

# Computational Treatment of the Parameter Estimation Problem in Mathematical Immunology

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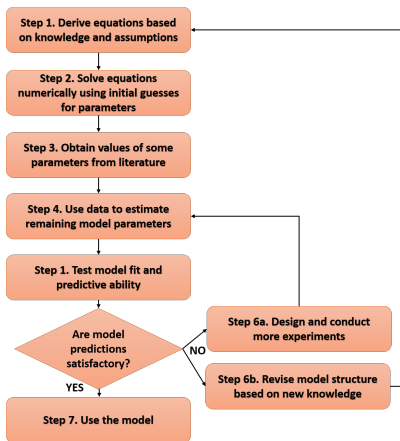
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# Objectives of the work

- Develop and solve the inverse problem for the model of population dynamics of the HIV infection;
- Develop and estimate parameters for the model of labelled cells division;
- Compare the numerical optimization methods for the formulated problems solution.

# Model development and parameter estimation

- The mathematical description of the immune processes across different scales calls for the development of multi-scale models characterized by a high dimensionality of the state space and a large number of parameters
- For complex models, only a small subset of the model parameters can be derived or measured from the available experimental data. Most of the remaining parameters have to be estimated by solving the inverse problem.
- For high-dimensional models the parameter estimation problem is usually computationally demanding.



# Parameter estimation problem

- Mathematical model:

$$\begin{cases} \frac{dy(t)}{dt} = F(y(t), p), t \in [0, T] & \text{— model equations;} \\ y(t) = \{y_i(t), i = 1, \dots, n, y_i(t) \in C^1(0, T)\} & \text{— time dependent variables;} \\ y(0) = y_0 & \text{— initial conditions;} \\ p = \{p_i\}, i = 1, \dots, m & \text{— parameter vector.} \end{cases} \quad (1)$$

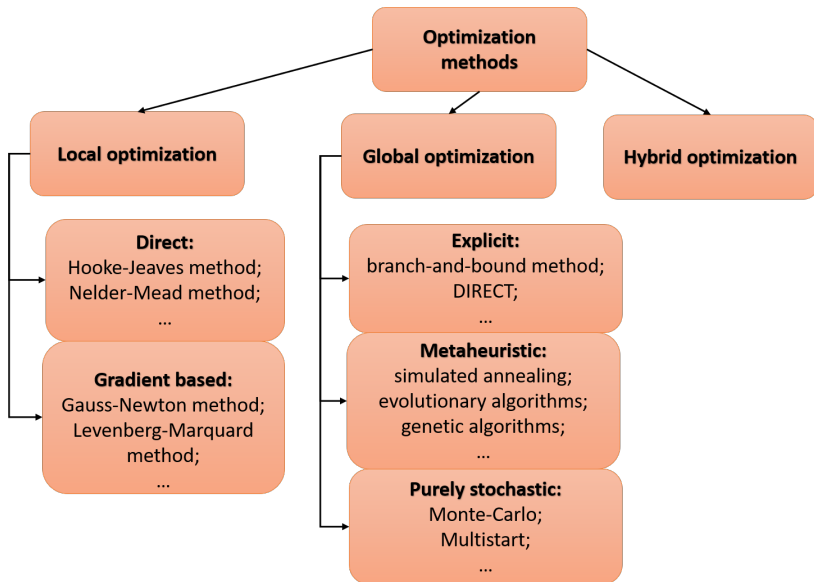
- $p = [a, b]$ , where  $[a]$  is a vector of estimated components;  $\{x_j, t_j\}, j = 1, \dots, K$  - experimental data. The parameter estimation problem can be formulated as:

$$p^* = \arg \min_{p \in \Omega \subseteq \mathbb{R}^m} \Phi(y, x, p) \quad (2)$$

- A general statistical framework for parameter estimation is the Bayesian approach which under the assumption of a uniform prior distribution of the model parameters reduces to a maximum likelihood estimation (*MLE*). Assuming that the observational errors are normally distributed, time- and component-independent and the variance of observation errors is the same for all the state variables and observation times, the *MLE* reduces to the minimization problem for the least-squares function

$$\Phi(p) = \sum_{j=1}^K \sum_{i=1}^n (x_{i,j} - y_i(t_j))^2, \quad (3)$$

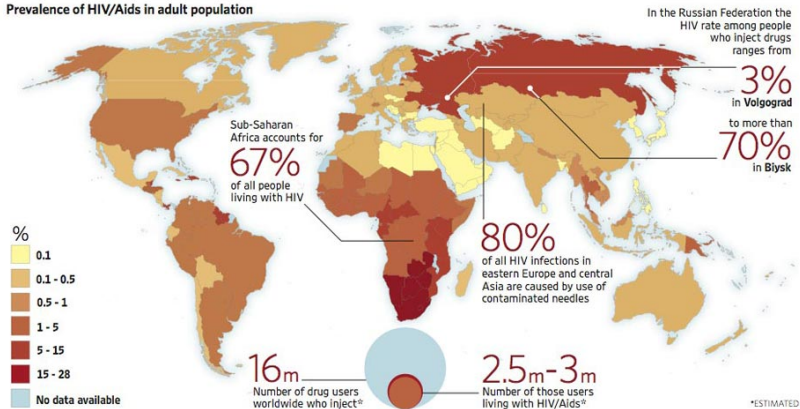
# Numerical optimization methods



# HIV epidemiology

## THE WORLDWIDE SCOURGE OF HIV/AIDS

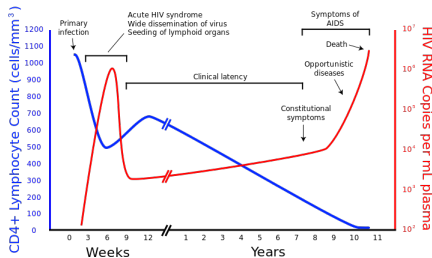
### Prevalence of HIV/Aids in adult population



GRAPHIC CAT DAVISON, PETE GUEST

SOURCE [WWW.UNAIDS.ORG](http://WWW.UNAIDS.ORG)

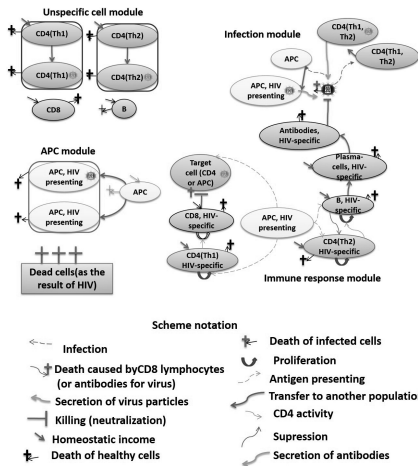
# Mathematical model of HIV infection



<https://en.wikipedia.org>

- Most of the models only account for the acute phase and asymptomatic latency phase and cannot explain the progression to AIDS.
- There are different hypothesis for AIDS: population dynamics, virus evolution, et. al.

# Mathematical model of HIV infection



- Marchuk-Petrov model of antiviral immune response was taken as a base;
- Model describes cellular and humoral immune reactions;
- The infection of target cells by HIV, i. e. the T helper lymphocytes (CD4 Th1 and CD4 Th2) and the antigen presenting cells (APC);
- The free virus- and the APC mediated modes of infection of CD4 T cells;
- The negative feedback of the infection and target cell destruction on the homeostasis of the lymphocytes is considered.
- Model contains 18 variables and 51 parameters, 32 parameters are estimated;
- Parameters were estimated for two datasets, characterizing different scenarios of infection dynamics;

Table: Model variables

Name	Variable	Initial value
$D$	number of antigen presenting cells (APC), cell/ml	$5 \cdot 10^5$
$D_V$	number of activated APC , cell/ml	0
$H_E$	number of CD4 Th1, cell/ml	$4.5 \cdot 10^5$
$H_B$	number of CD4 Th2, cell/ml	$4.5 \cdot 10^5$
$B$	number of B-lymphocytes, cell/ml	$2.7 \cdot 10^5$
$P$	number of plasma cells, cell/ml	10
$F$	number of antibodies, particle/ml	0
$E$	number of cytotoxic T-lymph., cell/ml	$4.5 \cdot 10^5$
$D_V^*$	number of inf. activated APC, cell/ml	0
$H_E^*$	number of inf. CD4 Th1, cell/ml	0
$H_B^*$	number of inf. CD4 Th2, cell/ml	0
$V$	number of vir. particles, particle/ml	100
$m$	number of dead target cells(as infection result), cell/ml	0
$H_{Esp}$	number of HIV specific CD4 Th1, cell/ml	5
$H_{Bsp}$	number of HIV specific CD4 Th2, cell/ml	5
$B_{sp}$	number of HIV specific B-cells, cell/ml	3
$E_{sp}$	number of HIV specific cytotoxic T-cells, cell/ml	5
$H_{Esp}^*$	number of infected HIV specific CD4 Th1, cell/ml	0
$H_{Bsp}^*$	number of infected HIV specific CD4 Th2, cell/ml	0

Equations for uninfected unspecific cells and antibodies are written as follows:

$$\begin{aligned}
 \frac{dD}{dt} &= \alpha_D(\xi D^0 - D) - \sigma_D VD - \gamma_{DV} VD; \\
 \frac{dD_V}{dt} &= \gamma_{DV} VD - \alpha_{D_V} D_V - \sigma_D VD_V; \\
 \frac{dH_B}{dt} &= \alpha_{H_B}(\xi H_B^0 - H_B) - \sigma_{H_B} H_B V - \sigma_{H_B}^D H_B D_V^*; \\
 \frac{dH_E}{dt} &= \alpha_{H_E}(\xi H_E^0 - H_E) - \sigma_{H_E} H_E V - \sigma_{H_E}^D H_E D_V^*; \\
 \frac{dB}{dt} &= \alpha_B(B^0 - B); \quad \frac{dE}{dt} = \alpha_E(E^0 - E); \\
 \frac{dP}{dt} &= b_P^p \xi \rho_P (D_V + D_V^*)(H_{Bsp} + H_{Bsp}^*) B_{sp} + \alpha_P(P_0 - P); \\
 \frac{dF}{dt} &= \rho_F P - \gamma_{VF} VF - \alpha_F F;
 \end{aligned}$$

Equations for infected unspecific cells are written as follows:

$$\begin{aligned}
 \frac{dD_V^*}{dt} &= \sigma_D V(D + D_V) - b_{D_V E} D_V^* E_{sp} - b_{D_V^*} D_V^*; \\
 \frac{dH_B^*}{dt} &= \sigma_{H_B} H_B V + \sigma_{H_B}^D H_B D_V^* - b_{H_B E} H_B^* E_{sp} - b_{H_B^*} H_B^*; \\
 \frac{dH_E^*}{dt} &= \sigma_{H_E} H_E V + \sigma_{H_E}^D H_E D_V^* - b_{H_E E} H_E^* E_{sp} - b_{H_E^*} H_E^*;
 \end{aligned}$$

Dynamics of viral particles and total number of dead cells are described by the following equations:

$$\begin{aligned}
 \frac{dV}{dt} &= \nu_{DV} D_V^* + \nu_{HE} (H_E^* + H_{Esp}^*) + \nu_{HB} (H_B^* + H_{Bsp}^*) + N_{DV} b_{DV}^* D_V^* \\
 &\quad + N_{HE} b_{HE}^* (H_E^* + H_{Esp}^*) + N_{HB} b_{HB}^* (H_B^* + H_{Bsp}^*) - \frac{kV(D_V + D_V^*)}{a(c + V)} \\
 &\quad - \gamma_{VHB} V(H_B + H_{Bsp}) - \gamma_{VHE} V(H_E + H_{Esp}) - \gamma_{VD} VD - \gamma_{VF} VF \\
 &\quad - \gamma_{VM} V; \\
 \frac{dm}{dt} &= b_{DVE} D_V^* E_{sp} + b_{DV}^* D_V^* + b_{HE}^* (H_E^* + H_{Esp}^*) + b_{HE} E(H_E^* + \\
 &\quad H_{Esp}^*) E_{sp} + b_{HB}^* (H_B^* + H_{Bsp}^*) + b_{HB} E(H_B^* + H_{Bsp}^*) E_{sp};
 \end{aligned}$$

Equations for uninfected HIV-specific cells are written as follows:

$$\begin{aligned}
 \frac{dH_{Bsp}}{dt} &= \alpha_{HB} (\xi \theta H_B^0 - H_{Bsp}) - \sigma_{HB} H_{Bsp} V - \sigma_{HB}^D H_{Bsp} D_V^* + \\
 &\quad 2b_{HB} (D_V + D_V^*) H_{Bsp} - b_{HB}^P (D_V + D_V^*) H_{Bsp} B_{sp}; \\
 \frac{dH_{Esp}}{dt} &= \alpha_{HE} (\xi \theta H_E^0 - H_{Esp}) - \sigma_{HE} H_{Esp} V - \sigma_{HE}^D H_{Esp} D_V^* + \\
 &\quad 2b_{HE} (D_V + D_V^*) H_{Esp} - b_{HE}^P (D_V + D_V^*) H_{Esp} E_{sp}; \\
 \frac{dB_{sp}}{dt} &= \alpha_B (\theta B^0 - B_{sp}) + 2b_B^P (D_V + D_V^*) (H_{Bsp} + H_{Bsp}^*) B_{sp}; \\
 \frac{dE_{sp}}{dt} &= \alpha_E (\theta E^0 - E_{sp}) + 2b_E^P (D_V + D_V^*) (H_{Esp} + H_{Esp}^*) E_{sp} - b_{EDV} D_V^* E_{sp} \\
 &\quad - b_{EH_E} H_E^* E_{sp} - b_{EH_B} H_B^* E_{sp};
 \end{aligned}$$

Equations for infected HIV-specific cells are written as follows:

$$\begin{aligned}\frac{dH_{Bsp}^*}{dt} &= \sigma_{H_B} H_{Bsp} V + \sigma_{H_B}^D H_{Bsp} D_V^* + 2b_{H_B} (D_V + D_V^*) H_{Bsp}^* - \\ &\quad b_{H_B}^P (D_V + D_V^*) H_{Bsp}^* B_{sp} - b_{H_B} E_{Bsp} H_{Bsp}^* E_{sp} - b_{H_B}^* H_{Bsp}^*; \\ \frac{dH_{Esp}^*}{dt} &= \sigma_{H_E} H_{Esp} V + \sigma_{H_E}^D H_{Esp} D_V^* + 2b_{H_E} (D_V + D_V^*) H_{Esp}^* - \\ &\quad b_{H_E}^P (D_V + D_V^*) H_{Esp}^* E_{sp} - b_{H_E} E_{Esp} H_{Esp}^* E_{sp} - b_{H_E}^* H_{Esp}^*;\end{aligned}$$

Negative feedback is described as follows:

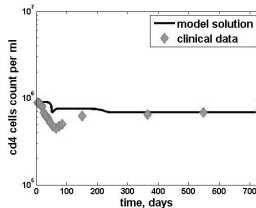
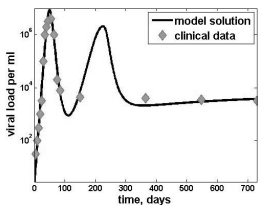
$$\xi = \frac{(1 - \epsilon m)}{\epsilon m + H_E^0 + H_B^0 + D^0};$$

## Minimized functional

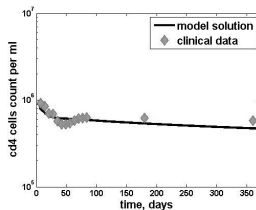
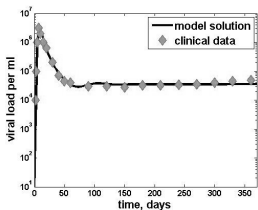
$$\begin{aligned}\Phi(\mathbf{p}) = & \sum_{j=1}^{17} [\log(CD4_{j,obs}) - \log(CD4(t_j))]^2 + \\ & \sum_{i=1}^{17} [\log(CD8_{j,obs}) - \log(CD8(t_j))]^2 + \\ & \sum_{i=1}^{17} [\log(V_j) - \log(V(T_j))]^2\end{aligned}\tag{4}$$

# HIV model solution

HIV dynamics model, data set 1:



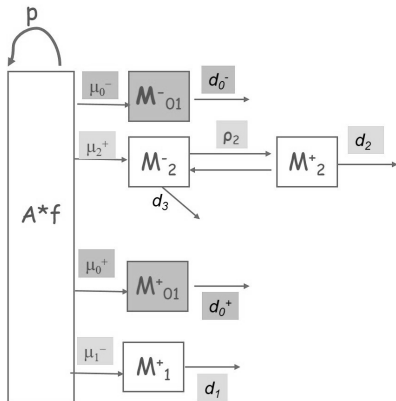
HIV dynamics model, data set 2:



# Mathematical model of labelled cells division

- Model describes the kinetics of proliferation of BrdU-labelled cells for SIV-infected primates;
- The main goal of the model is to check the hypothesis about chronic immune activation during the infection.
- The model version, describing also the dynamics of Ki67 was considered.

# Mathematical model of labelled cells division



Zvi Grossman, Gennady Bocharov, 2006

- Experimental data is given for control and infected groups of animals; synthetic data is also considered;
- Parameters are evaluated for control and infected group simultaneously;

# Mathematical model. Parameters

Table: Model parameters

Name	Biological meaning	Units	Range
$\mu_0^-$	transition rate from A to $M_{01}^-$	ml/day	0.001 - 2
$\mu_0^+$	transition rate from A to $M_{01}^+$	ml/day	0.001 - 2
$\mu_1^-$	transition rate from A to $M_1^+$	ml/day	0.001 - 2
$\mu_2^+$	transition rate from A to $M_2^-$	ml/day	0.001 - 2
$d_0^-$	death rate $M_{01}^-$	ml/day	
$d_0^+$	death rate $M_{01}^+$	ml/day	
$d_1$	death rate $M_1^+$	ml/day	
$d_2$	death rate $M_2^+$	ml/day	
$d_3$	death rate $M_2^-$	ml/day	
$\rho_2$	transition rate from $M_2^-$ to $M_2^+$	ml/day	0.001 - 1
$\rho_3$	transition rate from $M_2^+$ to $M_2^-$	ml/day	0.001 - 1
$\rho$	tuning parameter		0.3 - 3.0
$f$	tuning parameter		0.01 - 1
$p$	basic proliferation rate for A	ml/day	
$A_{0\max}$	maximal number for A	ml/day	0.1 - 2.0
$LT$	label injection interval delay	ml/day	1
			1.5

# Model equations

$$A^L(t) = \begin{cases} A_{0\max}(1 - \exp[-2pt]), & 0 < t < LT; \\ A_{0\max}(1 - \exp[-2pLT]), & LT \leq t \leq LT + \Delta; \\ A_{0\max}(1 - \exp[-2pLT]) \exp(-2p(t - LT - \Delta)), & LT + \Delta < t. \end{cases}$$

$$\frac{dM_{01}^{L-}}{dt} = \frac{\mu_0^-}{CCR5_{stac}^-} A^L f - d_0 M_{01}^{L-};$$

$$\frac{dM_{01}^{L+}}{dt} = \frac{\mu_0^+}{CCR5_{stac}^+} A^L f - d_0^+ M_{01}^{L+};$$

$$\frac{dM_1^{L+}}{dt} = \frac{\mu_1^-}{CCR5_{stac}^+} A^L f - d_1 M_1^{L+};$$

$$\frac{dM_2^{L-}}{dt} = \frac{\mu_2^+}{CCR5_{stac}^-} A^L f - \rho_2 M_2^{L-} - d_3 M_2^{L-} + \frac{CCR5_{stac}^+}{CCR5_{stac}^-} \rho_3 M_2^{L+};$$

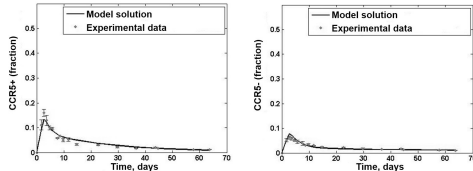
$$\frac{dM_2^{L+}}{dt} = \rho_2 \frac{CCR5_{stac}^-}{CCR5_{stac}^+} M_2^{L-} - \rho_3 M_2^{L+} - d_2 M_2^{L+};$$

## Minimized functional

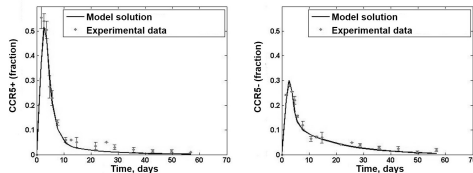
$$\begin{aligned} F = & \Phi_c^{WLS}(\mathbf{p}) + \Phi_i^{WLS}(\mathbf{p}) + \\ & \gamma_1 \left( \frac{CCR5^+_{CONTROL}}{(CCR5^+ + CCR5^-)_{CONTROL}} - 0.075 \right)^2 \\ & + \gamma_2 \left( \frac{CCR5^+_{INFECTED}}{(CCR5^+ + CCR5^-)_{INFECTED}} - 0.06 \right)^2 \\ & + \gamma_3 \left( \frac{(CCR5^+ + CCR5^-)_{INFECTED}}{(CCR5^+ + CCR5^-)_{CONTROL}} - 0.16 \right)^2 \end{aligned} \quad (5)$$

# BRDU-labeled cell division model solution

Cell-division model, control group:



Cell-division model, infected group:



Progressive CD4+ central memory T cell decline results in CD4+ effector memory insufficiency and overt disease in chronic SIV infection. Okoye A1, Meier-Schellersheim M, et. al. Picker, Grossman (unpublished data)

# Numerical methods used in numerical experiments

- TT** – TT global optimization method.
- CRS2** – Controlled Random Search with local mutation. The idea of the algorithm is similar to the idea of genetic algorithms, which start with a random "population" of points, and randomly change these points according to some heuristic rules.
- rMLSL** – Multi-Level Single-Linkage with pseudo-random start points. MLSL is a subtype of multistart algorithm, which implements a sequence of local optimizations from random start points. The algorithm uses a clustering heuristic to avoid the re-introducing the previously founded local optima.
- qrMLSL** – Multi-Level Single-Linkage with quasi-random start points.
- rMLSL+SBPLX** – Multi-Level Single-Linkage with pseudo-random start points, Sublex method used for local optimizations.
- qrMLSL+SBPLX** – Multi-Level Single-Linkage with quasi-random start points, Sublex method used for local optimizations.
- ISRES** – Improved Stochastic Ranking Evolution Strategy. The algorithm combines a mutation rule, realized with a log-normal step-size update and exponential smoothing, and differential variation, based on a Nelder-Mead-like update rule.
- ESCH** – Evolutionary Algorithm. This is a modification of Evolutionary Algorithm, developed by Carlos Henrique da Silva Santos's.

# TT global optimization method

- Method was introduced in INM RAS (Zheltkov, Tyrtysnikov, et. al.)
- Method is based on the useful properties of the TT-decomposition and TT-cross interpolation method.
- Sequential and parallel versions of the method were implemented.

# TT global optimization: algorithm

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**Algorithm 0.1:** TT OPTIMIZATION( $A \in \mathbb{R}^{n_1 \times \dots \times n_d}, r_{\max}, \max\_it$ )

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```
for  $k \leftarrow 1$  to  $d$ 
  do  $P_k \leftarrow \text{random}$ 
for  $it \leftarrow 1$  to  $\max\_it$ 
  do  $\begin{cases} [I_k, J_k] \leftarrow \text{construct\_submatrix}(n_k, n_{k+1}, P_k) \\ [U, V, P_k] \leftarrow \text{matrix\_cross}(A_k(I_k, J_k)) \\ P_k \leftarrow P_k \cup \text{optimized}(P_k) \\ P \leftarrow P_1 \cup \dots \cup P_d \\ P_k \leftarrow P_{k-1} \cup P_k \cup P_{k+1} \cup \text{best}(P, r_{\max}) \end{cases}$ 
return ( $\text{best}(P, 1)$ )
```

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- Complexity:  $O(dnr_{\max}^2)$  functional evaluations,  $O(dr_{\max})$  local optimizations and  $O(dnr_{\max}^3)$  arithmetic operations.
- For parallel version parallel complexity:  $O(r_{\max})$  functional evaluations,  $O(1)$  local optimizations and  $O(d + r_{\max}^2)$  arithmetic operations

# Numerical results

Locally optimized minimal values of the LSQ functional, obtained by global optimization methods. Results are given for HIV model (M. 1) for two datasets (data 1 and data 2), and for labelled cell division model (M. 2) for experimental data (data 1) and synthetic (data 2):

Method	M. 1, data 1	M. 1, data 2	M. 2 data 1	M. 2, data 2
TT	2.28	0.146	427	0.0055
CRS2	2.47	0.155	1164	49
rMLSL	2.50	0.186	759	2.4
qrMLSL	2.51	0.184	1062	67.2
rMLSL+SBPLX	2.13	0.144	428	0.04
qrMLSL+SBPLX	2.22	0.148	429	0.008
ISRES	2.34	0.156	526	1
ESCH	3.49	0.166	555	3.3

All methods were set to perform  $10^6$  functional evaluations for the first model and  $10^8$  for the second model.

# Conclusions

- We formulated a mathematical model of HIV infection by extending the Marchuk-Petrov model of an antiviral immune response. The model considered a detailed description of the infection and immune response processes operative in HIV infection.
- We considered a model of BrdU-labelled cell division for healthy and SIV-infected primates.
- A number of existing optimization methods were explored to treat the parameter estimation problem for proposed models;
- The TT-based and MLSL hybrid optimization methods are in a lead group in all the experiments.

# Thank you for your attention!

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