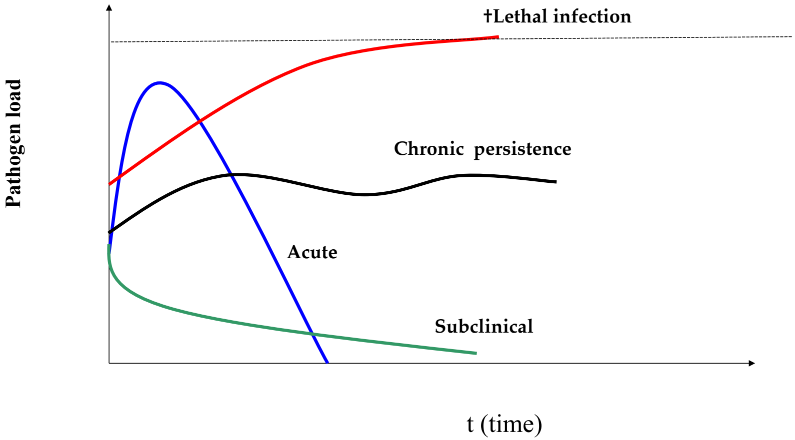
THE OPTIMAL DISTURBANCE APPROACH TO CONTROL OF VIRUS INFECTION MODEL WITH TIME-DELAYS

G.A.Bocharov, Yu.M.Nechepurenko, M.Yu.Khristichenko and D.S.Grebennikov, Maximum response perturbation-based control of virus infection model with time delays. *Russ. J. Numer. Anal. Math. Modeling, (2017).*

Dynamic patterns of infectious diseases



The aim of the work and the plan of the talk

Aim of the work: Proposing a new method for constructing the multi-modal impacts on the time-delay models of virus infections which is based on the so called optimal disturbances.

The plan of the talk:

- A model of LCMV infection
- Steady states and linearized equations
- Optimal disturbances
- Results of numerical experiments

A model of LCMV infection

$V(t)$ — concentration of viruses, $E_p(t)$ — population density of precursors, $E_e(t)$ —population density of effectors, $W(t)$ — the cumulative viral load.

$$\frac{d}{dt}V(t) = \overbrace{\beta V(t)\left(1-\frac{V(t)}{V_{mvc}}\right)}^{virus\ growth} - \overbrace{\gamma_{VE}E_e(t)V(t)}^{elimination\ of\ viruses},$$

$$\frac{d}{dt}E_p(t) = \overbrace{\alpha_{E_p}(E_p^0 - E_p(t))}^{maintenance\ of\ precursor} + \overbrace{\beta_p g_p(W)V(t-\tau)E_p(t-\tau)}^{increase\ in\ the\ number\ of\ precursors}$$

$$- \overbrace{\alpha_{AP}V(t-\tau_A)V(t)E_p(t)}^{cell\ death},$$

$$\frac{d}{dt}E_e(t) = \overbrace{b_d g_e(W)V(t-\tau)E_p(t-\tau)}^{appearance\ of\ effectors}$$

$$- \overbrace{\alpha_{AE}V(t-\tau_A)V(t)E_e(t) - \alpha_{E_e}E_e(t)}^{cell\ death\ and\ natural\ death},$$

$$\frac{d}{dt}W(t) = \overbrace{b_W V(t)}^{increase\ in\ viral\ antigen} - \overbrace{\alpha_W W(t)}^{decrease\ of\ inhibitory\ effect},$$

where $g_p(W) = 1/(1+W/\theta_p)^2$, $g_e(W) = 1/(1+W/\theta_E)^2$.

Steady states and linearized equations

Let us denote the vector of system variables as

$$U(t) = (V(t), E_p(t), E_e(t), W(t))^T$$

and express this system in the following compact form:

$$\frac{dU}{dt} = F(U(t), U(t-\tau), U(t-\tau_A)), \tau_A \geq \tau \quad (1)$$

U(t) is given for $-\tau_A \leq t \leq 0$.
Steady state $U = \overline{U}$ for system (1) can be computed from: $F(\overline{U}, \overline{U}, \overline{U}) = 0$
Representing arbitrary solution near the steady state as
$U(t) = \overline{U} + \varepsilon U'(t) + O(\varepsilon^2)$
we obtain the following system of linear differential equations for $U'(t)$:

$$\frac{dU'(t)}{dt} = L_0 U'(t) + L_\tau U'(t-\tau) + L_{\tau_A} U'(t-\tau_A) \quad (2)$$

Optimal disturbances

Family of local norms at time t: $\|U'\|_{D,t} = \left(\int\limits_{t-\tau_A}^{t} \|DU'(\xi)\|_2^2 \, d\xi \right)^{1/2}$

A solution $U'(t) = U'_{opt}(t)$ of the linearized system providing the maximum amplification of $\|U'\|_{D,t}$ will be referred to as the optimal disturbance. The optimal disturbance gives the maximum of

$$\max_{t \geq 0} \frac{\|U'\|_{D,t}}{\|U'\|_{D,0}}$$

Where $U' \in \mathcal{Q}$, and $\mathcal{Q}$ is the given subspace: $\mathcal{Q} \subset \{q : [-\tau_A, 0] \to \mathbb{R}^4\}$

Computation of optimal disturbances

We can find optimal disturbances in three steps:

- Compute the maximum amplification

$$\Gamma(t) = \max_{U' \in Q, U' \neq 0} \frac{\|U'\|_{D,t}}{\|U'\|_{D,0}}$$

- Find

$$t_{opt} = \min \arg \max_{t \geq 0} \Gamma(t)$$

- Find

$$U'_{opt} \in \arg \max_{U' \in Q, U' \neq 0} \frac{\|U'\|_{D,t_{opt}}}{\|U'\|_{D,0}}.$$

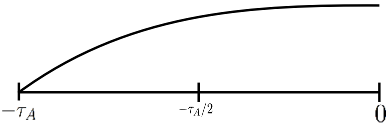
Using of optimal disturbance

We will use optimal disturbances for perturbing the stable steady states of the original non-linear model:

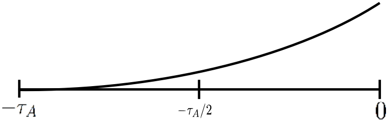
$$\frac{dU}{dt} = F(U(t), U(t-\tau_1), U(t-\tau_2)), t > 0$$
$$U(t) = \overline{U} + \epsilon U'_{opt}(t), -\tau_2 \leq t \leq 0$$

Subsape $\mathcal{Q}$ of basis functions for V, W

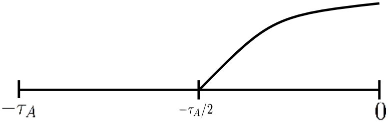
$$U' = \begin{cases} 0, -\tau_A \le t < t_0 \\ \exp(\beta(t - t_0)) - 1, t_0 \le t \le 0 \end{cases}$$



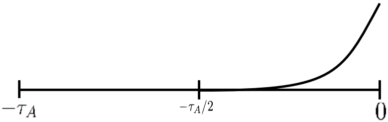
$\beta = -1, t_0 = -\tau_A$



$\beta = 1,\ t_0 = -\tau_A$



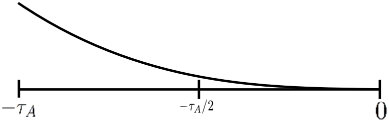
$\beta = -1,\ t_0 = -\tau_A/2$



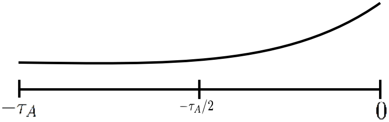
$\beta = 1,\ t_0 = -\tau_A/2$

Subsapce $\mathcal{Q}$ of basis functions for E_p, E_e

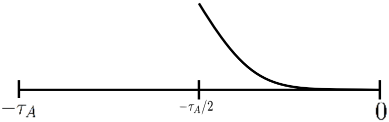
$$U' = \begin{cases} 0, -\tau_A \le t < t_0 \\ \exp(\beta(t - t_0)), t_0 \le t \le 0 \end{cases}$$



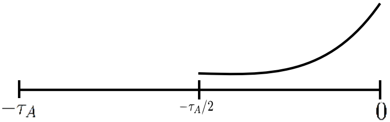
$\beta = -1,\ t_0 = -\tau_A$



$\beta = 1,\ t_0 = -\tau_A$



$\beta = -1,\ t_0 = -\tau_A/2$



$\beta = 1,\ t_0 = -\tau_A/2$

Low level of viral load. Traditional treatment scenario.

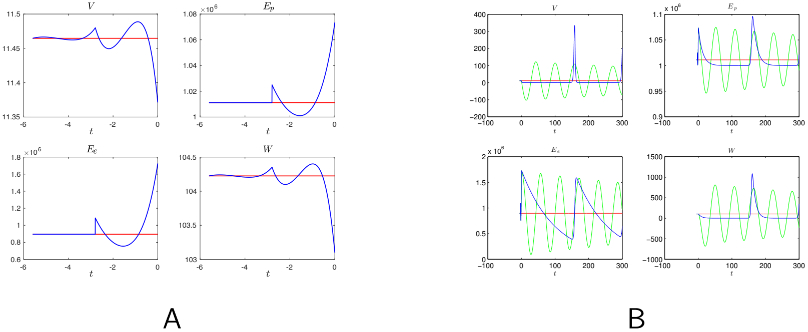


Fig. 1: The initial values (A) and the result of integration (B) for $\varepsilon = -0.45$

	V	E_p	E_e	W
Steady state	11.5	$1.01 \cdot 10^6$	$8.9 \cdot 10^5$	104
Minimum	$3.46 \cdot 10^{-14}$	10^6	$3.9 \cdot 10^5$	$9.09 \cdot 10^{-5}$
Maximum	334.7	$1.1 \cdot 10^6$	$1.73 \cdot 10^6$	$1.1 \cdot 10^3$

Low level of viral load. Treatment via exacerbation.

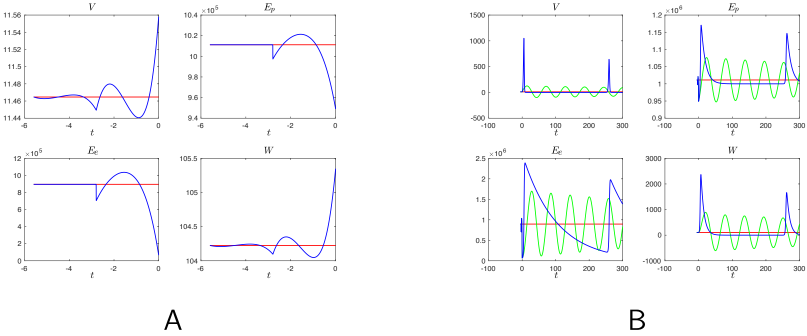


Fig. 2: The initial values (A) and the result of integration (B) for $\varepsilon = 0.45$

	V	E_p	E_e	W
Steady state	11.5	$1.01 \cdot 10^6$	$8.9 \cdot 10^5$	104
Minimum	$4.85 \cdot 10^{-36}$	$9.5 \cdot 10^5$	$6.5 \cdot 10^4$	$6.15 \cdot 10^{-8}$
Maximum	$1.05 \cdot 10^3$	$1.17 \cdot 10^6$	$2.39 \cdot 10^6$	$2.37 \cdot 10^3$

High level of viral load. Traditional treatment scenario.

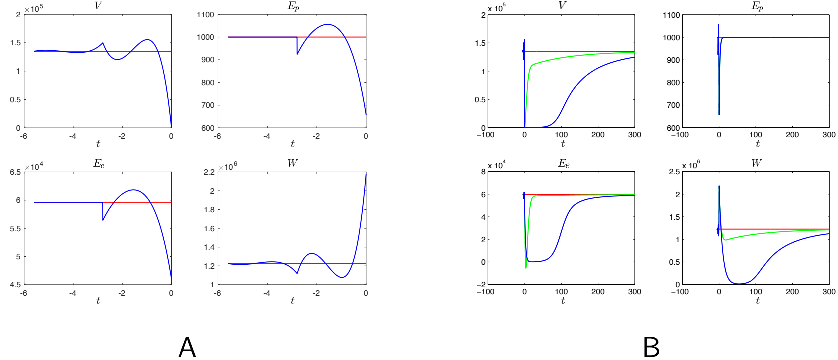


Fig. 3: The initial values (A) and the result of integration (B) for $\varepsilon = 0.5371$

	V	E_p	E_e	W
Steady state	$1.35 \cdot 10^5$	10^3	$5.95 \cdot 10^4$	$1.23 \cdot 10^6$
Minimum	21.18	656.9	81.7	$1.27 \cdot 10^4$
Maximum	$1.55 \cdot 10^5$	$1.06 \cdot 10^3$	$6.18 \cdot 10^4$	$2.18 \cdot 10^6$

High level of viral load. Treatment via exacerbation.

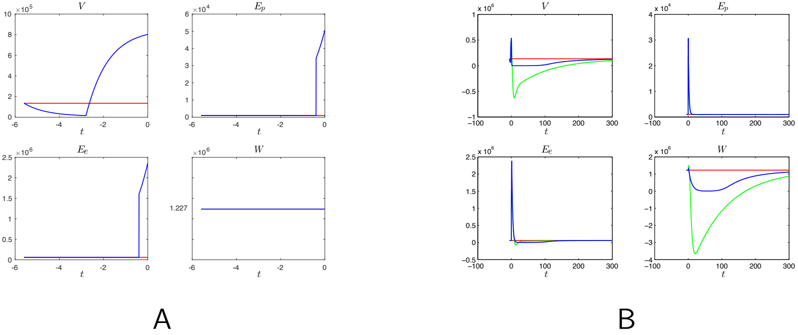
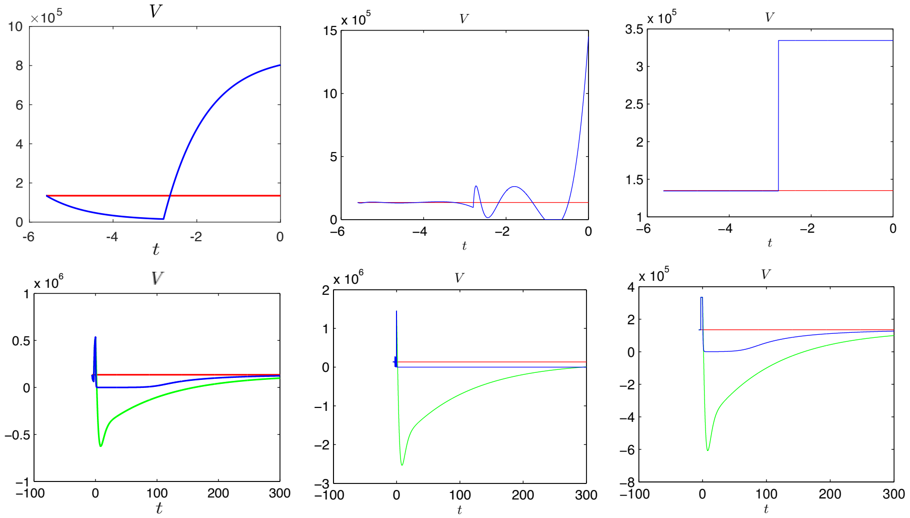


Fig. 4: The initial values (A) and the result of integration (B) for $\varepsilon = -20$

	V	E_p	E_e	W
Steady state	$1.35 \cdot 10^5$	10^3	$5.95 \cdot 10^4$	$1.23 \cdot 10^6$
Minimum	23.38	10^3	108.9	$6.93 \cdot 10^3$
Maximum	$5.34 \cdot 10^5$	$3.06 \cdot 10^4$	$2.38 \cdot 10^6$	$1.32 \cdot 10^6$

Other basis functions



Conclusions

- The concept of optimal disturbances for time delay systems is proposed
- The possibility of multi-component treatment of infectious diseases in chronic phase with the help of optimal disturbances was shown

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Thank you for your attention!

In the present work we use implicit scheme of the second order BDF2 on the uniform grid $t_k = k\delta$ built in interval $(-\tau_A, \infty)$ with step $\delta > 0$, $m = [\tau/\delta], m_A = [\tau_A/\delta]$,

$$\frac{1.5U_k - 2U_{k-1} + 0.5U_{k-2}}{\delta} = L_0 U_k + L_\tau U_{k-m} + L_{\tau_A} U_{k-m_A}, k = 1, 2, \ldots$$

Where $U_k = U(t_k)$. Let us write equation in the form:

$$U_k = C_1 U_{k-1} + C_2 U_{k-2} + C_m U_{k-m} + C_{m_A} U_{k-m_A}$$

It can be written in the form:

$$X_k = M X_{k-1}, \quad k = 1, 2, \ldots$$

where

$$X_k = \begin{pmatrix} U_k \\ \vdots \\ U_{k-m_A+1} \end{pmatrix}, \quad M = \begin{pmatrix} C_1 & C_2 & 0 & \ldots & 0 & C_m & 0 & \ldots & 0 & C_{m_A} \\ \mathrm{I} & 0 & 0 & \ldots & 0 & 0 & 0 & \ldots & 0 & 0 \\ 0 & \mathrm{I} & 0 & \ldots & 0 & 0 & 0 & \ldots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \ldots & 0 & 0 & 0 & \ldots & \mathrm{I} & 0 \end{pmatrix}$$

Grid analogue of norm:

$$\|U'\|_{D,t_k} = \left(\int\limits_{t_k-\tau_A}^{t_k} \|DU'(\xi)\|_2^2 \, d\xi \right)^{1/2} \sim \|HX_k\|_2, \quad H = \mathrm{I}_{m_A} \otimes D$$

Grid analogue of $\Gamma(t)$:

$$\Gamma_k = \max_{X_0 \in \mathrm{span}(Q), \|HX_0\|_2 = 1} \|HM^k X_0\|_2 = \|HM^k H^{-1} \widetilde{Q}\|_2$$

Let k_{opt} be the value of k, at which the maximum of Γ_k is reached:

$$k_{opt} = \min \arg \max_{k \geq 0} \Gamma_k$$

Computing the normalized right singular vector η of $HM^{k_{opt}} H^{-1} \widetilde{Q}$, corresponding to its largest singular value. According to:

$$\|HM^{k_{opt}} H^{-1} \widetilde{Q} \eta\|_2 = \Gamma_{k_{opt}}, \|\eta\|_2 = 1$$

Therefore $X_0^{opt} = H^{-1} \widetilde{Q} \eta$