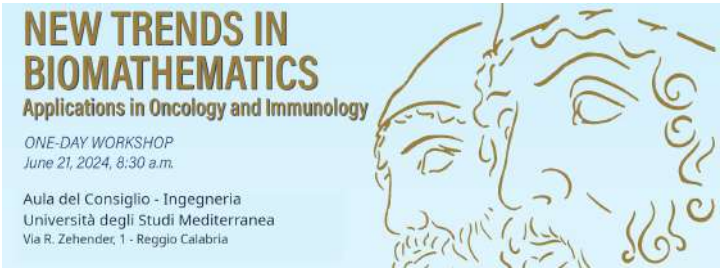



# Simulating to Predict: Computational Models in Infectious Diseases

*Francesco Pappalardo <francesco.pappalardo@unict.it>*
*Dept. Of Drug and Health Sciences, University of Catania, Italy.*
COMBINE Group, www.combine-group.org

# Actors i.e., agents!

| | Cells | Small molecules | Large molecules |
|---|---|---|---|
| **Who** | Cytotoxic T cells<br>Helper T cells (TH1, TH2, TH17)<br>Regulatory T cells<br>NK<br>M<br>DC | IL-2<br>IL-4<br>IL-6<br>IL-10<br>IL-12<br>IL-17<br>IL-23<br>IFN-γ<br>TNF<br>TGF-β<br>Type 1-IFN<br>D-signal<br>Vit. D<br>Chemokines | Antibody (Ab)<br>Ig (M, D, G1, G2, E)<br>Antigen (Ag)<br>IC |
| **Represented by** | Discrete variables (agents) | Continuous variables | Discrete variables (no internal states) |
| **Interaction based on** | Binary strings (n bits) | Only concentration on the lattice site is needed | Binary strings (n bits) |
| **How they move** | Chemotaxis and random diffusion | Diffusion equation (parabolic PDE)<br>$\frac{\partial C}{\partial t} = D\nabla^2 C - \lambda C$ | Random diffusion |

# State description

- At each time step, a cell can be found in one of the states reported in the first column if an X marks the corresponding entry in the table. TH1, TH2, TH17 and regulatory T cells all have the same state definitions as the TH.
- All other entities (i.e., the molecules) may be considered always ACTIVE, in other words, ready to interact. Note that specifying the behaviour of entities in terms of discrete states is an advantage in terms of memory parsimony since the cell state is stored in a **flag** byte for each cell.

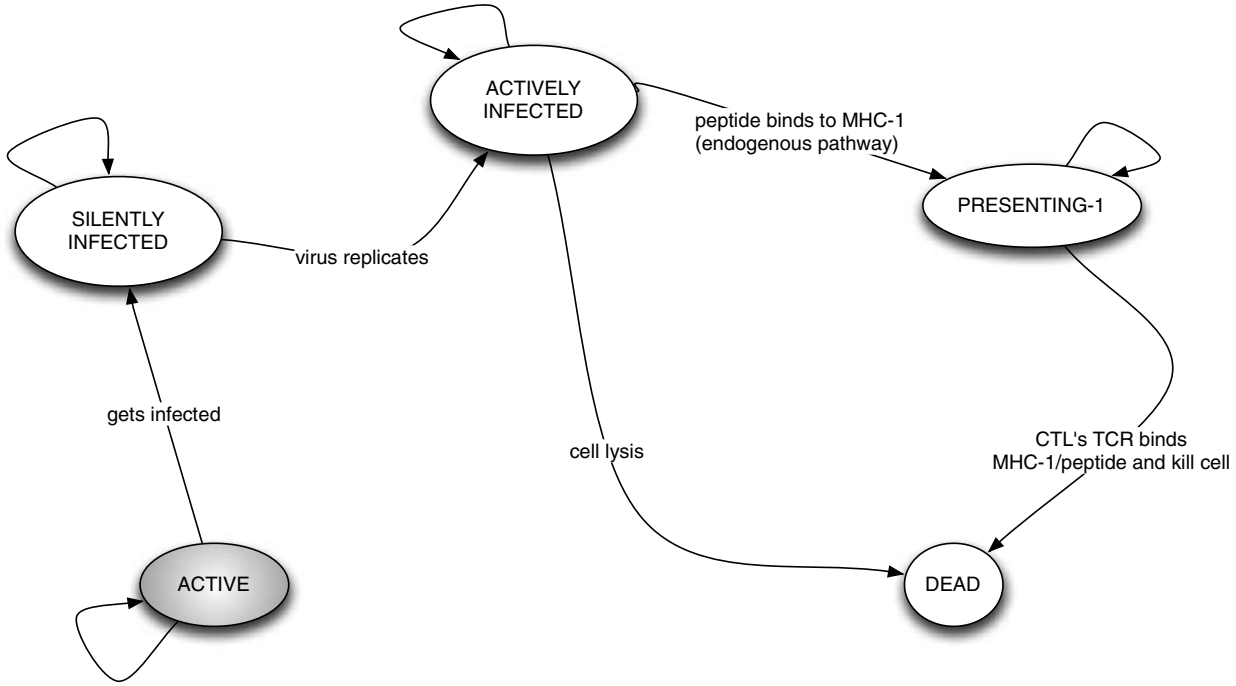
Specific *macro-instructions* have been defined to access, both in read and write mode, the flag byte. This access is also computationally very cheap.

| State | Description | B | TH | TC | M | DC | NK |
|---|---|---|---|---|---|---|---|
| **ACTIVE** | In this state, the cell is mature and ready to interact. This is the initial state for most cells. | X | X | X | X | X | X |
| **ANERGIC** | This is the anergic state. In this state, the cell does not interact. | X | X | X | | | |
| **INTERNALISED** | In this state, the cell has engulfed one antigen. | X | | | X | X | |
| **PRESENTING-1** | MHC-1 molecule is loaded with one antigen peptide. | | | | | X | |
| **PRESENTING-2** | The cell has processed the antigen it previously engulfed. The cell is now exposing the MHC-2 molecule bond with an antigen peptide. | X | | | X | X | |
| **DUPLICATING** | The cell is duplicating. It will remain in this state for a number of duplication steps. | X | X | X | | | |
| **RESTING** | The cell is in the resting state, waiting for a signal to be activated. | | X | X | X | | X |
| **SILENTLY INFECTED** | A virus has infected the cell and its DNA is already part of the cellular genome. The virus is not replicating. | | | | | X | |
| **ACTIVELY INFECTED** | The virus that has infected the cell is actively replicating. | | | | | X | |
| **DEAD** | The cell has been marked to die by lysis by a cytotoxic cell or is necrotic for other reasons. | X | X | | X | X | |

# UISS: State formal representation

How a generic epithelial cell change its status during a virus infection

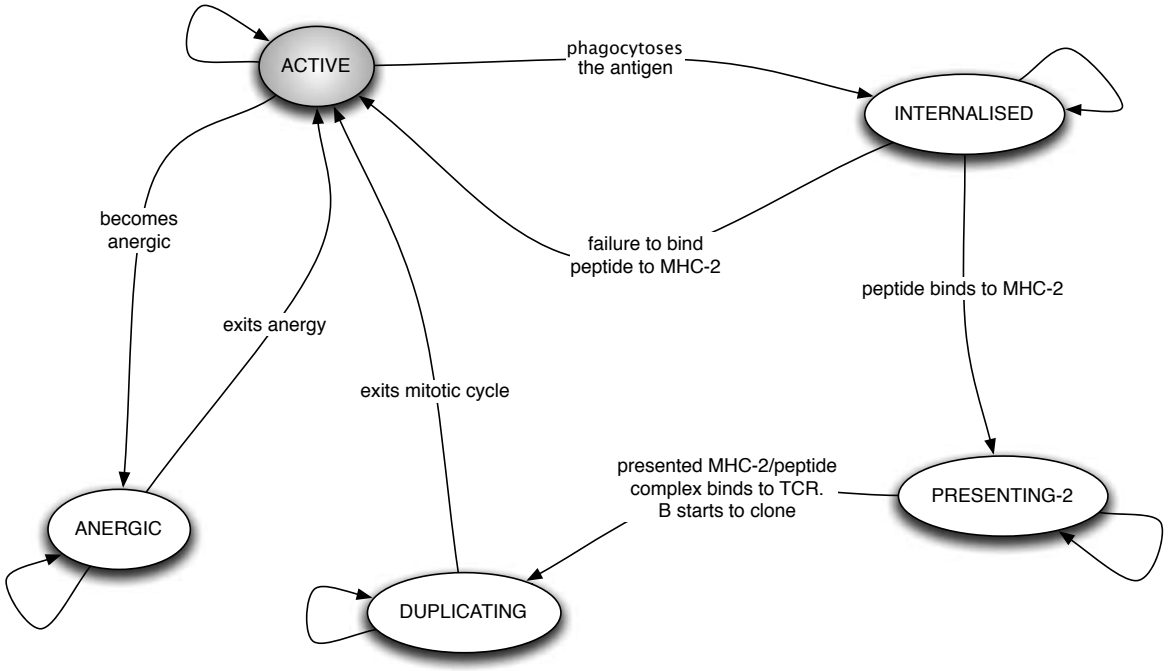
- ACTIVE epithelial cells are targets of the virus. A virus first integrates its DNA into the cell's DNA and later, upon activation, it starts replicating. This is when the epithelial cell changes from the state of SILENTLY to ACTIVELY INFECTED.
- In the latter state, the cell may release virus particles budding from the cell membrane. The fate of this cell is signed and it will die either because its membrane will break when its viral content reaches a threshold or because a cytotoxic T lymphocyte kills it.
- This happens if the TCR of the cytotoxic T binds to the MHC-1/peptide complex exposed on the infected cell membrane upon digestion of the viral peptides.



# UISS: State formal representation

UISS formal description of state changes is done by means of stochastic finite state machines

- B-cells start in the ACTIVE state. They can go back and forth between ACTIVE and ANERGIC according to the stimulation received.
- While ACTIVE, if they engulf an antigen, they go to the INTERNALISED state. If the MHC-2 succeeds in binding one antigen peptide, the B-cell goes into the PRESENTING-2 state.
- A cell in this state is able to stimulate a matching T helper lymphocyte and begin a clone expansion.

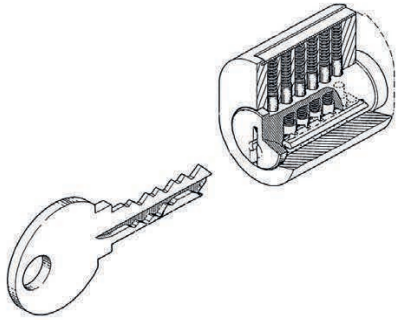


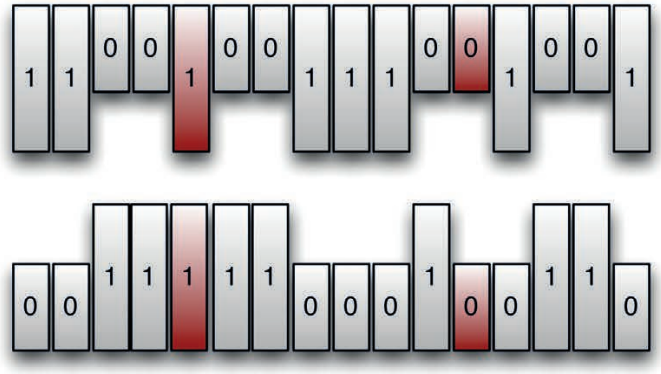
# UISS: molecular affinity

- UISS uses bit-string model (0s and 1s) to represent specific elements or binding properties in the same way that Farmer, Packard and Perelson did.

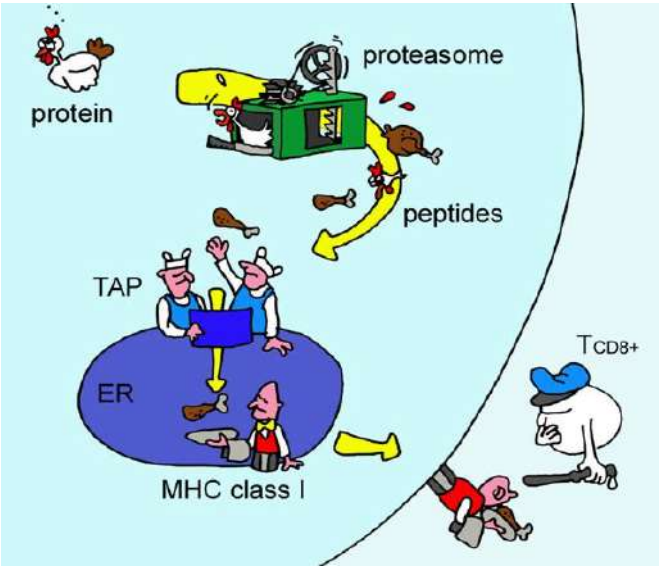
- Each different bit-string defines an element of the *repertoire*. An *m*-bit match is obtained when exactly *m* bits complement each other and the other NBIT – *m* are equal.

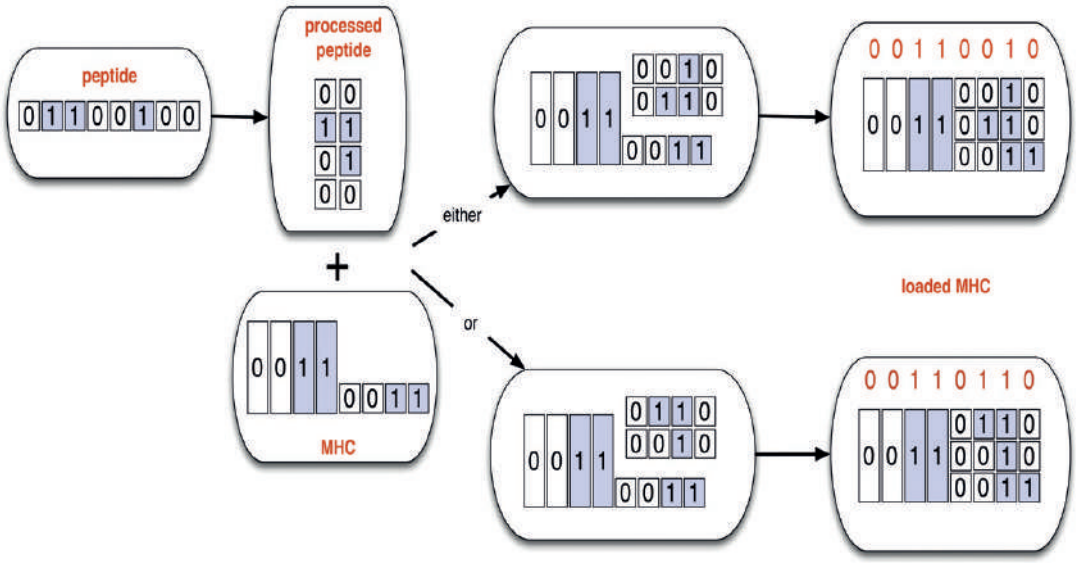
- The function match(*a*, *b*) = hamming(*a*, *b*) is defined to give us the number of matching bits between two strings *a* and *b* and is computed as the Hamming distance in the space of the bit- strings.





# UISS: antigen digestion and presentation

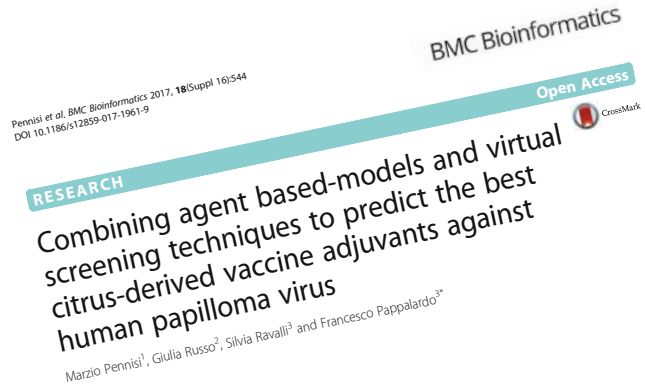



Internal digestion of the antigen peptides by antigen- presenting cells like the B lymphocytes or macrophages is done according to the following logic:
*ENTITY : B*
*SPECIFIC : Yes*
*MATCH : MHC-2(s), peptide(s)*
*CONDITION : B ≡ INTERNALISED*
*ACTION : B → PRESENTING-2*

**Analogously, the endogenous antigen is processed and presented on the class-1 MHC molecule (this is the cytosolic or endogenous pathway) instead of the class-2 MHC molecule as in this case of exogenous antigen processing (endocytic or exogenous pathway).**

# UISS



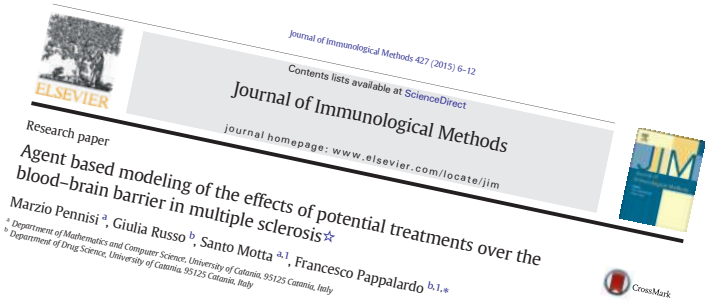
BMC Bioinformatics

Pennisi et al. BMC Bioinformatics 2017, 18(Suppl 16):544
DOI 10.1186/s12859-017-1961-9

RESEARCH Open Access

Combining agent based-models and virtual screening techniques to predict the best citrus-derived vaccine adjuvants against human papilloma virus

Marzio Pennisi[1], Giulia Russo[2], Silvia Ravalli[3] and Francesco Pappalardo[3*]



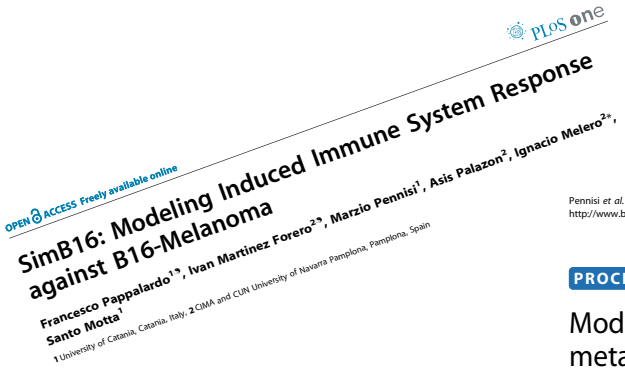
Journal of Immunological Methods 427 (2015) 6–12
Contents lists available at ScienceDirect
Journal of Immunological Methods
journal homepage: www.elsevier.com/locate/jim

Research paper

Agent based modeling of the effects of potential treatments over the blood–brain barrier in multiple sclerosis☆

Marzio Pennisi [a], Giulia Russo [b], Santo Motta [a,1], Francesco Pappalardo [b,1,*]

[a] Department of Mathematics and Computer Science, University of Catania, 95125 Catania, Italy
[b] Department of Drug Science, University of Catania, 95125 Catania, Italy



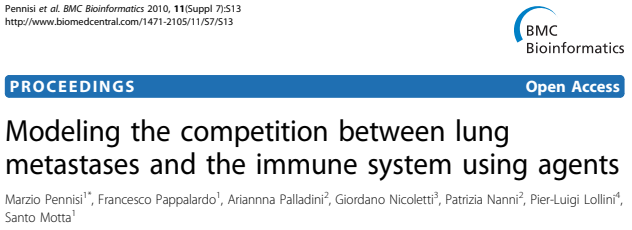
PLOS one

OPEN ACCESS Freely available online

SimB16: Modeling Induced Immune System Response against B16-Melanoma

Francesco Pappalardo[1,2], Ivan Martinez Forero[2,3], Marzio Pennisi[1], Asis Palazon[2], Ignacio Melero[2*], Santo Motta[1]

1 University of Catania, Catania, Italy, 2 CIMA and CUN University of Navarra Pamplona, Pamplona, Spain



Pennisi et al. BMC Bioinformatics 2010, 11(Suppl 7):S13
http://www.biomedcentral.com/1471-2105/11/S7/S13

BMC Bioinformatics

PROCEEDINGS Open Access

Modeling the competition between lung metastases and the immune system using agents

Marzio Pennisi[1*], Francesco Pappalardo[1], Ariannna Palladini[2], Giordano Nicoletti[3], Patrizia Nanni[2], Pier-Luigi Lollini[4], Santo Motta[1]

COMBINE Group
In Silico BioMedicine

## The team

HORIZON 2020

**STRITUVAD**

In Silico Trial for Tubercolosis Vaccine Development


UNIVERSITÀ degli STUDI di CATANIA

ETNA BIOTECH
Zydus Cadila Research Center

ARCHIVEL farma

The University Of Sheffield.

TBVI

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

IDRI

**Project Number:** 777123

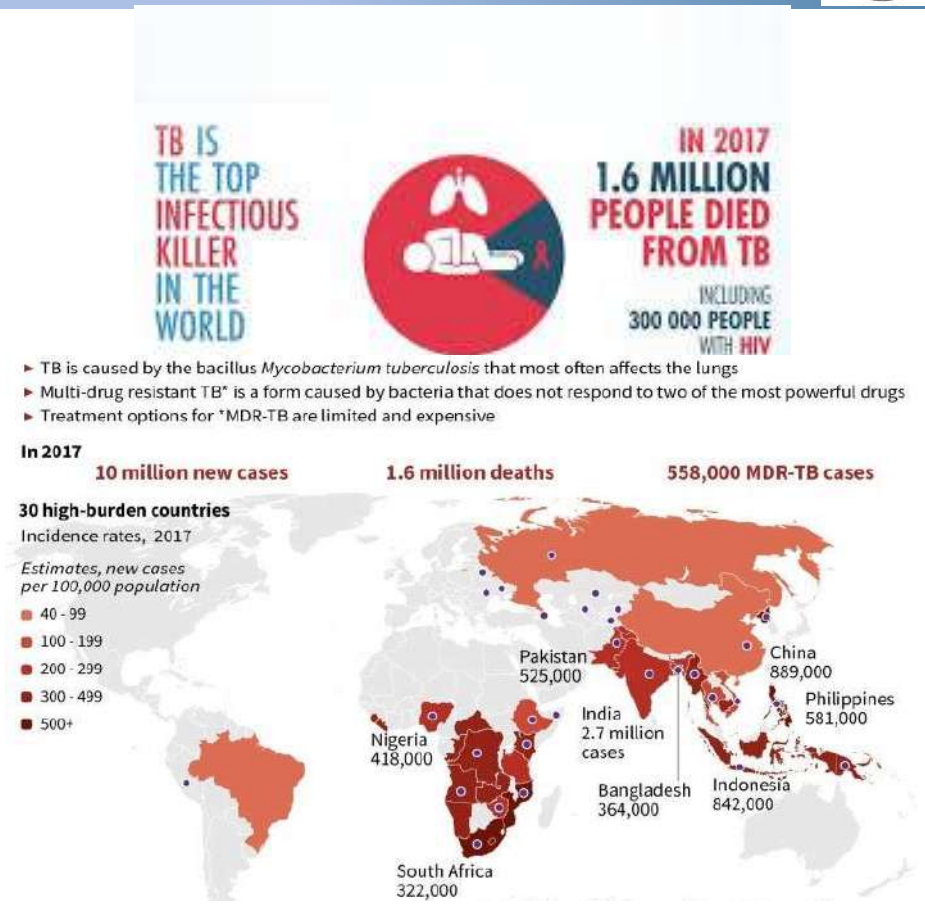
**Project Acronym:** STRITUVAD

**Project title:** In Silico Trial for Tuberculosis Vaccine Development

**Tuberculosis** is one of the world's deadliest diseases: it infects one third of the world's population in developing countries and it is becoming very dangerous in developed countries as well.

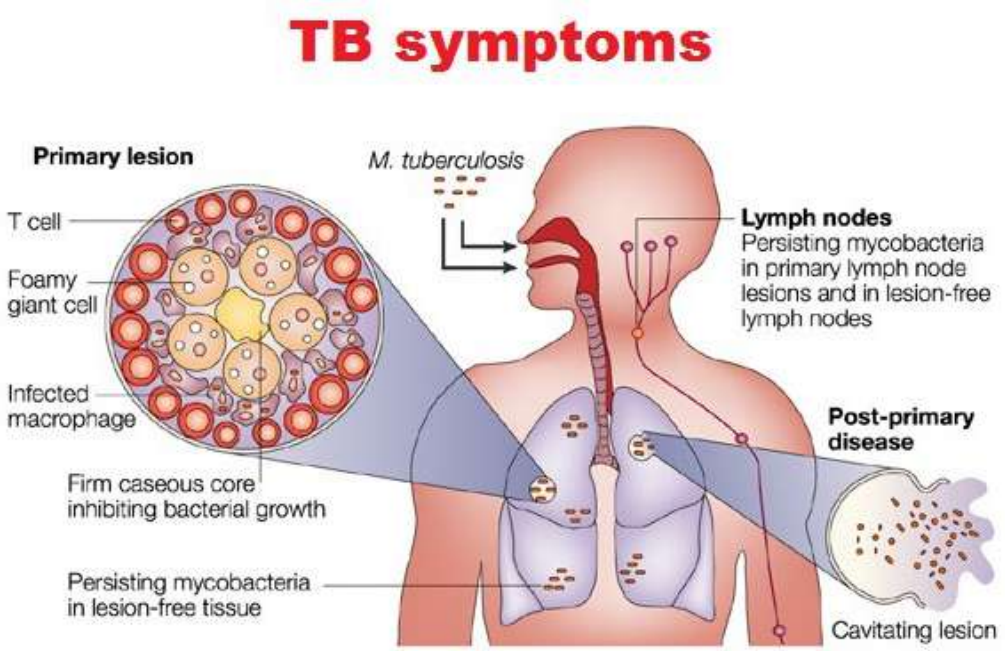
The high costs, long duration and poor compliance with the therapy, may lead to the development of multi-drug resistant bacterial strains, that make much harder to eradicate this disease.

**STriTuVaD** project aims to develop computer simulations to test the efficacy of new therapies, significantly reducing costs and duration of human clinical trials.

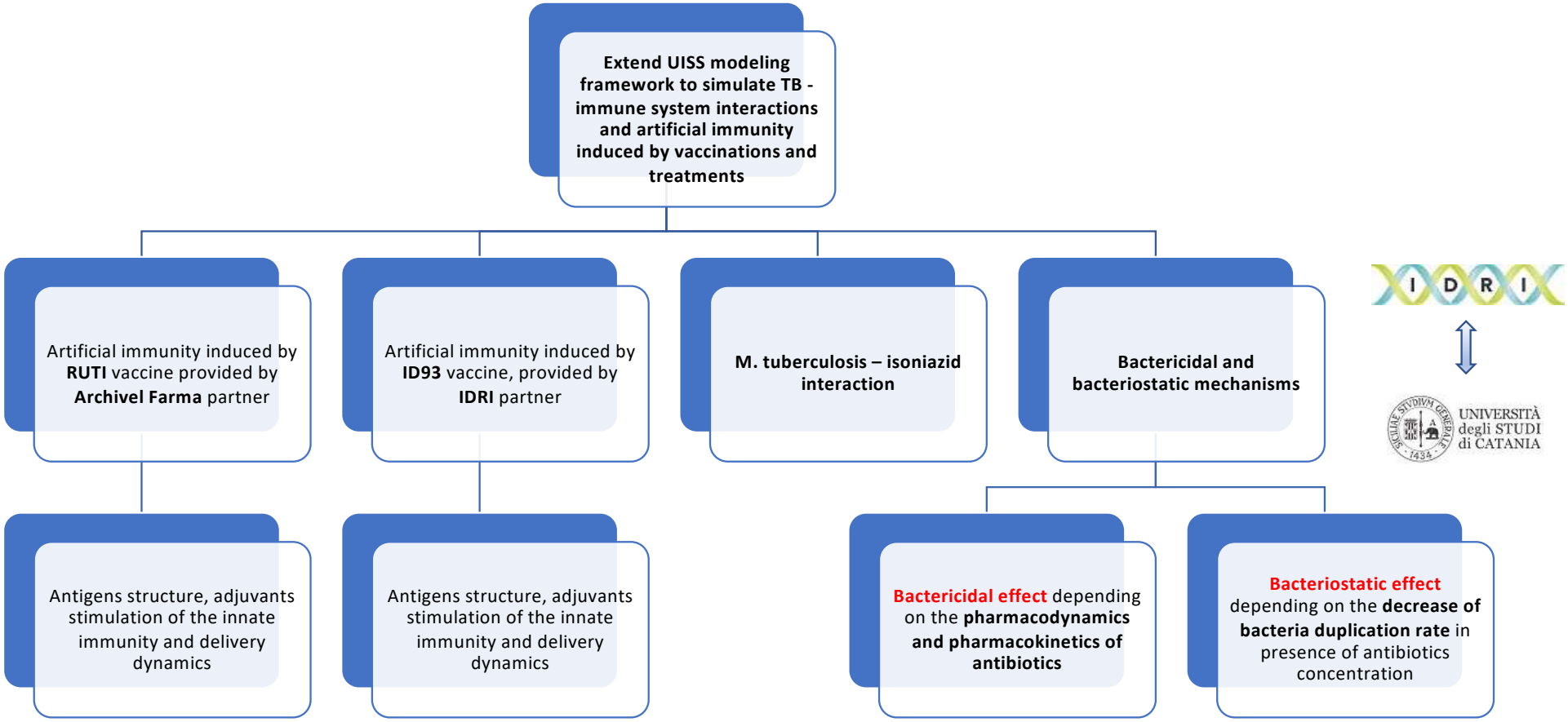


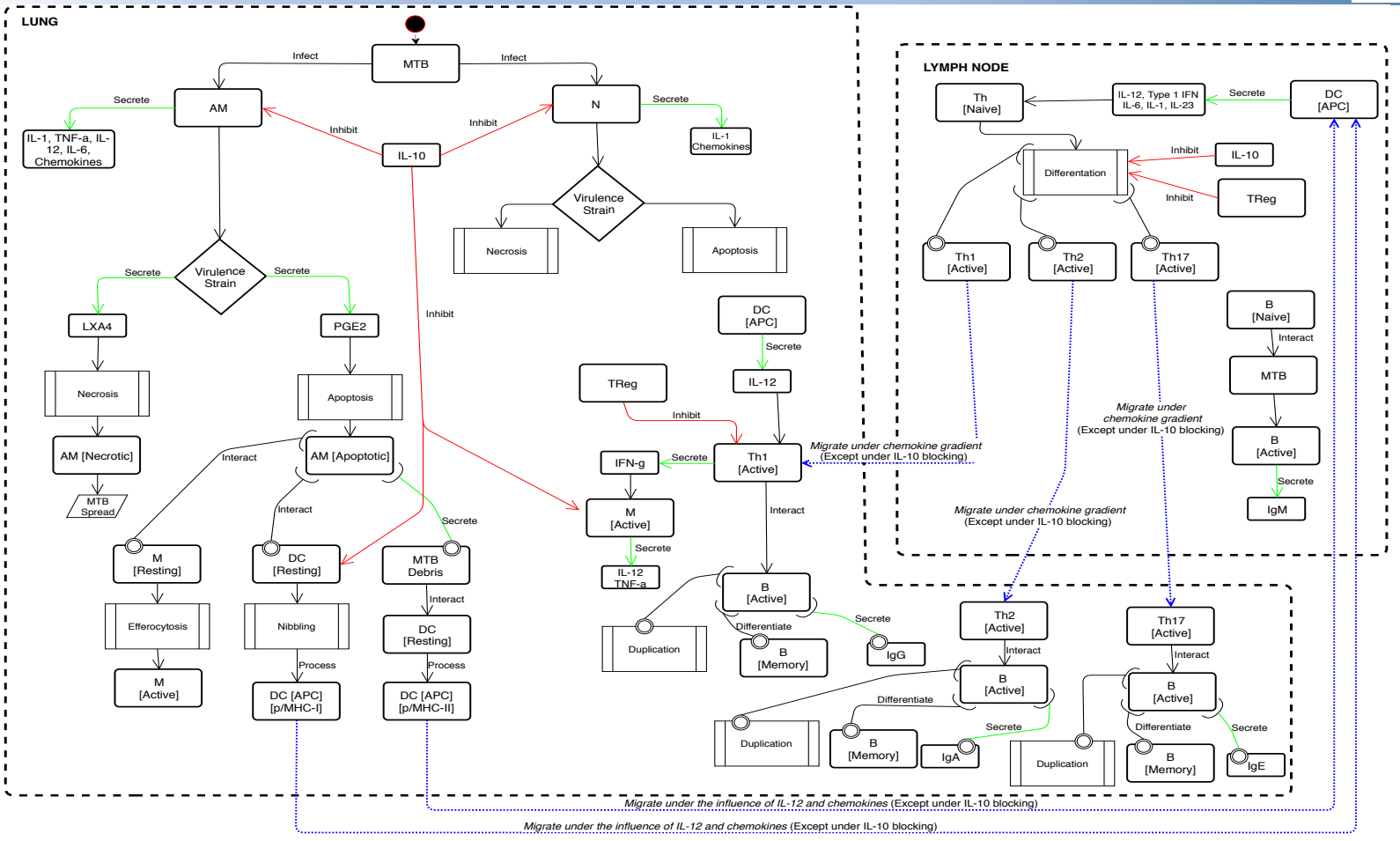
# Biological scenario

- To date non fully effective TB vaccines exists and, despite being both preventable and curable, it can be difficult for TB infected patients to get live-saving care.
- Current treatment can involve antibiotics administration for up to two years, potentially becoming a financial and social burden and resulting in patients stopping their medication.
- At times, TB is not diagnosed and dealt with the development and spread of drug-resistant strains.

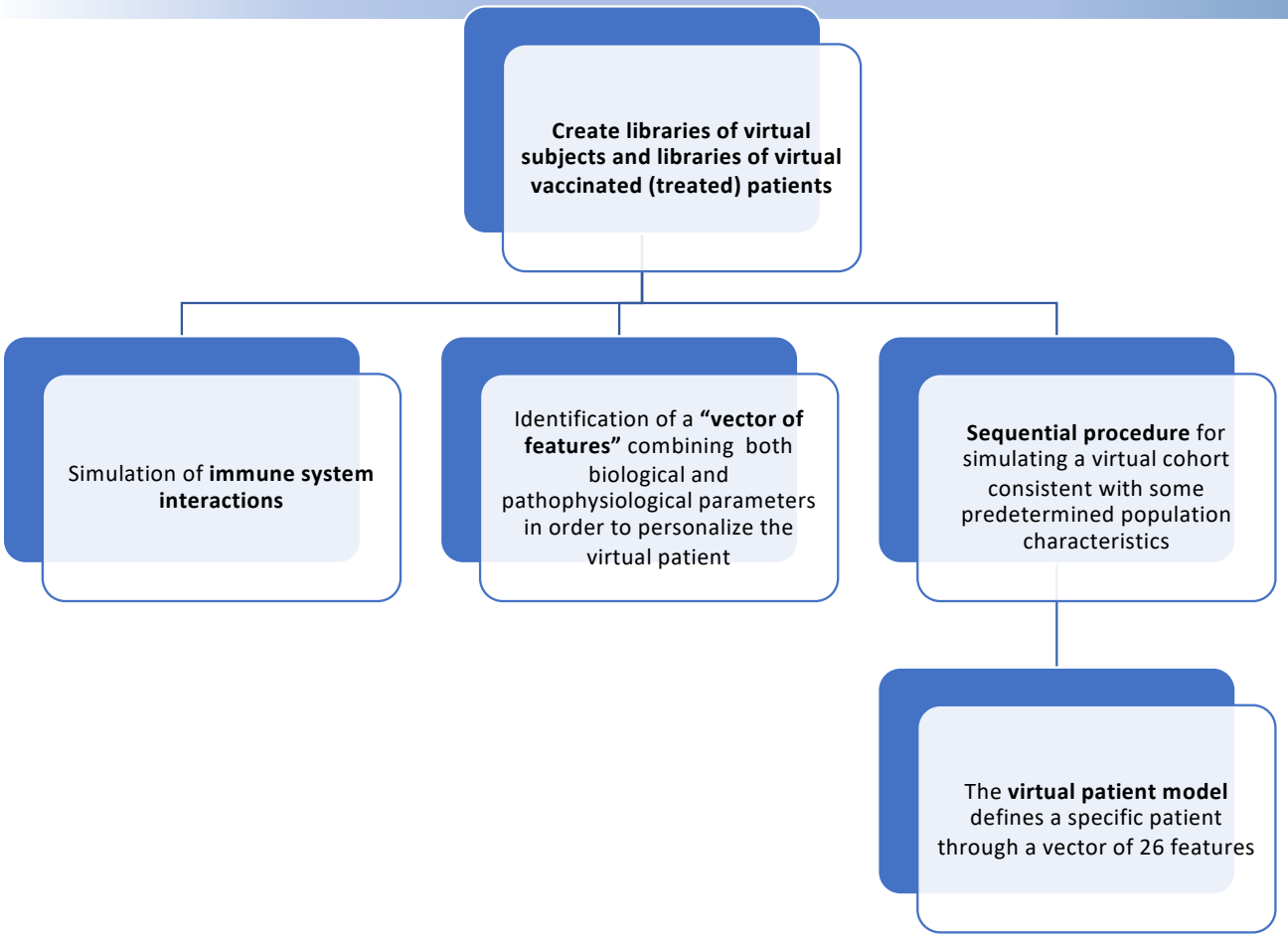


# Extending UISS for TB




LUNG
MTB
Infect
Infect
AM
N
Secrete
Secrete
IL-1, TNF-a, IL-12, IL-6, Chemokines
IL-1 Chemokines
Inhibit
Inhibit
IL-10
Virulence Strain
Necrosis
Apoptosis
Secrete
Secrete
Virulence Strain
LXA4
PGE2
Inhibit
Necrosis
Apoptosis
AM [Necrotic]
AM [Apoptotic]
MTB Spread
Interact
Interact
Secrete
M [Resting]
DC [Resting]
MTB Debris
Efferocytosis
Nibbling
Interact
DC [Resting]
M [Active]
Process
Process
DC [APC] [p/MHC-I]
DC [APC] [p/MHC-II]
DC [APC]
Secrete
IL-12
TReg
Inhibit
IFN-g
Secrete
Th1 [Active]
M [Active]
Secrete
IL-12 TNF-a
Interact
B [Active]
Duplication
Differentiate
Secrete
B [Memory]
IgG
Migrate under chemokine gradient (Except under IL-10 blocking)
LYMPH NODE
Th [Naive]
IL-12, Type 1 IFN IL-6, IL-1, IL-23
Secrete
DC [APC]
Differentation
Inhibit
IL-10
Inhibit
TReg
Th1 [Active]
Th2 [Active]
Th17 [Active]
B [Naive]
Interact
MTB
B [Active]
Secrete
IgM
Migrate under chemokine gradient (Except under IL-10 blocking)
Migrate under chemokine gradient (Except under IL-10 blocking)
Th2 [Active]
Interact
B [Active]
Differentiate
Secrete
Duplication
B [Memory]
IgA
Th17 [Active]
Interact
B [Active]
Differentiate
Secrete
Duplication
B [Memory]
IgE
Migrate under the influence of IL-12 and chemokines (Except under IL-10 blocking)
Migrate under the influence of IL-12 and chemokines (Except under IL-10 blocking)

# Digital Patients




The University Of Sheffield.

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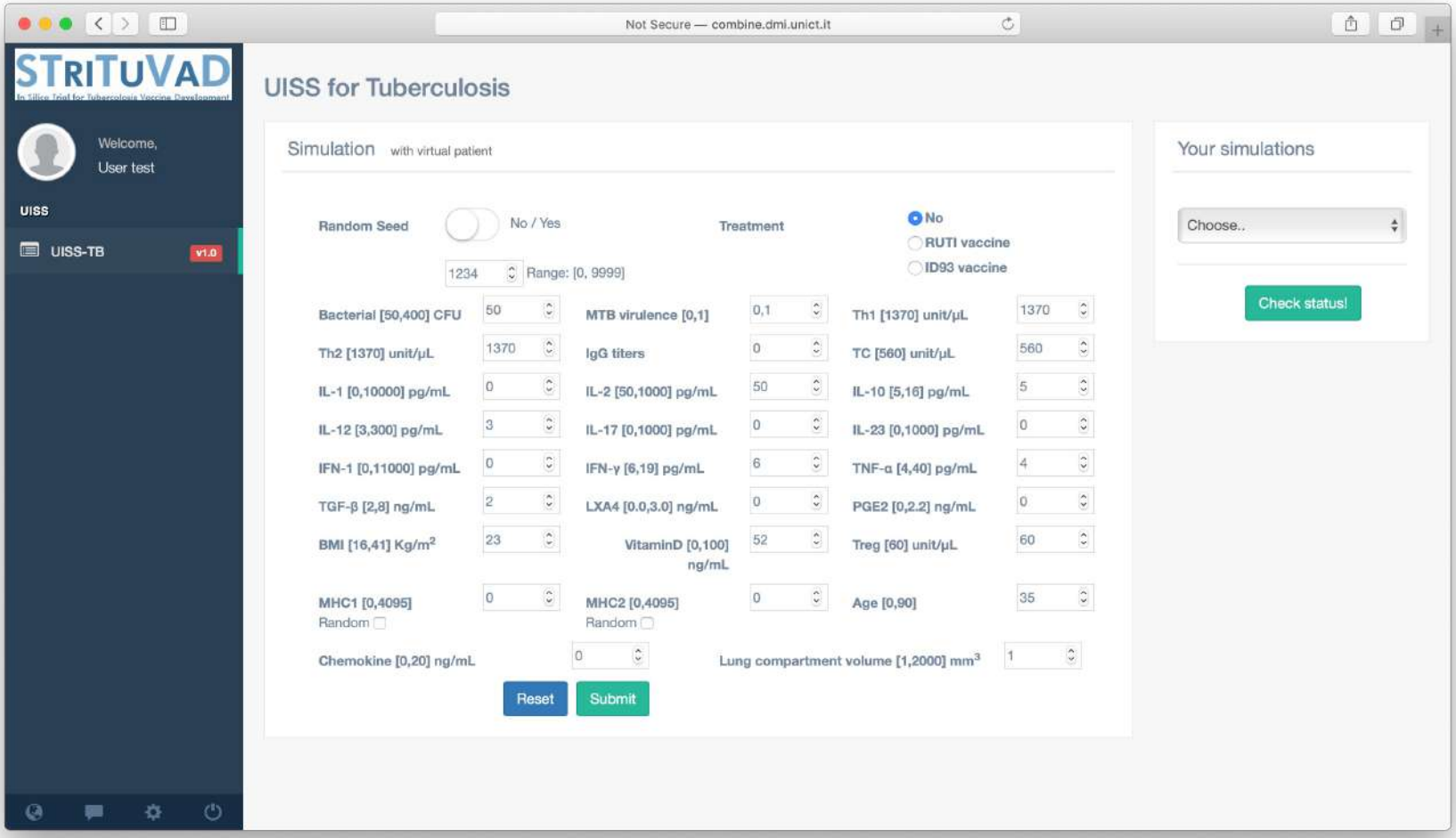
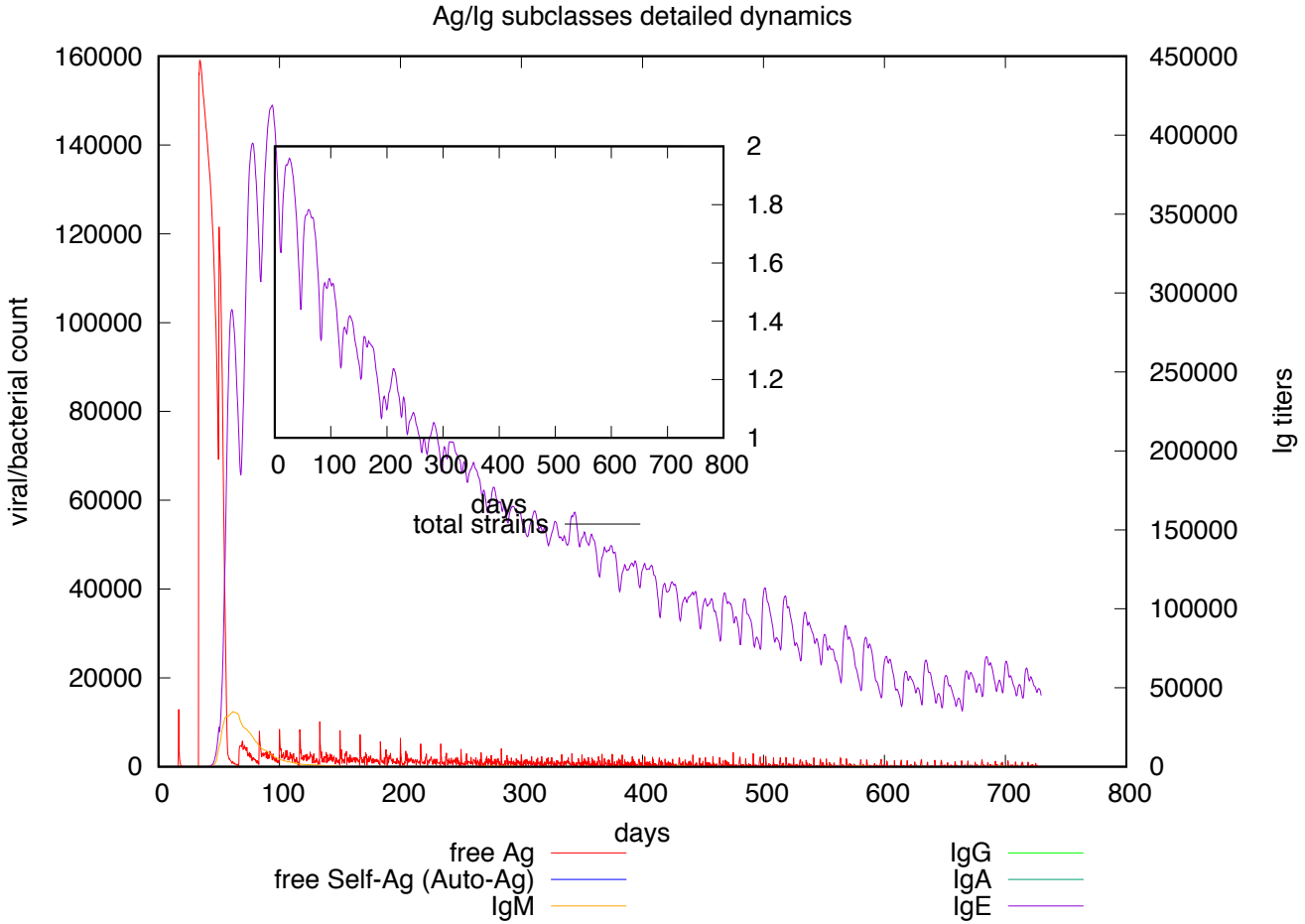
Still available only for project partners

Soon available to public



# Simulations: LTBI



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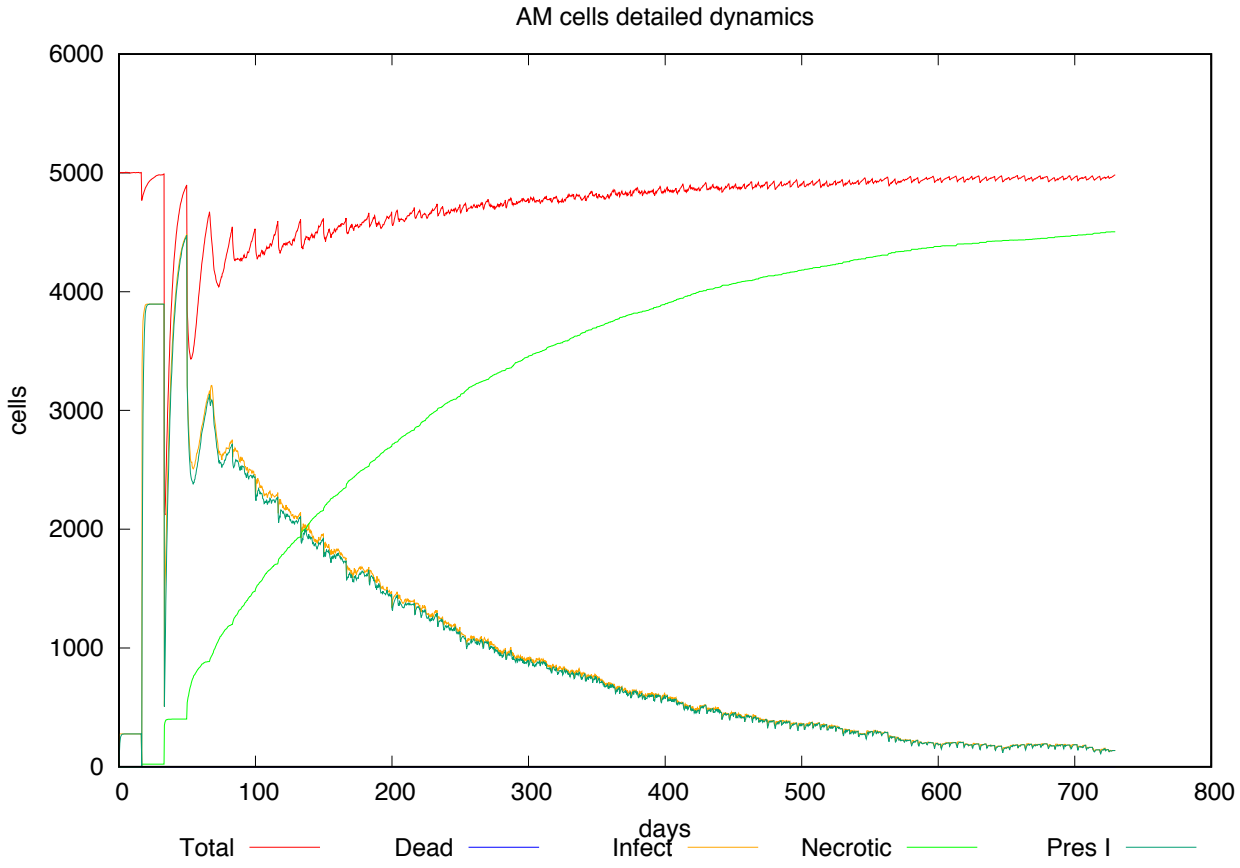

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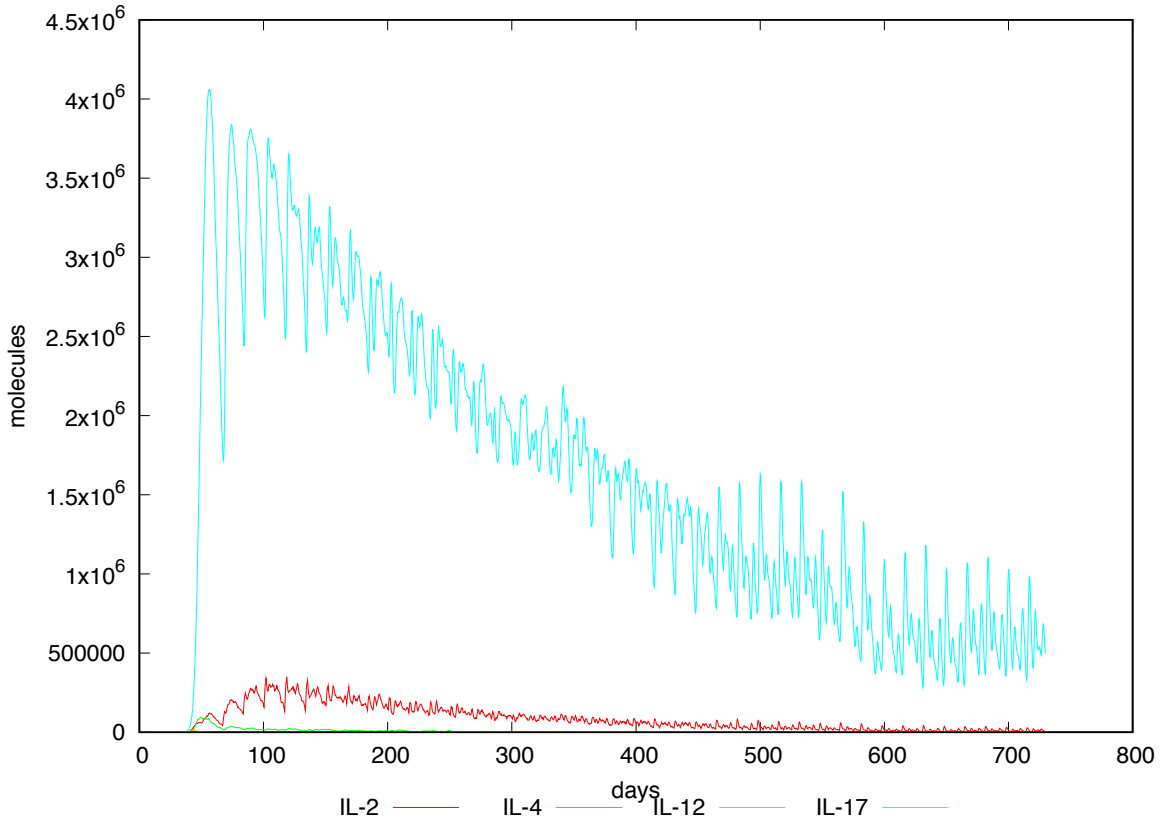
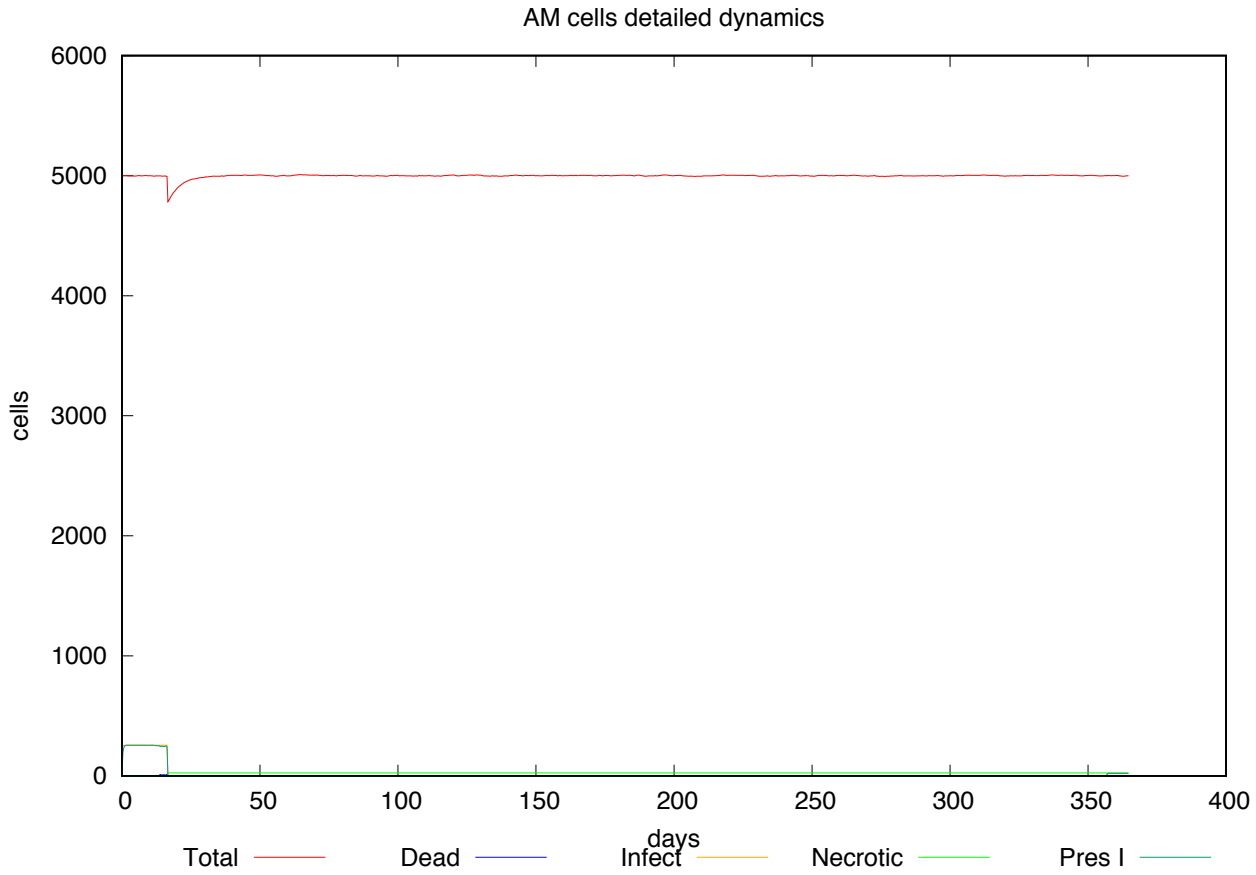
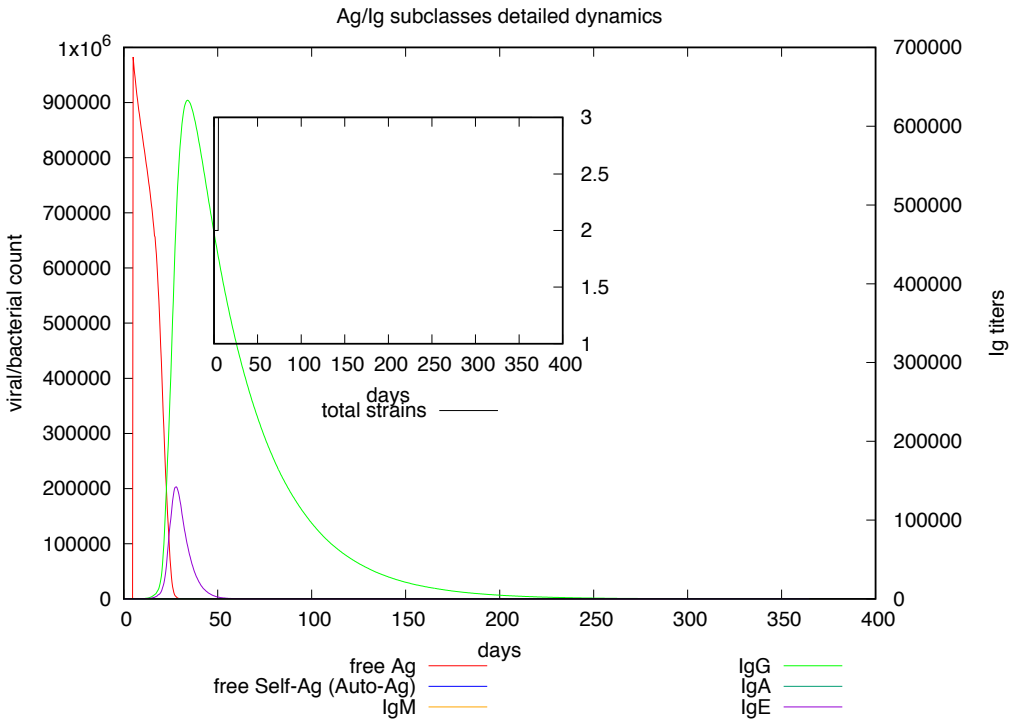


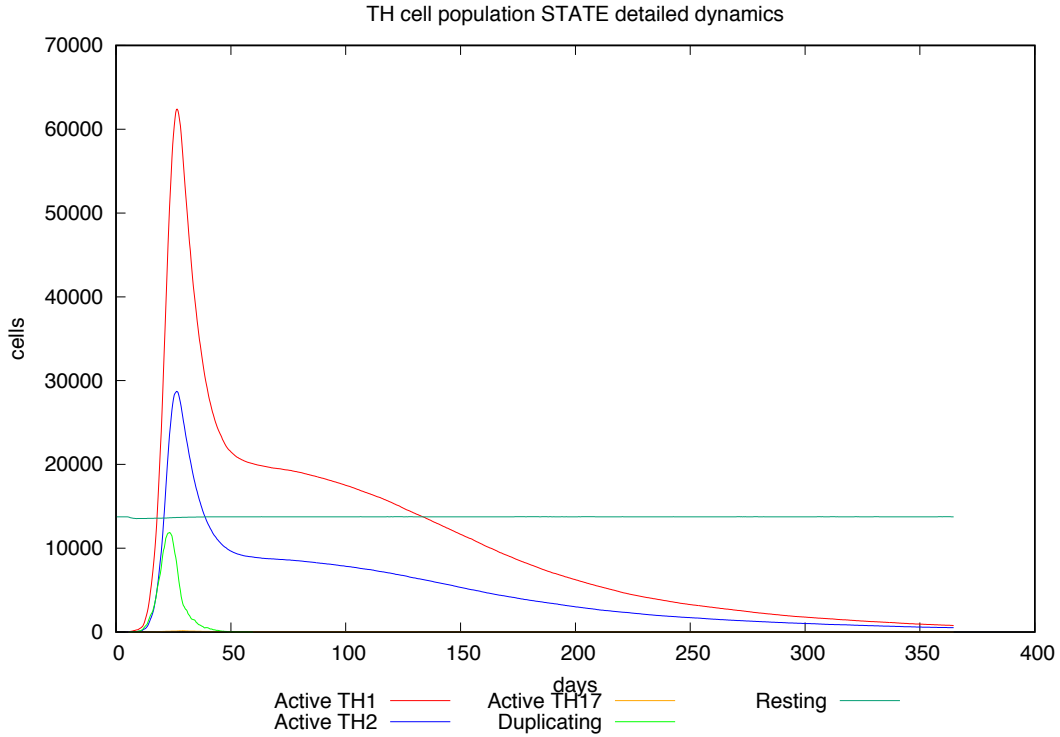
*Typical granuloma formation during latent TB infection*

# Simulations: vaccine administration

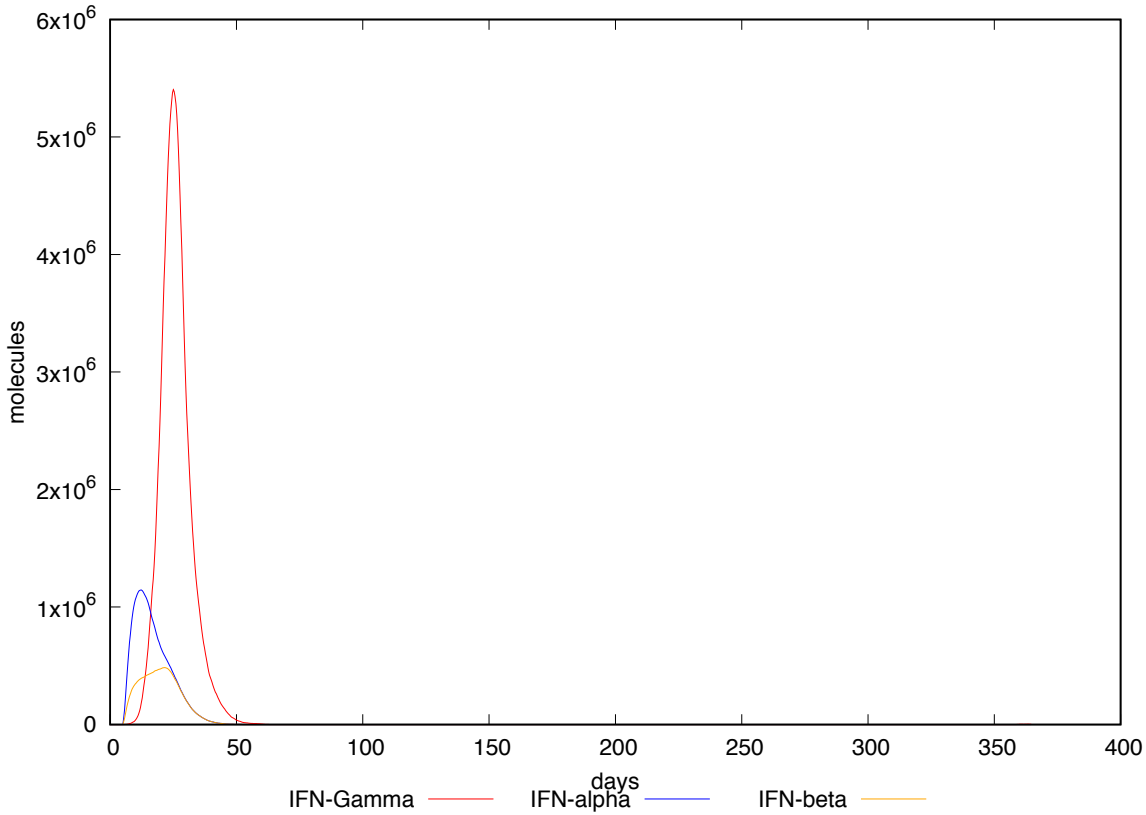


# Simulations: vaccine treated

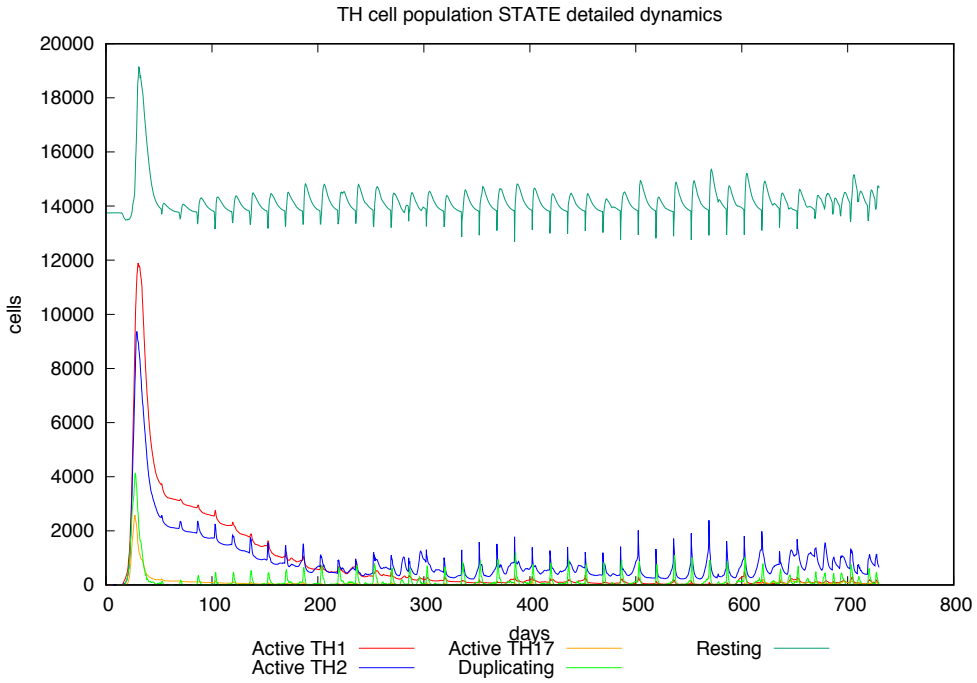


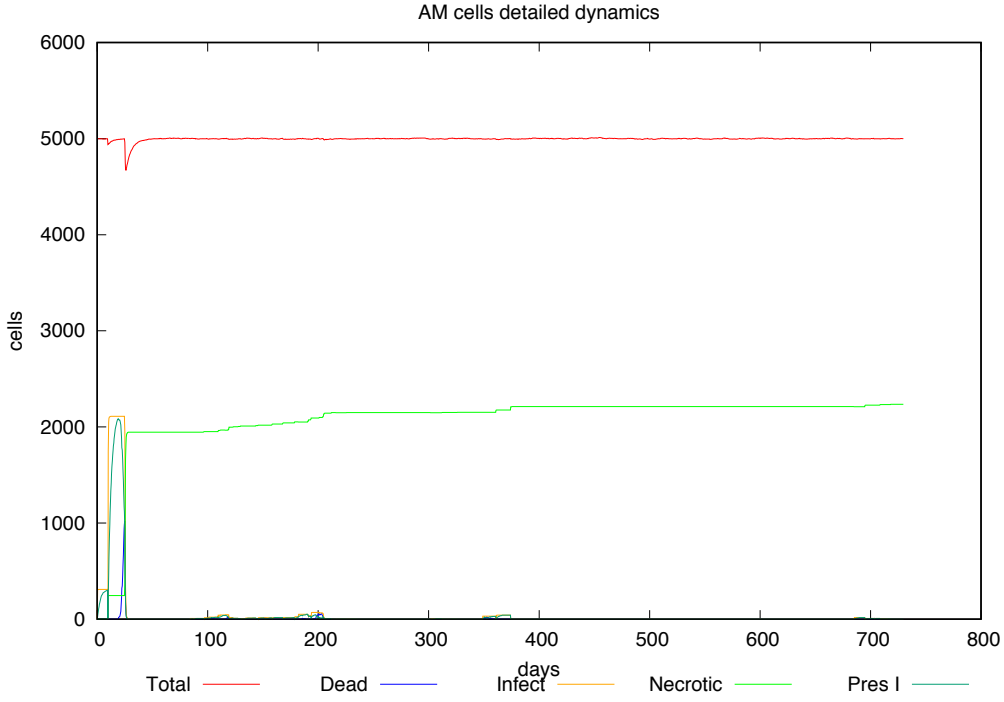



# Simulations: vaccine administration



# Simulations: vaccine administration
# No-responder



# Breaking News: UISS-TB-DR Final Process Letter of Support Released

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 January 2024
Doc ref: EMADOC-1700519818-1207681
Executive Director

## Letter of support for UISS-TB-DR

On 26 September 2022 the applicant Mimesis S.r.l. requested a qualification advice pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 25 – 28 September 2023, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 09 – 12 October 2023, the CHMP adopted the advice to be given to the applicant.

The current Letter of Support is issued on the basis of the qualification advice.

Mimesis Srl, on behalf of In Silico World (ISW) Consortium (https://insilico.world), requested a Qualification Advice for the use of UISS-TB-DR as a simulation platform to predict how the circulating interferon gamma (IFN-γ) changes over time as a function of the treatment dose in a cohort of virtual patients, to select the doses to be tested in escalating dose phase IIa trials of new therapeutic whole cell / fragmented based vaccines designed for latent pulmonary TB in adult, HIV negative, drug sensitive patients initially treated with isoniazid antibiotics pre-vaccination. According to the applicant, the focus is proposed to be made on selection of the middle dose in Phase 2a studies to also include the minimum effective dose (MED) and the maximum tolerated dose (MTD).

The Agency supports the application of model-informed drug development (MIDD) approaches, and in particular the use of mechanistic agent-based model such as UISS TB DR for dose regimen selection in the field of tuberculosis given the current need for effective therapies, vaccines, the challenge related to multidrug resistance and need for combination therapies.

However, the current context of use statement assumes that circulating interferon gamma (IFN-γ) changes over time can be considered as informative for clinical dose selection in TB. The value of IFN-γ (i.e. its prognostic and predictive value) as a biomarker for therapeutic vaccines/immune therapies in TB first needs to be established. IFN-γ is (currently) not an established surrogate for clinical endpoints in this clinical setting.

The implementation of the risk-based analysis and the credibility assessment by the Applicant are appreciated, and the overall approach proposed for technical model development, verification, validation and uncertainty quantification is in principle supported. However, the clinical data that the Applicant used to validate their platform (only including results obtained with RUTI vaccine PhIIa study), are considered limited for platform qualification in the claimed context of use. The applicant is currently narrowing the context of use to whole cell/fragmented based vaccines that are designed for latent pulmonary TB in adult subjects, who are HIV negative and drug sensitive after 1month treatment with INH. Although the rationale for limiting the scope of qualification is understood, the Agency encourages the applicant in the future to expand their approach to the other types of therapeutic vaccines, to widen the range of doses to be optimized and to assess the impact of concomitant antibacterial therapies.

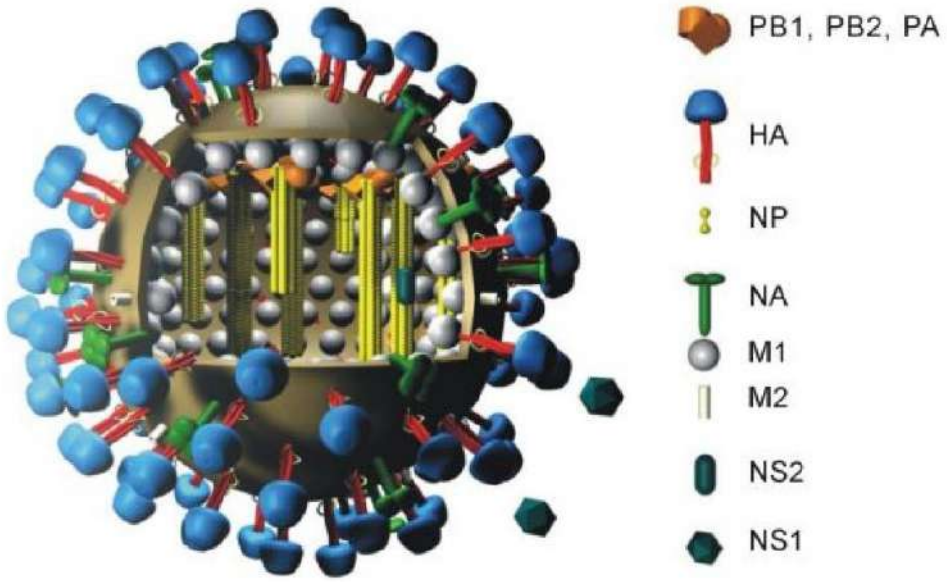
The objective of this letter of support is to foster clinical data sharing initiatives to advance exploratory development of latent TB therapeutic vaccines. It emphasizes the importance of collecting additional data, which are crucial for two primary purposes: firstly, to ascertain the value of IFN-γ as a reliable biomarker for dose regimen selection in therapeutic TB vaccines, and secondly, to address the current limitations in clinical validation of the platform. The Agency recognizes the potential of innovative approaches related to model-informed drug development (MIDD) in tuberculosis, an area that faces significant challenges such as multidrug resistance and the need for effective combination therapies. By encouraging the expansion of the platform's exploratory application to various types of therapeutic vaccines and a broader range of doses, once the limitations are addressed, the Agency underscores its support for advanced, comprehensive solutions in TB therapeutic vaccine development.

Sincerely,

Emer Cooke
Executive Director

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

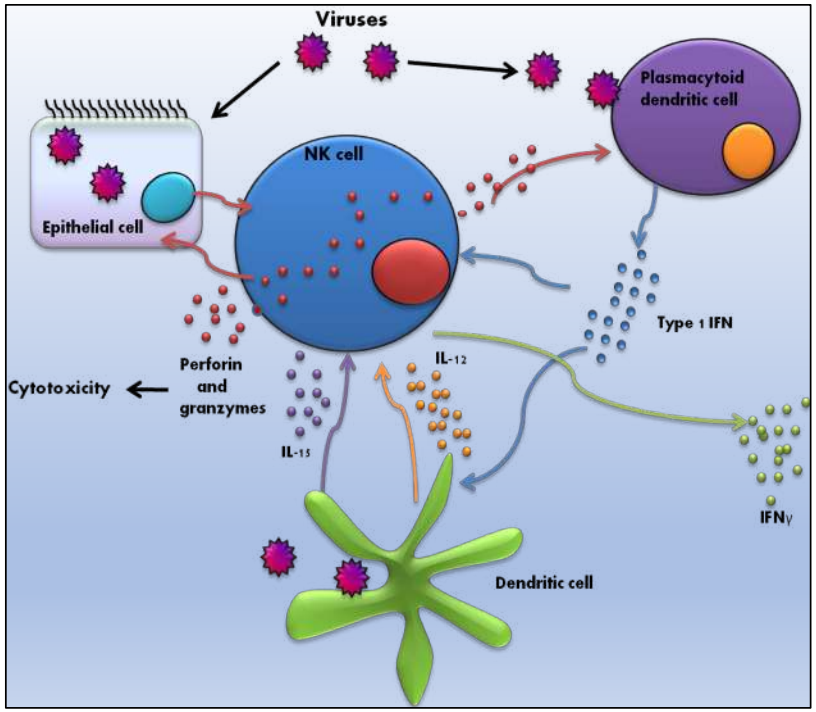
# Modeling Influenza with UISS

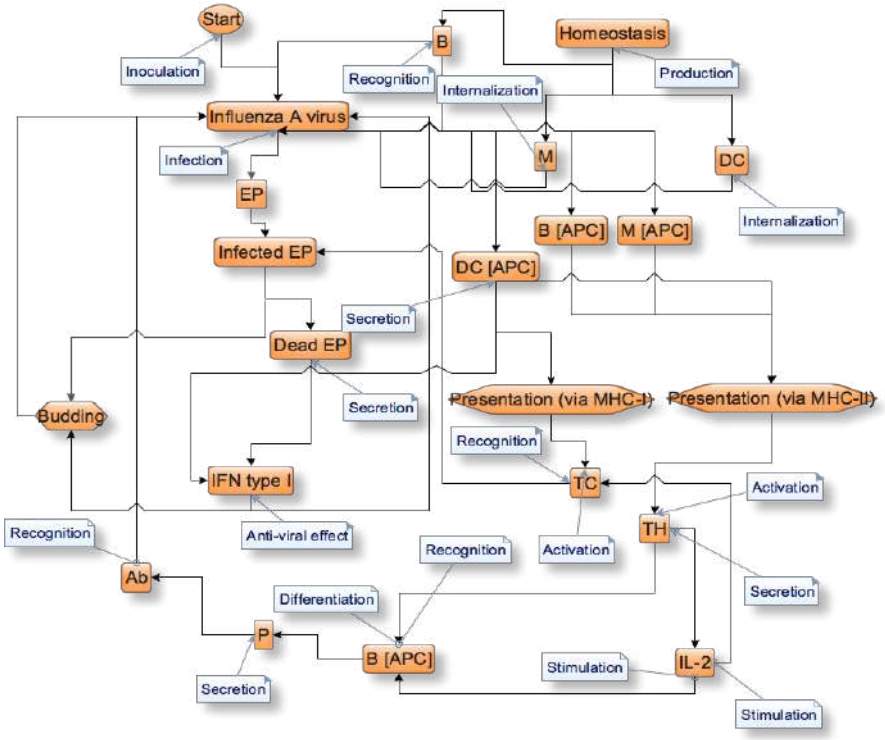



- In humans, replication of influenza subtypes seems to be limited to the respiratory epithelial cells.
- Once the virus enters a cell, it causes complex cytopathic effects, predominantly in the columnar epithelial cells, by shutting down the synthesis of host proteins.

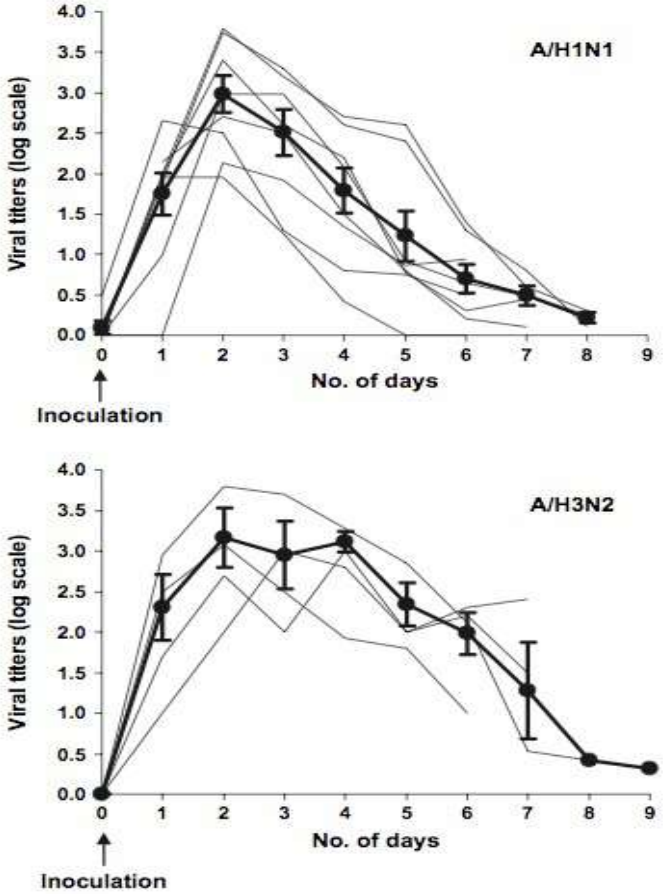
Figure 1. Structure of an influenza A virus.

Image copyright by Dr. Markus Eickmann, Institute for Virology, Marburg, Germany.



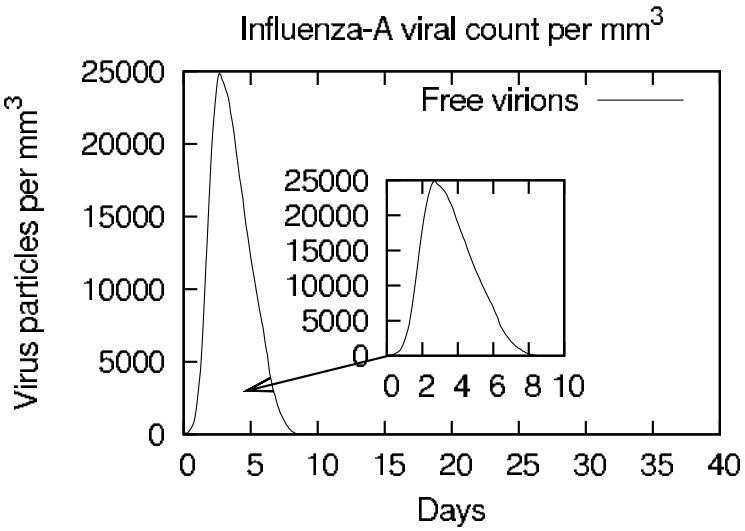



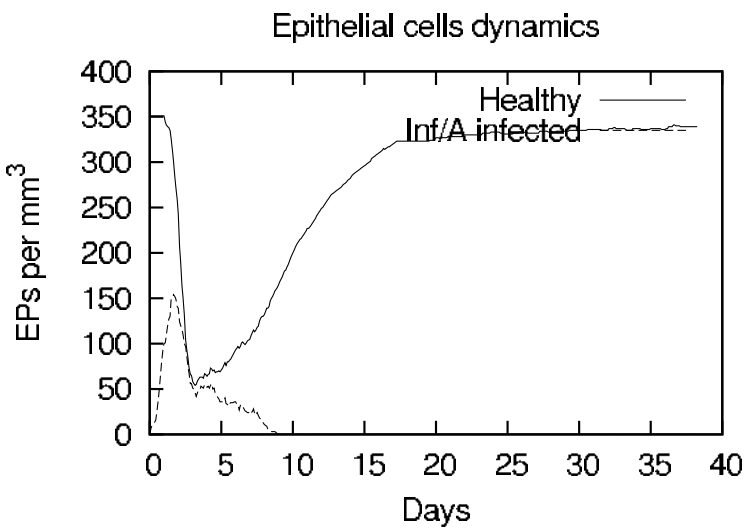

- The alpha/beta interferon (IFN-a/b) system represents one of the first lines of defense against virus infections.
- Influenza A is capable to produce these IFN-antagonistic factors. However, dendritic cells are capable of producing a large amount of IFN type I.
- The time of entry to the production of new virus is of **average 6 h**.



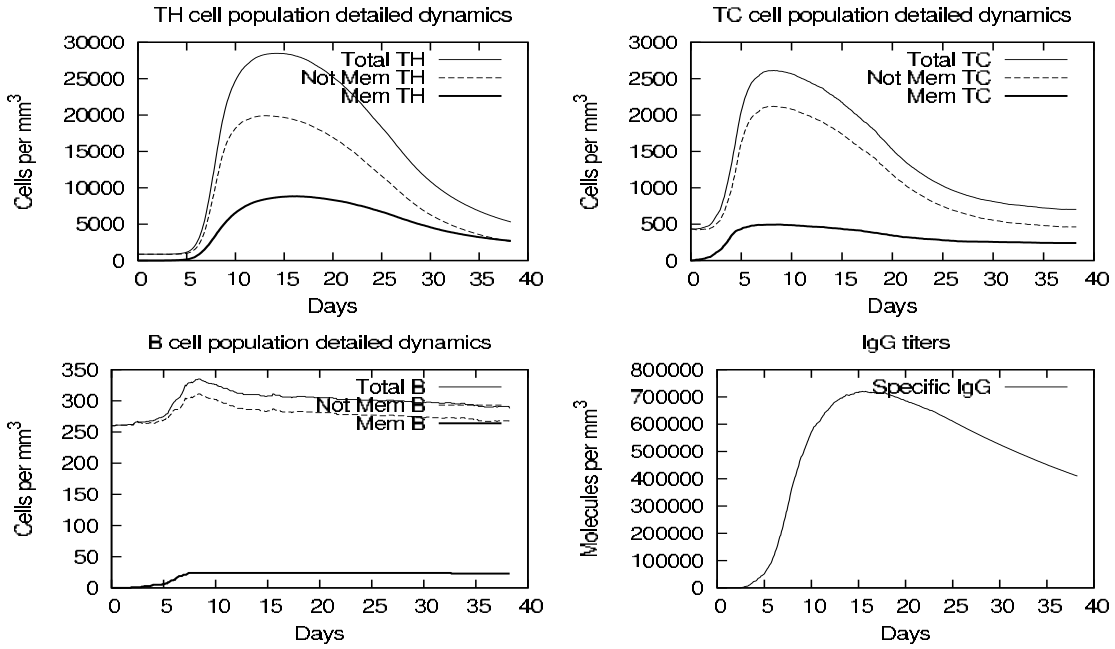

- The A/H1N1 and A/H3N2 curves showed a sharp increase during the first day following inoculation, and they reached their maximum values during the second day. Return to baseline values at day 8

- The summary curves did not differ markedly according to influenza virus type or subtype, although A/H3N2 infections gave sustained high viral titers by comparison with A/H1N1




***In silico results.*** *Viral dynamics of a typical INF/A infection. Viral load peaks around day 3-4. During an effective immune response, viral load decreases continuously to reach, at the end of day 7-8, undetectable values. On the right panel, it is depicted the dynamics of one of the most common influenza/A target i.e., epithelial cells. As one can appreciate, after day 15 the simulated tissue completely recovered its physiological condition, mirroring what commonly happens in in vivo settings.*




***In silico cellular and humoral immune system response.*** *Panel A shows the $CD4^+$ response to INF/A viral antigenic challenge. The response is detectable around day 4 and reaches its maximum level around day 13. Panel B depicts $CD8^+$response. It starts around day 4 and peaks around day 6-7. Cytotoxic response kills infected cells in order to remove all infection reservoir. Panel C and D show the humoral response. Only IgG are shown. Antibodies are present until 1 month afted the cleaning of the infection.*

# Another important step for influenza

Maleki *et al. BMC Bioinformatics* (2021) 22:617
https://doi.org/10.1186/s12859-022-04581-6

BMC Bioinformatics

RESEARCH Open Access

## In silico design of recombinant multi-epitope vaccine against influenza A virus

Avisa Maleki[1†], Giulia Russo[2†], Giuseppe Alessandro Parasiliti Palumbo[1] and Francesco Pappalardo[2*]

*From* 4th International Workshop on Computational Methods for the Immune System Function (CM-ISF 2020) Virtual. 16-19 December 2020

# Another important step for influenza

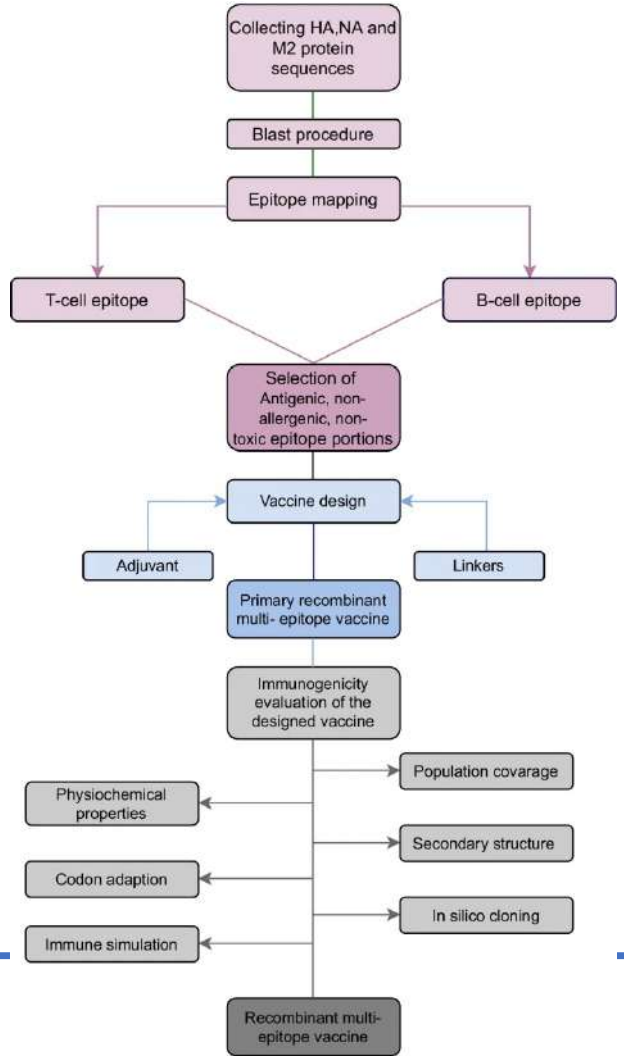
- This study utilized an immunoinformatic approach to design a **recombinant multi-epitope vaccine based on a highly conserved epitope** of **hemagglutinin**, **neuraminidase**, and **membrane matrix proteins** with fewer changes or mutate over time.

- The potential **B cells**, cytotoxic T lymphocytes (**CTL**), and **CD4 T cell epitopes** were identified. The recombinant multi-epitope vaccine was designed using **specific linkers** and a proper **adjuvant**.

- Moreover, some **bioinformatics online servers** and datasets were used to evaluate the **immunogenicity** and chemical properties of selected epitopes.

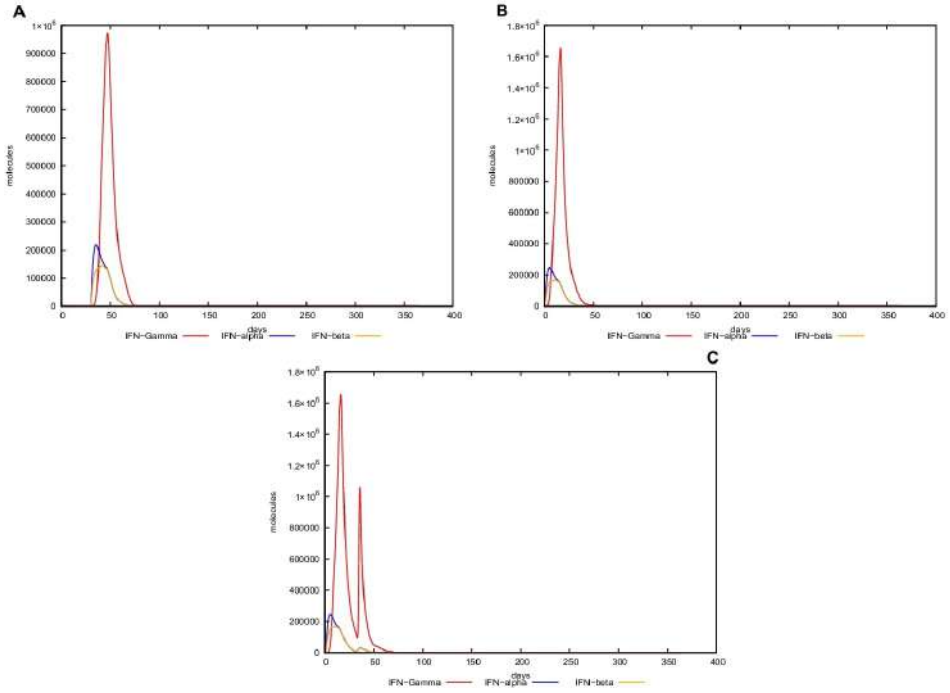
- In addition, **Universal Immune System Simulator (UISS)** in silico trial computational framework was run after influenza exposure and recombinant multi-epitope vaccine administration, showing a **good immune response in terms of immunoglobulins of class G (IgG), T Helper 1 cells (TH1), epithelial cells (EP) and interferon gamma (IFN-g) levels.**

- Furthermore, after a **reverse translation** (i.e., convertion of amino acid sequence to nucleotide one) and codon optimization phase, the optimized sequence was placed between the two EcoRV/MscI restriction sites in the PET32a$^{+}$ vector.

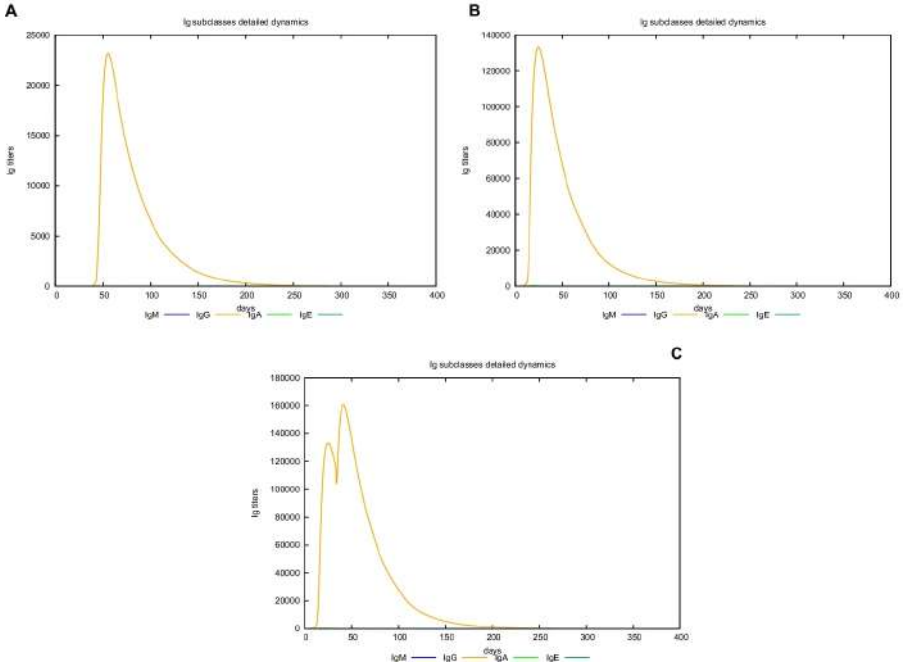



**Workflow of the multi-bioinformatic approach used.**

# In silico trial immune simulation

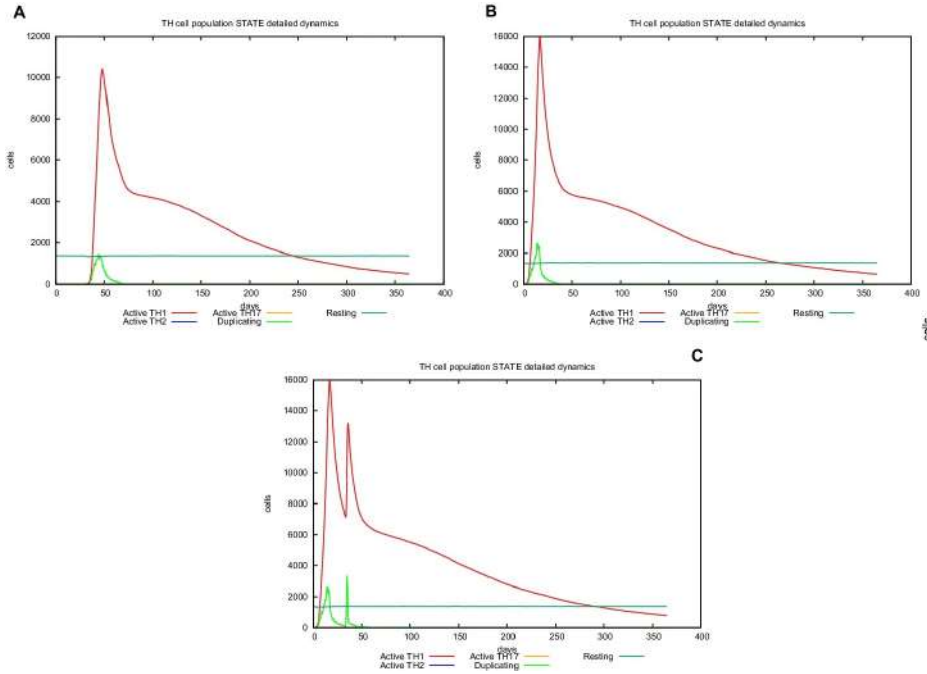



**In silico dynamics of IFN-g through the UISS simulation platform.**
**A** IFN-g level after influenza exposure. **B** IFN-g level after the recombinant multi-epitope vaccine. **C** IFN-g levels after influenza exposure and recombinant multi-epitope vaccine administration

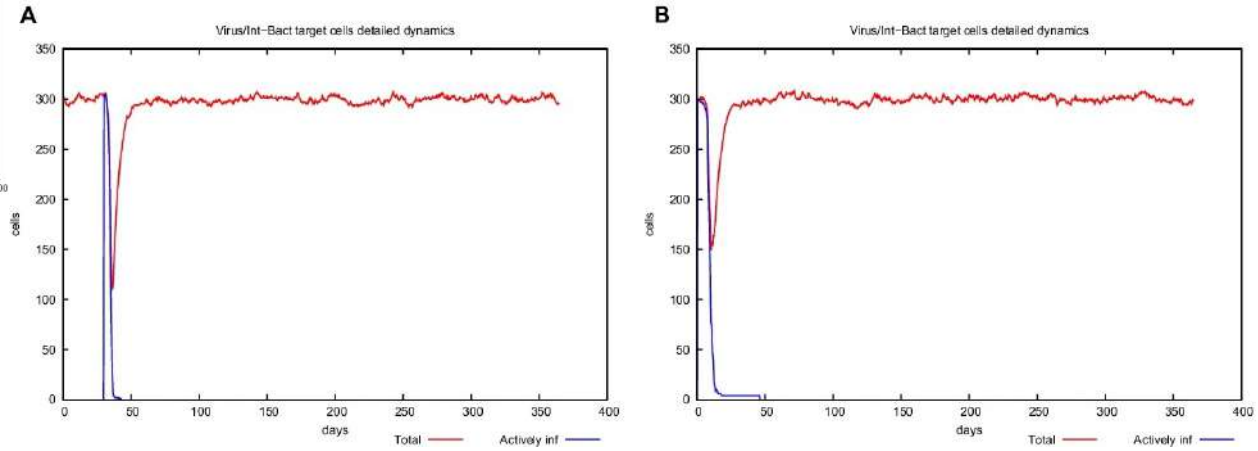



**In silico dynamics of IgG through the UISS simulation platform.**
**A** IgG level after influenza exposure. **B** IgG level after the recombinant multi-epitope vaccine. **C** IgG levels after influenza exposure and recombinant multi-epitope vaccine administration

# In silico trial immune simulation




**In silico dynamics of TH1 through the UISS simulation platform**.
**A** TH1 level after influenza exposure. **B** TH1 level after the recombinant multi-epitope vaccine. **C** TH1 levels after influenza exposure and recombinant multi-epitope vaccine administration




**In silico dynamics of EP cells through the UISS simulation platform.**
**A** EP level after influenza exposure. **B** EP level after the recombinant multi-epitope vaccine

> BMC Bioinformatics. 2020 Dec 14;21(Suppl 17):527. doi: 10.1186/s12859-020-03872-0.

# In silico trial to test COVID-19 candidate vaccines: a case study with UISS platform

Giulia Russo [1], Marzio Pennisi [2], Epifanio Fichera [3], Santo Motta [4], Giuseppina Raciti [5], Marco Viceconti [6], Francesco Pappalardo [7]

Affiliations + expand

PMID: 33308153 PMCID: PMC7733700 DOI: 10.1186/s12859-020-03872-0

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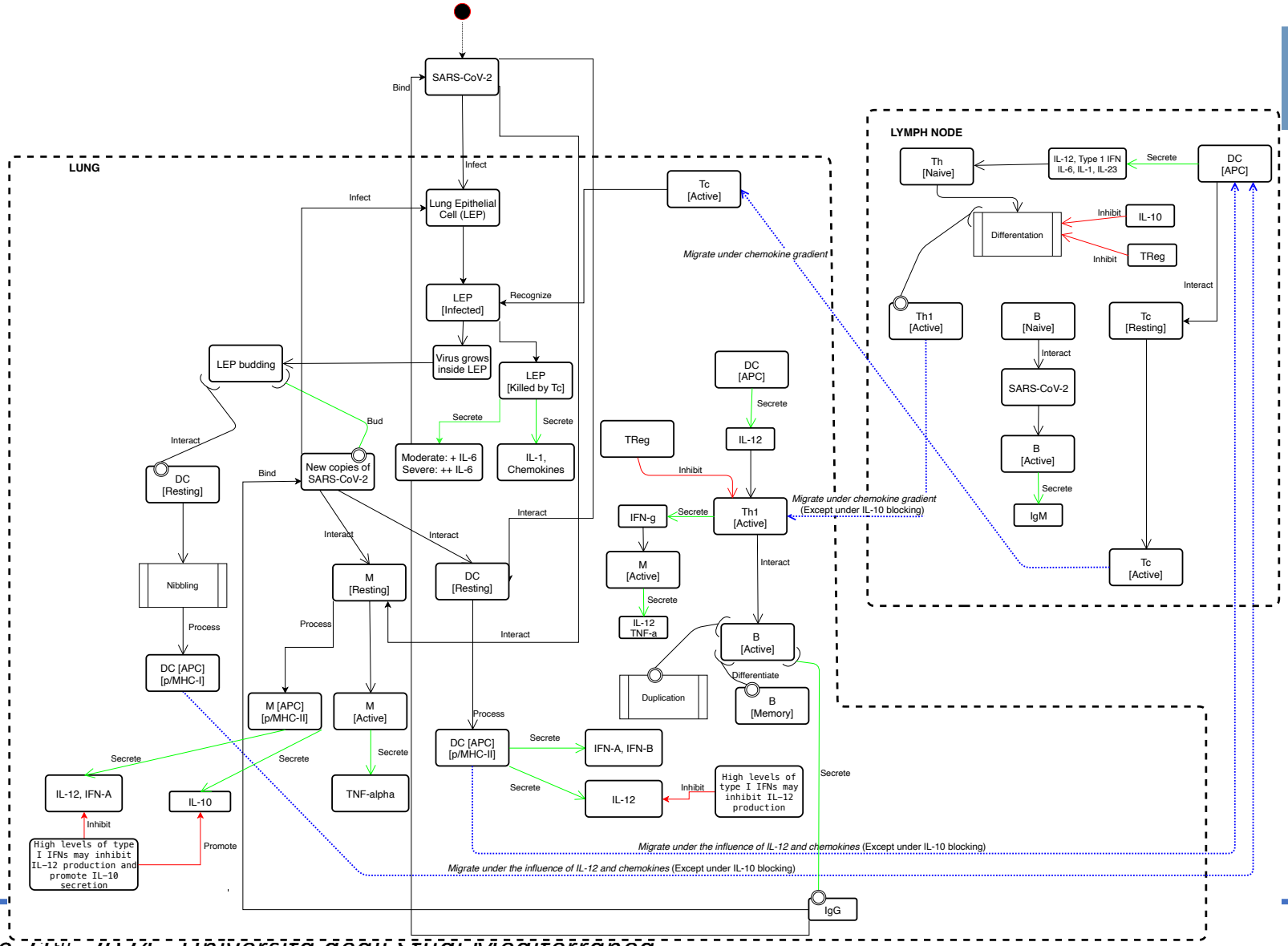

LUNG
SARS-CoV-2
Bind
Infect
Lung Epithelial Cell (LEP)
LEP [Infected]
Recognize
Virus grows inside LEP
LEP budding
LEP [Killed by Tc]
Bud
Secrete
Moderate: + IL-6 Severe: ++ IL-6
IL-1, Chemokines
Interact
DC [Resting]
New copies of SARS-CoV-2
Nibbling
Process
DC [APC] [p/MHC-I]
M [Resting]
DC [Resting]
M [APC] [p/MHC-II]
M [Active]
TNF-alpha
IL-12, IFN-A
IL-10
Inhibit
Promote
High levels of type I IFNs may inhibit IL-12 production and promote IL-10 secretion
DC [APC] [p/MHC-II]
IFN-A, IFN-B
IL-12
High levels of type I IFNs may inhibit IL-12 production
Tc [Active]
Migrate under chemokine gradient
TReg
IFN-g
Th1 [Active]
Migrate under chemokine gradient (Except under IL-10 blocking)
M [Active]
IL-12 TNF-a
Duplication
B [Active]
Differentiate
B [Memory]
IgG
Migrate under the influence of IL-12 and chemokines (Except under IL-10 blocking)
LYMPH NODE
Th [Naive]
IL-12, Type 1 IFN IL-6, IL-1, IL-23
DC [APC]
Differentation
IL-10
TReg
Th1 [Active]
B [Naive]
Tc [Resting]
SARS-CoV-2
B [Active]
IgM
Tc [Active]

# In silico SARS-CoV-2 viral dynamics and related CPE in a mild to moderate scenario

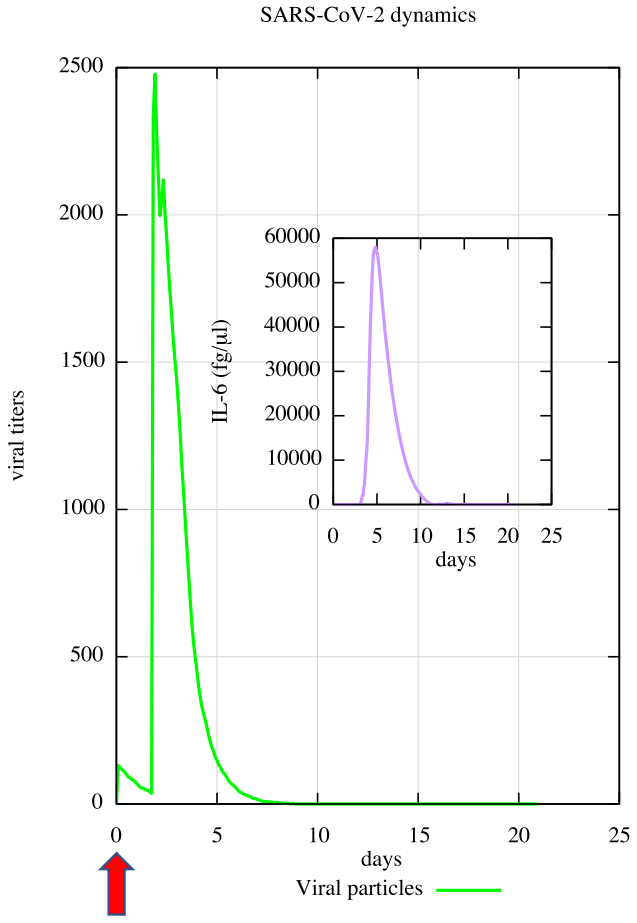
Peak viral titers are reached by 48 h post-inoculation.

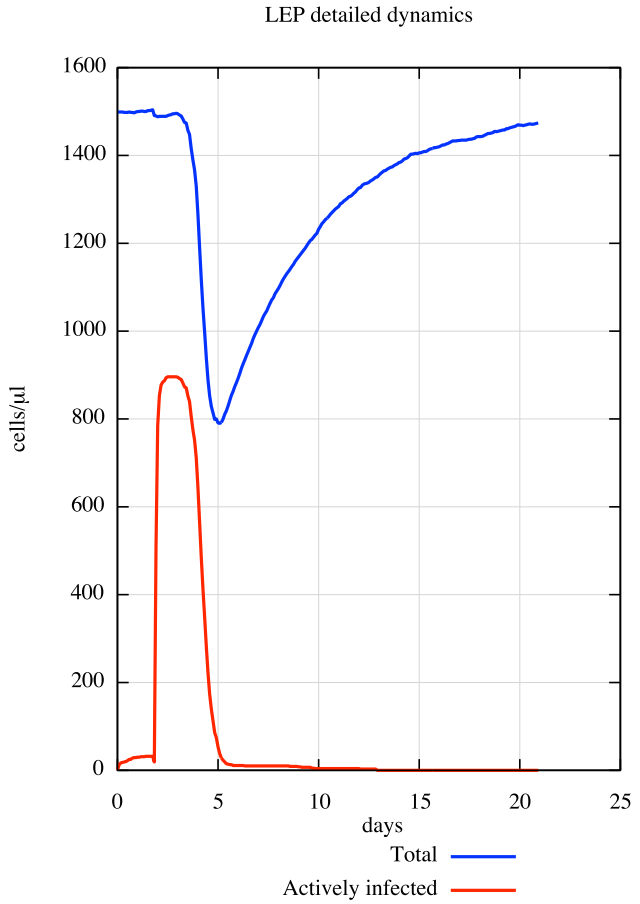
IL-6 dynamics and its related plasma levels (fg/µL) are also shown in the inner panel (purple line).

In the right one, the dynamics of CPE on the lung infected cells is measured (blue line): they started at day 3.5 and peak around day 5.

After about three weeks, the simulated digital patient almost recovers from the infection.

Accordingly to the recent literature, the early viral clearance appeared by day 10 post-onset in mild cases.



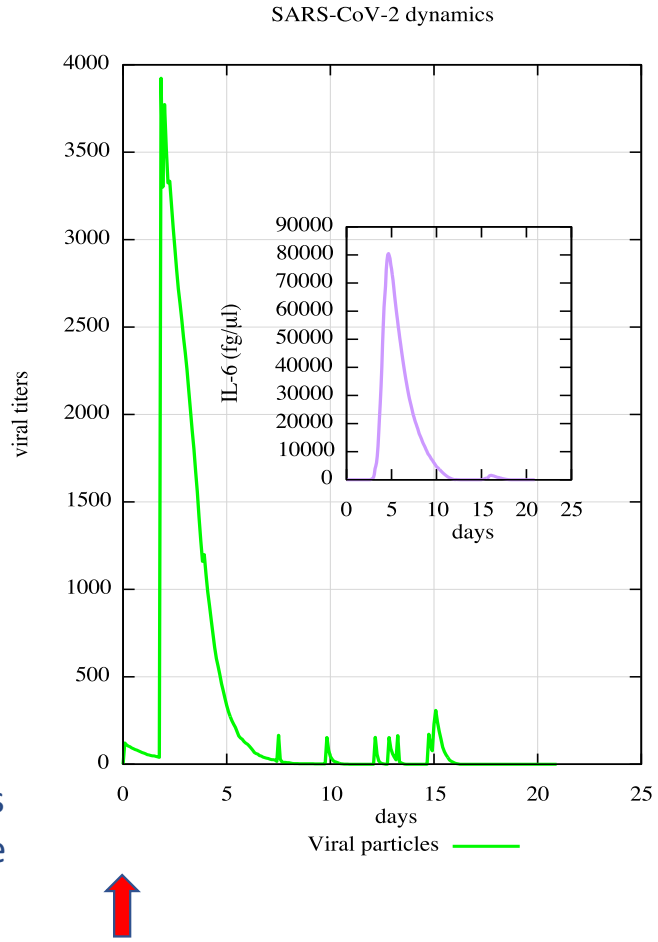



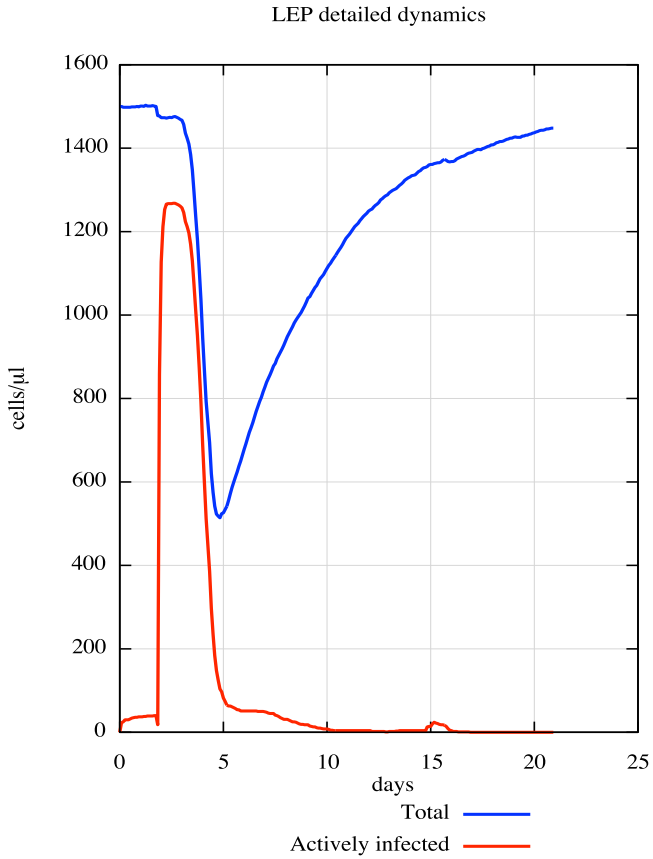
# In silico SARS-CoV-2 viral dynamics and related CPE in a severe scenario

Peak viral titers are reached by 48 h post-inoculation. In addition, it is worth to note that virus persists after day 10, until day 15, and its complete clearance is around day 19. In the inner panel (purple line), IL-6 dynamics and its related plasma levels (fg/µL) are shown.

IL-6 dynamics shows a much more prominent peak of values. This is in very good agreement with latest literature data.

UISS is capable to simulate, accordingly to the recent literature, how the severe cases tend to have a higher viral load both at the beginning and later on.



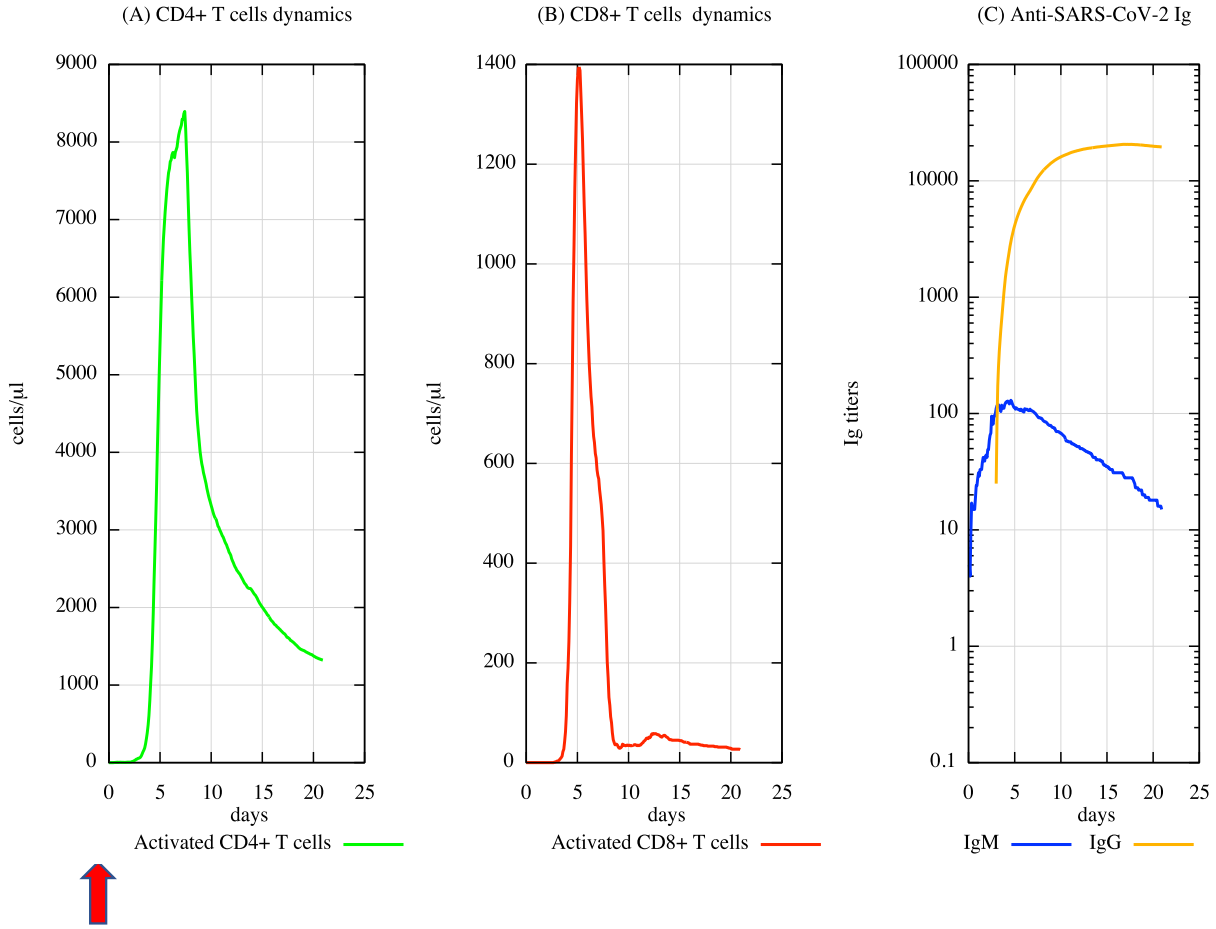



# Cellular and humoral response mounted by the host immune system against SARS-CoV-2

Panel A shows the dynamics of CD4$^{+}$T cells, subtype 1 (Th1). Th1 are primed by dendritic cells that present the viral particles complexed with MHC-II of the host. Th1 cells help the activation of B cells, eventually favoring their iso-type switching to IgG producing plasma cell.

B cells dynamics is depicted in panel B. Antigen activated B cells initially releases IgM.

Then, after interacting with Th1 and their released pro-inflammatory cytokines, they start to release specific IgG directed against SARS-CoV-2 virus.

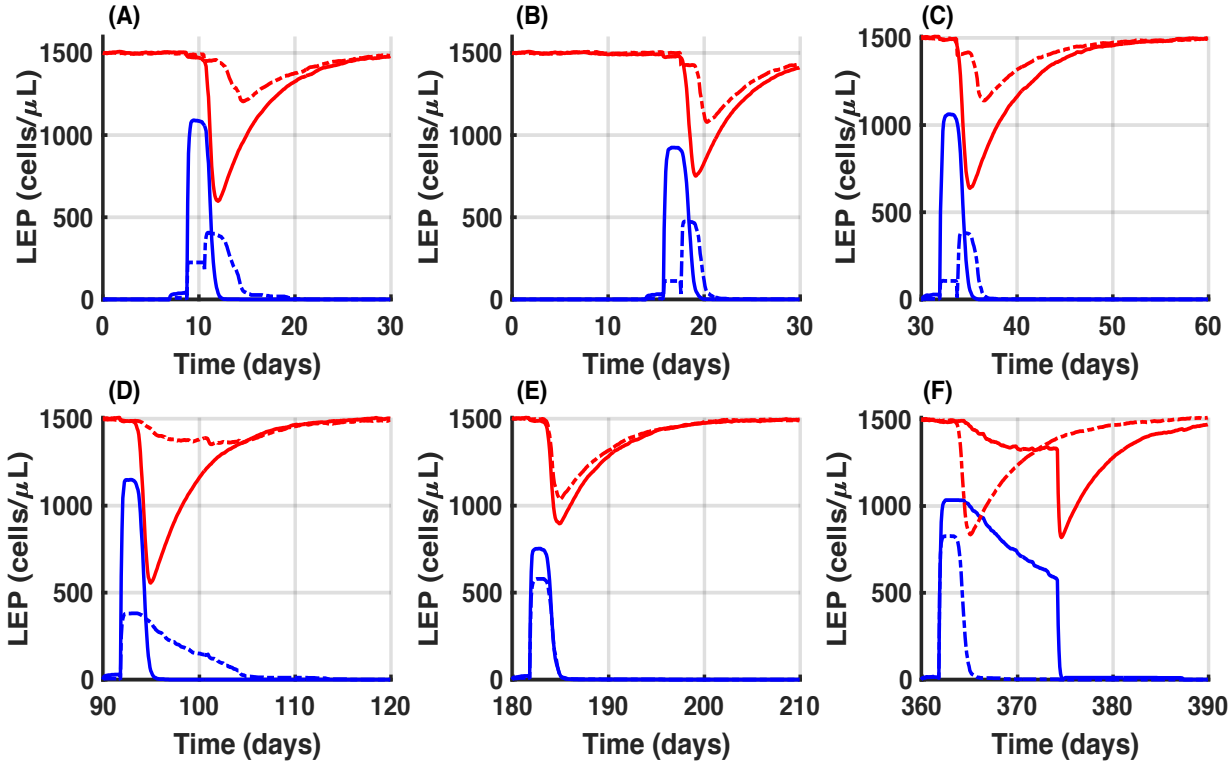


# In silico trial of 47D11 to predict preventive efficacy

The overall prediction dynamics of LEP at the **injection time of 47D11 mAb (day 1,** proposed by Wang et al. (doi:10.1038/s41467-020-16256-y) at a concentration of 10 µg/ml after different SARS-CoV-2 challenge in time (panels A to F) is depicted.

Specifically, one can observe the exposures at virus particles at day 7 (panel A), day 14 (panel B), month 1 (panel C), month 3 (panel D), month 6 (panel E) and after 1 year (panel F).

In panel E (subject infected after 6 months) and panel F (subject infected after one year) mAb vaccination is practically ineffective in protecting the onset of the disease.




Solid lines refer to the no-treated digital patient, while dashed lines refer to mAb treated one. Blue lines depict actively infected LEP, while red lines represent LEP to show the CPE.

# Take home messages

- ABM revealed as an effective modeling strategy to deal with complex adaptive systems i.e., immune system
- Modeling & simulation of biological systems is effective in helping healthcare research
- UISS-TB computational platform is a concrete example of working in progress qualification process of an in silico trial technology applied to medicinal products

# To learn more…

- **[UISS general description]** Pappalardo et al., The Potential of Computational Modeling to Predict Disease Course and Treatment Response in Patients with Relapsing Multiple Sclerosis. *Cells*, 9(3):586, 2020. (doi:10.3390/cells9030586)

- **[Tuberculosis]** Pennisi, Russo et al., Predicting the artificial immunity induced by RUTI vaccine against tuberculosis using universal immune system simulator (UISS). *BMC Bioinformatics*, 20(S6(504)), 2019. (doi:10.1186/s12859-019-3045-5)

- **[Influenza]** Pappalardo et al., A computational model to predict the immune system activation by citrus derived vaccine adjuvants. *Bioinformatics*, 32(17):2672–2680, 2016. (doi:10.1093/bioinformatics/btw293)

- **[COVID-19]** Russo et al., In Silico Trial to test COVID-19 candidate vaccines: a case study with UISS platform. *BMC Bioinformatics*. 2020;21(Suppl 17):527. doi: 10.1186/s12859-020-03872-0

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