

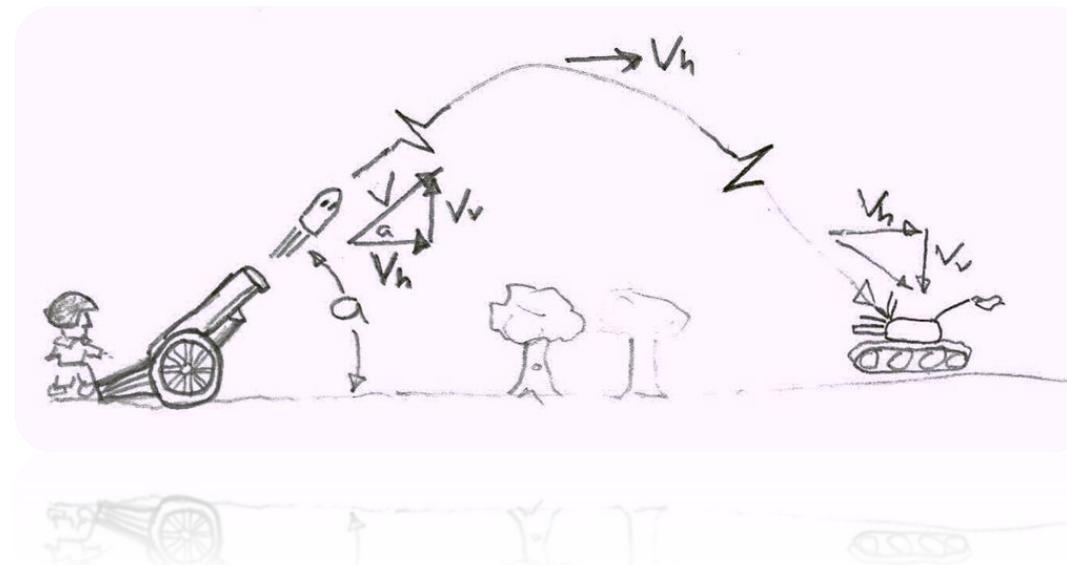
Numerical Immunology: a computer model of the immune response

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What is a mathematical model?

A mathematical model is a description of a (real, i.e., physical, biological, economic, social) system using mathematical language.



$$\begin{aligned}\frac{dS}{dt} &= \mu(N - S) - \beta \frac{SI}{N} - \nu S \\ \frac{dE}{dt} &= \beta \frac{SI}{N} - (\mu + \sigma)E \\ \frac{dI}{dt} &= \sigma E - (\mu + \gamma)I \\ \frac{dR}{dt} &= \gamma I - \mu R + \nu S \\ N &= S + E + I + R\end{aligned}$$

\downarrow

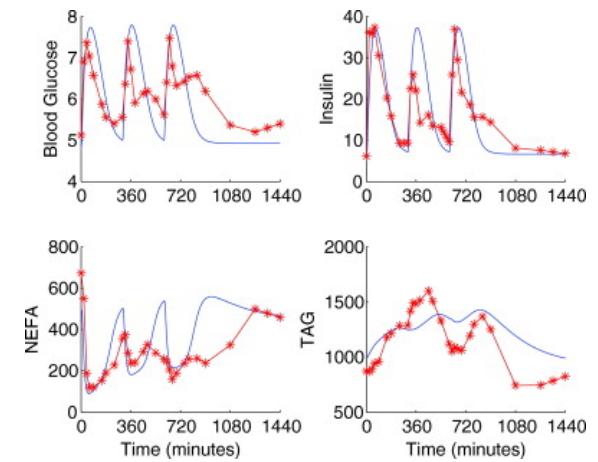
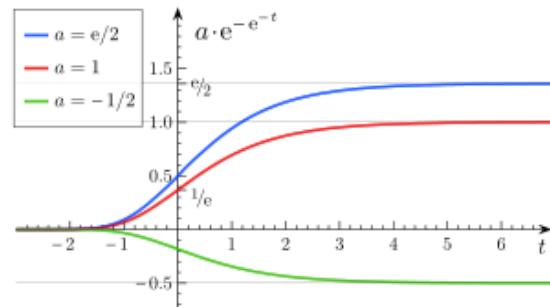
$$f(t) = ae^{-be^{-ct}}$$

<https://www.wikihow.com/Make-a-Mathematical-Model>

What is a mathematical model?

The **parameters** of the mathematical model are adjusted to study different **possible outcomes**.

$$f(t) = ae^{-bt}e^{-ct}$$



Models can reveal hidden patterns and/or counterintuitive mechanisms in complex systems.

<https://www.nibib.nih.gov/science-education/science-topics/computational-modeling>

Mathematics in biology

Mathematical or theoretical biology is a branch of biology which employs theoretical analysis, mathematical models and abstractions of the living organisms to investigate the principles that govern the structure, development and behavior of the systems

This is opposed to experimental biology which deals with the conduction of experiments to prove and validate the scientific theories.

https://en.wikipedia.org/wiki/Mathematical_and_theoretical_biology

Modeling is an interdisciplinary endeavor

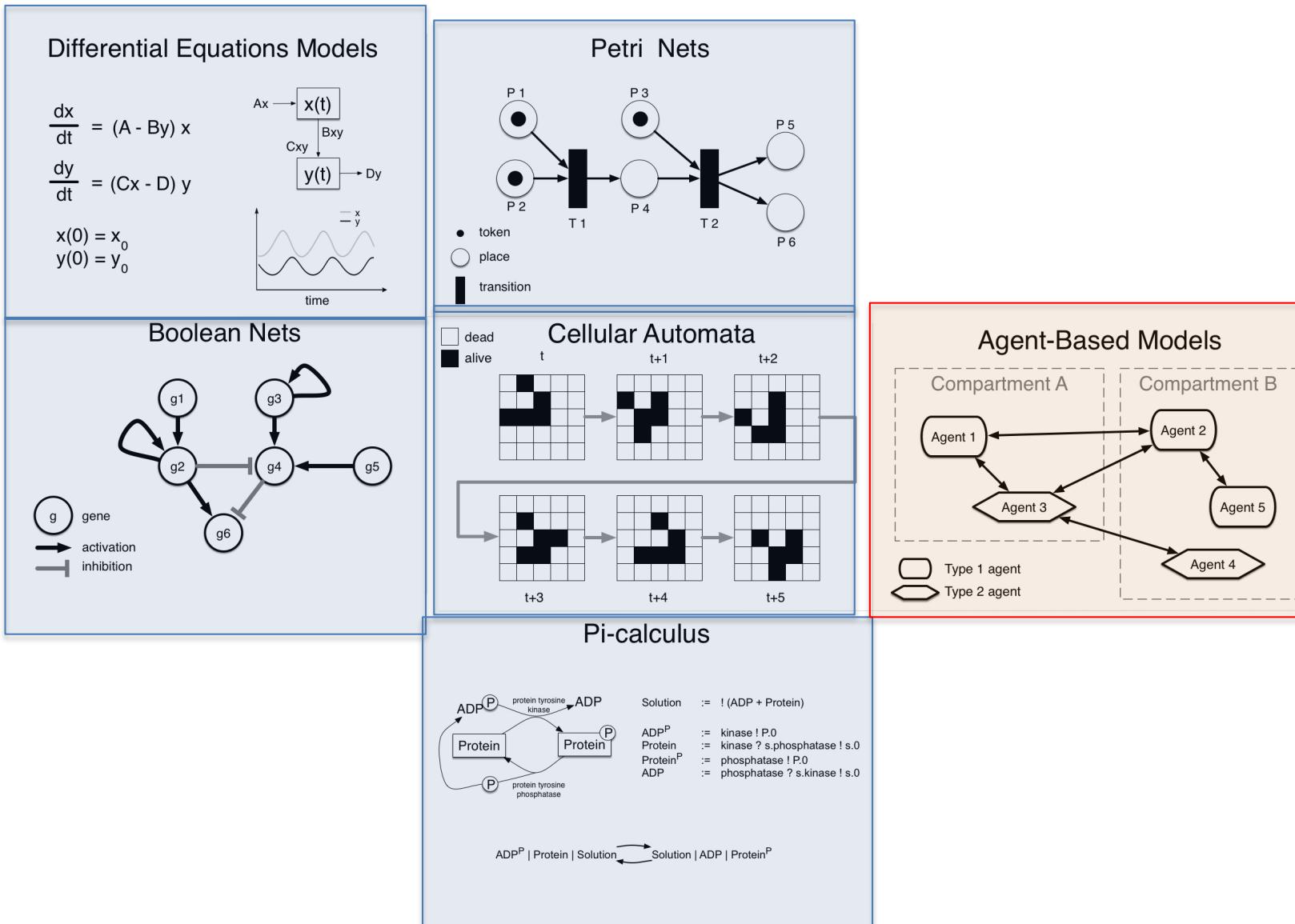
A biologist understand a mechanism or a phenomena

A mathematician is able to express this knowledge in a formal language

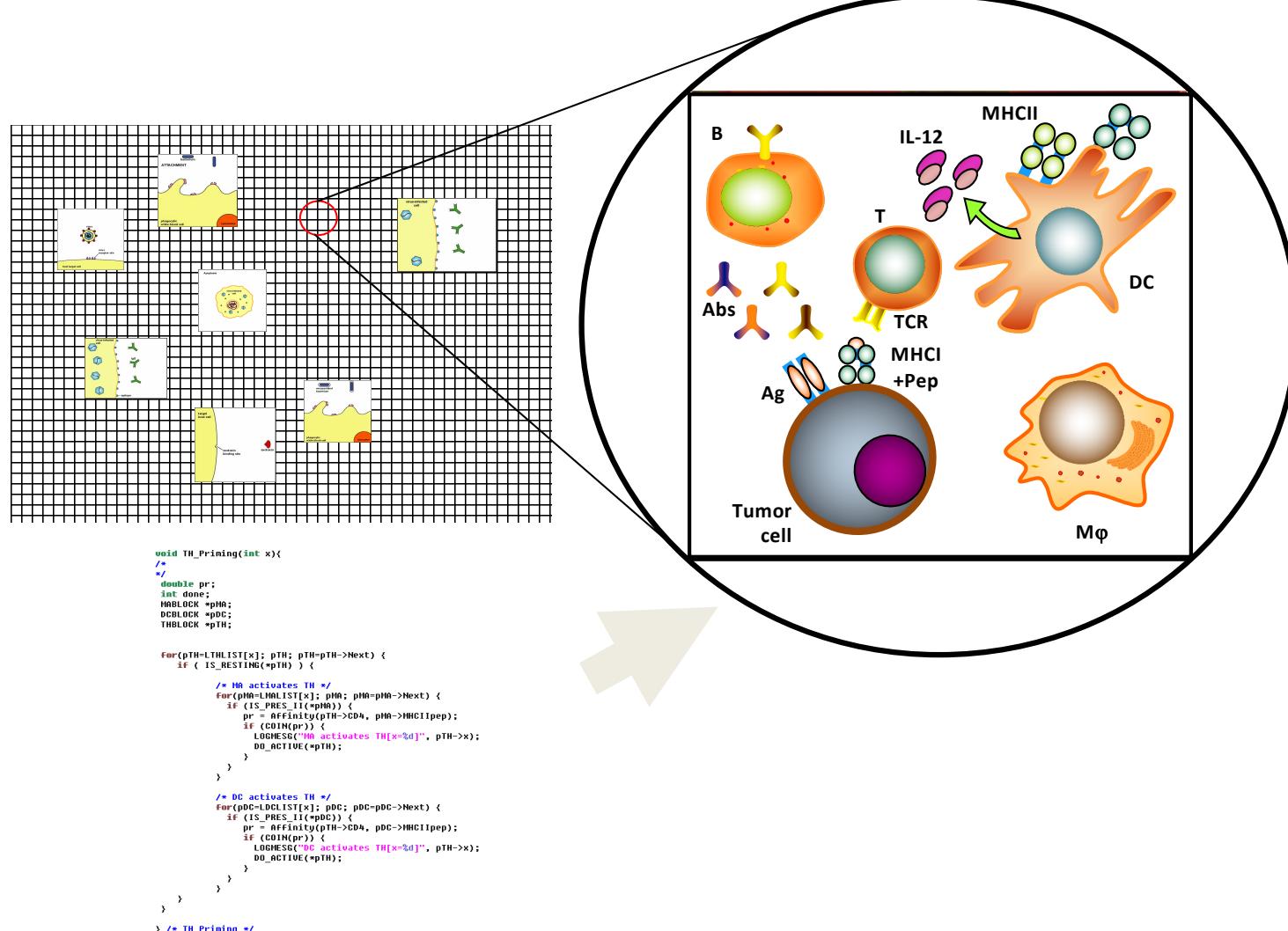
Together they have a model

Why is it useful to have a computational model?	<u>Abductive reasoning</u> is a form of logical inference which goes from an observation to a theory which accounts for the observation, ideally seeking to find the <u>simplest</u> and most likely <u>explanation</u> .
What is useful for?	To simulate, to compare, to formulate new (vested) hypothesis: systematic in silico experiments results are predictions to be tested in lab

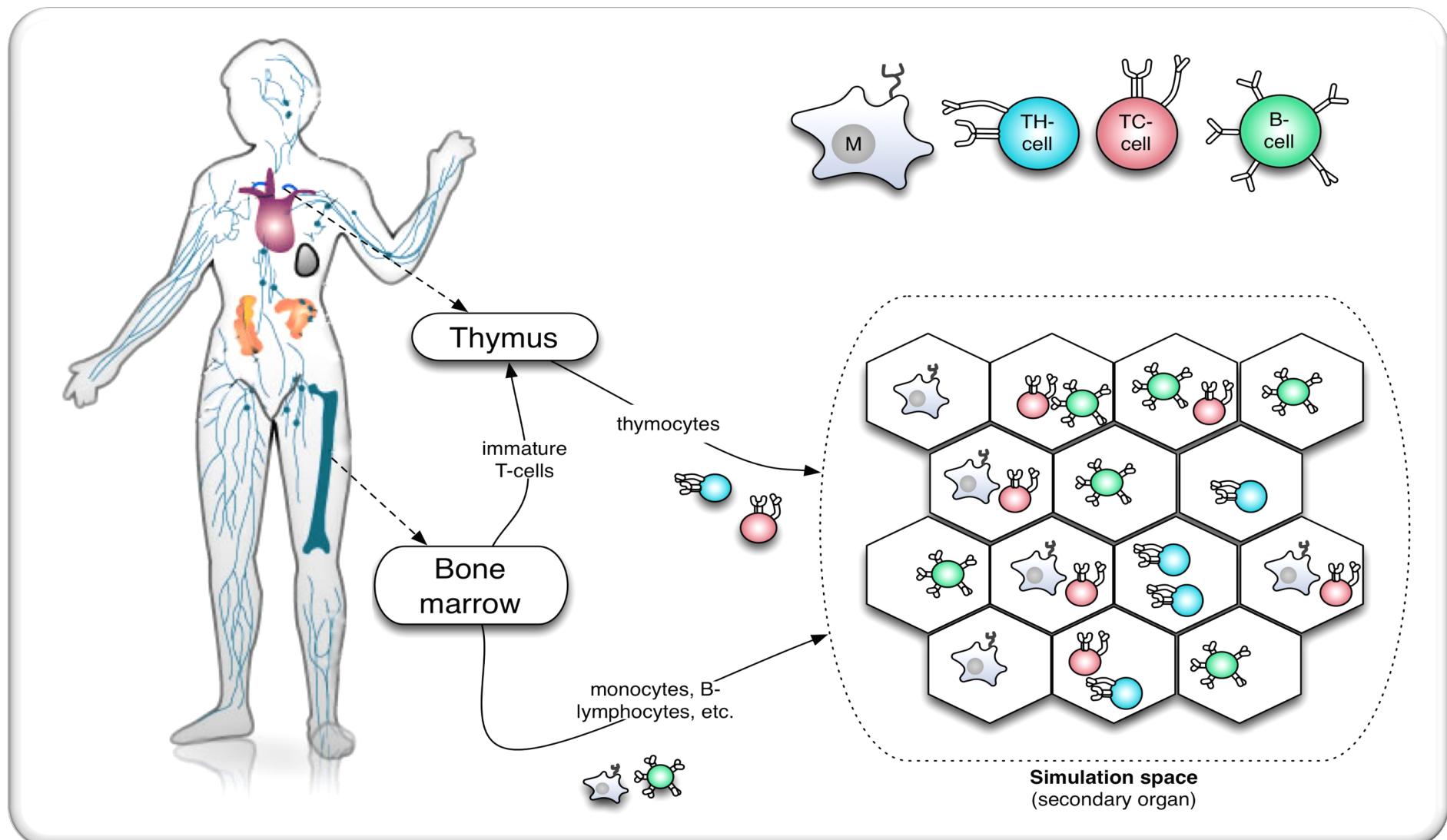
Mathematical/Computational modeling approaches



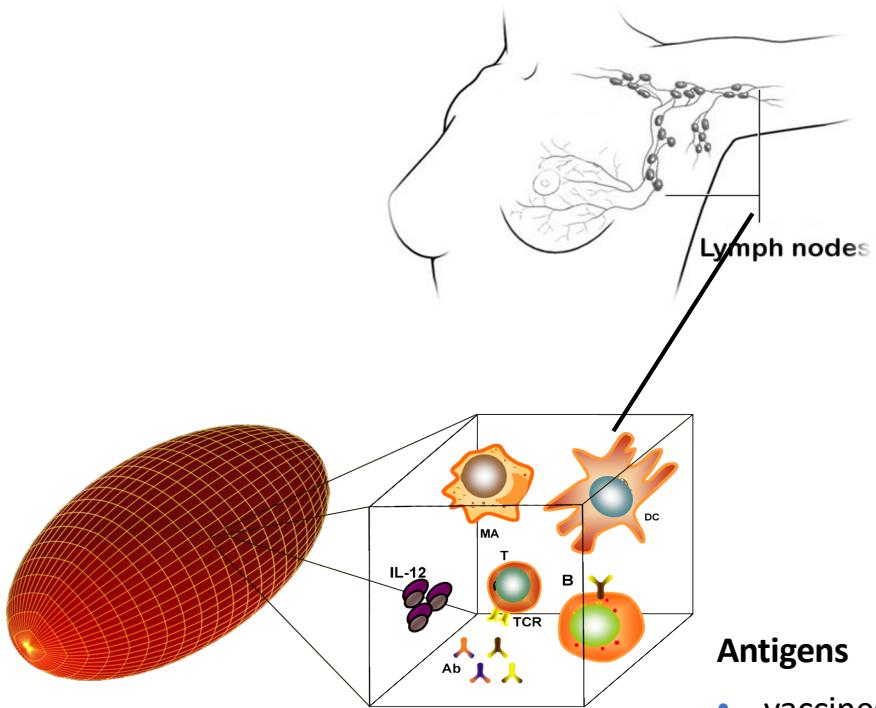
Agent-based modeling and simulations



C-IMMSIM: a model of the IS response



a computational (agent-based) stochastic model



Antigens

- vaccines
- virus
- bacteria
- cancer cells
- ...

Cells

- B-cell
 - B-1
 - B-2
 - PLB
- CD4 T-cell
 - Th1
 - Th2
 - Th17
 - Treg
- CD8 T-cell
- NK
- Mφ
 - M1
 - M2

DC

EP (virus target)

Immunoglobulins

- IgM
- IgG
 - IgG1
 - IgG2
- IC

Interleukins/cytokines

- Danger
- IL-2
- IL-12
- IFN- γ
- IL-4
- TNF- α
- TGF- β
- IL-6
- IL-10
- IL-18
- IL-23
- IFN- β
- IL-1 β

events / rules

1. Infection: An infection dose $V(0) = V_0$ is injected into the simulated volume
2. Endocytosis: the virus enters epithelial cells (EP)
3. Biosynthesis: the viral RNA and viral proteins are made and assembled into new virions that are released by budding (exocytosis) from infected cells (SARS-CoV-2 follows a *lysogenic cycle*, that is, it does not kill the host). At this stage, infected/injured EP
 - DAMPs release: release danger signal (D) (generally indicating interferon, cytokines, DAMPs = damage associated molecular patterns)
 - Inflammation: release IL-6
 - Endocytic presentation: process the viral proteins leading to their presentation on class I HLA molecules
4. B phagocytosis: B cells phagocytose, internalise, process and present viral peptides on class II HLA
5. Response to Danger:
 - NK response: Natural killer cells (NKs) release IFNg upon bystander stimulation by danger
 - M response: Macrophages (M) respond to danger (e.g., DAMPs) via TLR4 releasing TNFa and IL-6
6. M activation: macrophages become activated by IFNg (activated M have a greater phagocytic activity)
7. Active M
 - M phagocytosis: M internalise, process and present viral peptides on class II HLA; in presence of IFNg they release IL-12; they also release TNFa
 - DC activation: M release TNFa which activate dendritic cells (DC)
8. DC phagocytosis & endocytosis: DC phagocytose, internalise, process and present viral peptides on class II HLA (exocytic pathway) but also on class I HLA (endocytic pathway)
9. Th activation: in presence of danger signal, resting T helper lymphocytes are activated by interaction with peptide-bound HLAs on professional antigen presenting cells (M and DC, mainly DC) surface by means of specific interaction with their T-cell receptors (TCR); if no danger is present, the Th cells becomes anergic upon interaction of its TCR with the HLApeptide complex
10. Th stimulation by APCs: activated Th interacting with antigen presenting cells (M, DC)
 - Th duplication: start clone expansion; part of the clones become memory cells
 - Th cells release IL-2
 - M release IL-6
 - Th1 release IFNg
 - Th2 release IL-4
 - release IL-12 in presence of high local concentration of IFNg
 - Treg release TGFb and IL-10
11. Th stimulation by B: activated Th interacting with B cells
 - B duplication: stimulate B cells to start clone expansion; part of the clone become memory
 - Th duplication: start clone expansion; part of the clones become memory cells
 - release IL-2, IL-12
 - Th1 release IFNg
 - Th2 release IL-4
 - Treg release TGFb and IL-10
12. Th differentiation: depending on the local concentration of IFNg, IL-10, IL-4, IL-6, IFNb, IL-12, IL-18, IL-2, TGFb and IL23, active T helper cells undergo class switch into Th1 and Th2
13. B differentiation: B cells differentiate to antibody-secreting plasma B cells (PLB);
14. Isotype switch: B cells perform immunoglobulin class switching, that is, change production of immunoglobulin from the isotype IgM to the isotype IgG
15. Antibodies production: Plasma cells secrete antibodies
16. Humoral response: antibodies inhibit viral particles by opsonization; the result are the immuno-complexes that are eventually cleared by macrophages
17. Tc activation: in presence of IL-2, resting cytotoxic T cells (Tc) are activated by the interaction of their TCR with DC presenting on class I HLA the viral peptides but only in presence of IL-2
18. Tc duplication: activated Tc interact with infected EP cells presenting viral peptides on class I HLA molecule
 - Cytotoxic response: kill infected EP (this will further release danger signal)
 - Tc start duplication

Int_B_Ag
 Int_MA_Ag
 Int_MA_IC
 Int_TH_B
 Int_TH_MA
 Int_Ab_Ag
 Int_TH_DC
 Int_DC_Ag
 Int_TC_EP
 Int_EP_Virus
 Int_TH_DC_TC

Int_B_Ab /* idiotypic network */
 Int_B_IC /* idiotypic network */

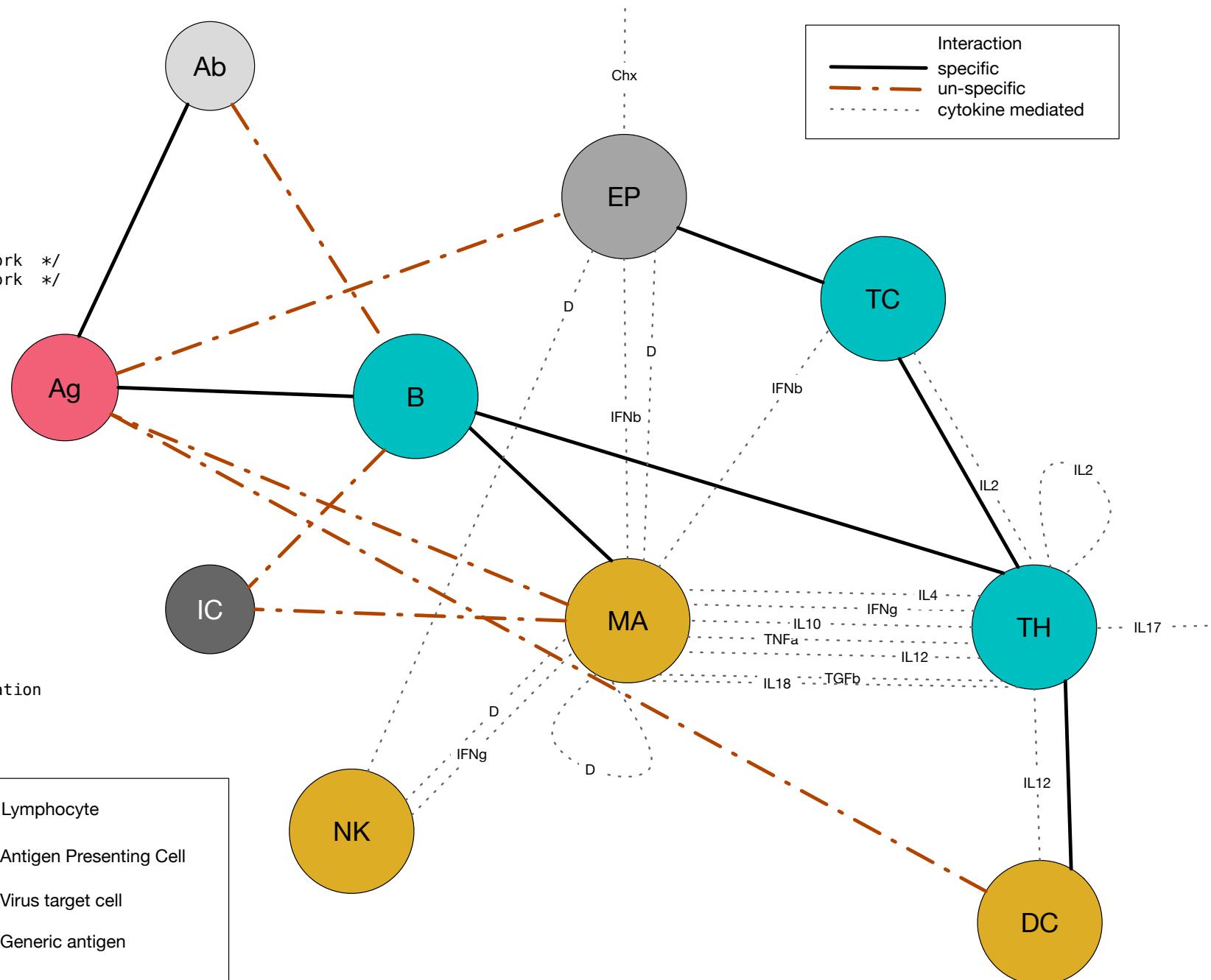
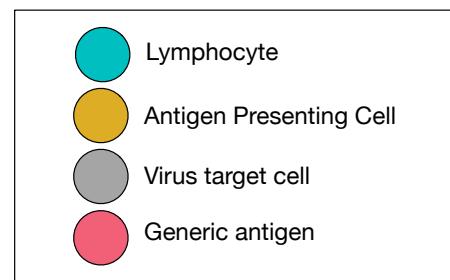
ClassSwitchTH
 ClassSwitchMA

MA_ActDeact
 DC_ActDeact
 B_Anergy
 TH_Anergy
 TH_Priming
 TC_Anergy

NK_ActbyDanger;
 MA_ReleaseIFNb_by_Danger
 ParacrineInhibitionOf_TC
 ParacrineInhibitionOf_TH
 TR_ActDeact;

TC_FinishingMaturation

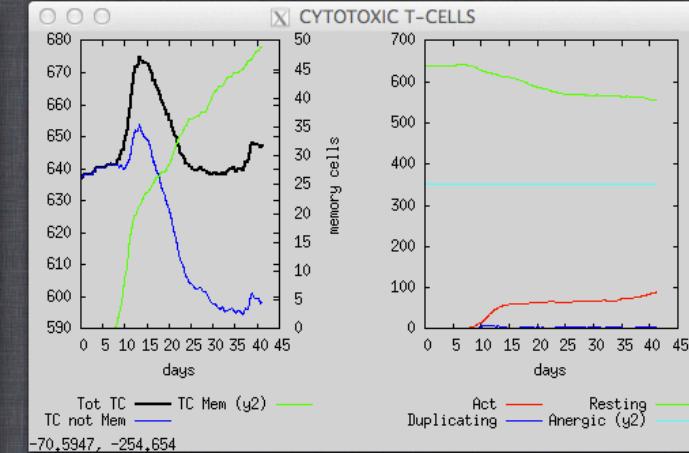
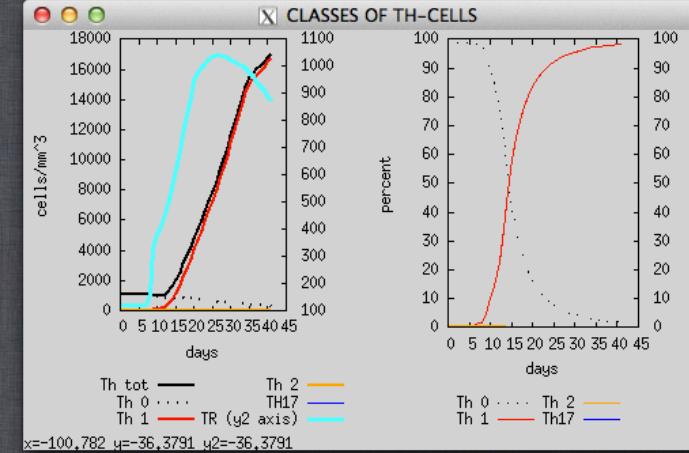
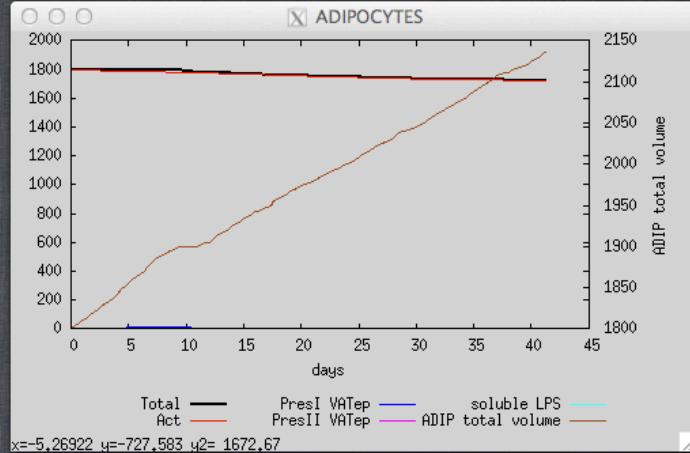
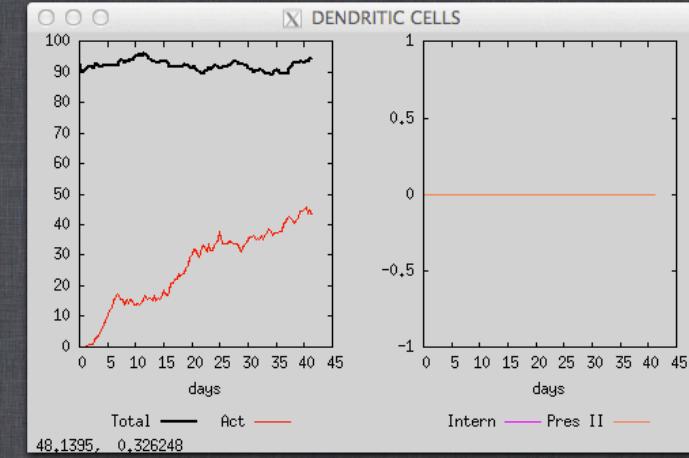
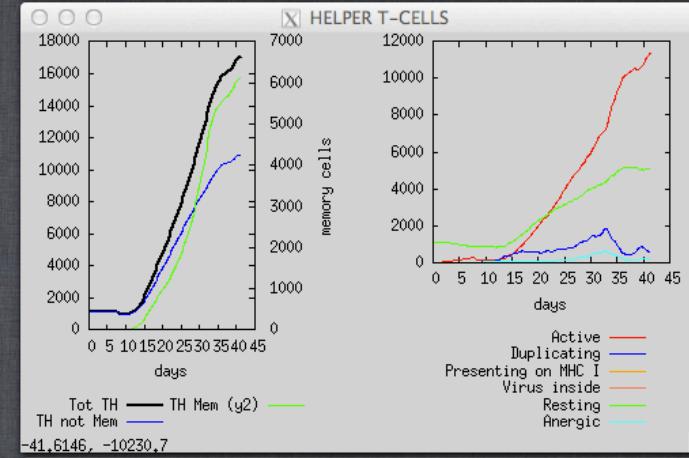
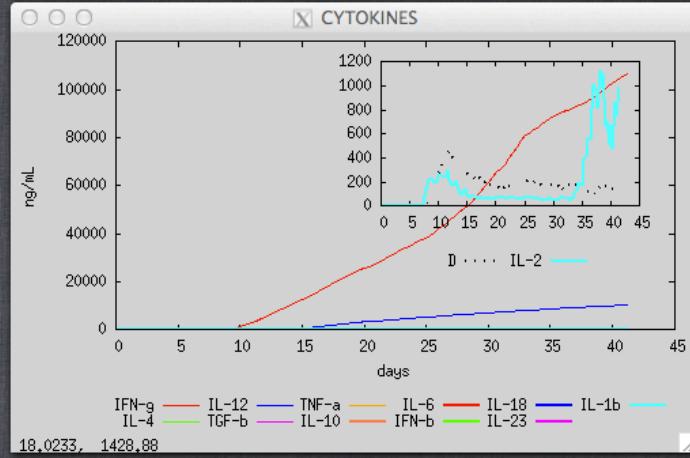
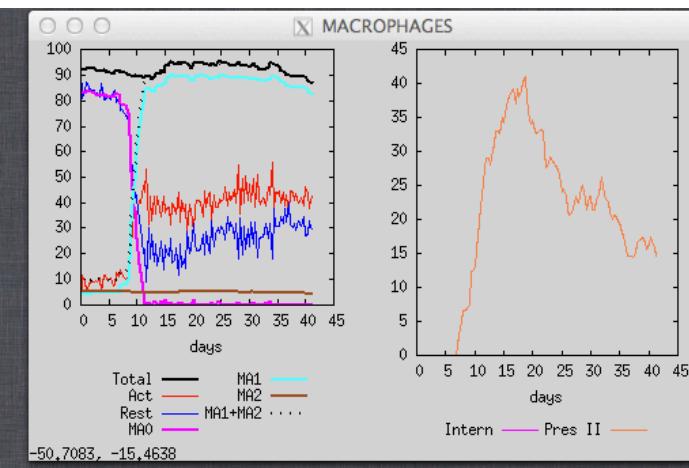
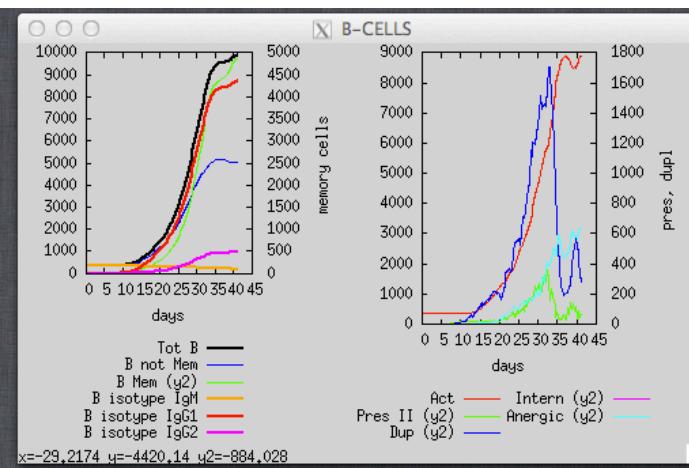
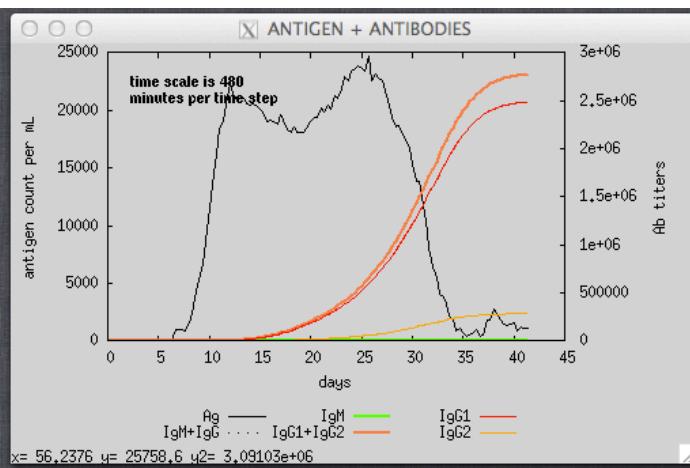
ComplementActivation
 MAReact2Complement
 ComplementBacterialOpsonization
 IC_fires_C1q



Immunological features

- Clonal selection theory (random generation of TCRs and BCRs)
- Clonal deletion theory (positive/negative selection of T-cells in the thymus)
- Innate + adaptive immunity
- Humoral + cellular immunity
- Immunological memory
- Homeostasis
- Affinity maturation and hypermutation
- Peptide digestion and presentation (class-1, class-2 MHC)
- Cytokine activation/inhibition of immune cells' functions
- Matzinger's danger signal theory
- T-cells replicative senescence (the Hayflick limit)
- T-cell anergy (lack of second signal)
- B-cell anergy (overstimulation)
- Peripheral tolerance by Tregs
- *IFN-Induced Attrition of CD8 T cells*
- *Idiotypic network*

Disease course



Past and present studies

Modeling viral infections

- HIV (and HAART therapy)
- EBV
- H1N1 vaccine
- SARS-CoV-2

Modeling bacterial infections

- MTB (*Mycobacterium tuberculosis*)

Modeling parasites

- Leishmania

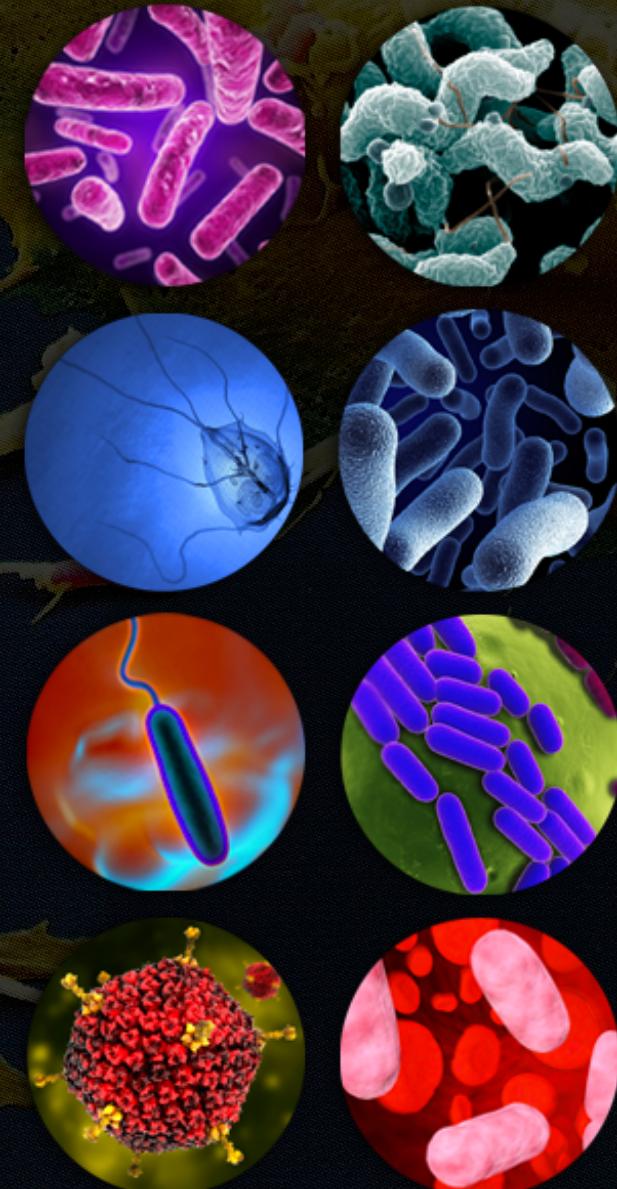
Modeling hypersensitivity (i.e., type-1 allergies)

Modeling cancer-immune interaction

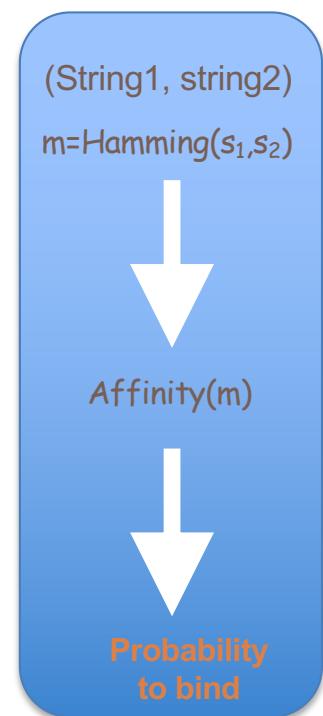
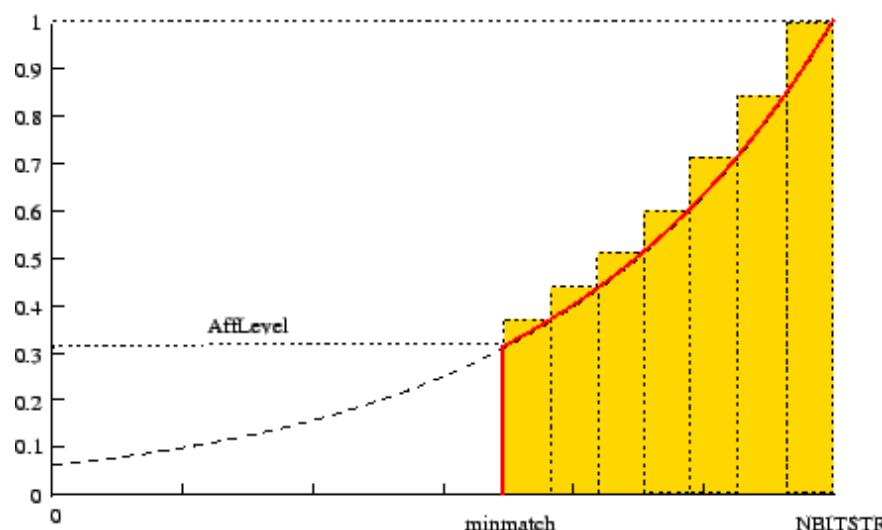
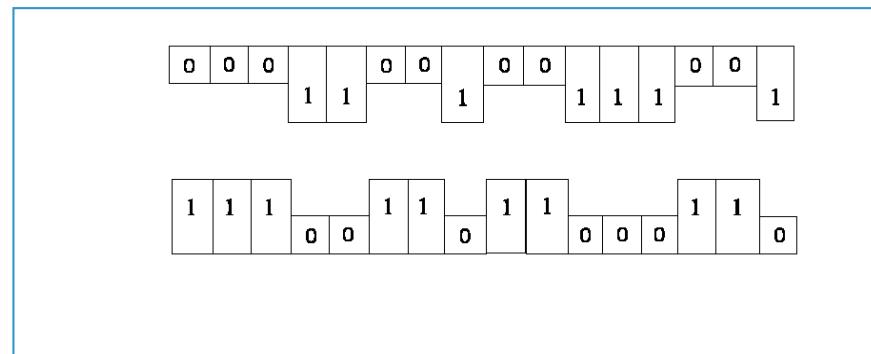
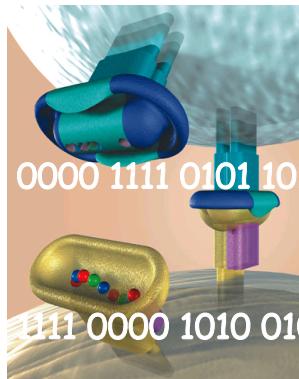
- Immuno-prevention (therapy)

Modeling inflammation

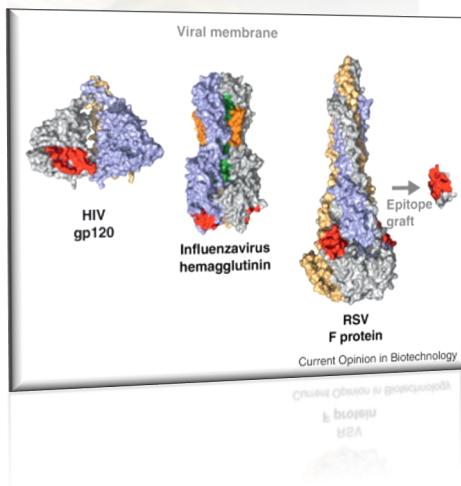
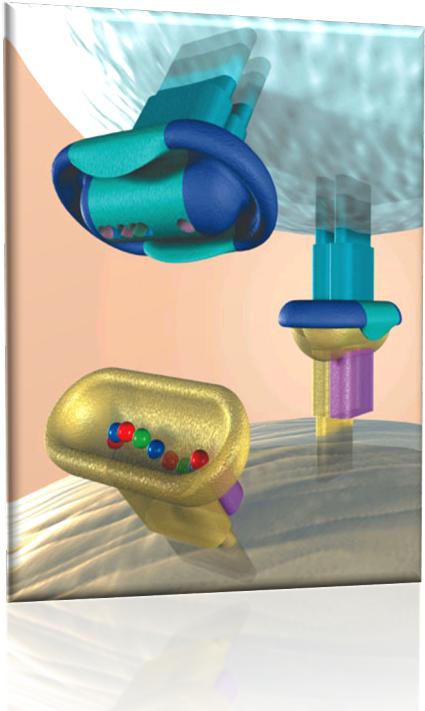
- in type-2 diabetes



Definition of the molecular of Affinity



Represent specificity by molecular primary structure



Cell receptors' binding site

{ EKQEGMSASVQWENKKGVKY

HLAs

{
A0201
A0301
B2705
B2705
DRB1_0401
DRB1_0401

Antigen primary structure

>matrix protein 1
MSLLTEVETPIRNEWGCRCNDSSDPLVVAANIIIGILHLILWILDRLFFKCIYRLF
KHGLKRGPSSEGVPESMREYRKEQQSAVDADDHFVNIELE

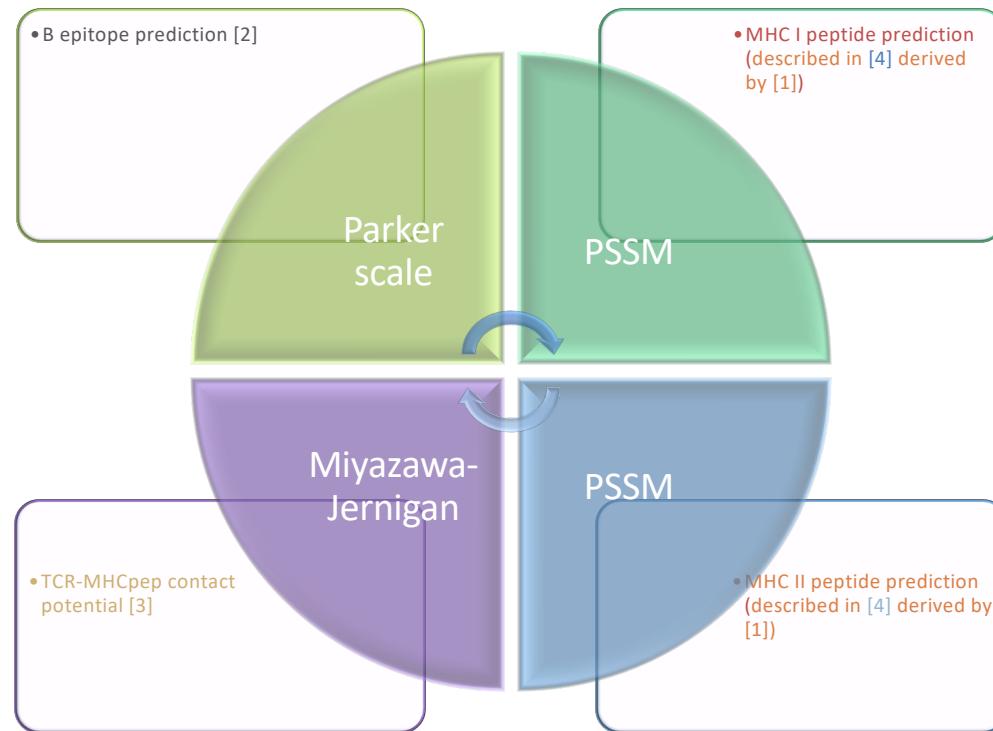
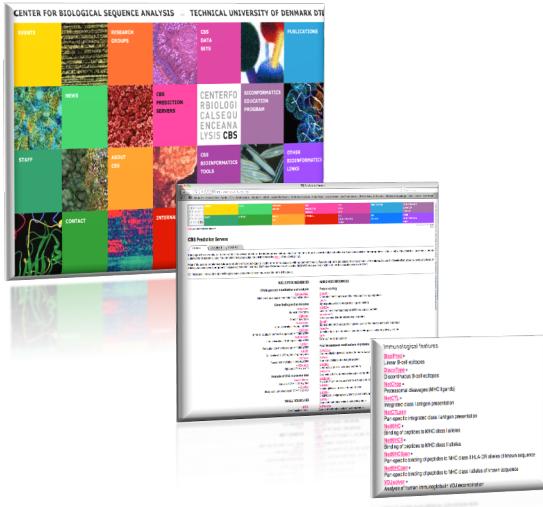
>matrix protein 2
MSLLTEVETYVLSIVPSGPLKAEIAQRLEDVFAGKNTDLEALMEWLKTRPILSPL
TKGILGFVFTLTVPSERGLQRRRFVQNALNGNGDPNNMDRAVKLYRKLKREITFH
GAKEIALSYSAGALASCMGLIYNRMRGAVTTEVAFGLVCATCEQIADSQHRSRQM
VTTTNPLIRHENRMVLASTTAKAMEQMASSEQAAEAMEVASQARQMVQAMRTIG
THPSSAGLKDDILENLQAYQKRMGVQMQRFK

>nonstructural protein 1
MDPNTVSSFQVDCFLWHVRKRVADQELGDAPFLDRLLRDQKSILRGRGSTLGLNIE
TATRVGKQIVERILKEESDEALKMTMASALASRYLTDMTIEEMSRDWFMMPKQK
VAGPLCIRMDQAIMDKSIILKANFSVIFGRLETLILLRAFTEEGAIVGEISPLPS
LPGHTNEDVKNAIGVLIGGLEWNDNTVRVSCTLQRFAWRSSNENGRRPLTPKQKR
KMAUTIRSEV

>matrix protein 2

...

Exploiting peptide-discovery tools



[1] Nielsen M, Lundsgaard C, Worning P, Hvid CS, Lamberth K, et al. (2004) Improved prediction of MHC class I and class II epitopes using a novel Gibbs sampling approach. *Bioinformatics* 20:1388-1397

[2] Parker JM, Guo D, Hodges RS (1986) New hydrophilicity scale derived from high-performance liquid chromatography peptide retention data: correlation of predicted surface residues with antigenicity and X-ray-derived accessible sites. *Biochemistry* 25: 5425–5432

[3] Miyazawa S, Jernigan RL (2000) Identifying sequence-structure pairs undetected by sequence alignments. *Protein Eng* 13: 459–475

[4] N. Rapin, O. Lund, M. Bernaschi and F. Castiglione. Computational Immunology Meets Bioinformatics: The Use of Prediction Tools for Molecular Binding in the Simulation of the Immune System. *PLoS ONE*. 5(4): e9862 (2010)

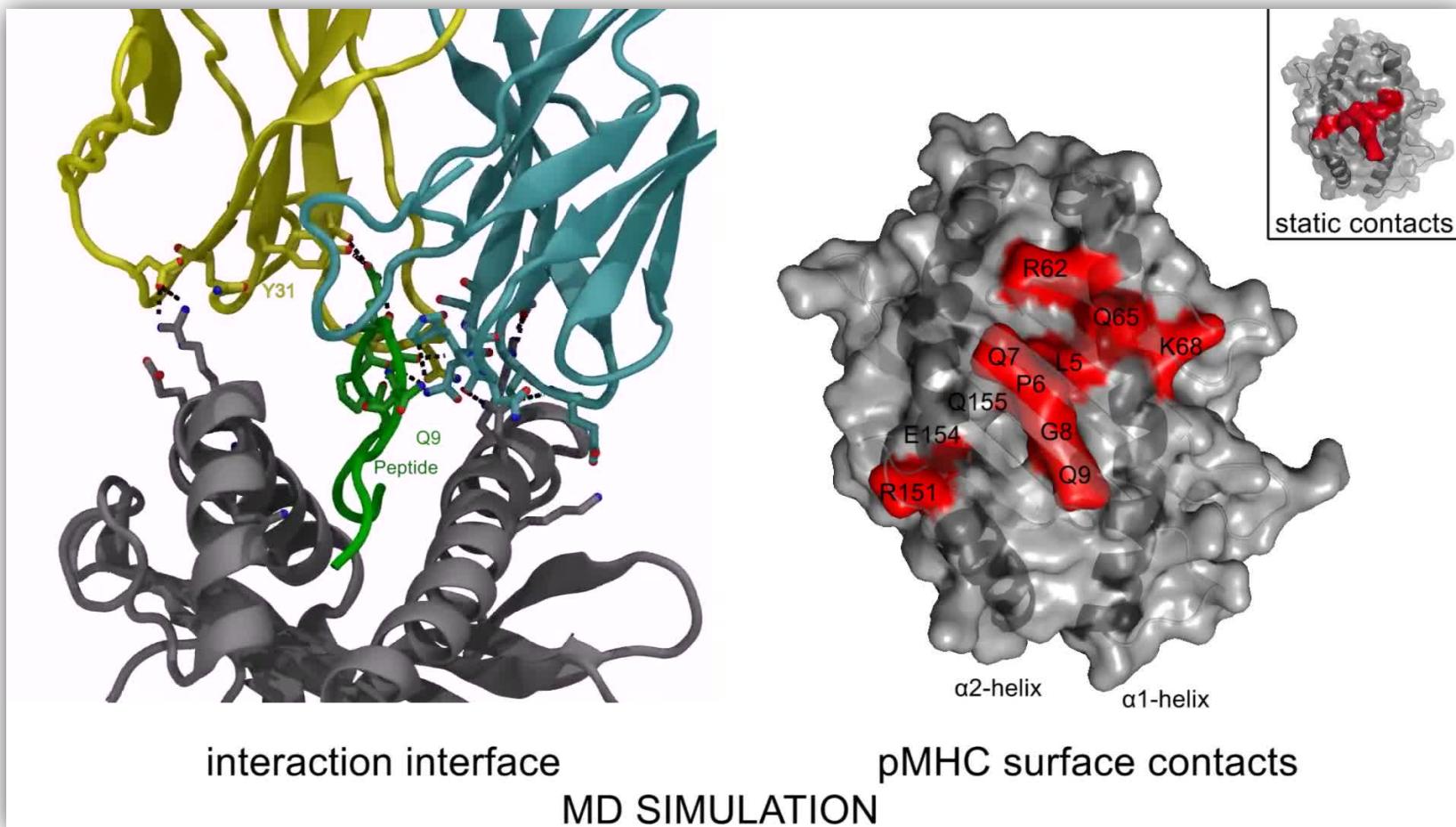
J. von Eichborn, A-L. Woelke, F. Castiglione, R. Preissner. Vacclimm: Simulating peptide vaccination in cancer therapy. *BMC Bioinformatics* 14:127 (2013) doi:10.1186/1471-2105-14-127

L. Woelke, J. von Eichborn, M.S. Murgueitio, C.L. Worth, F. Castiglione, R. Preissner. Development of Immune-Specific Interaction Potentials and Their Application in the Multi-Agent-System Vacclimm. *PLoS ONE* 6(8): e23257 (2011)

N. Rapin, O. Lund and F. Castiglione. Immune System Simulation Online. *Bioinformatics, Application note*. 27(14):2013-2014 (2011)

Using Molecular Dynamics results

(credits: team Bioinformatique Structures et Interactions, Institut de Biologie et Chimie des Protéines, CNRS, Lyon)

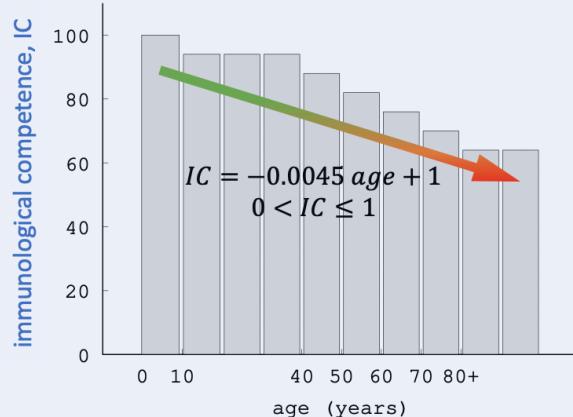


SARS-CoV-2 infection

- Host factors
 - Immuno-competence to model immuno-aging effects
- Pathogen (virus) factors
 - Viral load
 - Virus' spike affinity to ACE2 receptor

Host factors

We define the **immunological competence, IC** (can also be called immuno-senescence^[1] factor, is the dual concept of immune deficiency)

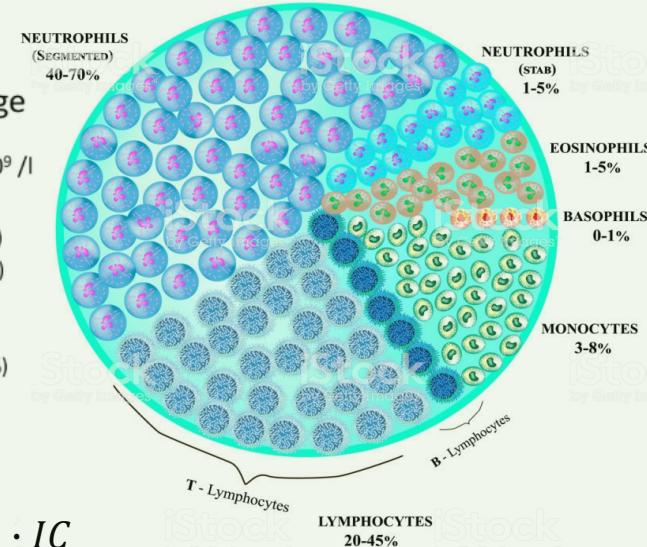


[1] Aiello Anna, et al. (2019) Immunosenescence and Its Hallmarks. *Frontiers in Immunology*, 10:2247
<https://www.frontiersin.org/article/10.3389/fimmu.2019.02247>

Adaptive immuno-senescence: Reduced leukocyte counts

LEUKOCYTE FORMULA

THE PERCENTAGE OF THE DIFFERENT TYPES OF LEUKOCYTES



Normal Reference Range

- White blood cell count $4.0-11.0 \times 10^9 / l$
- Differential white cell count
 - Neutrophils $2.0-7.0 \times 10^9 / l$ (40-80%)
 - Lymphocytes $1.0-3.0 \times 10^9 / l$ (20-40%)
 - Monocytes $0.2-1.0 \times 10^9 / l$ (2-10%)
 - Eosinophils $0.02-0.5 \times 10^9 / l$ (1-6%)
 - Basophils $0.02-0.1 \times 10^9 / l$ (<1-2%)



$$\text{Lymphocytes} \sim N(\mu, \sigma) \cdot IC$$

Creator: Timoninalryna | Credit: Getty Images/iStockphoto

Information extracted from [IPTC](#) Photo Metadata.

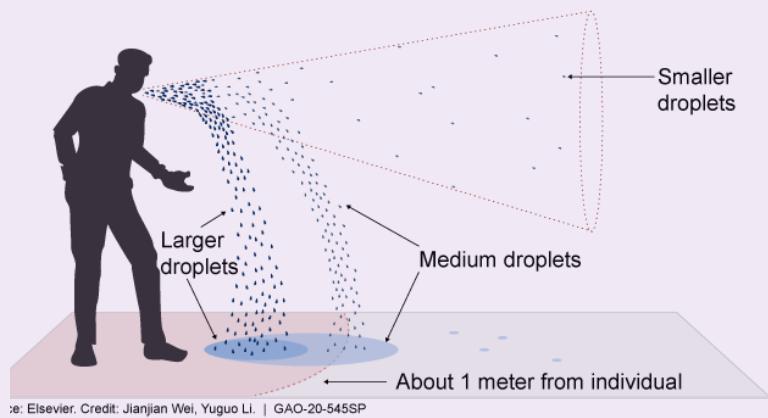
Phagocytic activity of Antigen Presenting Cells (i.e., Macrophages, Dendritic cells)

$$p_M = IC \cdot u \quad u \sim U_{[a,b]}$$

$$p_{DC} = IC \cdot v \quad v \sim U_{[c,d]}$$

pathogen (virus) factors

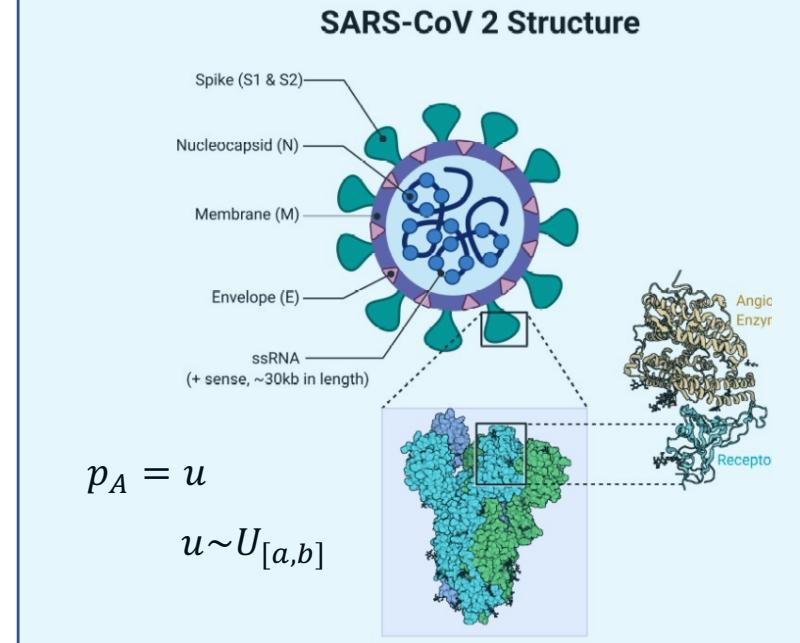
The **viral load** infecting an individual is diverse.



$$V(0) = V_0 = u$$

$$u \sim U_{[a,b]}$$

The SARS-CoV-2's spike molecule **affinity** to ACE2 receptor on target cells

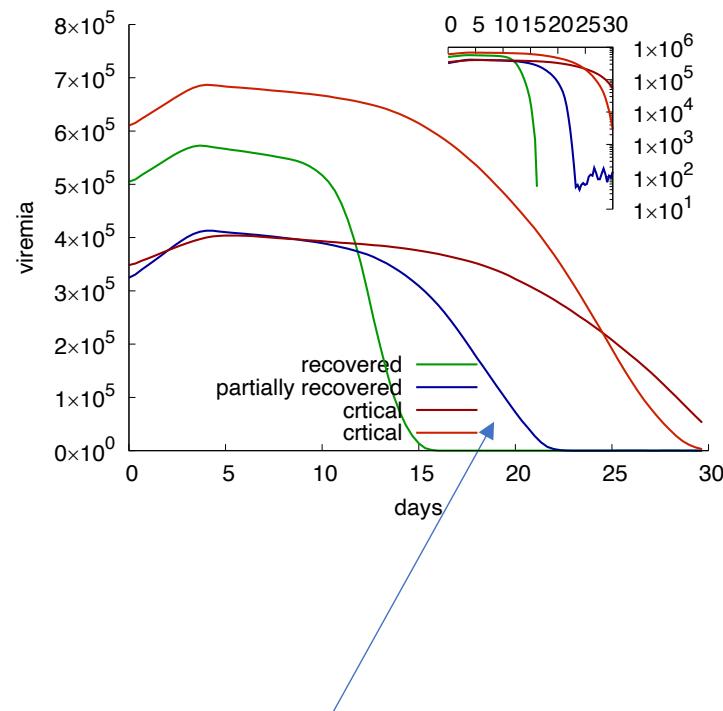


case stratification

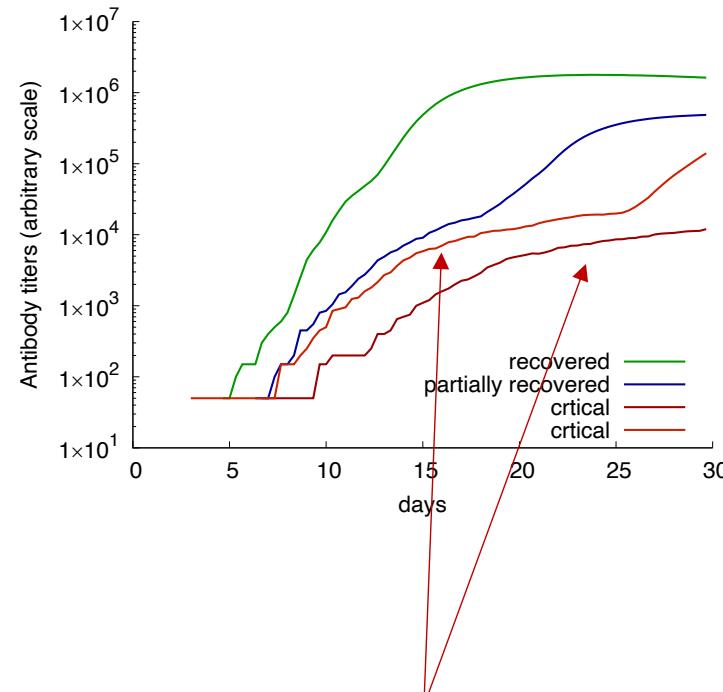
$$\text{CRITICAL} \Leftrightarrow V_{30} > \theta$$

$$\text{PARTIALLY RECOVERED: } \Leftrightarrow 0 < V_{30} < \theta$$

$$\text{FULLY RECOVERED} \Leftrightarrow V_{30} = 0$$

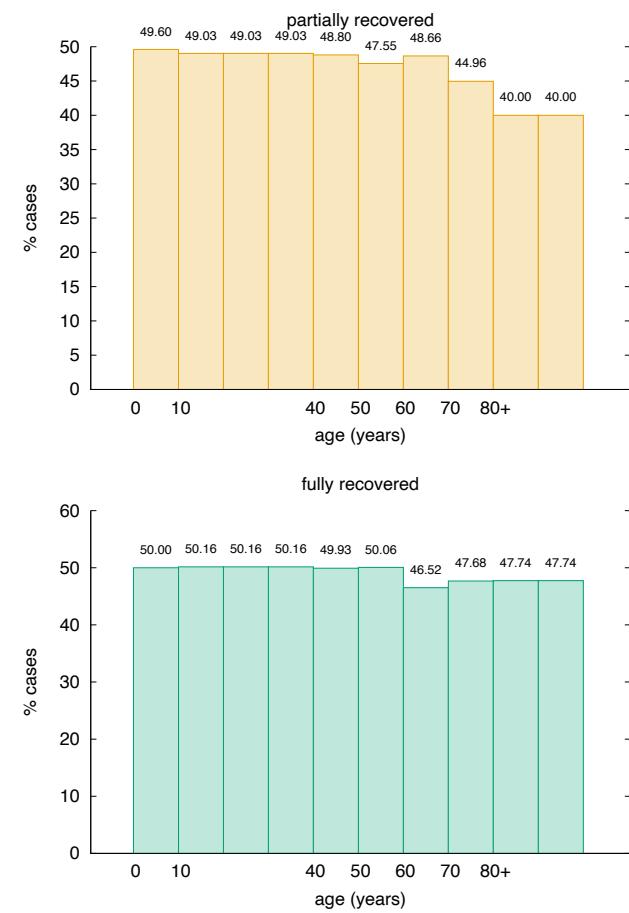
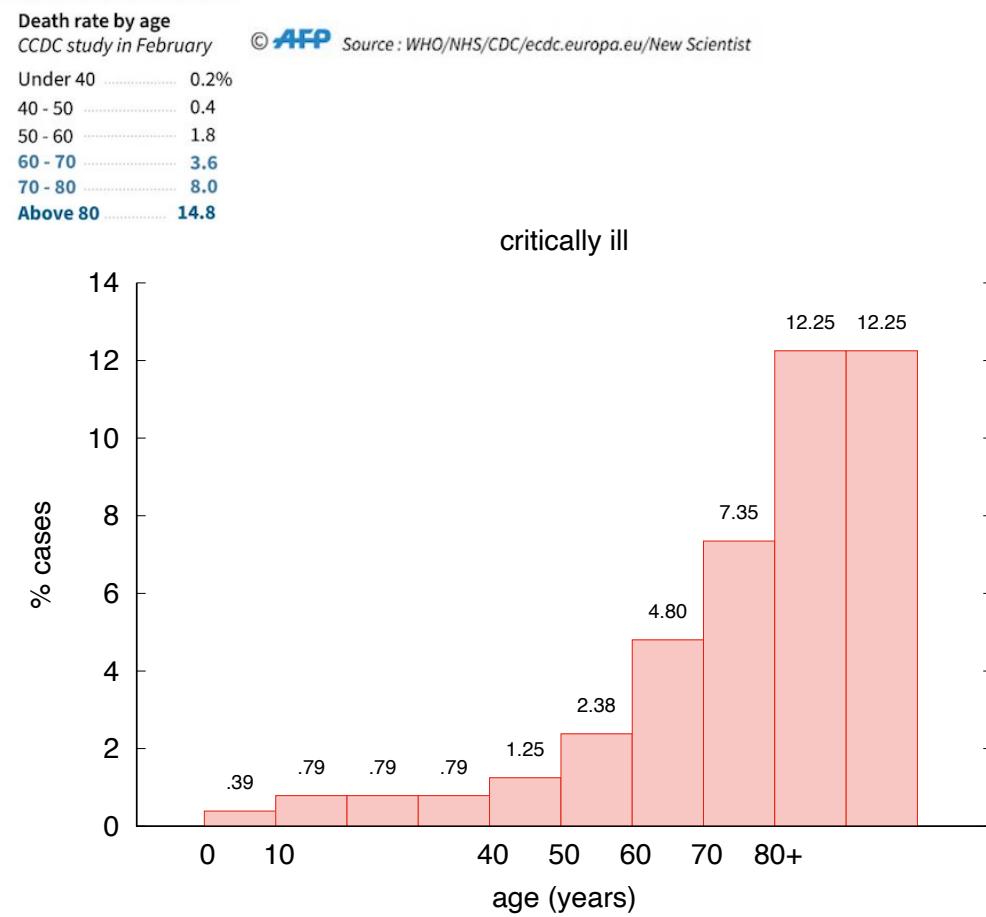


Partially recovered \supset
{asymptomatic}

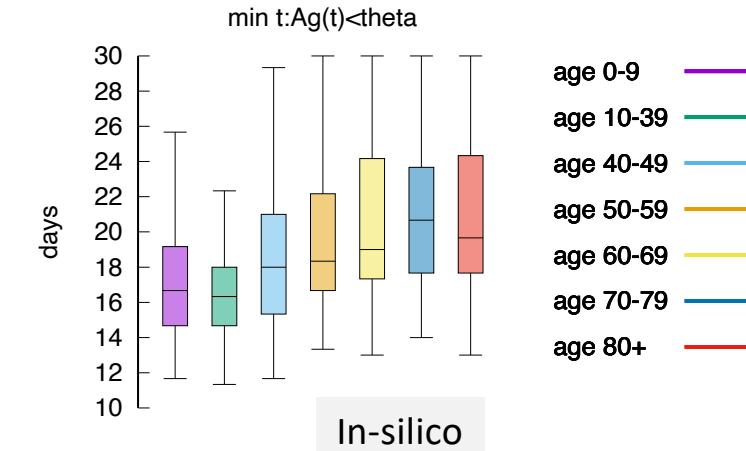
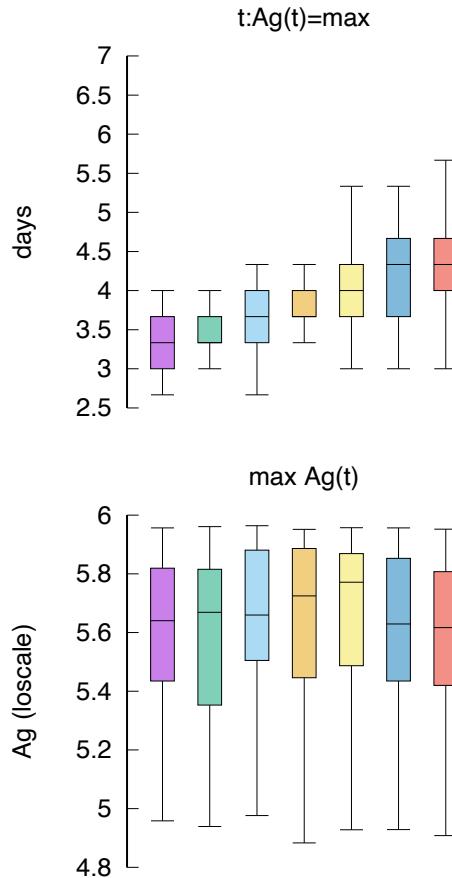


Critical \equiv {late responders} \cup
{weak responders}

numerical case studies



match to reality



In-silico

In-vivo

- ✓ time of viral peak:
- ✓ time virus below detection:
- ✓ time of seroconversion:
- ✓ time of antibodies peak:

3-5 days
12-28 days

- (critical 28-30)
- (carriers 25-29)
- (recovered 24-29)

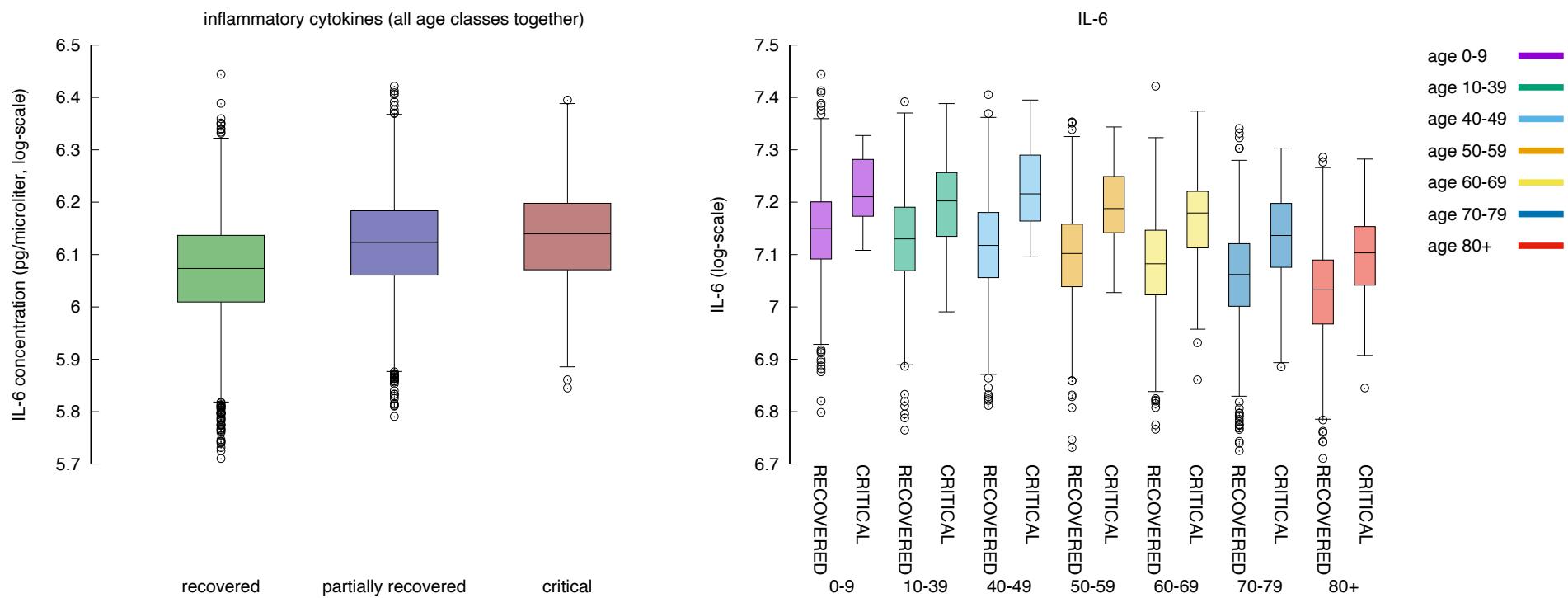
- (pharyngeal swab):
days
- time to recovery:
~20 days
- time of seroconversion:
6-12 days
- time of antibodies peak:
16-39 days
 - (critical 22-39)
 - (mild 16-21)

4

<https://doi.org/10.1038/s41586-020-2196-x>

- Zheng Shufa, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January–March 2020: retrospective cohort study *BMJ* 2020; 369 :m1443
- Juanjuan Zhao, et al., Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019, *Clinical Infectious Diseases*, , ciaa344, <https://doi.org/10.1093/cid/ciaa344>

IL-6 correlates with disease severity



Tobias Herold, Vindi Jurinovic, Chiara Arnreich, Johannes C Hellmuth, Michael von Bergwelt-Baileon, Matthias Klein, Tobias Weinberger. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv 2020.04.01.20047381; doi:<https://doi.org/10.1101/2020.04.01.20047381>. *Journal of Allergy and Clinical Immunology (in press)* doi: [10.1016/j.jaci.2020.05.008](https://doi.org/10.1016/j.jaci.2020.05.008)

Thank you

For your attention