XIV конференция «Математические модели и численные методы в биологии и медицине»

Математическое моделирование инфицирования SARS-CoV-2 в группе индивидов, случайно перемещающихся в ограниченном помещении

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- Modeling of the relative chaotic movement of individuals in a limited area in a panic. Examples of calculations, the influence of the intensity of chaotic movement, the influence of obstacles on the rate of evacuation
- Simulation of COVID-19 infection in the local atmosphere. The traditional model of pathogen development in the human body. A modified model that takes into account the penetration of infection from the atmosphere into the body and the degree of immunity. The effect of fluctuations in the concentration of the virus in the atmosphere and an explosive increase in the concentration of the virus in the body
- Examples of numerical simulation of infection in the local atmosphere with a random concentration of COVID-19 virions. The impact of medical care. The method of the probability density function.
- Main conclusions

Modeling of chaotic movement of individuals in a group during evacuation from a limited area

A model of random movement of individuals taking into account their collisions in a limited area

The equation of random movement of individuals. Elastic collision model

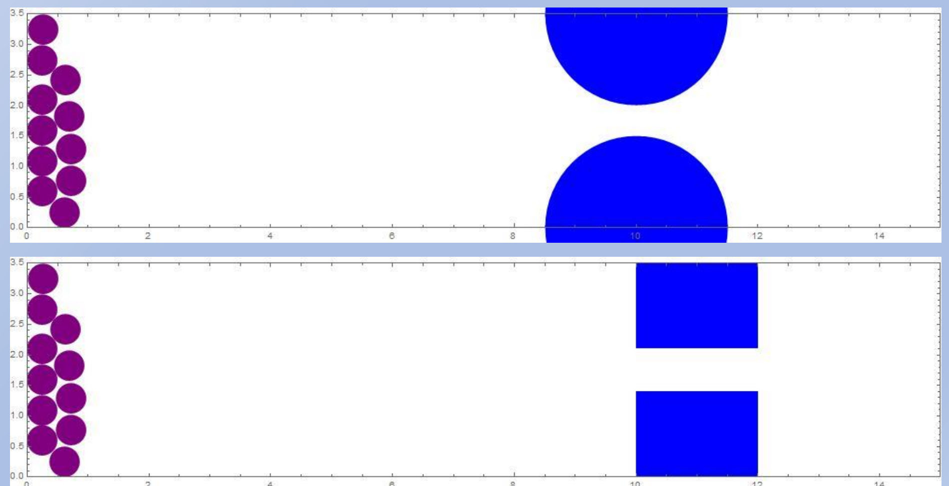
$$\frac{d\mathbf{V}^{(\alpha)}}{dt} = \frac{1}{\tau^{(\alpha)}}\left(\mathbf{U}\left(\mathbf{R}^{(\alpha)},t\right)-\mathbf{V}^{(\alpha)}\right)+\frac{1}{m^{(\alpha)}}\left\{\mathbf{F}_{\mathrm{Wall}}\left(\mathbf{R}^{(\alpha)}\right)+\sum_{\beta\neq\alpha}^{N}\mathbf{F}_{\mathrm{Repl}}\left(\mathbf{R}^{(\alpha)}-\mathbf{R}^{(\beta)}\right)\right\} \qquad \mathbf{F}_{\mathrm{Wall}}(\mathbf{x}) = -\frac{\partial U_{\mathrm{Wall}}\left(|\mathbf{x}|\right)}{\partial \mathbf{x}}$$

$$\frac{d\mathbf{X}(t)}{dt} = \mathbf{V}(t) \qquad \mathbf{V}(0)=\mathbf{V}_0 \qquad \mathbf{X}(0)=\mathbf{X}_0$$

Random desired speed of movement of an individual

$$\mathbf{U}(t)=\left\langle \mathbf{U}(t)\right\rangle+\mathbf{u}(t) \qquad \frac{d\mathbf{u}(t)}{dt}=\frac{1}{T_E}\left(\zeta(t)-\mathbf{u}(t)\right) \qquad \left\langle \mathbf{u}(t)\right\rangle = 0$$

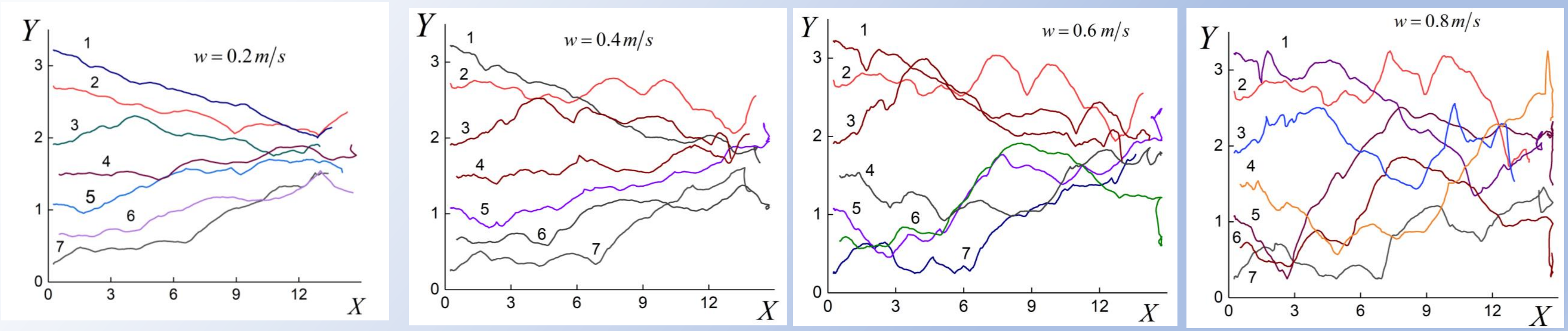
$$\left\langle \zeta_i(t')\zeta_j(t'')\right\rangle = 2\delta_{ij}\tau_0\left\langle \zeta^2\right\rangle \delta(t'-t'')$$



Example of the initial location of individuals in a group

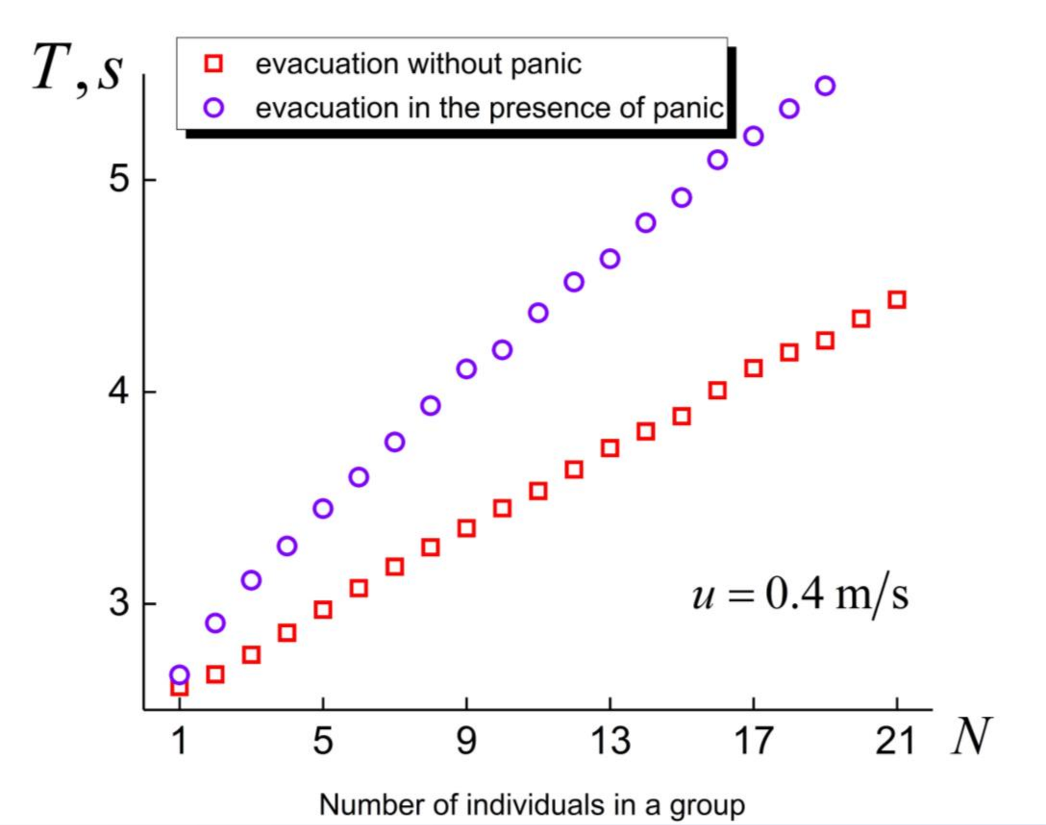
Results of simulation of movement in conditions of panic

Examples of bottlenecks in the presence of obstacles

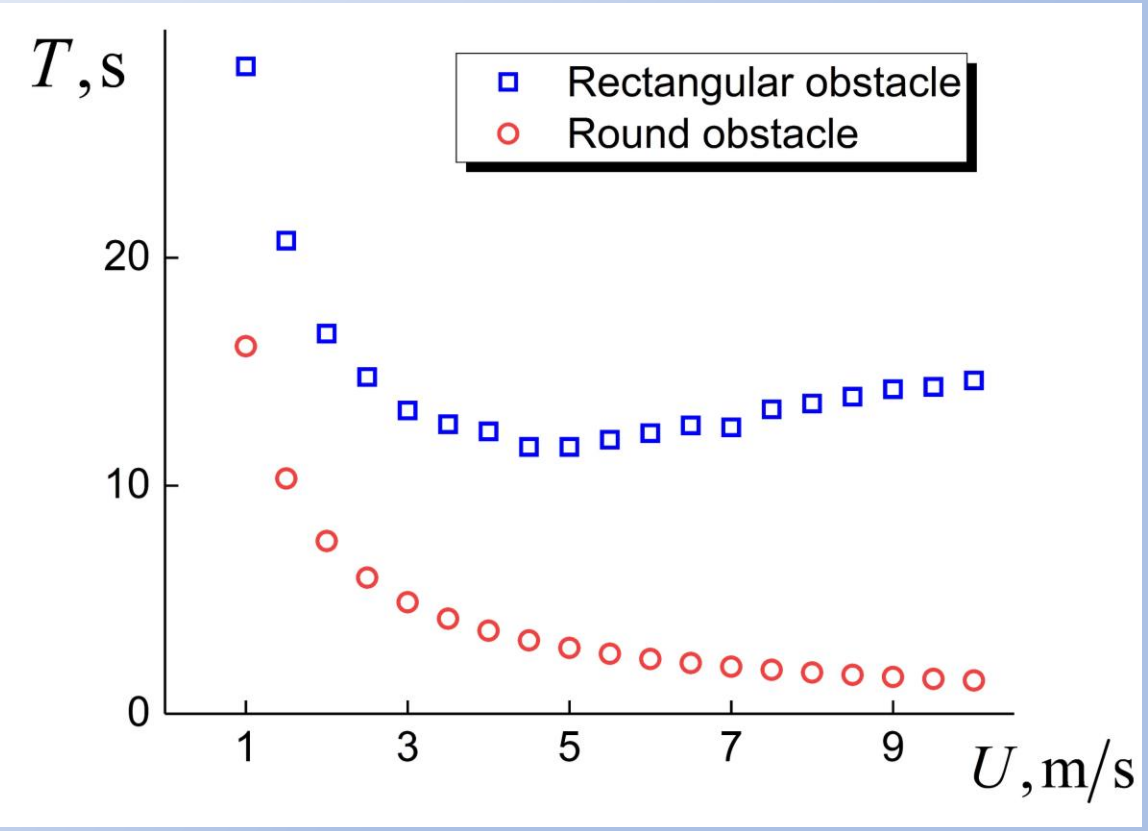


Examples of random trajectories of individuals during evacuation in panic conditions

The effect of panic on the evacuation time from a limited space



Evacuation in panic conditions from a limited space without obstacles



The effect of the average speed of movement of a group of persons on evacuation in a panic, taking into account obstacles

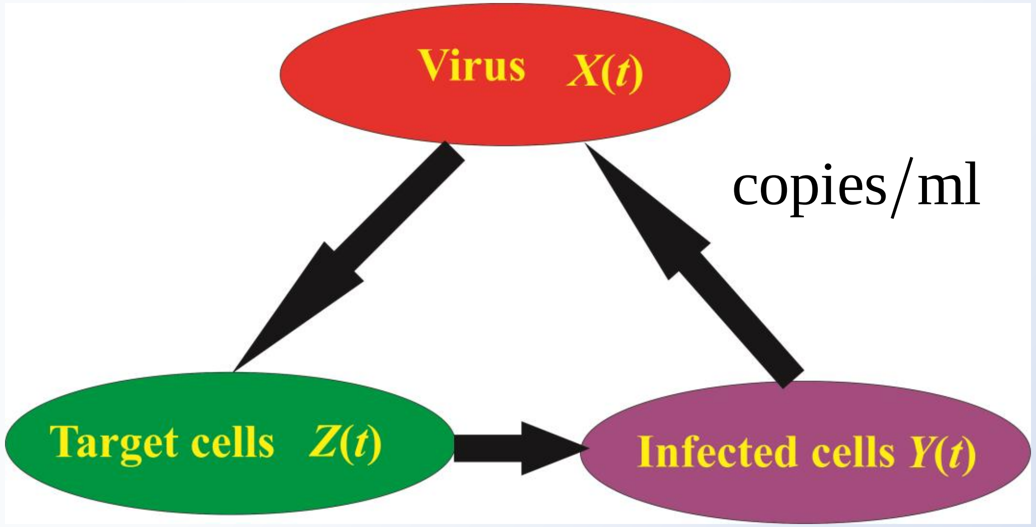
Summary of the results of the first part of the study

- ✓ Chaotic movement of individuals leads to the formation of local areas with an increased concentration of people
- ✓ The presence of persons infected with viral diseases may increase the local concentration of virions exceeding the critical value
- ✓ A model of COVID-19 infection and pathogen development in the body of any individual in a group in a local atmosphere with virion concentration fluctuations is proposed

Traditional and modified models of the growth of the concentration of pathogens COVID-19 in the human body

The traditional model of infection development in the human body

Model constants for SARS – CoV



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$$\frac{dX}{dt} = \frac{1}{T_X} Y - \frac{1}{\tau_X} X \qquad X(0) = X_0$$

concentrations of pathogenic cells

$$\frac{dY}{dt} = \frac{1}{T_Y} \frac{Z}{Z_0} X - \frac{1}{\tau_Y} Y \qquad Y(0) = Y_0$$

concentration of infected cells

$$\frac{dZ}{dt} = -\frac{1}{T_Y} \frac{Z}{Z_0} X - \frac{1}{\tau_Z} Z \qquad Z(0) = Z_0$$

concentration of target cells affected by the virus

T_X, T_Y characteristic generation time of pathogenic cells and virus-infected cells

τ_X, τ_Y, τ_Z characteristic lifetimes of pathogenic cells, infected cells and target cells

1K.S. Kim, K. Ejima, S. Iwanami, Y. Fujita, H. Ohashi, Y. Koizumi, et al., PLoS Biol. 19 (2021), e3001128. https://doi.org/10.1371/journal.pbio.3001128
S. Iwanami, K. Ejima, K.S. Kim, K. Noshita, Y. Fujita, T. Miyazaki, et al., PLoS Med. 18 (2021), e1003660. https://doi.org/10.1371/journal

Dimensionless variables

$X^* = \dfrac{X}{X_{\mathrm{cr}}}$ $\quad Y^* = \dfrac{Y}{X_{\mathrm{cr}}}$ $\quad Z^* = \dfrac{Z}{Z_0}$ dimensionless concentrations of virus, infected and susceptible cells

$t^* = t/\tau_X$ dimensionless time

X_{cr} the critical value of the concentration of virions absorbed by the body, starting from which there is an explosive increase in the concentration of the pathogen

$T_X^* = T_X/\tau_X \quad T_Y^* = T_Y/\tau_Y \quad \tau_Y^* = \tau_Y/\tau_X$ dimensionless characteristic times

$Z_0^* = Z_0/X_{\mathrm{cr}} \quad Z_0^* >> 1$ the ratio of the initial concentration of target cells of the body to the critical level of pathogen concentration in the body

Equations in dimensionless form

Concentrations of pathogen and target cells

$$\frac{\mathrm{d}X^*(t^*)}{\mathrm{d}t^*} = \frac{1}{T_X^*} Y^*(t^*) - X^*(t^*)$$

$$\frac{\mathrm{d}Z^*(t^*)}{\mathrm{d}t^*} = -\frac{1}{T_Y^* Z_0^*} Z^*(t^*) X^*(t^*) - \frac{1}{\tau_Z^*} Z^*(t^*)$$

$$\frac{\mathrm{d}Y^*(t^*)}{\mathrm{d}t^*} = \frac{1}{\tau_Y^*}\left\{\frac{\tau_Y^*}{T_Y^*} Z^*(t^*) X^*(t^*) - Y^*(t^*)\right\}$$

$$Y^*(t^*) \approx \frac{\tau_Y^*}{T_Y^*} Z^*(t^*) X^*(t^*)$$

quasistationary condition

$$X^*(0) = X_0^* \qquad Y^*(0) = Y_0^* \qquad Z^*(0) = 1$$

The final system of equations for COVID-19 infection

$$\boxed{\frac{\mathrm{d}X^*(t^*)}{\mathrm{d}t^*} = \Gamma_X Z^*(t^*) X^*(t^*) - X^*(t^*)}$$

$$\boxed{\frac{\mathrm{d}Z^*(t^*)}{\mathrm{d}t^*} = -\mathrm{B}_Z Z_0^* Z^*(t^*) X^*(t^*) - \frac{1}{\tau_Z^*} Z^*(t^*)}$$

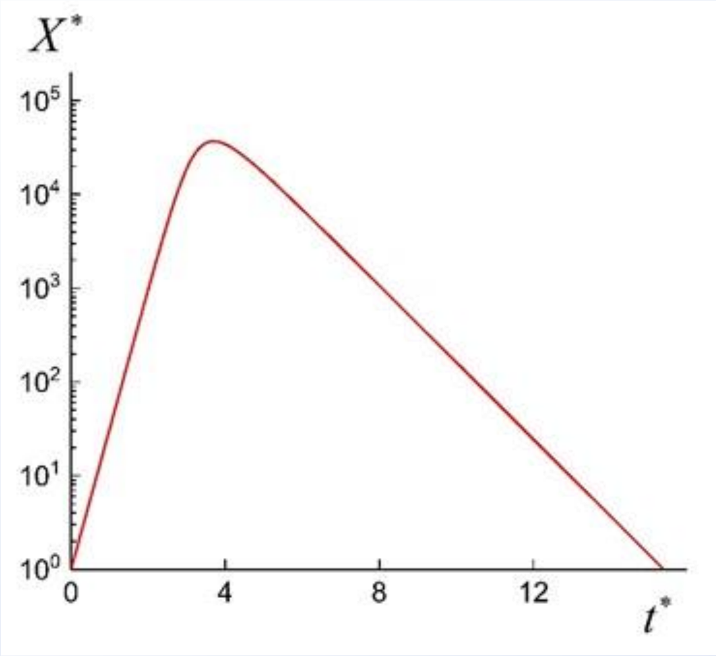
Example of calculation according to the traditional model

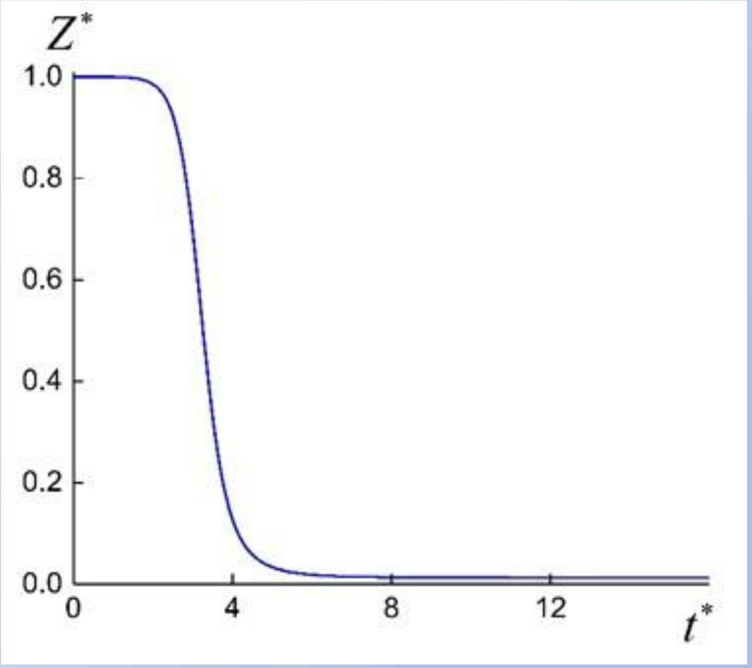
Model constants for SARS – CoV – 2

δ	Death rate of infected cells, 1/day	0.93
γ	Maximum rate constant for viral replication, 1/day	4.13
β	Rate constant for virus infection, 1/day	4.9 E-8
$1/\tau_Z$	Death rate of target cells, 1/day	1.0 E-8

Model coefficients

$$\mathrm{B}_Z = \frac{1}{T_Y^* Z_0^*} = \frac{\beta}{\delta} \qquad \Gamma_X = \frac{1}{T_X^*} \frac{\tau_Y^*}{T_Y^*} = \frac{\gamma}{\delta}$$

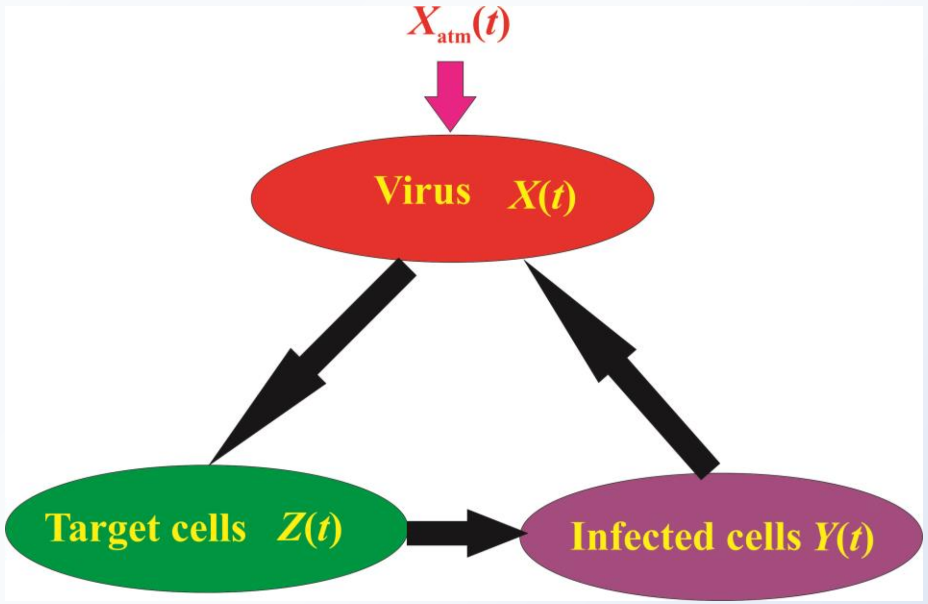




Dynamics of concentrations of pathogen cells and target cells of the body

Modified model

Introduction of the degree of immunity, critical concentration of pathogen concentration and virion concentration in the local atmosphere



Modified COVID-19 infection model

Equation for the concentration of pathogenic cells

$$\frac{dX^*(t^*)}{dt^*} = \frac{1}{T_X^*} Y^*(t^*) + \frac{X_{atm}^*(t^*)}{T_{in}^*} - X^*(t^*)$$

Equation for the concentration of infected cells

$$\frac{dY^*(t^*)}{dt^*} = \frac{1}{\tau_Y^*}\left\{\frac{\tau_Y^*}{T_Y^*} Z^*(t^*)\left(\frac{X^*(t^*)}{1+\alpha_{im}^* X^*(t^*)} - 1\right) X^*(t^*) - Y^*(t^*)\right\}$$

Equation for the concentration of target cells of the body

$$\frac{dZ^*(t^*)}{dt^*} = -\frac{1}{T_Y^* Z_0^*} Z^*(t^*) X^*(t^*) - \frac{1}{\tau_Z^*} Z^*(t^*)$$

$$\alpha_{im}^* = \frac{\Gamma_X}{1+\Gamma_X}\alpha_{im}$$

α_{im} the degree of initial immunity

X_{atm}^* concentration of virions in the local atmosphere

T_{in}^* characteristic time of transport of absorbed virions to the organs affected by the virus

The system of equations of the modified model

Reduction of the system using the hypothesis of quasi-stationarity

Equation for the concentration of pathogenic cells

$$\boxed{\frac{\mathrm{d}X^*(t^*)}{\mathrm{d}t^*} = \Gamma_X Z^*(t^*)\left(\frac{X^*(t^*)}{1+\alpha_{\mathrm{im}}^* X^*(t^*)} - 1\right) X^*(t^*) + \frac{X_{\mathrm{atm}}^*(t^*)}{T_{\mathrm{in}}^*} - X^*(t^*)} \qquad X^*(0) = X_0^*$$

$$\alpha_{\mathrm{im}}^* = \frac{\Gamma_X}{1+\Gamma_X}\alpha_{\mathrm{im}}$$

Equation for the concentration of target cells of the body

$$\boxed{\frac{\mathrm{d}Z^*(t^*)}{\mathrm{d}t^*} = -\mathrm{B}_Z Z_0^* Z^*(t^*) X^*(t^*) - \frac{1}{\tau_Z^*} Z^*(t^*)} \qquad Z^*(0) = 1$$

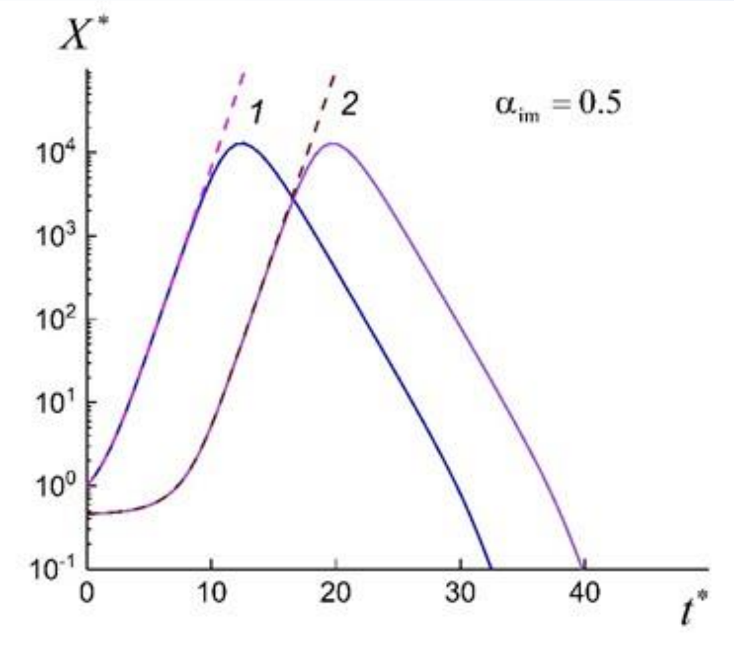
Reduction of the modified model at the initial stage of infection

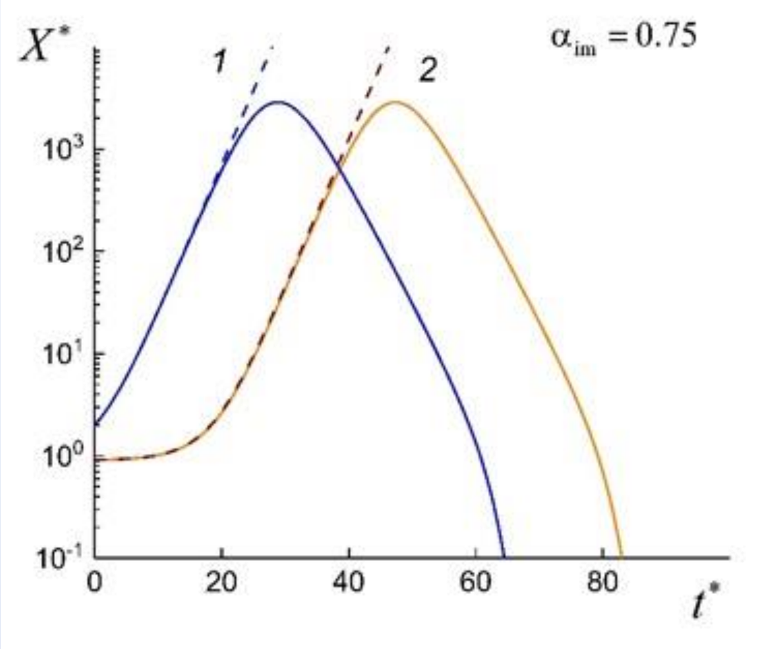
At the initial stage of infection until the peak value of the pathogen concentration is reached

$$Z^*\left(t^*\right) \approx Z^*\left(0\right) = 1$$

Equation for the concentration of pathogenic cells

$$\frac{\mathrm{d}X^*\left(t^*\right)}{\mathrm{d}t^*} = \Gamma_X\left(\frac{X^*\left(t^*\right)}{1+\alpha^*_{\mathrm{im}}X^*\left(t^*\right)} - 1\right)X^*\left(t^*\right) + \frac{X^*_{\mathrm{atm}}\left(t^*\right)}{T^*_{\mathrm{in}}} - X^*\left(t^*\right)$$

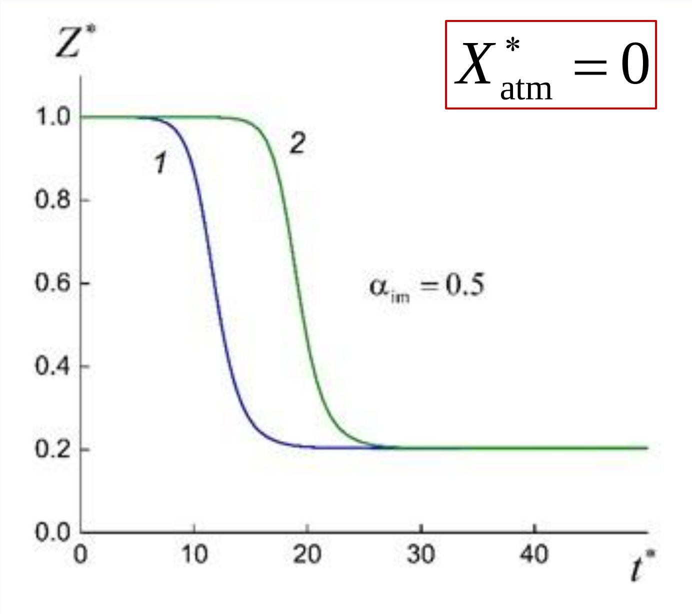


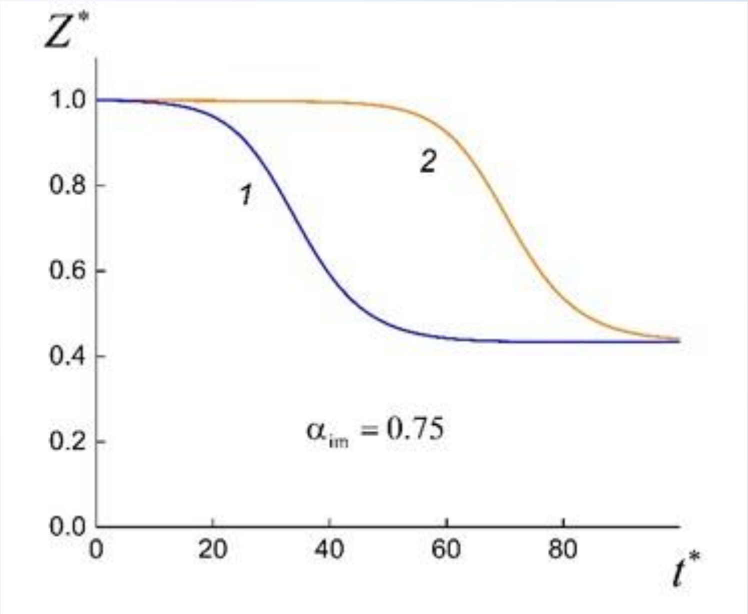


$$X^*_{\mathrm{atm}} = 0$$

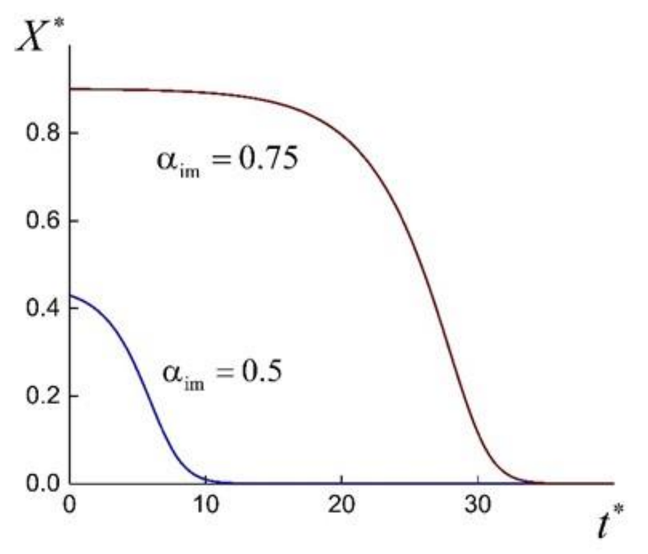
Calculation of the concentration of pathogen cells for two values of the degree of immunity. Calculation of solid curves in accordance with the complete system of equations dotted curves – calculation in accordance with the above equation

The influence of the degree of initial immunity on the dynamics of infection



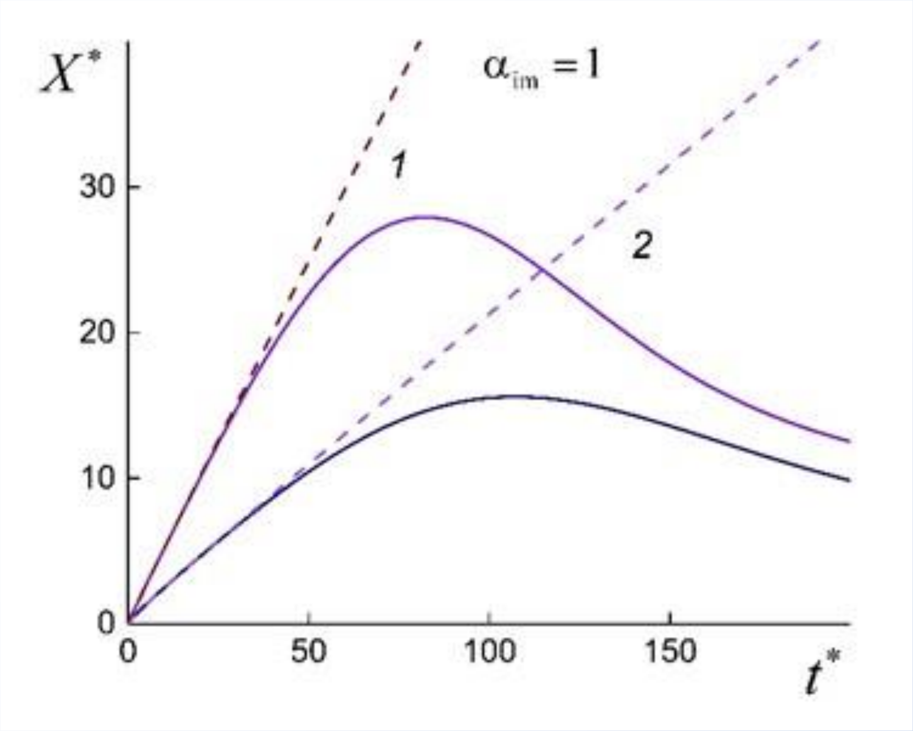


Dynamics of the concentration of cells of the affected organs. Curves 1 2 correspond to curves 1 and 2 in the previous Figure



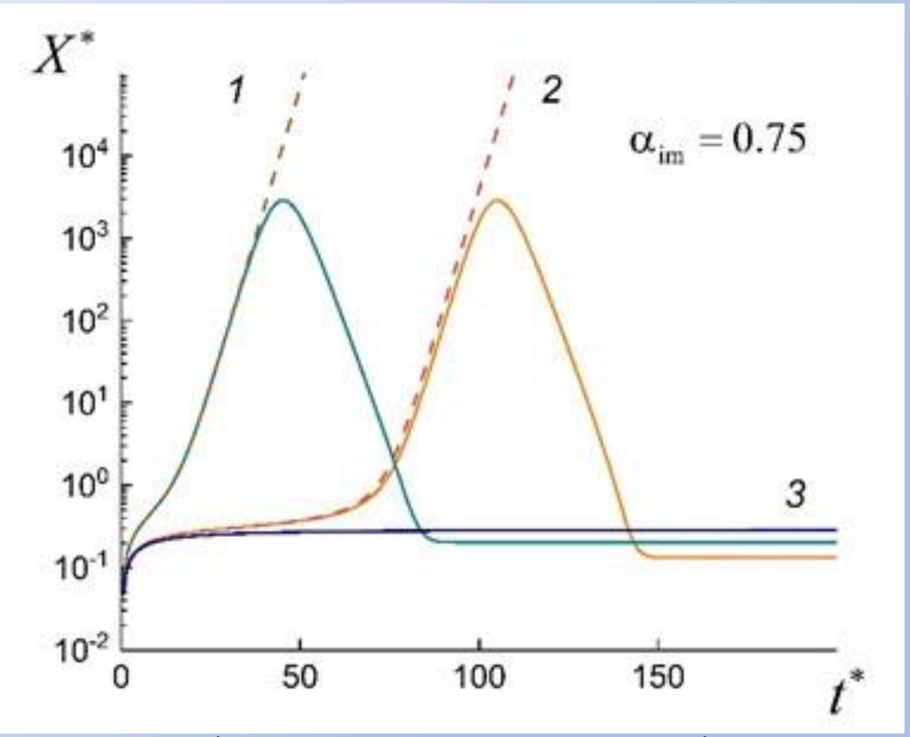
Degeneration of the virus in the body at the initial concentration of the pathogen below the critical value

Influence of virion concentration in the atmosphere



$1 - X_{atm}/T_{in} = 0.429$; $2 - X_{atm}/T_{in} = 0.714$

$\boxed{X_0^* = 0}$



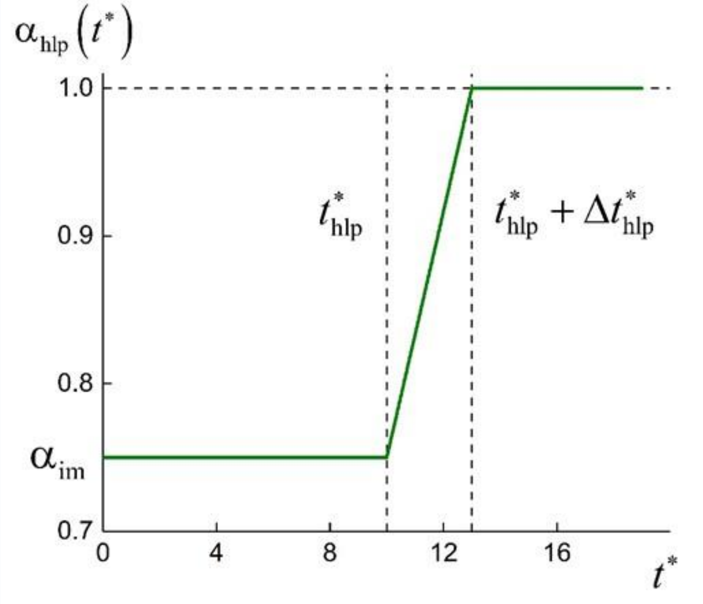
$1 - X_{atm}^*/T_{in}^* = 0.14$; $2 - X_{atm}^*/T_{in}^* = 0.12$;

$3 - X_{atm}^*/T_{in}^* = 0.1$

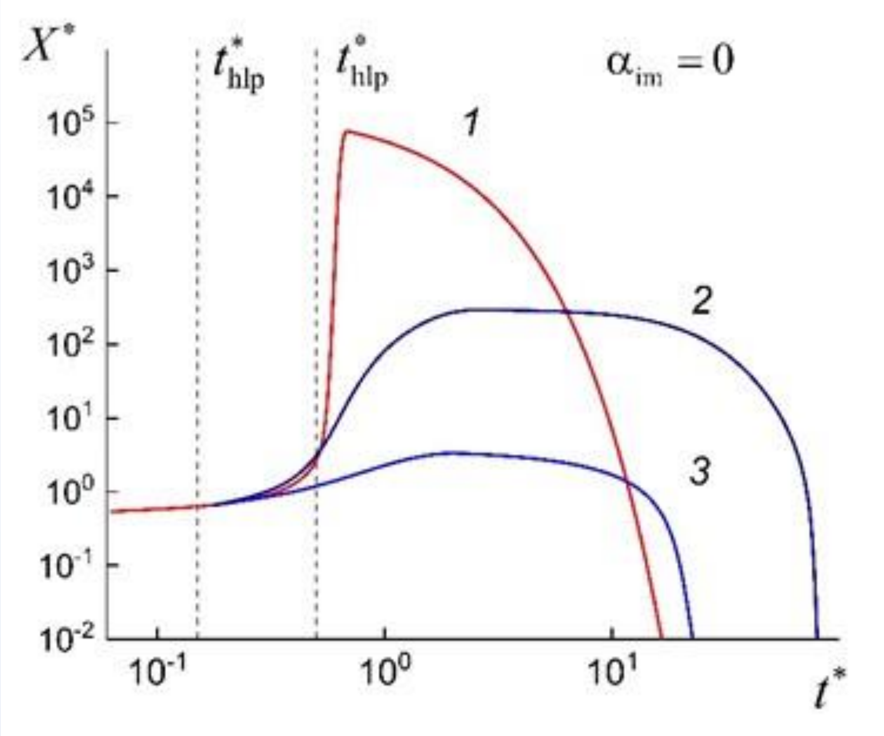
Dynamics of the concentration of pathogen cells in the affected organs at a given constant concentration of virions in the atmosphere and zero initial concentration of pathogen cells in the body

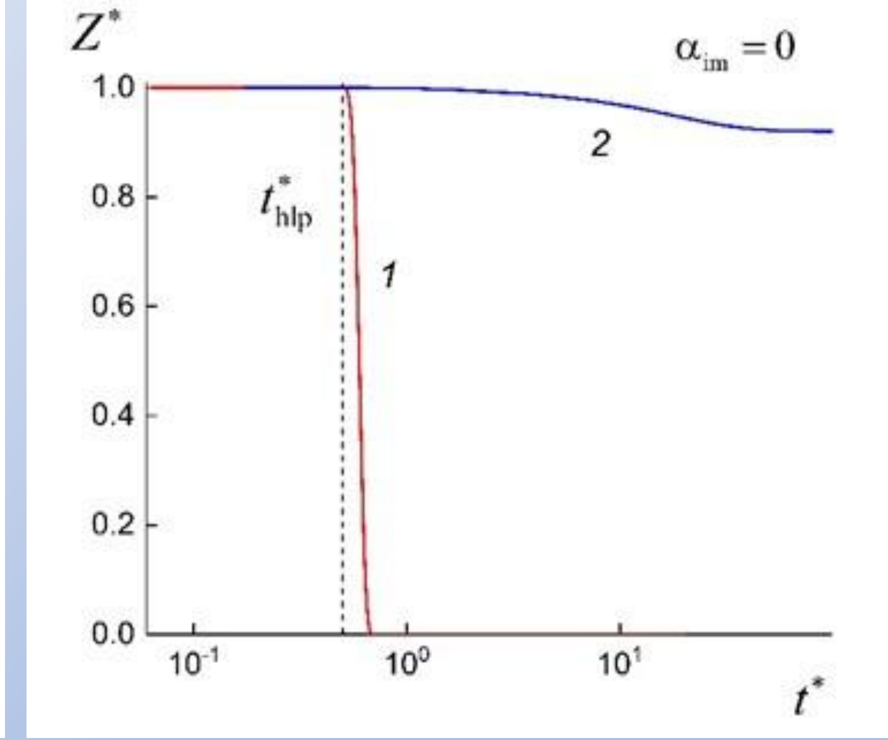
Modeling of medical care

Increasing the degree of immunity during medical intervention



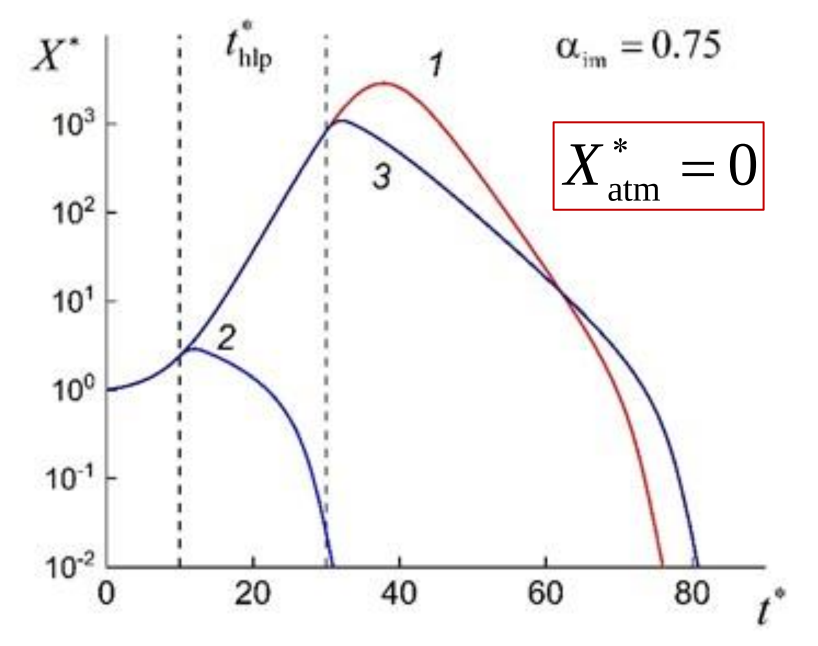
An example of an increase in the degree of immunity as a result of medical care

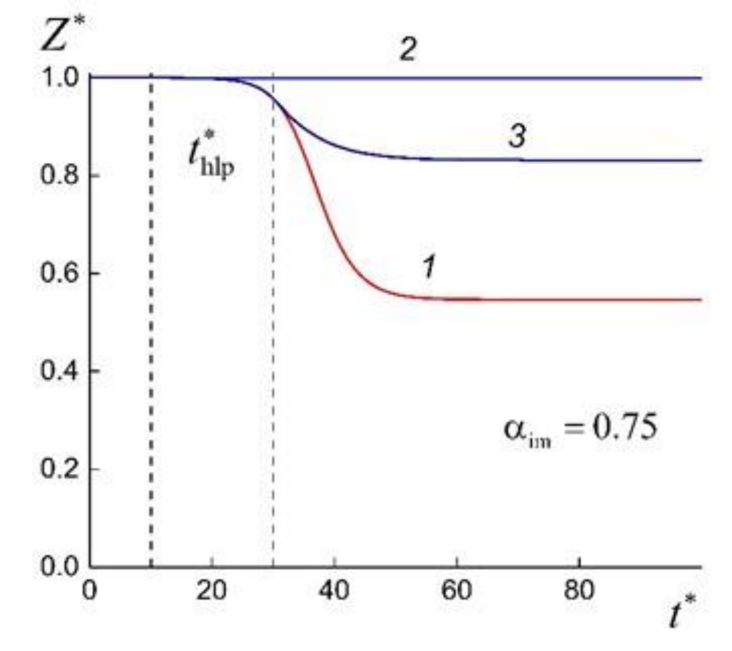


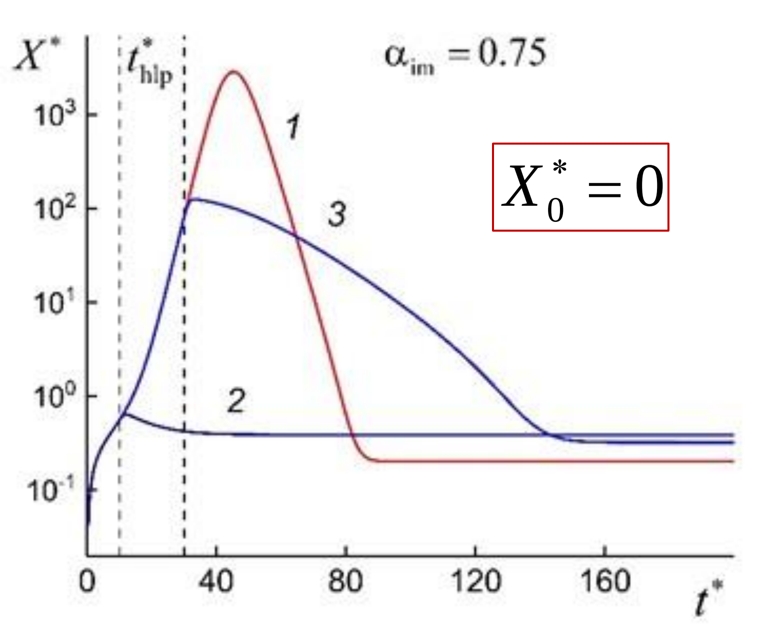


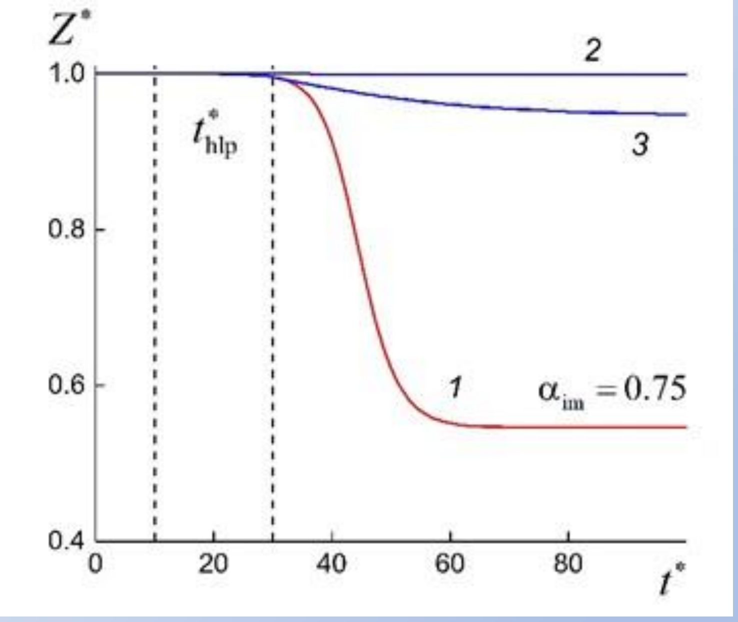
An example of changes in the concentration of pathogen cells and target cells affected by the virus in the absence of immunity and medical care (curve 1) and taking into account medical intervention (curves 2 and 3).

Medical care in an atmosphere with a constant concentration of virions









An example of the influence of medical care on the dynamics of changes in the concentration of pathogen and target cells of the body: 1 – without taking into account medical care; 2, 3 – taking into account medical care.

Stochastic model of COVID-19 infection

Simulation of virion concentration fluctuations in the local atmosphere

We model the concentration of virions in the local atmosphere as a statistically stationary logarithmically normal random process

$$X^*_{\mathrm{atm}}\left(t^*\right)=\left\langle X^*_{\mathrm{atm}}\right\rangle \exp\left[\Xi^*\left(t^*\right)\right] \qquad \left\langle \Xi^*\left(t^*\right)\right\rangle = 0$$

$\left\langle X^*_{\mathrm{atm}}\right\rangle$ is an average value of the virion concentration in the atmosphere; angle brackets denote averaging over an ensemble of realizations; $\Xi^*\left(t^*\right)$ random Gaussian process with autocorrelation function

$$\left\langle \Xi^*\left(t^{*\prime}\right)\Xi^*\left(t^{*\prime\prime}\right)\right\rangle = \left\langle \Xi^{*2}\right\rangle \Psi_{\Xi}\left(t^{*\prime\prime}-t^{*\prime}\right)$$

Integral time scale of concentration fluctuations $\qquad T^*_{\mathrm{atm}}=\int_0^\infty \Psi_{\Xi}\left(t^*\right)\mathrm{d}t^*$

Stochastic ordinary differential equation for virion concentration in the atmosphere

$$\boxed{\frac{\mathrm{d}\Xi^*\left(t^*\right)}{\mathrm{d}t^*}=\frac{1}{T^*_{\mathrm{atm}}}\left(\eta^*\left(t^*\right)-\Xi^*\left(t^*\right)\right)}$$

$\eta^*\left(t^*\right)$ Is a source of fluctuations (white noise) modeled by a random Gaussian process with an autocorrelation function $\tau_0^* << T^*_{\mathrm{atm}}$

$$\left\langle\eta^*\left(t^{*\prime}\right)\eta^*\left(t^{*\prime\prime}\right)\right\rangle=2\tau_0^*\left\langle\eta^{*2}\right\rangle\delta\left(t^{*\prime\prime}-t^{*\prime}\right)$$

Dispersion of virion concentration fluctuations in the atmosphere

$$\left\langle\Xi^{*2}\right\rangle=\frac{\tau_0^*}{T^*_{\mathrm{atm}}}\left\langle\eta^{*2}\right\rangle$$

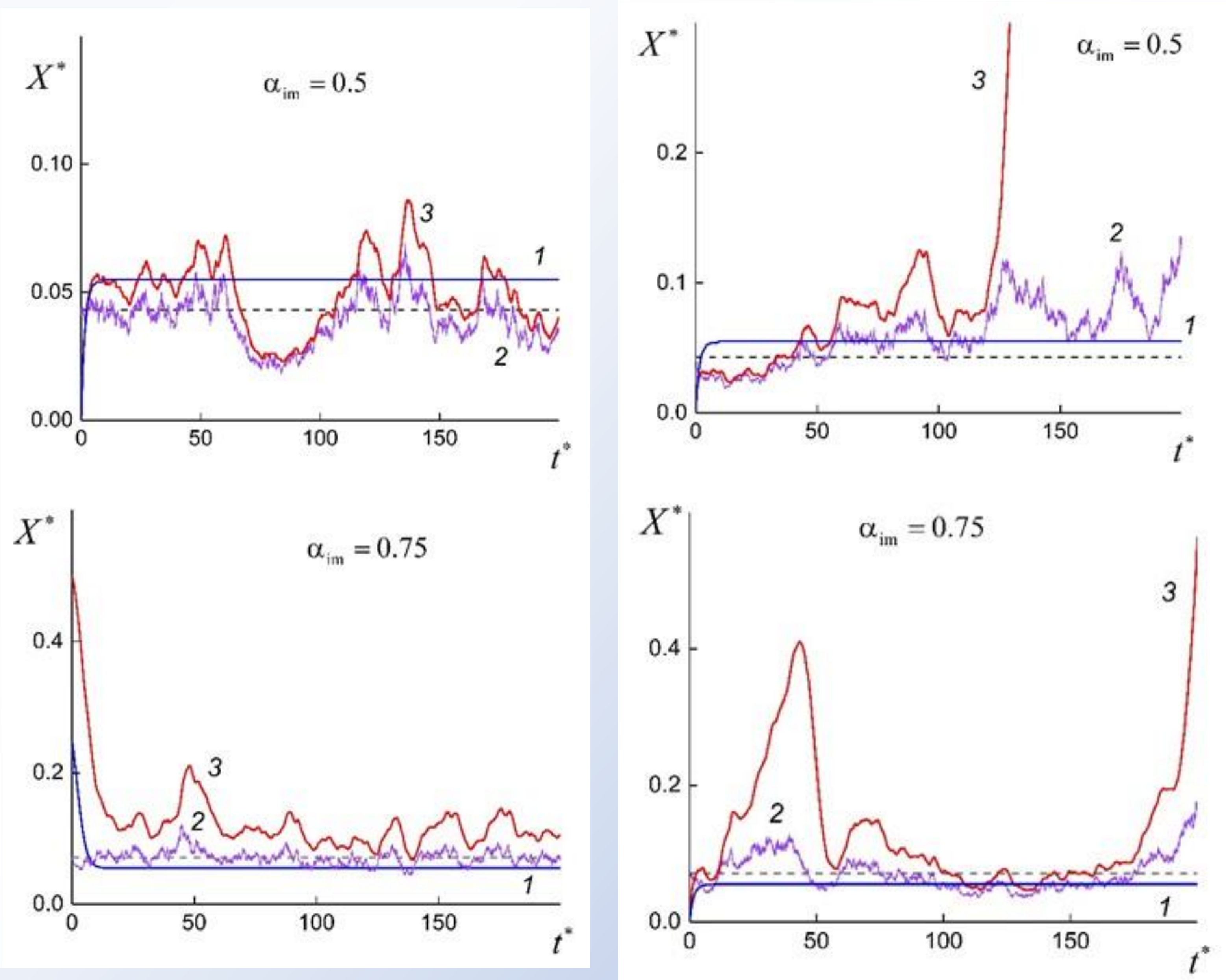
Autocorrelation function of the process

$$\Psi_{\Xi}\left(t^*\right)=\exp\left(-\frac{t^*}{T_{\mathrm{atm}}}\right)$$

The average value of the random concentration of virions in the local atmosphere

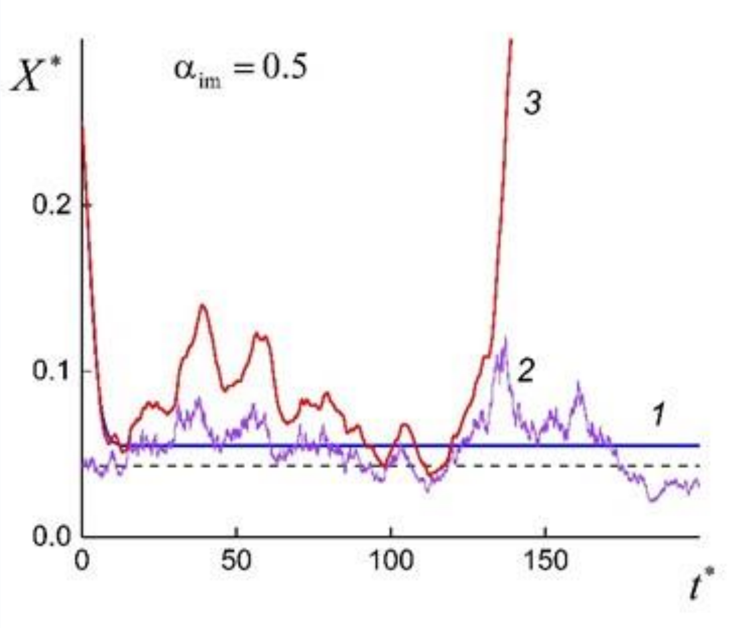
$$\boxed{\left\langle X^*_{\mathrm{atm}}\left(t^*\right)\right\rangle=\left\langle X^*_{\mathrm{atm}}\right\rangle\left\langle\exp\left[\Xi^*\left(t^*\right)\right]\right\rangle=\left\langle X^*_{\mathrm{atm}}\right\rangle\exp\left(\frac{\left\langle\Xi^{*2}\right\rangle}{2}\right)}$$

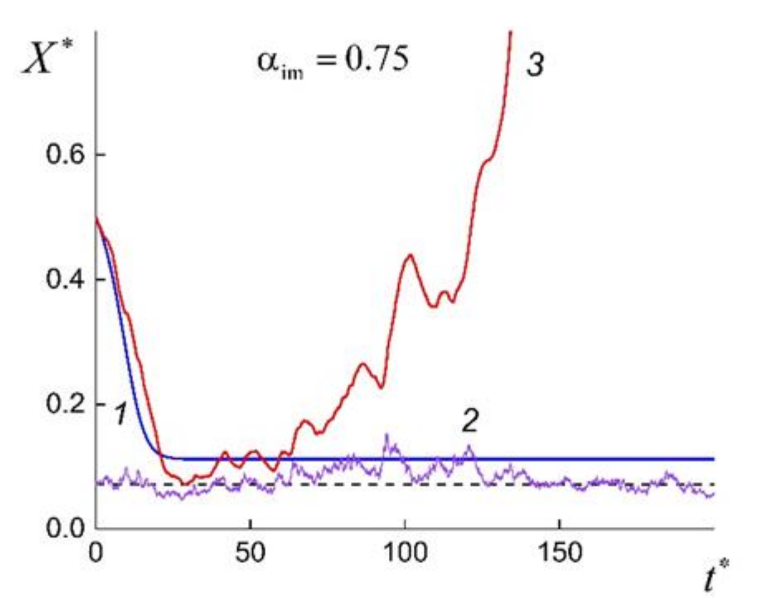
Direct numerical simulation I



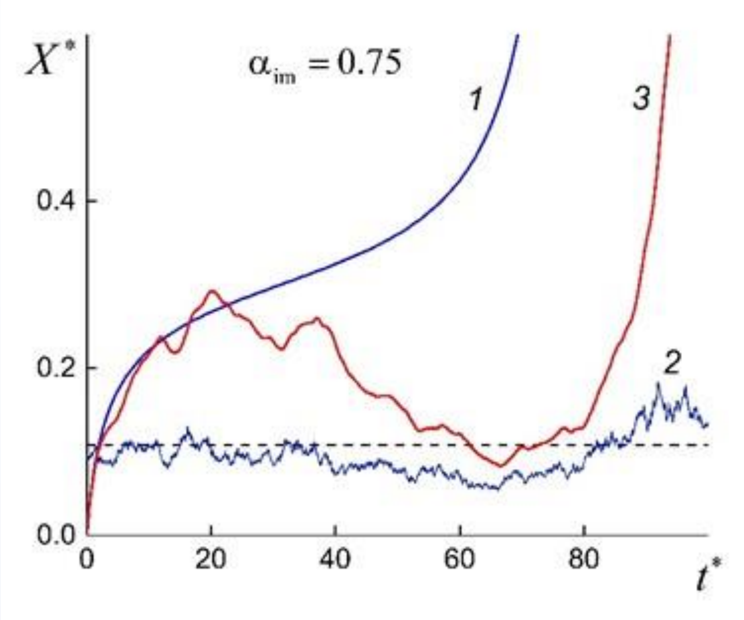
An example of random trajectories of the concentration of pathogen cells in an initially uninfected organism in a local atmosphere with fluctuations in the concentration of virions: 1 – stable concentration of pathogen in the body; 2 – concentration of virions in the atmosphere $X^*_{\text{atm}}\left(t^*\right)/T^*_{\text{in}}$; 3 – random concentration of pathogen cells in the body

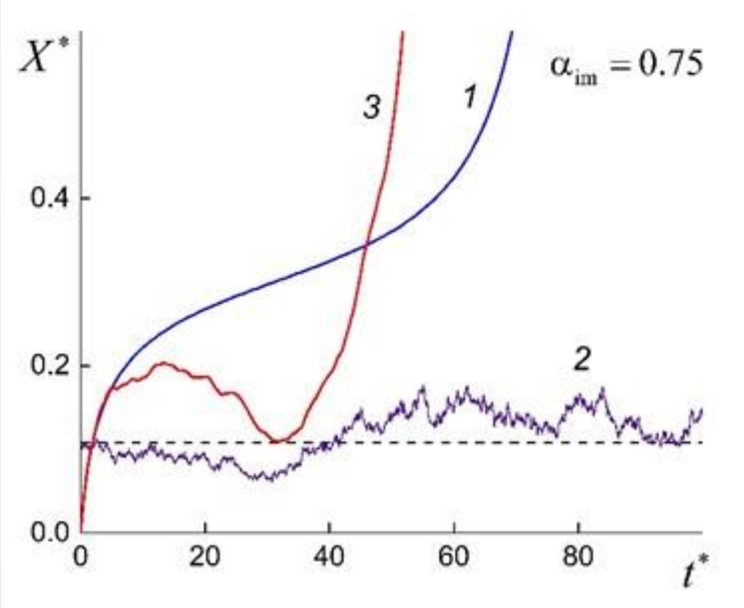
Direct numerical simulation II





Example of random pathogen concentration trajectories in an organism with a given initial pathogen concentration





Random trajectories of pathogen concentration in the body with an average concentration of virions in the atmosphere above the critical level

Probability density function method (PDF)

$$\Phi\left(X^*,t^*\right)=\left\langle\varphi\left(X^*,t^*\right)\right\rangle=\left\langle\delta\left(X^*-X^*\left(t^*\right)\right)\right\rangle$$

X^* is the point of the phase space; $X^*\left(t^*\right)$ is random concentration

Reduced equation for pathogen concentration

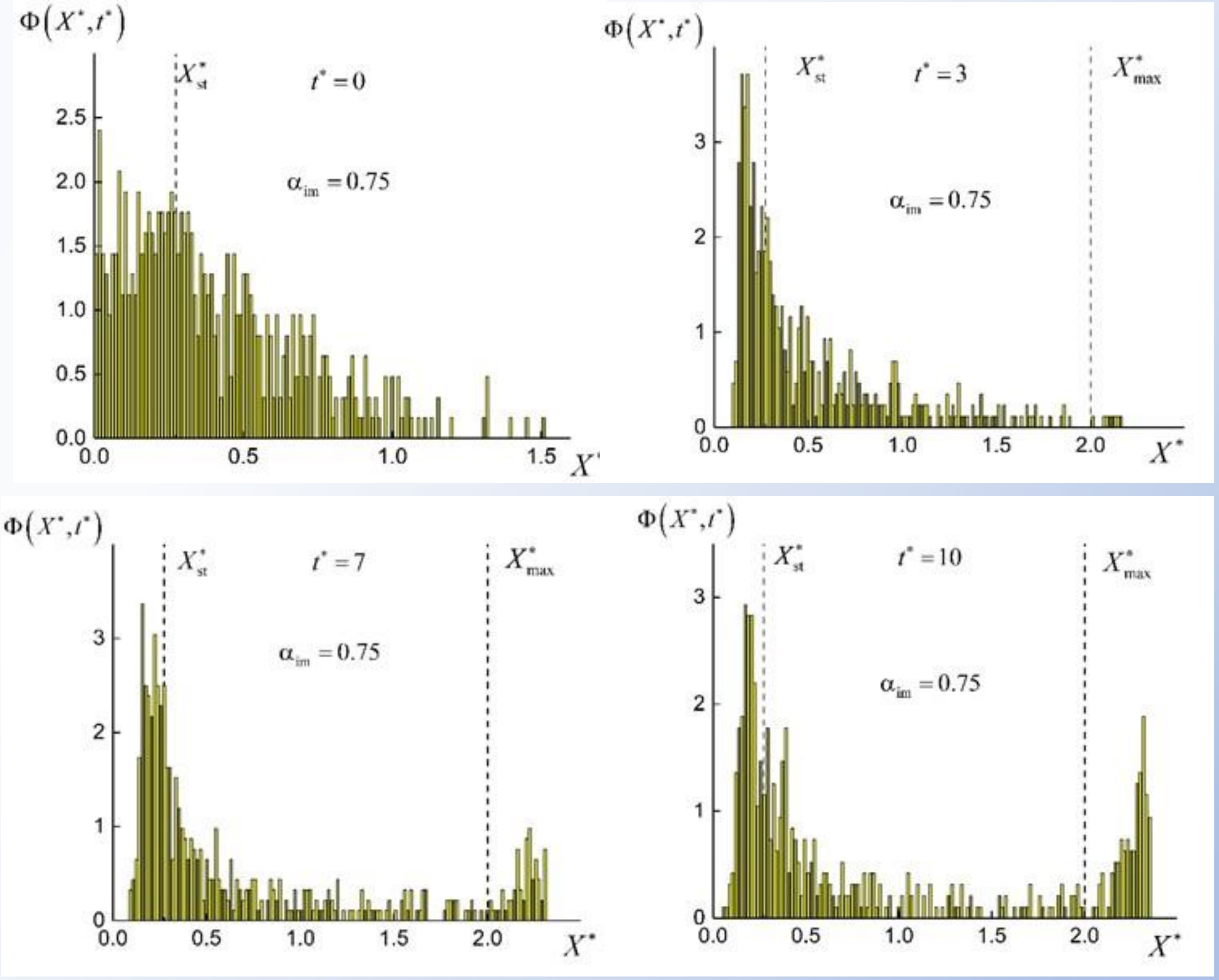
$$\boxed{\frac{\mathrm{d}X^*\left(t^*\right)}{\mathrm{d}t^*}=\left\{\Gamma_X\frac{X^*\left(t^*\right)}{1+\Gamma_X\alpha_{\mathrm{im}}X^*\left(t^*\right)}X^*\left(t^*\right)+\frac{X^*_{\mathrm{atm}}\left(t^*\right)}{T^*_{\mathrm{in}}}-X^*\left(t^*\right)\right\}F_{\max}\left(X^*\left(t^*\right)\right)}$$

Limiting function

$$F_{\max}\left(X^*\right)=\frac{1}{2}\left[1-\mathrm{erf}\left(\frac{X^*-X^*_{\max}}{\Delta X^*_{\max}}\right)\right]$$

$$\Delta X^*_{\max}\ll X^*_{\max}$$

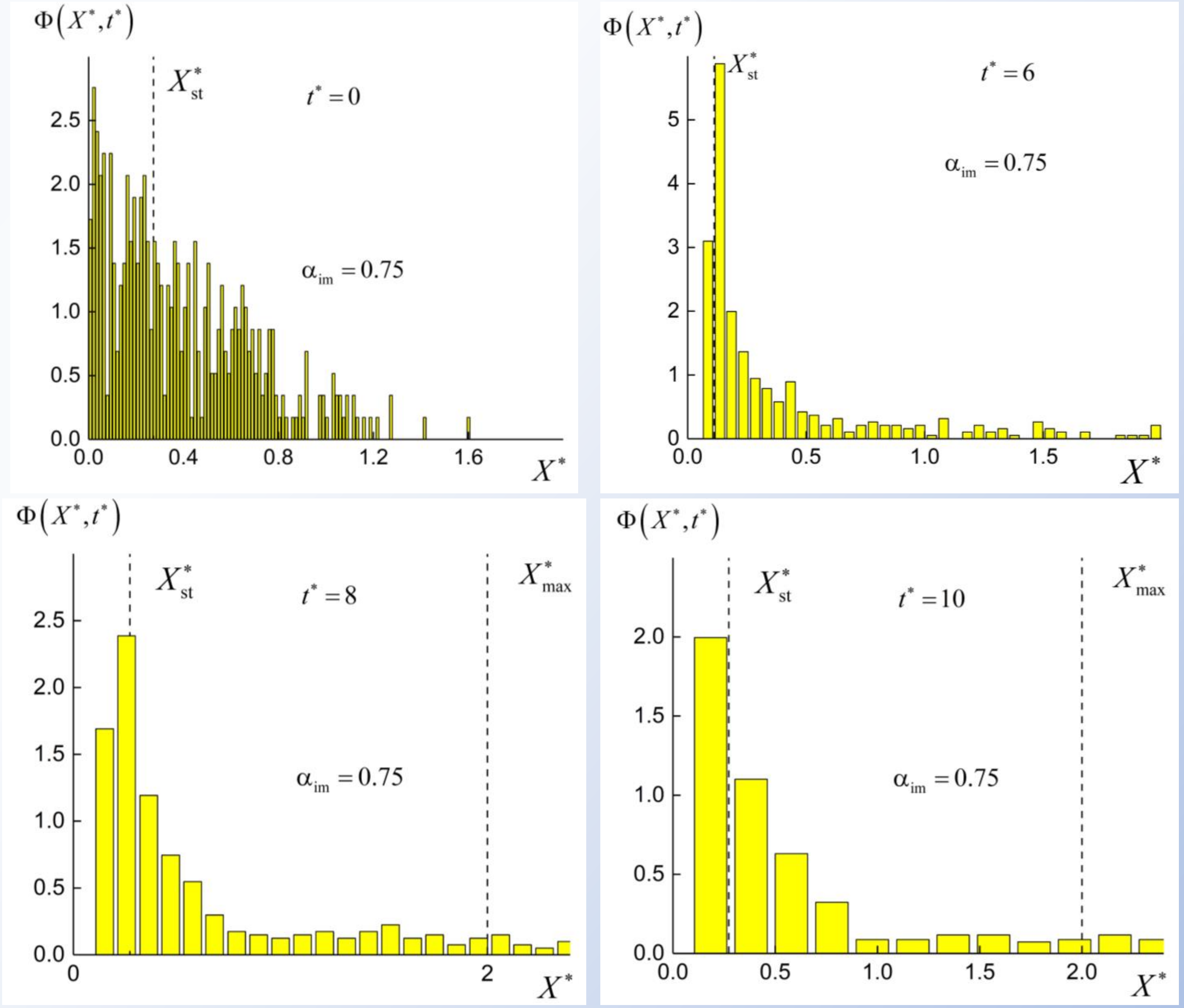
Empirical PDF with a limiting function



X^*_{st} is the stationary concentration of the pathogen in the body when the concentration of virions in the atmosphere is below the critical value

An example of an empirical PDF in the case when a part of the population passes into the stage of an active disease

Empirical PDF based on the solution of a complete system of equations



Simulation of the probability density function of the pathogen concentration in the body based on the solution of a complete system of equations

Main conclusions

A mathematical model of COVID-19 infection of an individual in a small group of people, among whom there are carriers of infection, has been developed

- ✓ A mathematical model of the random movement of a group of people in a limited area is proposed. The process of evacuation from a dangerous zone with obstacles in conditions of panic is considered
- ✓ The traditional COVID-19 infection model has been modified. The initial degree of immunity, the change in the rate of generation of pathogen cells from infected body cells, the absorption of virions from the local atmosphere are taken into account
- ✓ The results of calculations of the dynamics of the concentration of pathogen cells in an organism with varying degrees of immunity and the concentration of virions in the atmosphere are presented
- ✓ A qualitative difference in the dynamics of infection in a local atmosphere with a constant and fluctuating concentration of virions is shown
- ✓ A method for analyzing the dynamics of infection of a group of people based on the empirical probability density function of the random concentration of the pathogen in the body is proposed

Acknowledgements

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Thanks for your attention