REGULATORY SCIENCE AND IN SILICO TRIALS:

CREDIBILITY OF UISS-TB MODELLING AND SIMULATION FRAMEWORK

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- ✓ Tuberculosis (TB) is one of the world's deadliest diseases: one third of the world's population, mostly in developing countries, is infected with TB.

- ✓ In-Silico Trials (IST) represent an innovative application of Virtual Human technology helpful in assisting and supporting the refinement, the reduction, or the replacement of pre-clinical and clinical trials.

- ✓ In the context of **EC HORIZON 2020** framework, the funded project "**STriTuVaD – In silico trial for tuberculosis vaccine development**" aims to develop computer simulations to test the efficacy of new therapies for tuberculosis infection. The core modeling and simulation platform of the STriTuVaD project is the Universal Immune System Simulator for TuBerculosis (UISS-TB).

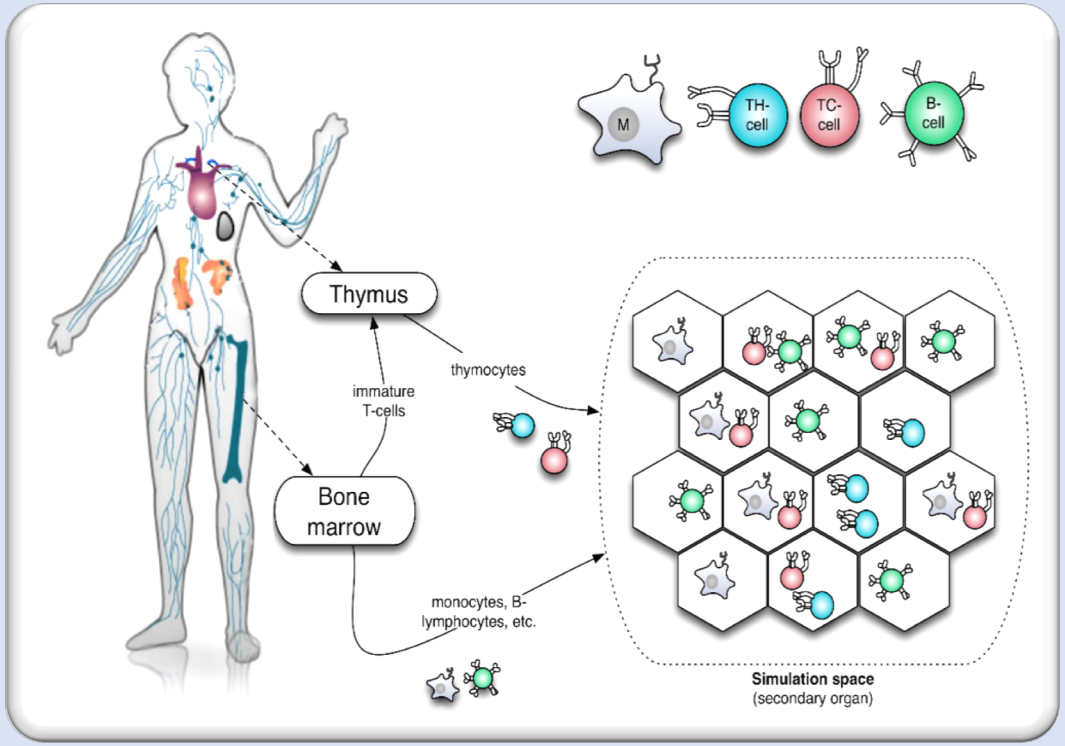
This approach, where found effective, could drastically significantly reduce the cost of innovation and duration of human clinical trials in this critical sector of public healthcare.

UISS IN BRIEF

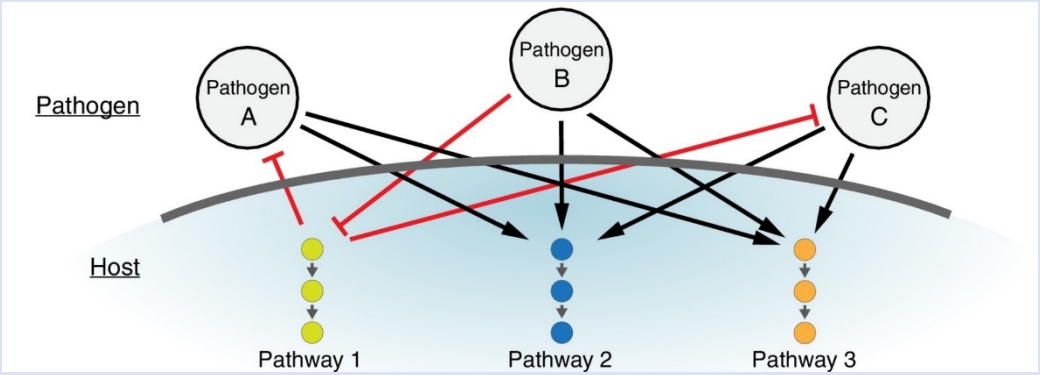
UISS

CrOSSBAR

The **U**niversal **I**mmune **S**ystem **S**imulator Framework (**UISS**) is a multi-scale (at cellular and molecular level), multi-compartment, polyclonal, agent based simulator of the immune system dynamics



COmputational **S**trategie**S** for the analysis of **B**iological p**A**thways and molecula**R** surface/binding



UISS KEYPOINTS

Anatomical compartment

Cells and molecules

Repertoire

Molecular affinity

Haematopoiesis

Cell maturation and thymus selection

Hayflick limit

Aging and memory

Hypermutation of antibodies

Bystander effect

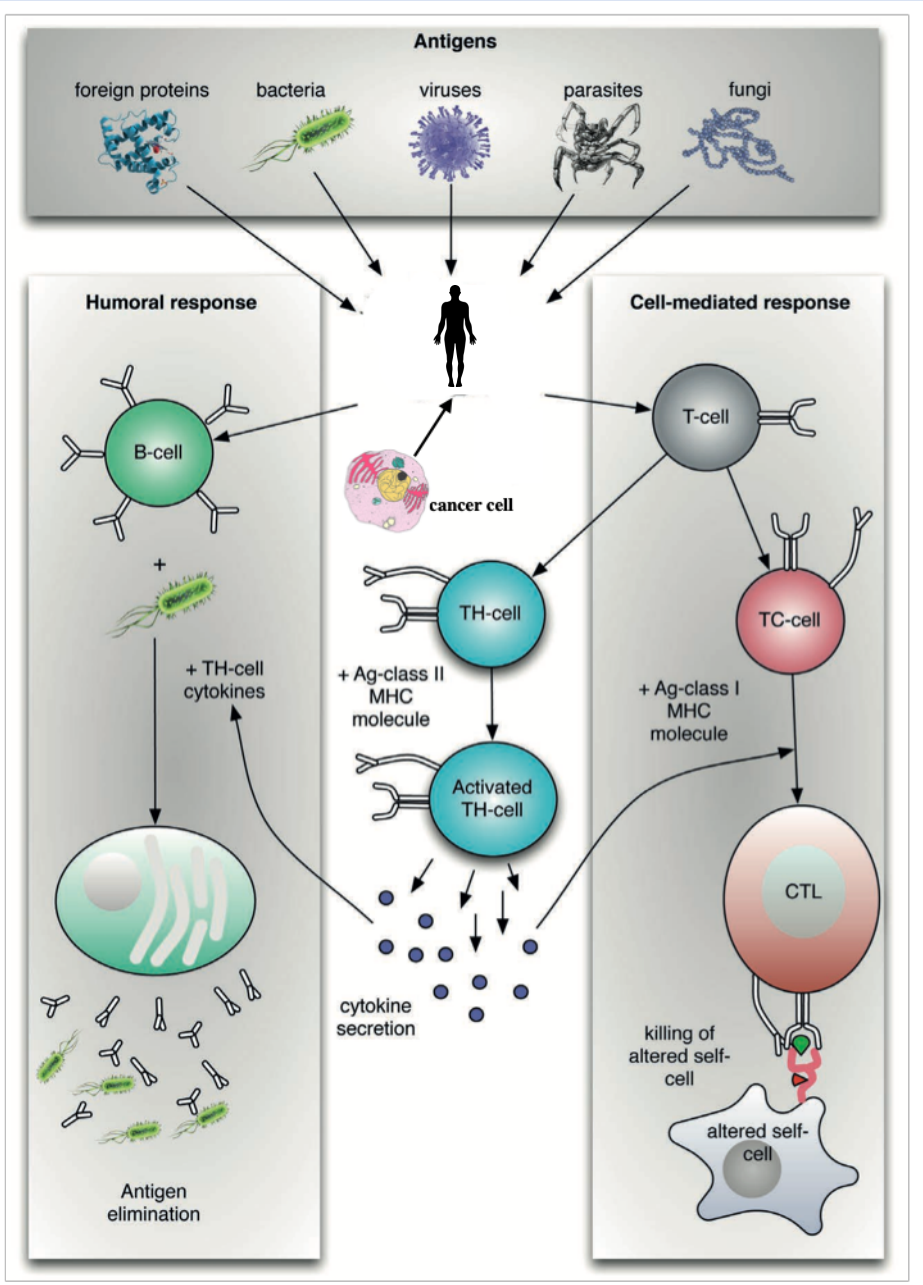
Cell activation and anergy

Cell interaction and cooperation

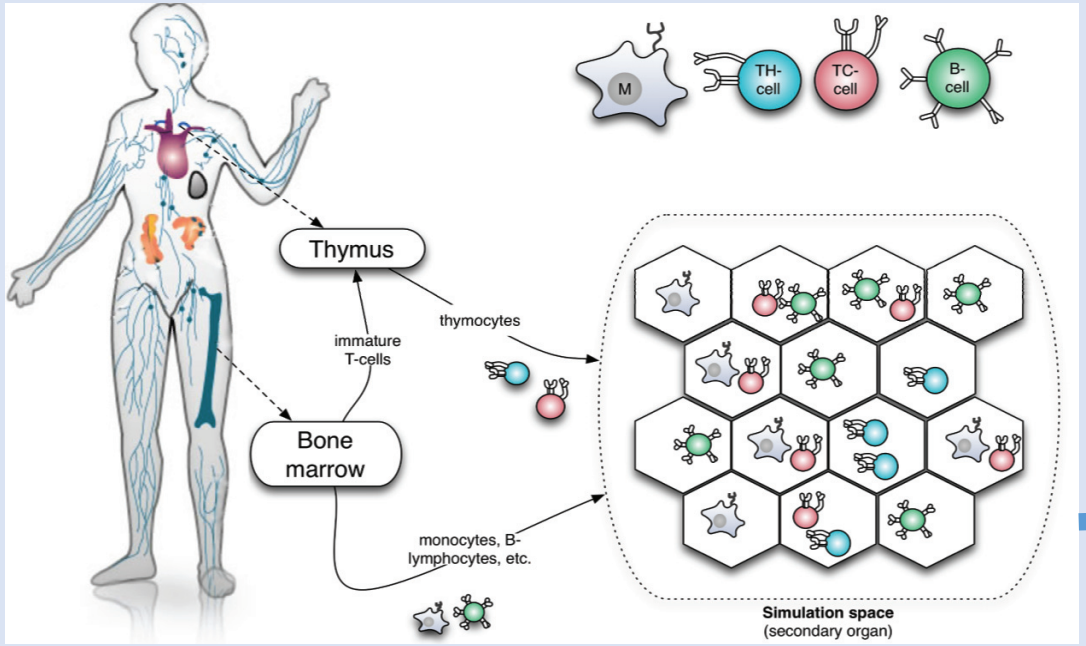
Antigen digestion and presentation

UISS: THE BIG PICTURE

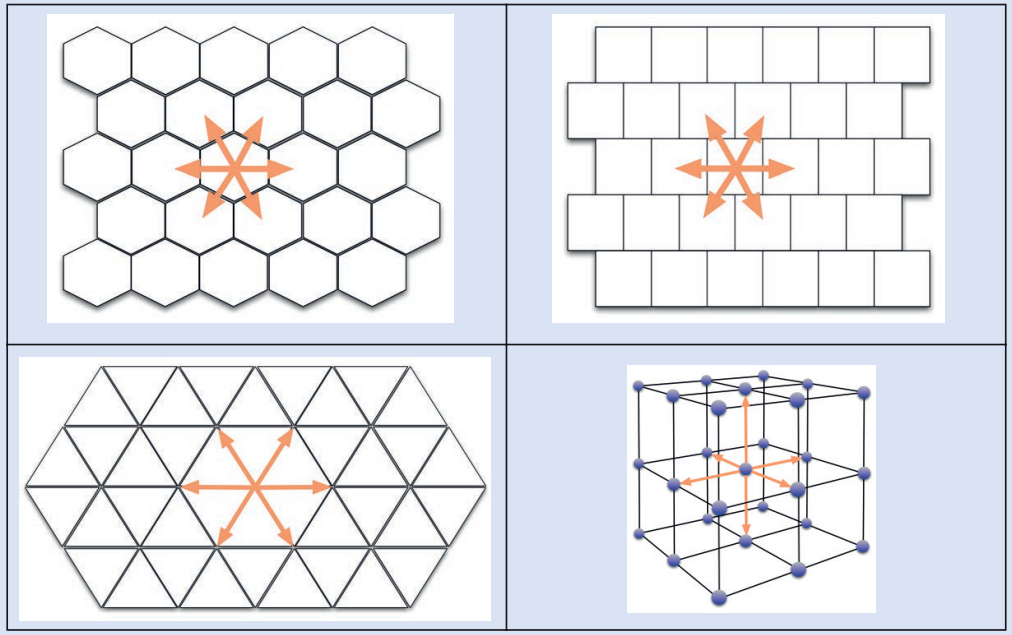
- The two branches of the immune response to an offending antigen/cancer cell: humoral response, mediated by the production of antibodies, and the cellular response, mediated by the action of activated cytotoxic T lymphocytes.
- UISS implements both and enables the representation of various pathogens as virus and bacteria. Cancer cells are represented as well.
- In UISS we considered both cellular and molecular entities.



UISS: COMPARTMENTS AND HOW ENTITIES MOVE



The three anatomical compartments modelled in UISS are the thymus, the bone marrow and a portion of a generic secondary organ



The space is discrete. UISS grid is a **hexagonal lattice** (top, left) or square-shifted (top, right). This is equivalent to the triangular lattice if you look at the edges instead of the nodes (bottom-left). For specific purposes, three-dimensional version could be implemented. In this case, the space is a Cartesian lattice (bottom-right).

IST: THE REGULATORY CHALLENGE

- In increasingly IST adoption perspective, the regulatory authorities are facing with an increasing number of projects developing and applying ISTs ranging from validating underway *in-silico* models of specific pathophysiology or applied virtual populations, via technological and infrastructural demands.

- The last few years have been characterised by an intense activity around the so-called regulatory science, aimed to ensure a robust approach to assess the credibility of individual *in-silico* methods as sources of regulatory evidence.

Why not use computer simulation in healthcare?

In healthcare

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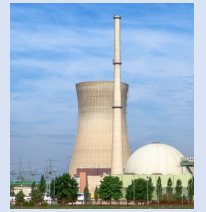
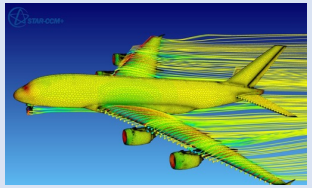
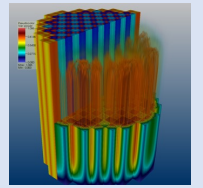
We test safety and efficacy of new products only by trial and error

In any other industrial sector

Testing is now done mostly with computer simulation

QUALIFICATION IN REGULATORY FIELD

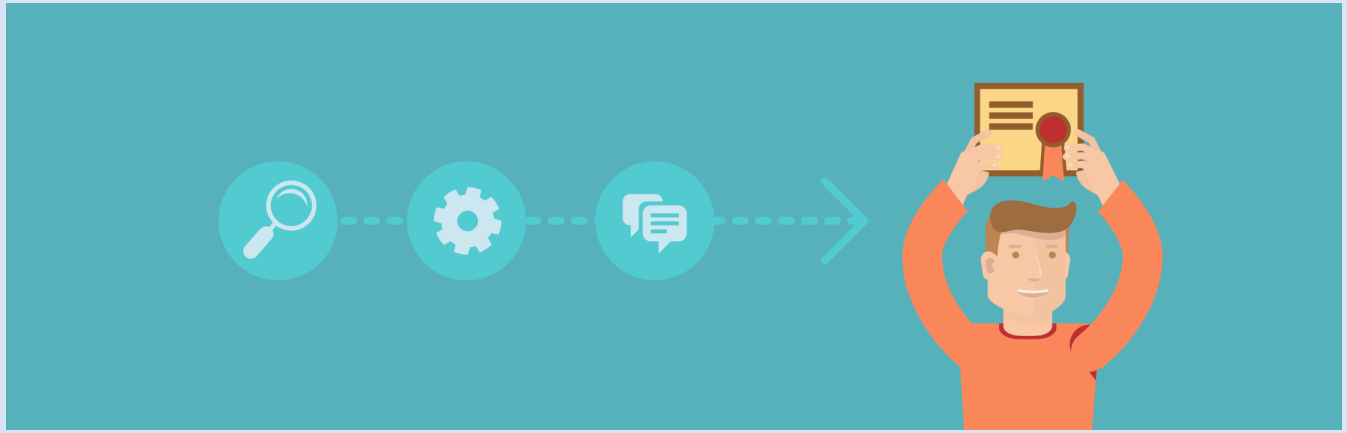
- In the regulatory field, the term **qualification** indicates the overall process that a regulator uses to establish the **credibility** of a novel method.

- This process is not entirely codified yet, although some aspects of it are addressed by the **ASME V&V-40** standard for medical devices, and in other regulatory documents for drugs. In addition to the ASME V&V-40 standard, we used as references the **EMA** 2017 advisory document on the qualification process, and a recent draft guidance document from **FDA** on Biomarkers qualification.

ASME, 2018. V&V 40 - 2018: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices.

European Medicine Agency, 2017. Essential considerations for successful qualification of novel methodologies (No. EMA/750178/2017).

Food & Drug Administration, 2018. Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff (No. Draft Guidance, Dec 2018).

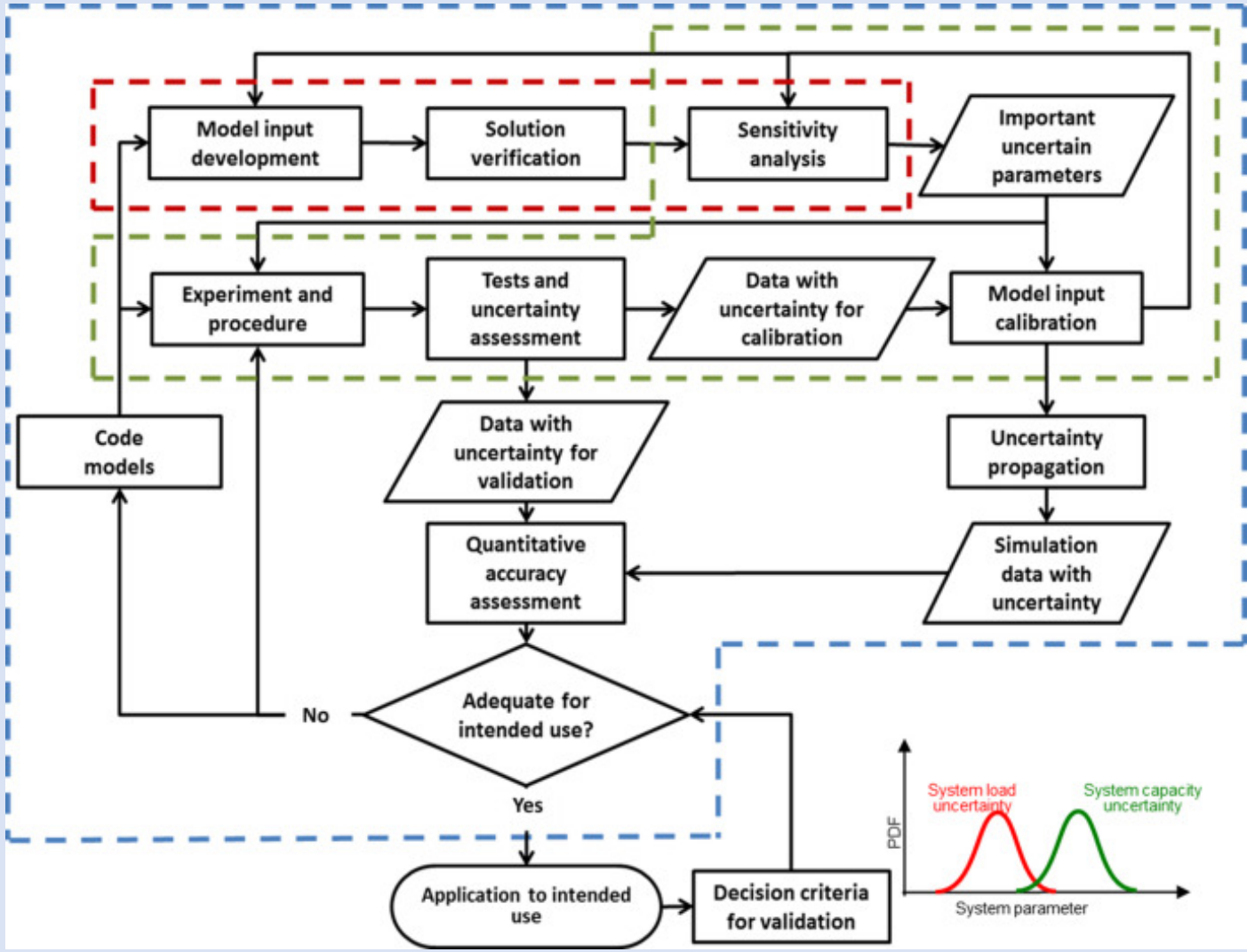


CREDIBILITY IN UISS-TB

Credibility analysis consists on Technical Validation, which is developed within the traditional framework of Verification, Validation, and Uncertainty Quantification (VV&UQ) already well established for other industrial sectors, and Clinical Validation, where the principles of general biomarkers qualification are followed.

TECHNICAL VERIFICATION IN UISS-TB

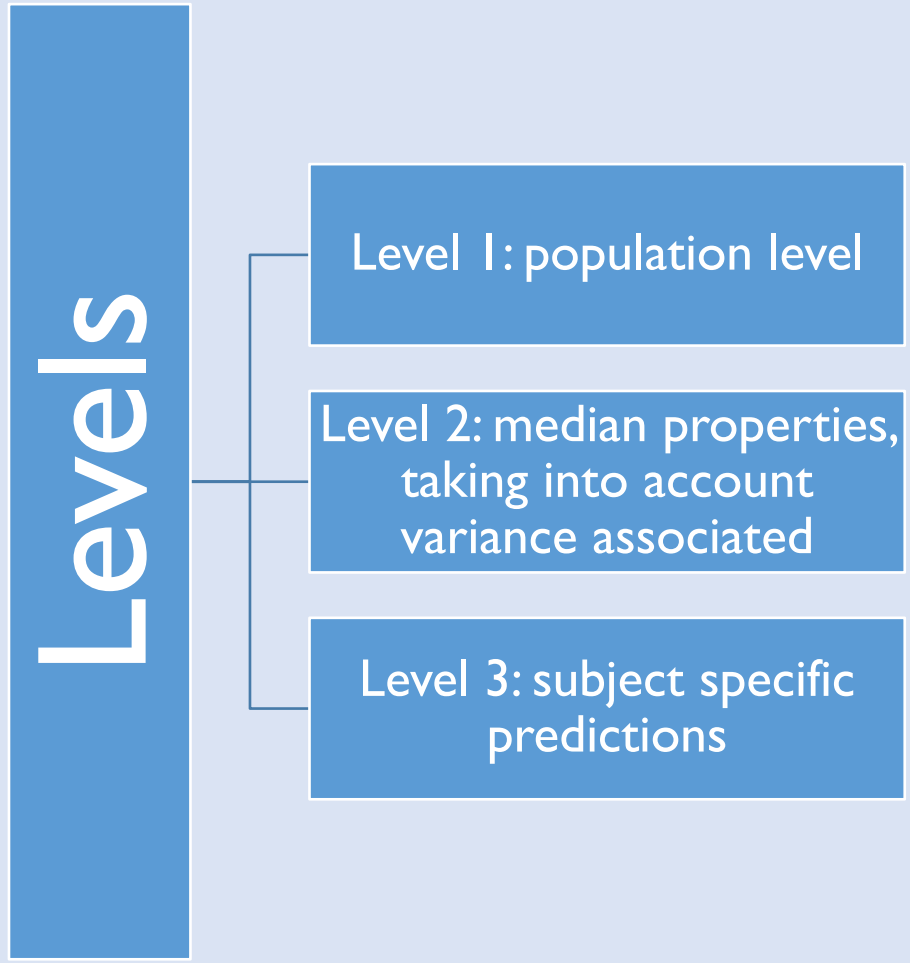
- UISS-TB is a predictive modeling framework. So its verification can be separated in code verification and model verification.
- Code verification: UISS-TB code includes a complete set of unit tests (both functional and non-functional), some that ensure the correct algorithmic behaviour of the program, other that monitor the model's logic and adherence to the available knowledge.
- The verification of agent-based models (ABM) is a complex topic. ABMs treat as discrete all quantities.
- A systematic exploration of all admissible input ranges, in order to highlight possible ill-conditioning scenarios, must be conducted. Sensitivity analysis is the way through we try to reach this goal.



TECHNICAL VALIDATION IN UISS-TB

Depending on the purpose of the model being validated, there are three levels of validation.

- (L1) → we expect the model to predict any value among those observed within a reference population, or in a set of controlled experiments.
- (L2) → validation means that we expect the model to predict a median property (for example the average value) of the distribution of values observed in the reference population.
- (L3) → **represents the most stringent validation**, applies when the model predicts each of the values observed in the reference population or in the set of controlled experiments, when properly parametrised with subject-specific information.



TECHNICAL VALIDATION IN UISS-TB (CONTD)

- UISS-TB technical validation needs to be done in steps.

- The first is to show that the simulation of the human immune system responds to well-defined challenges as expected. This is an L2 validation, as we can only compare the model's predictions to the average response of the population, as reported in the specific literature.

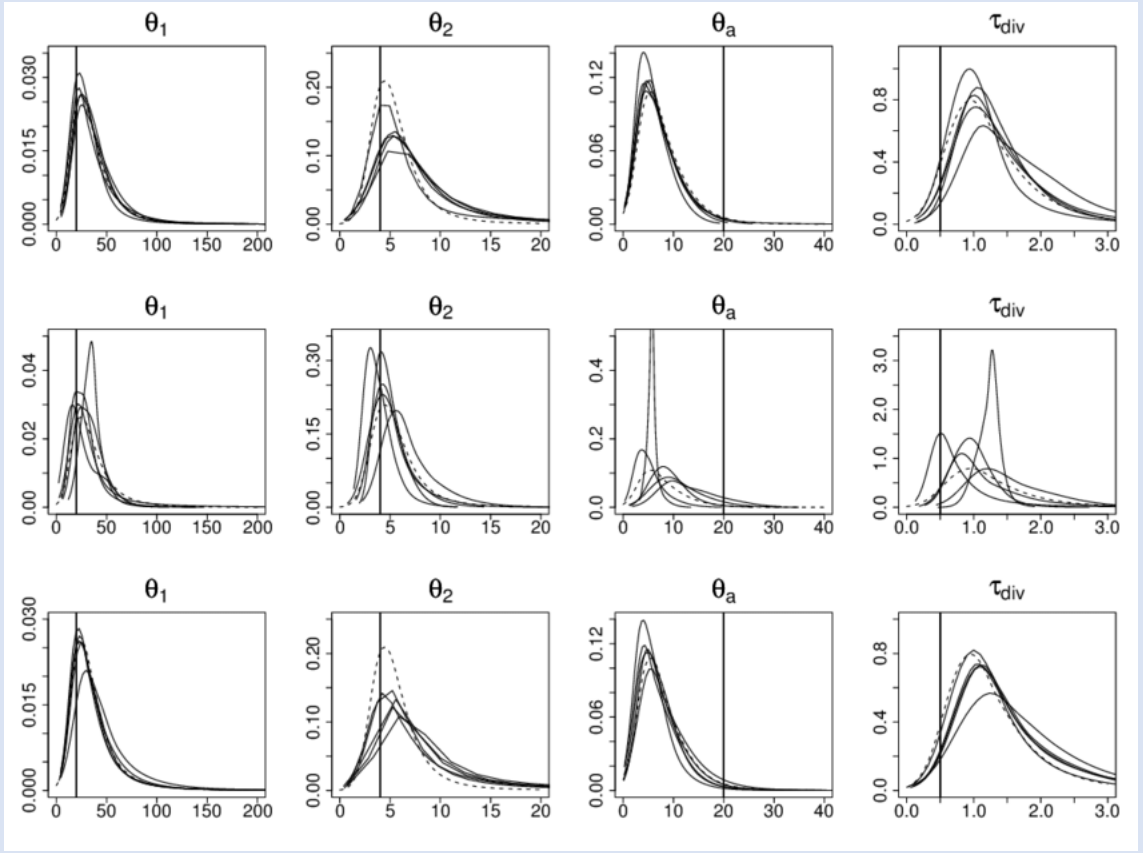
- The second step is to validate the disease progression model. Here it is possible to use animal experiments, where the conditions are well controlled; for human validation the amount of information available on the progression of TB in untreated patients is somehow limited and mostly historical.

- So, while such comparison can provide secondary evidences that reinforce the credibility, a robust validation of the model of intervention can be done only from a clinical point of view in this case (L3 validation).

UISS-TB UNCERTAINTY QUANTIFICATION

The UISS-TB model is personalised to predict the response of each patient with a specific set of information coming from real data.

For each of these quantities, the reproducibility of the information must be quantified, and the propagation of such uncertainties into the model's prediction needs to be evaluated, using a full-scale Monte Carlo scheme.



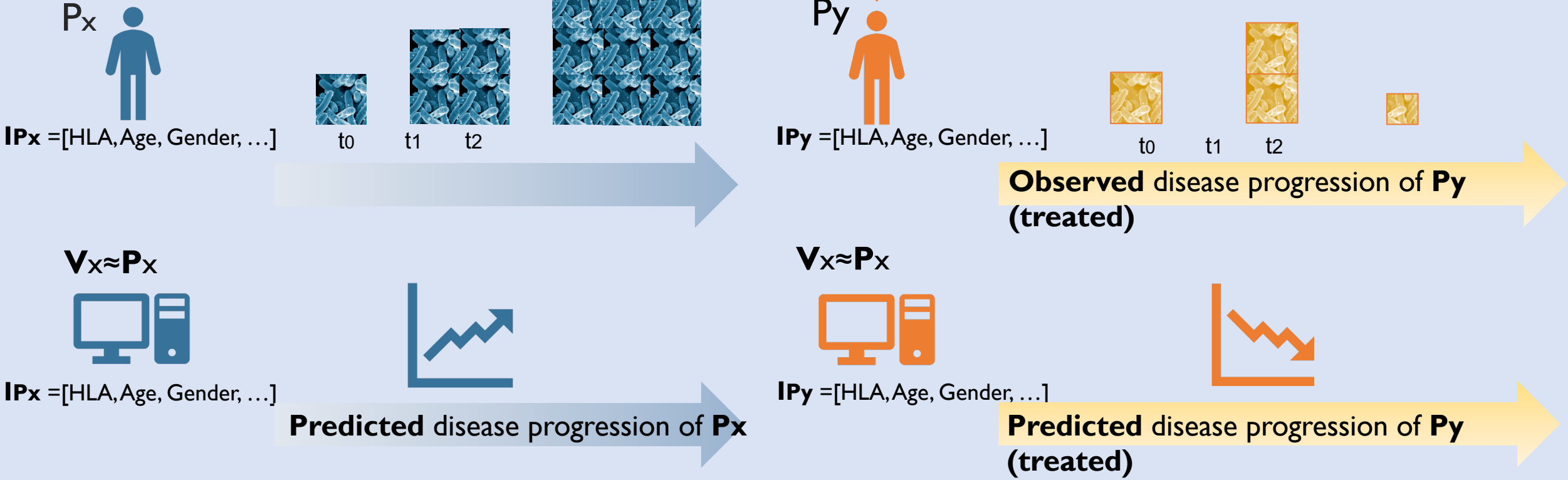
EXTRAPOLATION OF UISS-TB VALIDATION AND CLINICAL VALIDATION

The extrapolation credibility as formulated in the ASME V&V-40 standard revolves around two assumptions: regularity, and similar prediction error within the limits of validity of the model.

Regularity of UISS-TB predictions is explored in the sensitivity analysis. UISS-TB should be considered validated only for the range of input values that are explored in the clinical validation; any prediction outside such range should be used with much greater care.

Clinical validation studies are run in parallel to the clinical trial of a new therapy (done in comparison to the standard-of-care therapy). As for the clinical trial, also the clinical validation requires the modelers to be blinded, although the information to be blinded are different.

SUMMARY



Validated patient-specific model of **disease progression**

Validated patient-specific model of **treatment response**