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Междисциплинарный научный центр
«Математическое моделирование в биомедицине»

Моделирование распространения вирусной инфекции в культуре клеток с учётом внутриклеточной регуляции

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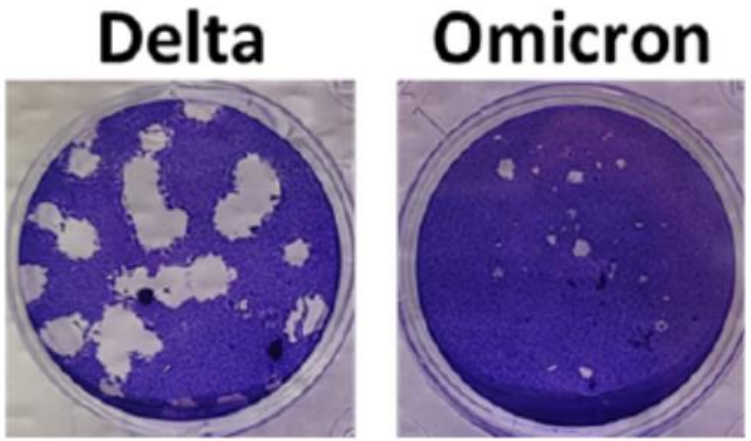
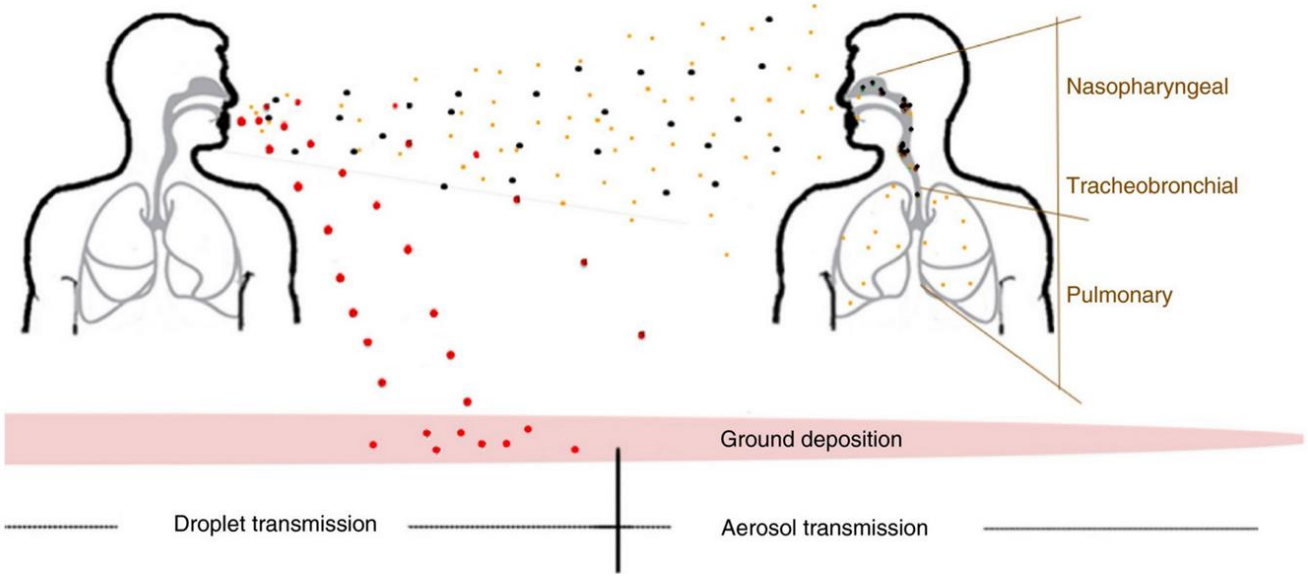
XIV конференция «Математические модели и численные методы в биологии и медицине», ИВМ РАН, 1-2 ноября 2022

Вирулентность и инфекционность

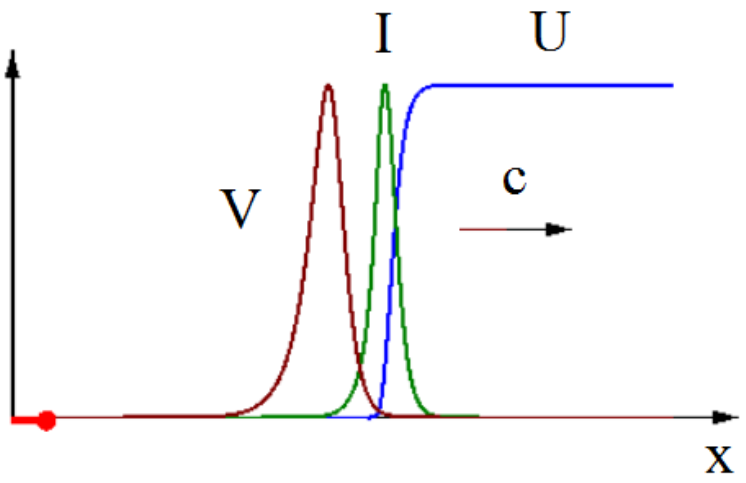




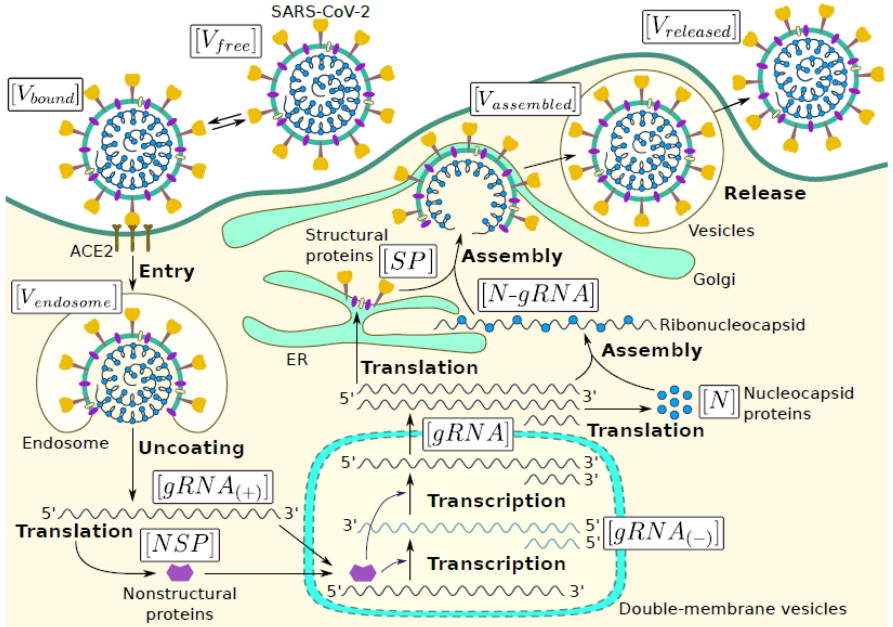
$$\frac{\partial U}{\partial t} = -aUV,$$

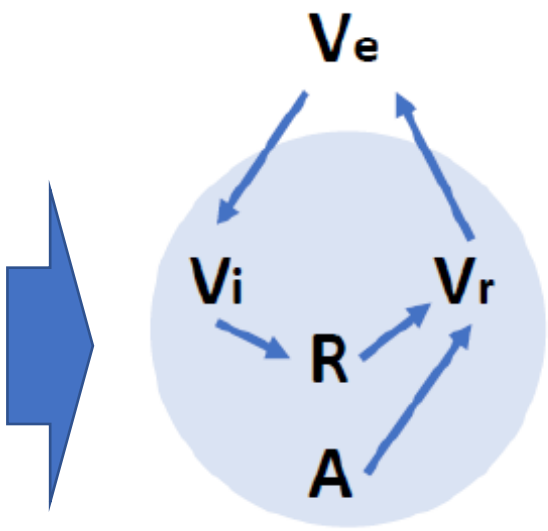
$$\frac{\partial I}{\partial t} = aUV - \beta I,$$

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



Модель





$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,$$

$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

$$\frac{\partial V_r}{\partial t} = k_3 A R - q_2 V_r,$$

$$\frac{\partial A}{\partial t} = -k_4 A R.$$

Dmitry Grebennikov et al. "Intracellular Life Cycle Kinetics of SARS-CoV-2 Predicted Using Mathematical Modelling". In: *Viruses* 13.9 (Aug. 2021), p. 1735. DOI: 10.3390/v13091735. URL: https://doi.org/10.3390/v13091735.

- клетки не делятся
- клетки не двигаются

Nikolay Bessonov; Gennady Bocharov; Anastasiia Mozokhina; Vitaly Volpert. Viral Infection Spreading in Cell Culture with Intracellular Regulation. *Mathematics* **2023**, *11*, 1526 . doi: **10.3390/math11061526**

Число репликации вируса

$$\frac{dV_e}{dt} = q_2 V_r - q_1 V_e - \sigma_1 V_e,$$
$$\frac{dV_i}{dt} = q_1 V_e - k_1 V_i,$$
$$\frac{dR}{dt} = k_1 V_i - \sigma_2 R,$$
$$\frac{dV_r}{dt} = k_3 A R - q_2 V_r,$$
$$\frac{dA}{dt} = -k_4 A R.$$

- стационарные точки: $V_r = 0,\ V_e = 0,\ V_i = 0,\ R = 0,$ and any A.
- линеаризуем в окрестности точки ($A=A_0$, 0, 0, 0, 0):

$$\mathcal{A} = \begin{pmatrix} -q_1 - \sigma_1 & 0 & 0 & q_2 \\ q_1 & -k_1 & 0 & 0 \\ 0 & k_1 & -\sigma_2 & 0 \\ 0 & 0 & k_3 A_0 & -q_2 \end{pmatrix}$$

- система имеет положительный корень при выполнении условия:

$$det(\mathcal{A}) = (q_1 + \sigma_1) k_1 \sigma_2 q_2 - q_2 q_1 k_1 k_3 A_0 < 0.$$

$$R_v = \frac{q_1 k_3 A_0}{\sigma_2 (q_1 + \sigma_1)} > 1$$

=> инфекция распространяется

Вирусная нагрузка

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,$$

$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

$$\frac{\partial V_r}{\partial t} = k_3 AR - q_2 V_r,$$

$$\frac{\partial A}{\partial t} = -k_4 AR.$$

Consider the travelling wave solution $V_e(x,t) = v(x-ct)$, $R(x,t) = u(x-ct)$, $A(x,t) = w(x-ct)$, $V_i(x,t) = y(x-ct)$, $V_r(x,t) = z(x-ct)$ with the limits at infinity:

$$v(\pm\infty) = u(\pm\infty) = y(\pm\infty) = z(\pm\infty) = 0,\ w(-\infty) = w_f,\ w(+\infty) = w_0, \qquad (2.16)$$

$$Dv'' + cv' + q_2 z - q_1 v - \sigma_1 v = 0,$$

$$cy' + q_1 v - k_1 y = 0,$$

$$cu' + k_1 y - \sigma_2 u = 0,$$

$$cz' + k_3 wu - q_2 z = 0,$$

$$cw' - k_4 wu = 0,$$

интегрируем по $\xi \in (-\infty, +\infty)$,

$$q_2 J(z) = (q_1 + \sigma_1) J(v),$$

$$q_1 J(v) = k_1 J(y),$$

$$k_1 J(y) = \sigma_2 J(u),$$

$$c \ln \frac{w_f}{w_0} = -k_4 J(u),$$

$$\frac{ck_3}{k_4}(w_0 - w_f) = q_2 J(z).$$

исключаем интегралы

$$R_v(\tilde{w} - 1) = \ln \tilde{w}, \quad \tilde{w} = w_f / w_0,$$

ненулевое решение существует при Rv > 1

$$J(v) = \int_{-\infty}^{+\infty} v d\xi = -\frac{c\sigma_2}{q_1 k_4} \ln \tilde{w} = \frac{cw_0}{q_1 + \sigma_1} \frac{k_3}{k_4}(1 - \tilde{w}).$$

- вирусная нагрузка

If $\tilde{w} \ll 0$, then $\ln \tilde{w} \approx -R_v$ and

$$J(v) \approx \frac{cw_0 k_3}{(q_1 + \sigma_1) k_4},$$

Скорость волны

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,$$

$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

$$\frac{\partial V_r}{\partial t} = k_3 A R - q_2 V_r,$$

$$\frac{\partial A}{\partial t} = -k_4 A R.$$

Consider the travelling wave solution

w -> w0

$$Dv'' + cv' + q_2 z - q_1 v - \sigma_1 v = 0,$$

$$cy' + q_1 v - k_1 y = 0,$$

$$cu' + k_1 y - \sigma_2 u = 0,$$

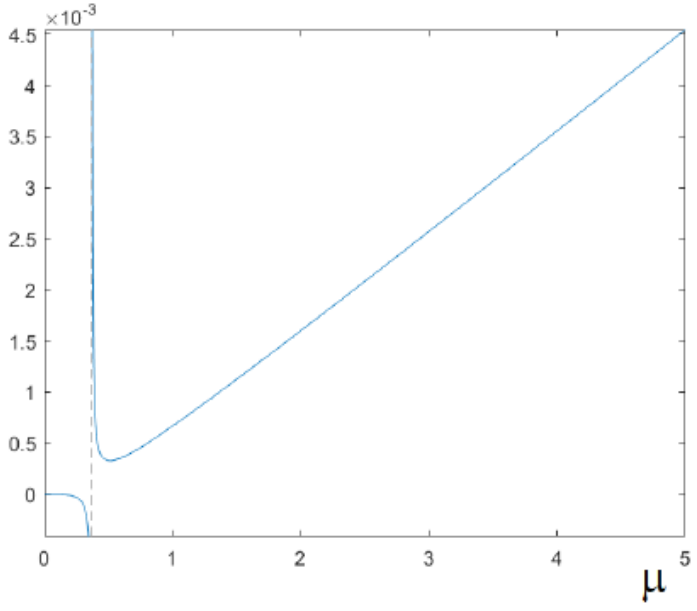
$$cz' + k_3 w_0 u - q_2 z = 0.$$

Будем искать решение в виде: $v(\xi) = pe^{-\lambda\xi}, \; u(\xi) = qe^{-\lambda\xi}, \; y(\xi) = me^{-\lambda\xi}, \quad z(\xi) = le^{-\lambda\xi}.$

$$\begin{vmatrix} D\lambda^2 - c\lambda - (q_1+\sigma_1) & 0 & 0 & q_2 \\ q_1 & -c\lambda - k_1 & 0 & 0 \\ 0 & k_1 & -c\lambda - \sigma_2 & 0 \\ 0 & 0 & k_3 w_0 & -c\lambda - q_2 \end{vmatrix} = 0,$$

Denote $\mu = c\lambda$ and express c^2, thus we get:

$$c^2 = \min_{\mu > \mu_0} \frac{D\mu^2(\mu+k_1)(\mu+\sigma_2)(\mu+q_2)}{(\mu+q_1+\sigma_1)(\mu+k_1)(\mu+\sigma_2)(\mu+q_2) - q_1 q_2 k_1 k_3 w_0},$$



Зависимость от параметров

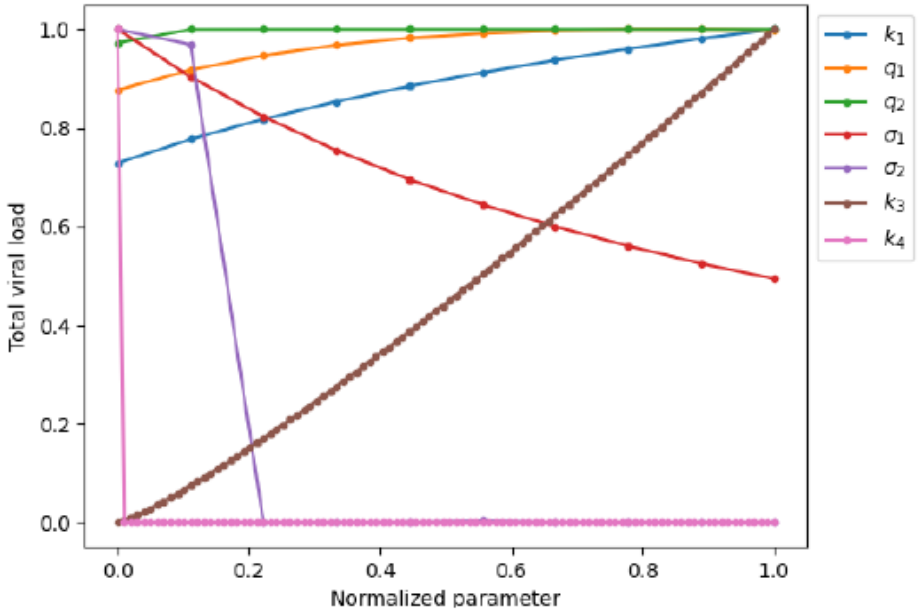
$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

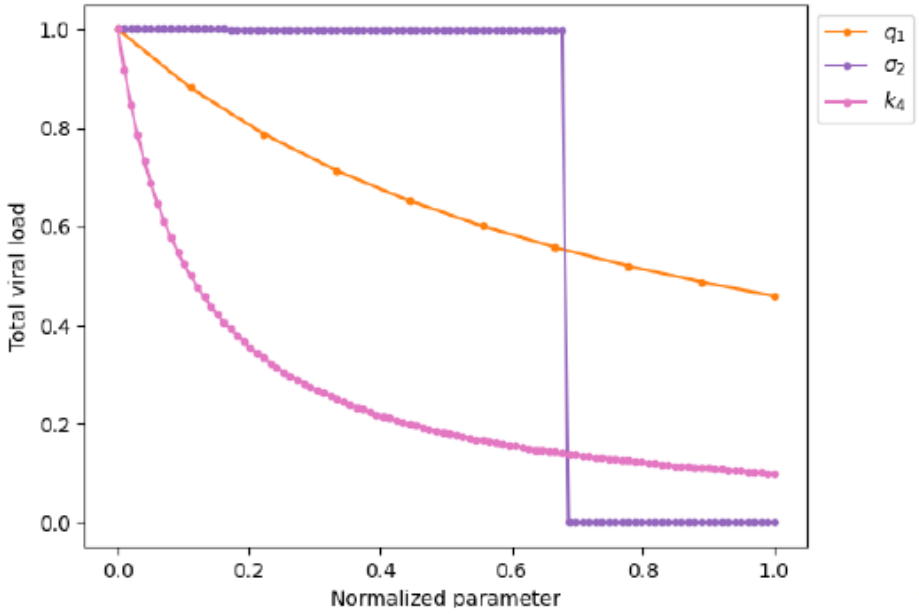
$$\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,$$

$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

$$\frac{\partial V_r}{\partial t} = k_3 A R - q_2 V_r,$$

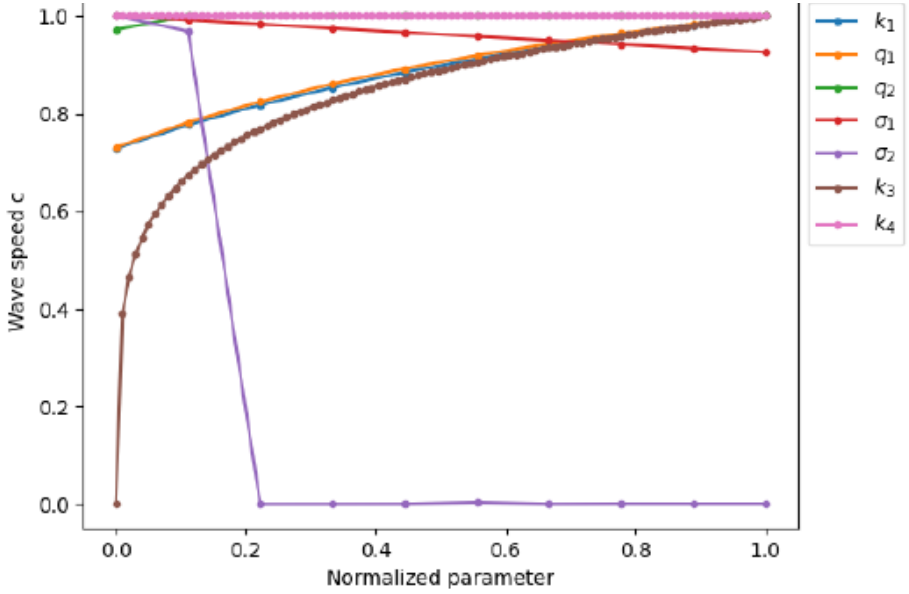
$$\frac{\partial A}{\partial t} = -k_4 A R.$$

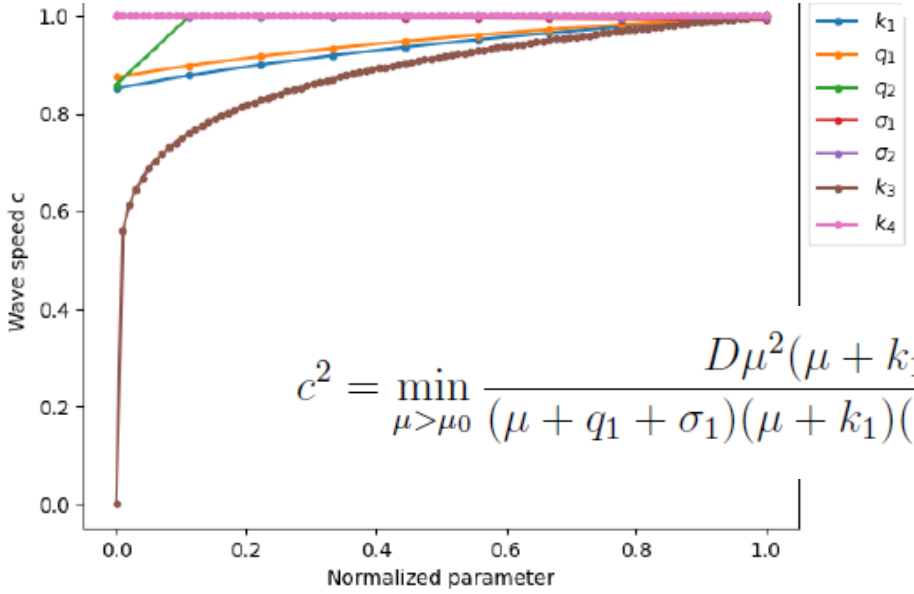




$$J(v) \approx \frac{c w_0 k_3}{(q_1+\sigma_1)k_4},$$

$$J(v) = \int_{-\infty}^{+\infty} v\, d\xi = -\frac{c\sigma_2}{q_1 k_4}\ln \tilde{w}$$





$$R_v = \frac{q_1 k_3 A_0}{\sigma_2(q_1+\sigma_1)}.$$

$$c^2 = \min_{\mu>\mu_0} \frac{D\mu^2(\mu+k_1)(\mu+\sigma_2)(\mu+q_2)}{(\mu+q_1+\sigma_1)(\mu+k_1)(\mu+\sigma_2)(\mu+q_2) - q_1 q_2 k_1 k_3 w_0},$$

Редукция модели 1

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\boxed{\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,}$$

q1 and k1 are big

$$V_i = \frac{q_{10}}{k_{10}} V_e.$$

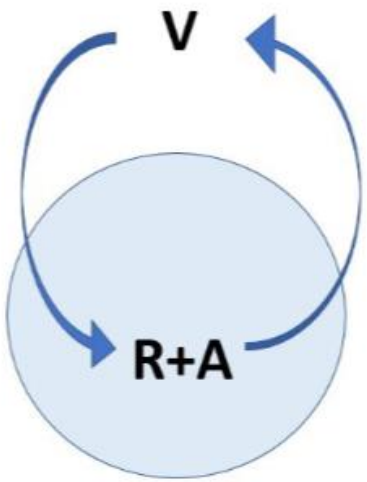
$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

$$\boxed{\frac{\partial V_r}{\partial t} = k_3 AR - q_2 V_r,}$$

k3 and q2 are big

$$V_r = \frac{k_{30}}{q_{20}} AR.$$

$$\frac{\partial A}{\partial t} = -k_4 AR.$$



$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + k_3 AR - (q_1 + \sigma_1) V_e,$$

$$\frac{\partial R}{\partial t} = q_1 V_e - \sigma_2 R,$$

$$\frac{\partial A}{\partial t} = -k_4 AR.$$

$$k_1 \sim k_3 = k_4,\ k_2 \sim q_1,\ V \sim V_e$$

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} + k_1 AR - k_2 V - \sigma_1 V,$$

$$\frac{\partial R}{\partial t} = k_2 V - \sigma_2 R,$$

$$\frac{\partial A}{\partial t} = -k_1 AR.$$

Редуцированная модель 1

$$\frac{dV}{dt} = k_1 AR - k_2 V - \sigma_1 V,$$

$$\frac{dR}{dt} = k_2 V - \sigma_2 R,$$

$$\frac{dA}{dt} = -k_1 AR.$$

- R_v и $J(v)$ – такие же, как в полной модели
- при больших k1 и q2 формула для c в полной модели сходится к формуле для c в редуцированной модели

$$R_v = \frac{k_1 k_2 A_0}{(k_2 + \sigma_1)\sigma_2}$$

$$c^2 = \min_{\mu > \mu_0} \frac{D\mu^2(\mu + k_1)(\mu + \sigma_2)(\mu + q_2)}{(\mu + q_1 + \sigma_1)(\mu + k_1)(\mu + \sigma_2)(\mu + q_2) - q_1 q_2 k_1 k_3 w_0},$$

$$J(v) = c\frac{w_0}{k_2 + \sigma_1}$$

$$c^2 = F(\mu) \equiv \frac{D\mu^2(\mu + \sigma_2)}{(\mu + \sigma_2)(\mu + k_2 + \sigma_1) - k_1 k_2 w_0}. \qquad c_0^2 = \min_{\mu > \mu_0} F(\mu),$$

Редукция 2

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\boxed{\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,}$$

q1 and k1 are big

$$V_i = \frac{q_{10}}{k_{10}} V_e.$$

$$\boxed{\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,}$$

k1 and sigma2 are big

$$R = \frac{k_{10}}{\sigma_{20}} V_i = \frac{q_{10}}{\sigma_{20}} V_e,$$

$$\frac{\partial V_r}{\partial t} = k_3 A R - q_2 V_r,$$

$$\frac{\partial A}{\partial t} = -k_4 A R.$$

$$\frac{\partial A}{\partial t} = -\frac{k_4 q_{10}}{\sigma_{20}} A V_e,$$

$$\frac{\partial V_r}{\partial t} = \frac{k_3 q_{10}}{\sigma_{20}} A V_e - q_2 V_r,$$

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - (q_1 + \sigma_1) V_e.$$

$$U = \kappa_1 A,\ I = \kappa_2 V_r,\ V = V_e.$$

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

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

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

$$a \sim \frac{k_4 q_1}{\sigma_2} = \frac{k_3 q_1 \kappa_2}{\sigma_2 \kappa_1}*,\ \beta \sim q_2,\ b \sim \frac{q_2}{\kappa_2},\ \sigma \sim (q_1 + \sigma_1),\ U_0 \sim \kappa_1 A_0.$$

Редуцированная модель 2

[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.

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

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

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

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

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

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

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

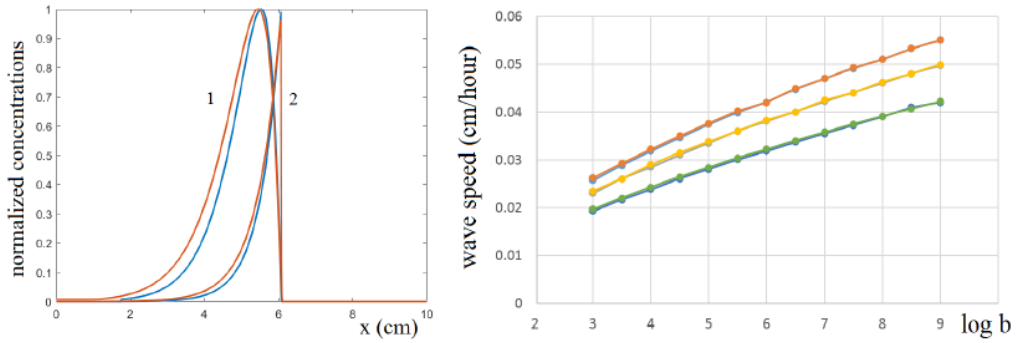


Figure 1: Left: virus concentration (curve 1) and concentration of infected cells (curve 2) in numerical simulations (red) and analytical approximation (blue) for the values of parameters: $a = 0.1$ $(1/(hour \cdot virus))$, $b = 1000$ $(copies/(hour \cdot cell))$, $\beta = 0.1$ $(1/hour)$, $\sigma = 0.1$ $(1/hour)$, $D = 10^{-4}$ $(cm^2/hour)$. 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).

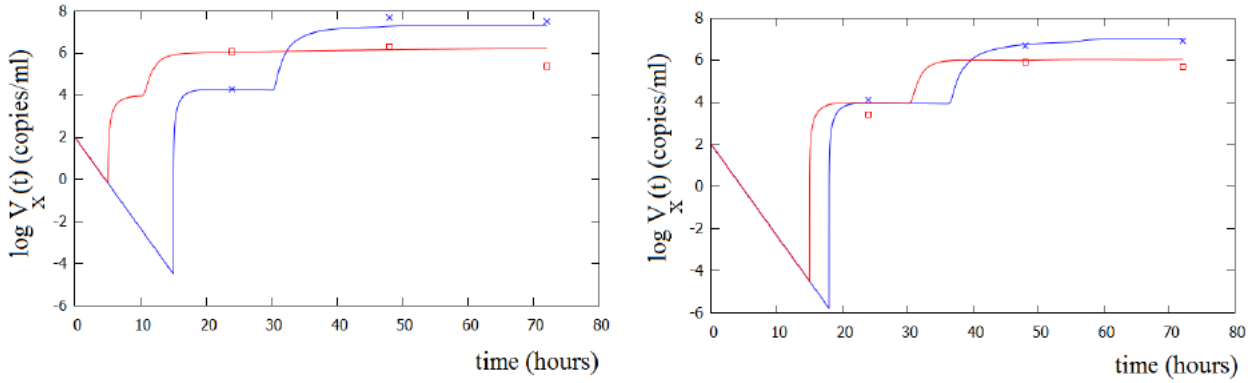
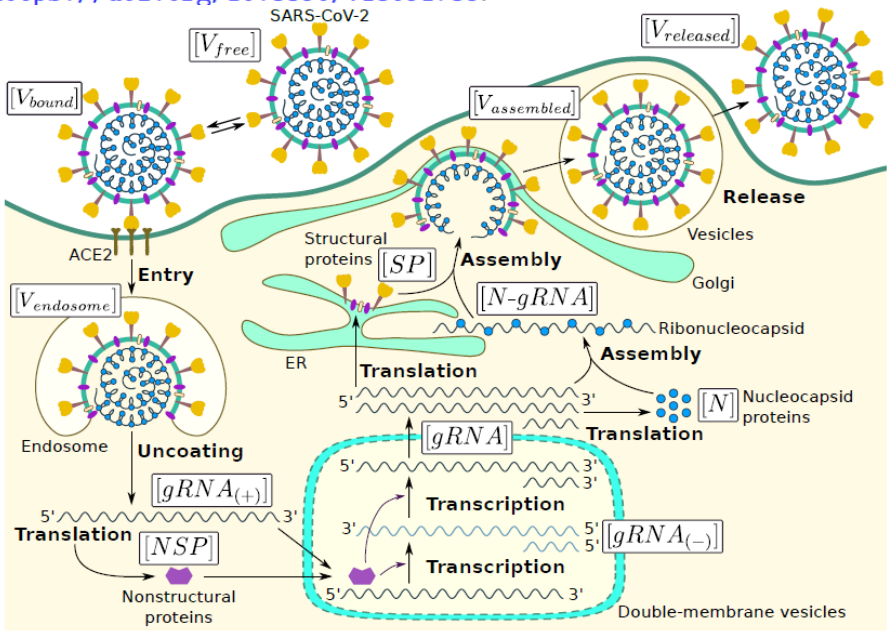


Figure 3: Left: human nasal cells, experimental results from [5] (dots) and numerical simulations with the values of parameters for Delta (blue): $a = 10^{-5}, b = 2 \cdot 10^7, \beta = 0.01, \sigma = 1, \tau = 15$; for Omicron (red): $a = 10^{-4}, b = 10^6, \beta = 0.01, \sigma = 1, \tau = 8$. Right: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

Валидация полной модели

Dmitry Grebennikov et al. "Intracellular Life Cycle Kinetics of SARS-CoV-2 Predicted Using Mathematical Modelling". In: *Viruses* 13.9 (Aug. 2021), p. 1735. DOI: 10.3390/v13091735. URL: https://doi.org/10.3390/v13091735.



$$\frac{d[V_{free}]}{dt} = -k_{bind}[V_{free}] - d_V[V_{free}] + k_{diss}[V_{bound}]$$

$$\frac{d[V_{bound}]}{dt} = k_{bind}[V_{free}] - (k_{fuse} + k_{diss} + d_V)[V_{bound}]$$

$$\frac{d[V_{endosome}]}{dt} = k_{fuse}[V_{bound}] - (k_{uncoat} + d_{endosome})[V_{endosome}]$$

$$\frac{d[gRNA_{(+)}]}{dt} = k_{uncoat}[V_{endosome}] - d_{gRNA}[gRNA_{(+)}].$$

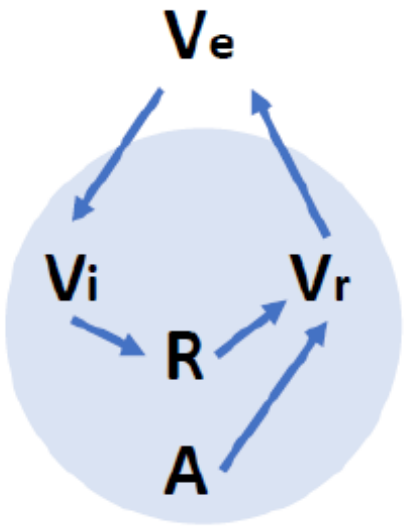
$$\frac{d[NSP]}{dt} = k_{transl} f_{ORF1}[gRNA_{(+)}] - d_{NSP}[NSP]$$

$$\frac{d[gRNA_{(-)}]}{dt} = k_{tr_{(-)}}[gRNA_{(+)}]\theta_{RdRp} - d_{gRNA_{(-)}}[gRNA_{(-)}]$$

$$\frac{d[gRNA]}{dt} = k_{tr_{(+)}}[gRNA_{(-)}]\theta_{RdRp} - (k_{complex}\theta_{complex} + d_{gRNA})[gRNA]$$

where

$$\theta_{RdRp} = \frac{[NSP]}{[NSP] + K_{NSP}}, \quad \theta_{complex} = \frac{[N]}{[N] + K_N}$$



$$\frac{d[N]}{dt} = k_{transl} f_N[gRNA] - k_{complex} n_N \theta_{complex}[gRNA] - d_N[N]$$

$$\frac{d[SP]}{dt} = k_{transl} f_{SP}[gRNA] - k_{assemb} n_{SP} \theta_{assemb}[N\text{-}gRNA] - d_{SP}[SP]$$

where

$$\theta_{assemb} = \frac{[SP]}{[SP] + K_{V_{rel}} n_{SP}}$$

$$\frac{d[N\text{-}gRNA]}{dt} = k_{complex}\theta_{complex}[gRNA] - (k_{assemb}\theta_{assemb} + d_{N\text{-}gRNA})[N\text{-}gRNA]$$

$$\frac{d[V_{assembled}]}{dt} = k_{assemb}\theta_{assemb}[N\text{-}gRNA] - (k_{release} + d_{assembled})[V_{assembled}]$$

$$\frac{d[V_{released}]}{dt} = k_{release}[V_{assembled}] - d_V[V_{released}]$$

$$\frac{d[V_{free}]}{dt} = k_{release}[V_{assembled}] - (k_{fuse} + d_V)[V_{free}],$$

$$\frac{d[V_{endosome}]}{dt} = \frac{k_{fuse}k_{bind}}{k_{diss}}[V_{free}] - (k_{uncoat} + d_{endosome})[V_{endosome}],$$

$$\frac{d[gRNA_{(+)}]}{dt} = k_{uncoat}[V_{endosome}] - d_{gRNA}[gRNA_{(+)}],$$

$$\frac{d[V_{assembled}]}{dt} = k_3[SP][gRNA_{(+)}]^3 - (k_{release} + d_{assembled})[V_{assembled}],$$

$$\frac{d[SP]}{dt} = -k_4[SP][gRNA_{(+)}]^3,$$

Валидация полной модели

$$\frac{\mathrm{d}[V_{free}]}{\mathrm{d}t} = k_{release}[V_{assembled}] - (k_{fuse} + d_V)\,[V_{free}],$$

$$\frac{\mathrm{d}[V_{endosome}]}{\mathrm{d}t} = \frac{k_{fuse}k_{bind}}{k_{diss}}[V_{free}] - (k_{uncoat} + d_{endosome})\,[V_{endosome}],$$

$$\frac{\mathrm{d}[gRNA_{(+)}]}{\mathrm{d}t} = k_{uncoat}[V_{endosome}] - d_{gRNA}[gRNA_{(+)}],$$

$$\frac{\mathrm{d}[V_{assembled}]}{\mathrm{d}t} = k_3[SP][gRNA_{(+)}]^3 - (k_{release} + d_{assembled})[V_{assembled}$$

$$\frac{\mathrm{d}[SP]}{\mathrm{d}t} = -k_4[SP][gRNA_{(+)}]^3,$$

$$k_3 = \frac{k_{assemb}}{k_{V_{rel}} n_{SP}} W, \; k_4 = \frac{k_{assemb}}{K_{V_{rel}}} W,$$

$$W = \frac{k_{transl} f_N}{d_{N-gRNA} n_N} \frac{k_{tr_{(+)}} k_{tr_{(-)}}}{d_{gRNA} K_{NSP}^2 d_{gRNA_{(-)}}} \left(\frac{k_{transl} f_{ORF1}}{d_{NSP}}\right)^2.$$

Parameter	Corresponding parameter from [23]	Value from [23, Table 2]
σ_1	d_V	$0.12\ h^{-1}$, range: $(0.06, 3.5)$, tuned to $(0.06, 0.2)$
q_1	k_{fuse}	$0.5\ h^{-1}$, range: $(0.33, 1)$
q_2	$k_{release}$	$8\ h^{-1}$ range: $(8, 7200)$
k_1	k_{uncoat}	$0.5\ h^{-1}$, range: $(0.33, 1)$
σ_2	d_{gRNA}	$0.2\ h^{-1}$, range: $(0.069, 0.69)$, tuned to $(0.069, 0.4)$
k_3	eq. (4.9)	0.003, range: $(1.05 \cdot 10^{-10}, 3.7 \cdot 10^6)$, range using tuned values: $(8.6 \cdot 10^{-9}, 7.5 \cdot 10^5)$
k_4	eq. (4.9)	6.093, range: $(2.35 \cdot 10^{-7}, 4.2 \cdot 10^9)$, range using tuned values: $(1.9 \cdot 10^{-5}, 8.4 \cdot 10^8)$

$$\frac{\partial V_e}{\partial t} = D\frac{\partial^2 V_e}{\partial x^2} + q_2 V_r - q_1 V_e - \sigma_1 V_e,$$

$$\frac{\partial V_i}{\partial t} = q_1 V_e - k_1 V_i,$$

$$\frac{\partial R}{\partial t} = k_1 V_i - \sigma_2 R,$$

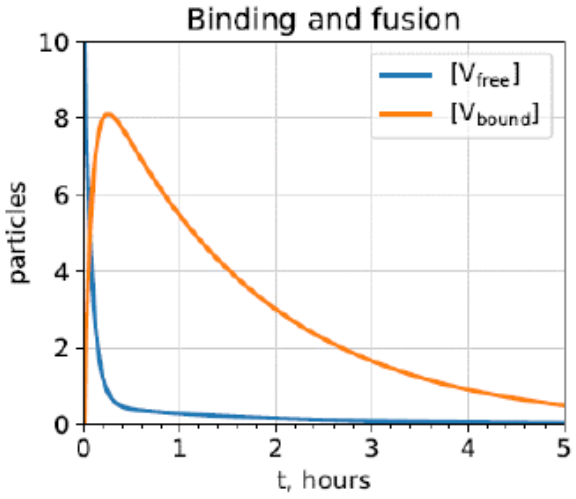
$$\frac{\partial V_r}{\partial t} = k_3 AR - q_2 V_r,$$

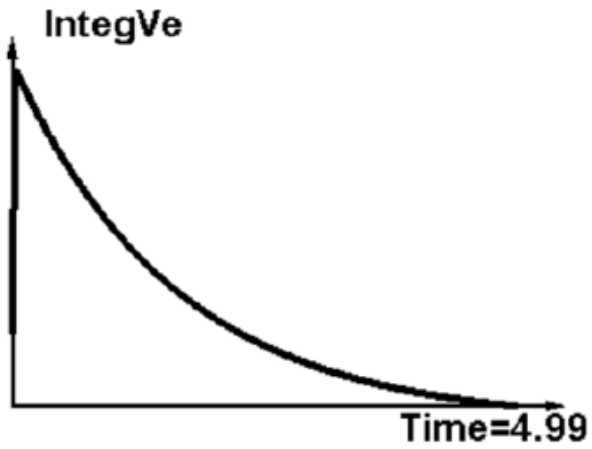
$$\frac{\partial A}{\partial t} = -k_4 AR.$$

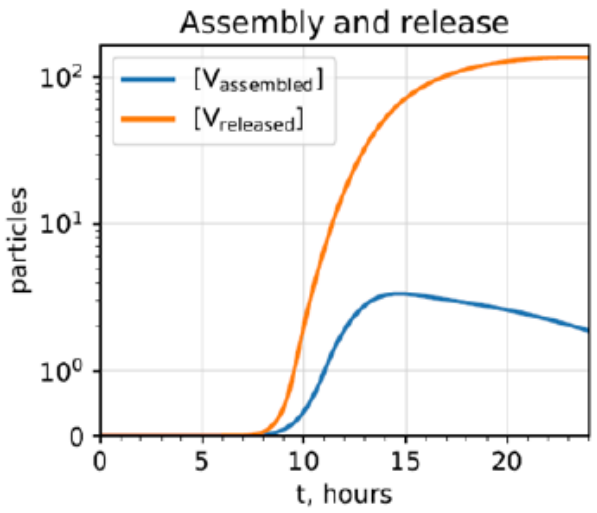
$$V_e \sim [V_{free}],\; V_i \sim [V_{endosome}],\; R \sim [gRNA_{(+)}],\; V_r \sim [V_{assembled}],\; A \sim [SP]$$

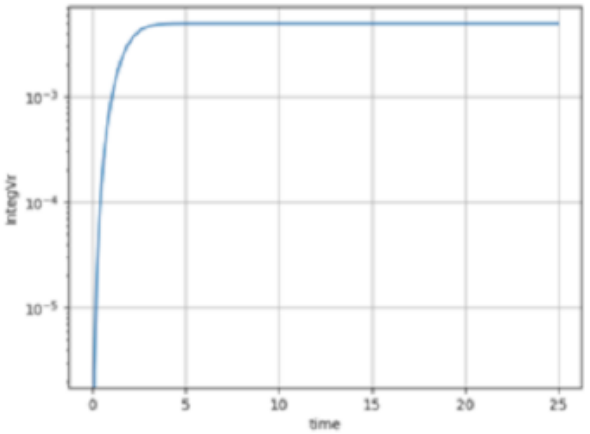
$$q_1 \sim k_{fuse},\; \sigma_1 \sim d_V,\; k_1 \sim (k_{uncoat} + d_{endosome}) \approx k_{uncoat},\; \sigma_2 \sim d_{gRNA},\; q_2 \sim k_{release}.$$

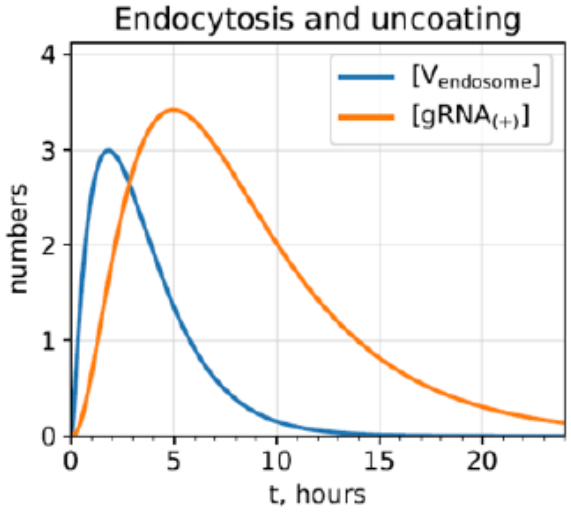
Результаты сравнения

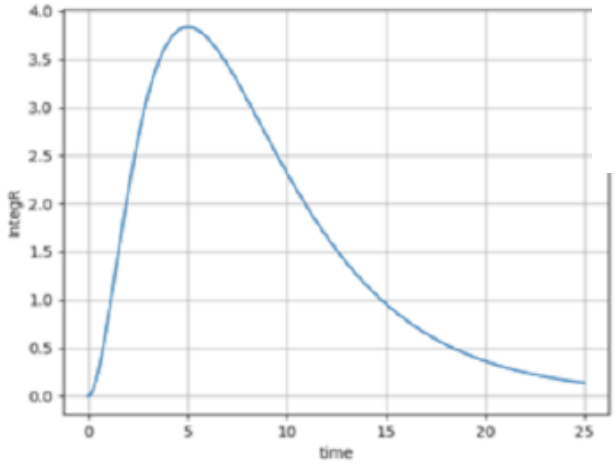












Заключение

- Получена зависимость скорости волны от параметров внутриклеточного регулирования
  - скорость волны соотносится с вирулентностью вируса
- Получена зависимость вирусной нагрузки от параметров внутриклеточного регулирования
  - для респираторных вирусных инфекций вирусная нагрузка соотносится с инфекционностью вируса (=скоростью передачи вируса между индивидами)
- Увеличение скорости проникновения вируса в клетку (q1) увеличивает скорость волны, и может как увеличивать, так и уменьшать вирусную нагрузку
  - для COVID-19: мутации в спайке, увеличивающие скорость проникновения вируса в клетку, увеличивают вирулентность, но не обязательно увеличивают инфекционность заболевания

Спасибо за внимание!