Sensitivity study of parameters in a mathematical model of Intracellular SARS-CoV-2 replication Course Project

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Background

In the project we will develop reliable and efficient algorithms implemented in Matlab for solution of ODE system which describes the major replication stages of SARS-CoV-2.

It is expected that application of the obtained algorithms and software will be in further research related to the parameter identification in the life cycle model of SARS-CoV-2 which will lead to development of antiviral drugs against SARS-CoV-2 infection.

The project will be done in collaboration with mathematical biologists from Marchuk Institute of Numerical Mathematics, Moscow; Sechenov First Moscow State Medical University and Sobolev Institute of Mathematics, Novosibirsk, Russia.

Description of the project

The main model considered in this project will be the mathematical model of life circle of SARS-CoV-2 proposed in [2]. It provides a kinetic description of the major replication stages of SARS-CoV-2 (cell entry; genome transcription and replication; translation of structural and accessory proteins; assembly and release of new virions). Sensitivity analysis of the net viral progeny with respect to model parameters (see [2], Table 2) enables the identification of the life cycle stages that have the strongest impact on viral replication. These three most influential parameters in this model are:

- (i) degradation rate of positive sense vRNAs in cytoplasm (negative effect),
- (ii) threshold number of non-structural proteins enhancing vRNA transcription (negative effect), and
- (iii) translation rate of non-structural proteins (positive effect).

The results of the mathematical model analysis could be used for guiding the search for antiviral drug targets to combat SARS-CoV-2 infection.

Table 1 of [2] Time-dependent variables of the mathematical model of intracellular SARS-CoV-2 replication.

System (5)	Variable	Meaning Characteristics	Quantitative
u_1	$[V_{free}]$	number of free virions outside the cell membrane	10
u_2	$[V_{bound}]$	number of virions bound to ACE2 and activated by TMPRSS2	$1-10$
u_3	$[V_{endosome}]$	number of virions in endosomes	$1-10$
u_4	$[gRNA_{(+)}]$	single strand positive sense genomic `RNA`	$1-5$
u_5	$[NSP]$	population of non-structural proteins	–
u_6	$[gRNA_{(-)}]$	negative sense genomic and subgenomic `RNA`s	10
u_7	$[gRNA]$	positive sense genomic and subgenomic `RNA`s	$10,000$
u_8	$[SP]$	total number of structural proteins	$2000 \in (1125, 2230)$
u_9	$[N]$	N proteins per virion [N]	456; $1465 \in (730, 2200)$
u_{10}	$[N-gRNA]$	ribonucleocapsid molecules	–
u_{11}	$[V_{assembled}]$	assembled virions in endosomes	–
u_{12}	$[V_{released}]$	virus burst size	$10-10,000$ virions in 7 to 24 h

A kinetic description of the major replication stages of SARS-CoV-2 considered in [2] such that cell entry; genome transcription and replication; translation of structural and accessory proteins; assembly and release of new virions, is described by system of ODE equations which are briefly presented below for every stage.

Cell Entry

Binding of the virion to the cellular transmembrane protein ACE2, and entry and release of the viral RNA into the host cell are described by equations specifying the rates of changes of free-, receptor-bound, and fused virions, as well as the viral RNA genome in the cytoplasm.

$$\begin{aligned}
\frac{d[V_{free}]}{dt} &= -k_{bind}[V_{free}] - d_V[V_{free}] + k_{diss}[V_{bound}],\\
\frac{d[V_{bound}]}{dt} &= k_{bind}[V_{free}] - (k_{fuse} + k_{diss} + d_V)[V_{bound}],\\
\frac{d[V_{endosome}]}{dt} &= k_{fuse}[V_{bound}] - (k_{uncoat} + d_{endosome})[V_{endosome}],\\
\frac{d[gRNA_{(+)}]}{dt} &= k_{uncoat}[V_{endosome}] - d_{gRNA}[gRNA_{(+)}].
\end{aligned} \tag{1.1}$$

Genome Transcription and Replication

In [2] authors describe the abundance of the populations of non-structural proteins $[NSP]$, the set of negative sense genomic and subgenomic $[gRNA_{(-)}]$, and the set of positive

sense genomic and subgenomic $[gRNA]$ with the following differential equations:

$$\begin{aligned}
\frac{d[NSP]}{dt} &= k_{transl} f_{ORF1}[gRNA_{(+)}] - d_{NSP}[NSP], \\
\frac{d[gRNA_{(-)}]}{dt} &= k_{tr(-)}[gRNA_{(+)}]\theta_{RdRp} - d_{gRNA(-)}[gRNA_{(-)}], \\
\frac{d[gRNA]}{dt} &= k_{tr(+)}[gRNA_{(-)}]\theta_{RdRp} - (k_{complex}\theta_{complex} + d_{gRNA})[gRNA],
\end{aligned} \tag{1.2}$$

where

$$\theta_{RdRp} = \frac{[NSP]}{[NSP] + k_{NSP}}, \quad \theta_{complex} = \frac{[N]}{[N] + k_N}.$$

Translation of Structural and Accessory Proteins

The translation rates of $[N]$ and $[SP]$ proteins are described by the following two equations:

$$\begin{aligned}
\frac{d[N]}{dt} &= k_{transl} f_N[gRNA] - k_{complex} n_N \theta_{complex}[gRNA] - d_N[N], \\
\frac{d[SP]}{dt} &= k_{transl} f_{SP}[gRNA] - k_{assemb} n_{SP} \theta_{assemb}[N - gRNA] - d_{SP}[SP],
\end{aligned} \tag{1.3}$$

where

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

Assembly and Release of Virions

The rates of changes of the ribonucleocapsid and the assembled and released virions are described by the following three equations:

$$\begin{aligned}
\frac{d[N - gRNA]}{dt} &= k_{complex}\theta_{complex}[gRNA] - (k_{assemb}\theta_{assemb} + d_{N-gRNA})[N - gRNA], \\
\frac{d[V_{assembled}]}{dt} &= k_{assemb}\theta_{assemb}[N - gRNA] - (k_{release} + d_{assembled})[V_{assembled}], \\
\frac{d[V_{released}]}{dt} &= k_{release}[V_{assembled}] - d_V[V_{released}].
\end{aligned} \tag{1.4}$$

Combining all ODE systems (1)-(4) for all stages we finally get the system of ODE consisting of 12 equations:

$$
\begin{aligned}
\dot{u_1} &= -(k_{bind} + d_V) \cdot u_1 + k_{diss} \cdot u_2, \\
\dot{u_2} &= k_{bind} \cdot u_1 - (k_{fuse} + k_{diss} + d_V) \cdot u_2, \\
\dot{u_3} &= k_{fuse} \cdot u_2 - (k_{uncoat} + d_{endosome}) \cdot u_3, \\
\dot{u_4} &= k_{uncoat} \cdot u_3 - d_{gRNA} \cdot u_4, \\
\dot{u_5} &= k_{transl} f_{ORF1} \cdot u_4 - d_{NSP} \cdot u_5, \\
\dot{u_6} &= k_{tr(-)} \theta_{RdRp} \cdot u_4 - d_{gRNA(-)} \cdot u_6, \\
\dot{u_7} &= k_{tr(+)} \theta_{RdRp} \cdot u_6 - (k_{complex} \theta_{complex} + d_{gRNA}) \cdot u_7, \\
\dot{u_8} &= (k_{transl} f_N - k_{complex} n_N \theta_{complex}) \cdot u_7 - d_N \cdot u_8, \\
\dot{u_9} &= k_{transl} f_{SP} \cdot u_7 - k_{assemb} n_{SP} \theta_{assemb} \cdot u_{10} - d_{SP} \cdot u_9, \\
\dot{u_{10}} &= k_{complex} \theta_{complex} u_7 - (k_{assemb} \theta_{assemb} + d_{N-gRNA}) u_{10}, \\
\dot{u_{11}} &= k_{assemb} \theta_{assemb} \cdot u_{10} - (k_{release} + d_{assembled}) \cdot u_{11}, \\
\dot{u_{12}} &= k_{release} \cdot u_{11} - d_V \cdot u_{12}.
\end{aligned}
\tag{1.5}
$$

with initial conditions for functions $(u_1, .., u_{12})$ taken from Table 1 and values of parameters presented in Table 2 of [2].

Purpose of the project

The main purpose of this project is to develop efficient and reliable numerical method implemented in Matlab for solution of system (5) with different initial conditions taken from Table 1.

The specific goals of this project are:

- Study methods and results of papers [1, 2].
- Study and modify the Matlab code of [1] for solution of system (5) (forward problem) for different initial conditions and different values of parameters. Compare obtained results with results of [2].
- Optional: formulate parameter identification problem and modify the Matlab code of [1] for solution of adjoint problem corresponding to problem (5).

  Matlab programs of [1] are available for download from the link

  `https://github.com/larisa70/AFEM_HIV`

Contact information

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References

[1] L. Beilina, AM. Eriksson, I. Gainova, Time-Adaptive Determination of Drug Efficacy in Mathematical Model of HIV Infection, *Differ. Equ. Dyn. Syst. (2021)*. https://doi.org/10.1007/s12591-021-00572-w

[2] D. Grebennikov, E. Kholodareva, I. Sazonov, A. Karsonova, A. Meyerhans, G. Bocharov, Intracellular Life Cycle Kinetics of SARS-CoV-2 Predicted Using Mathematical Modelling, *Viruses*, 13, 1735, 2021.https://doi.org/10.3390/v13091735