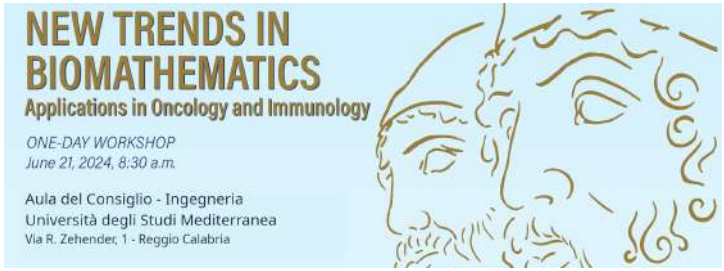
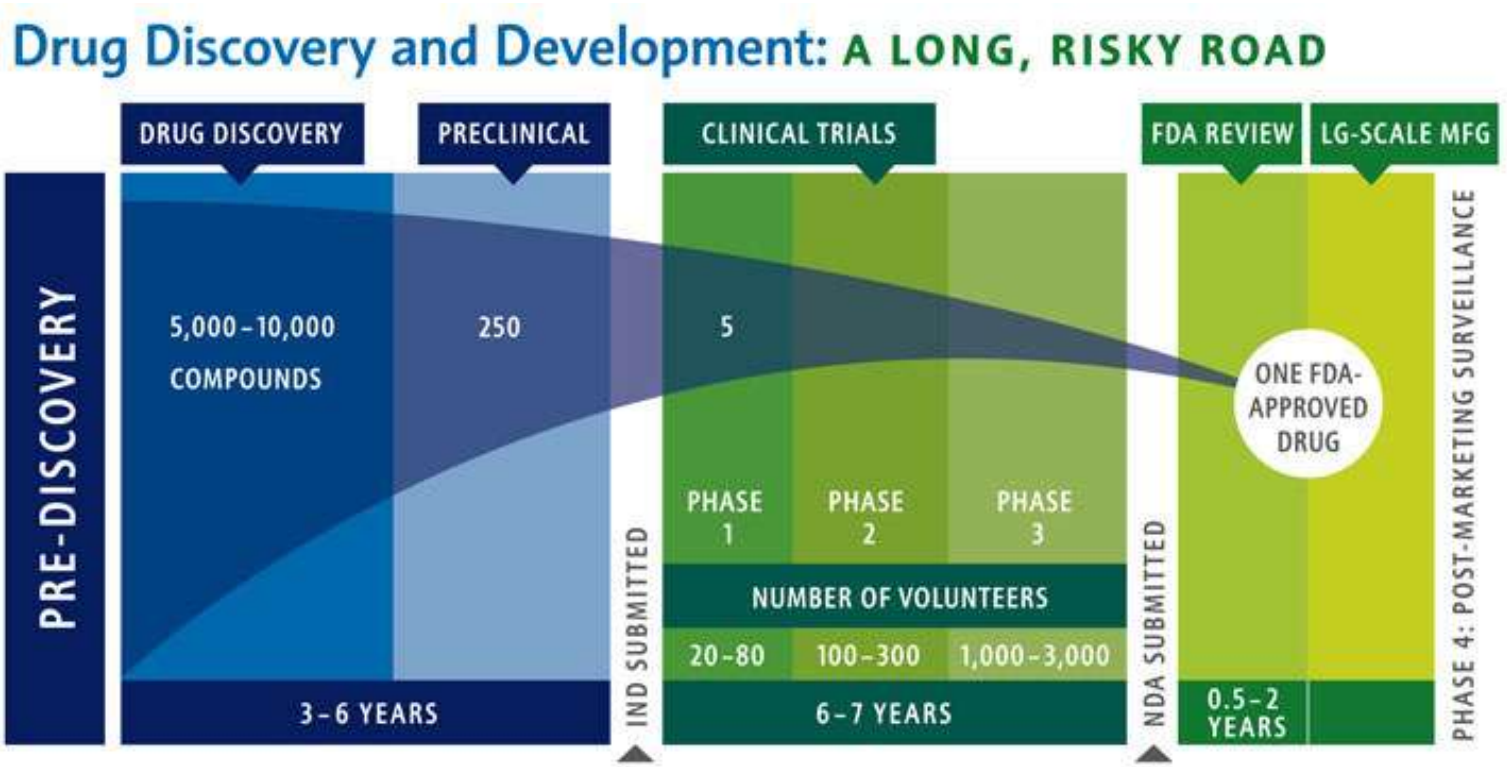


Beyond the data: computational modeling as a tool in oncology and immunology

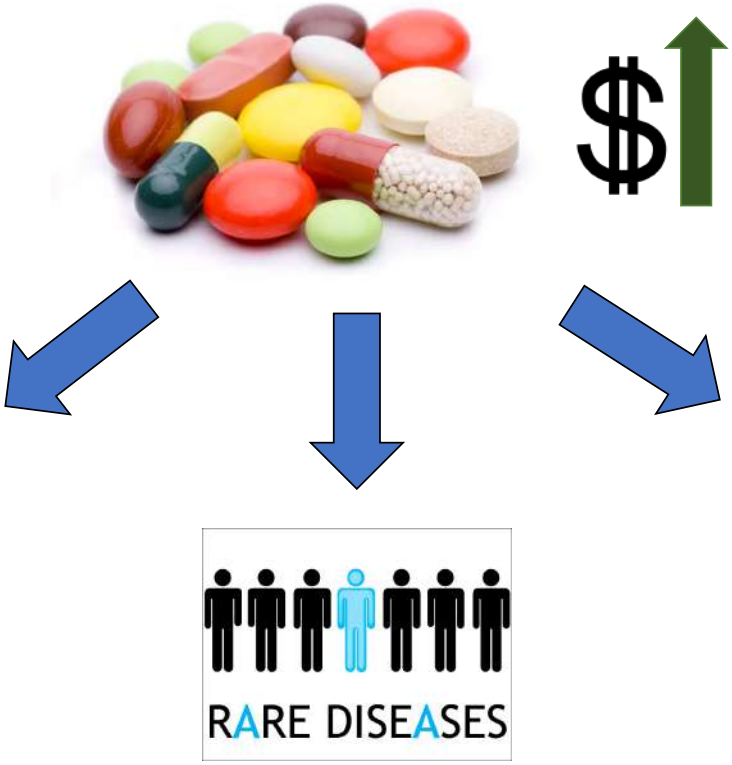
Francesco Pappalardo <francesco.pappalardo@unict.it>
Dept. Of Drug and Health Sciences, University of Catania, Italy.
COMBINE Group, www.combine-group.org

This is the problem



Source: Pharmaceutical Research and Manufacturers of America

The impact of growing prices



Universal Healthcare Sustainability

Improve health in developing countries

M&S in the medical industry: drugs

- In drugs design, computer models are used routinely in lead optimisation (molecular dynamics) and in dose-response studies (PKPD, PBPK), usually to inform experimental studies
- Binding affinity simulation (MD) is growing in drug discovery
- There is a growing demand for the so-called *Quantitative Systems Pharmacology* (QSP) model to link drug design to clinical outcomes

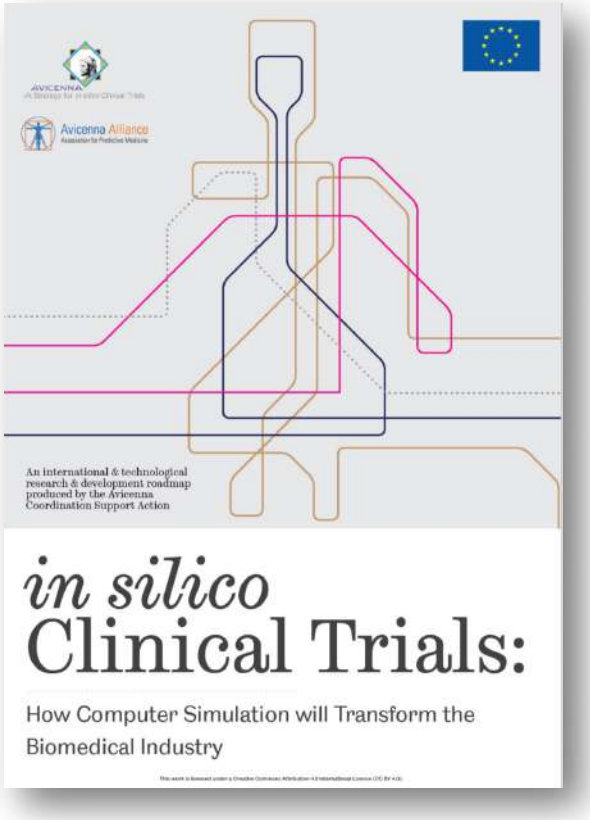
M&S in the medical industry: device

- Computer modelling & simulation is routinely used in the design of medical devices (Biophysics & physiology models)
- FDA has opened a pathway for producing regulatory evidence of safety and efficacy using M&S (VV-40)
- There is a growing interest in using M&S to refine, reduce and to some extent replace:
  - In Vitro and ex vivo experimentation (cost, time to market)
  - Animal experimentation (ethical issues)
  - Human experimentation (both)

In Silico Trials

- In Silico Trials are a sub-class of QSP models
- where cohorts of subject-specific models capable of predicting the response of individuals to the treatment with a new medical product
- are used to refine, reduce, and partially replace in vivo/ex vivo, animal, or human experimentation

2015: Avicenna roadmap

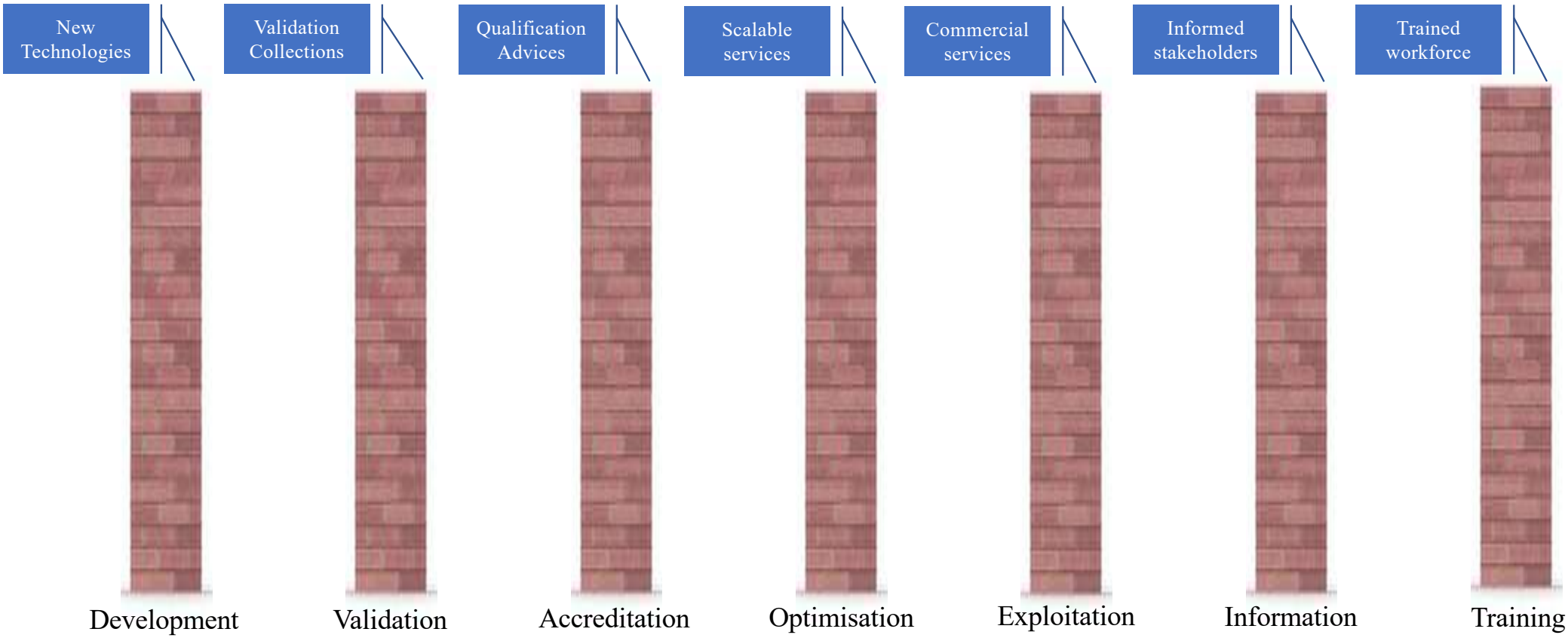


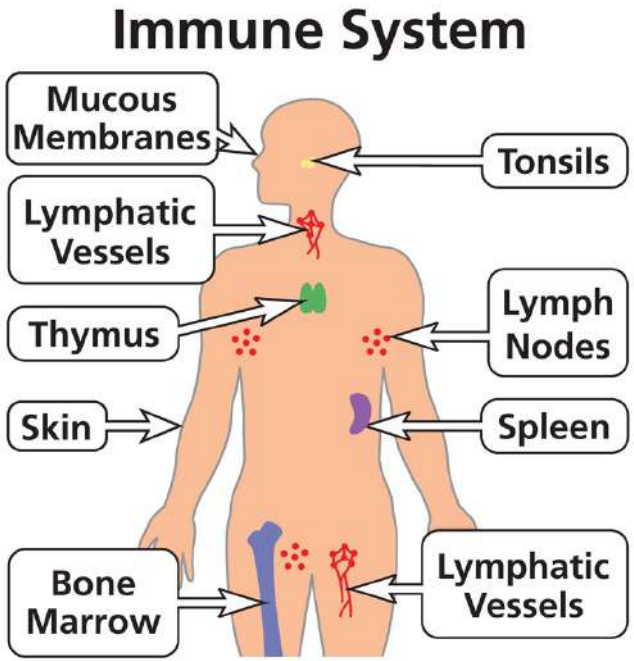
In Silico Trials = "The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/intervention"

http://www.vph-institute.org/documents.html

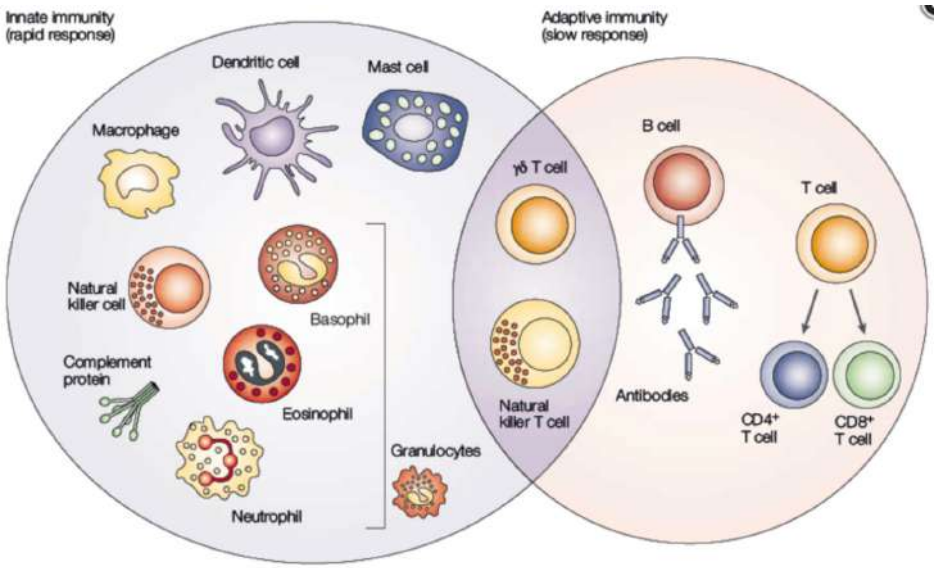
What is preventing a wider adoption?

- Seven years after the publication of the Avicenna roadmap on In Silico Trials the adoption of modelling and simulation in the assessment of medical products is still spotty
- While for some classes of products the use of In Silico methodologies produce regulatory evidence is becoming normal, for others this is still impossible


New Technologies
Validation Collections
Qualification Advices
Scalable services
Commercial services
Informed stakeholders
Trained workforce
Development
Validation
Accreditation
Optimisation
Exploitation
Information
Training



The immune system is **a complex distributed system** that constitutes the defense mechanism of higher level organisms to pathogens.



- The Immune System is a ***complex adaptive system***.

- Complex adaptive system (CAS): An ensemble of (inhomogeneous and) adaptive particles with the following characteristics:
  - Particles can interact each other and with the outside environment
  - The collective behavior cannot be simply inferred from the behavior of its elements.
  - The alteration of only one agent or one interaction reverberates on the whole system.
- Other CAS examples: the brain, social systems, insects swarms, crowds.

- CAS are characterized by a global organization, which emerges from the interacting constitutive particles.
- An Emergent Property of a CAS is a property of the system as a whole which does not exist at the individual level.

(Some) **Emergent properties** of the IS:

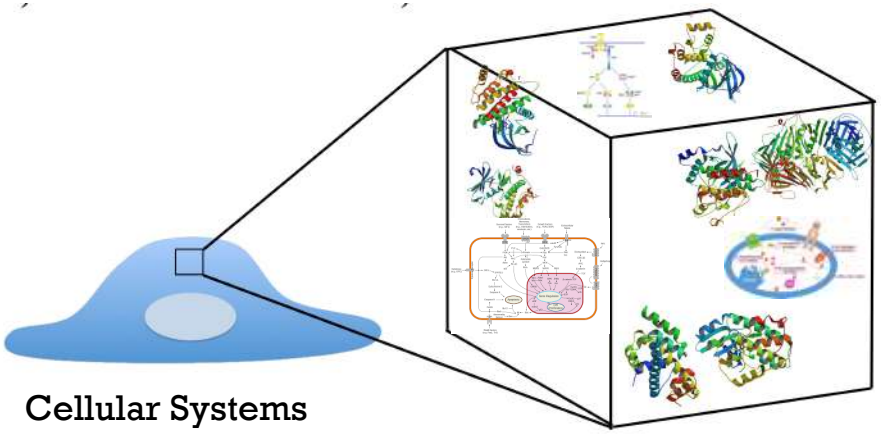
- **The ability to distinguish** any substance (typically called antigen) and determine whether it is self or nonself.
- **The ability to memorize** most previously encountered antigens, which enables it to mount a more effective reaction in any future encounters.

- Homeostasis!

So, the IS is a a very complex adaptive system!

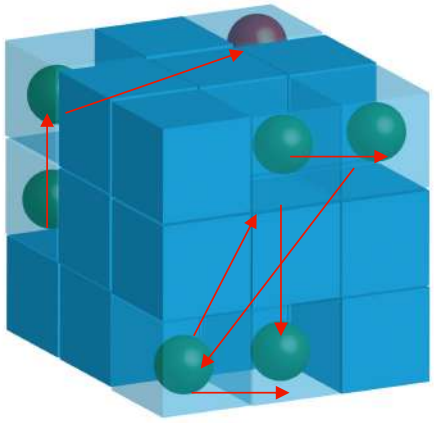
Agent-based models (ABMs)

- A generalization of the concept of **Cellular Automata** initially proposed by Alan Turing.
- ABMs represents the physical reality through a large number of autonomous discrete particles (called **Agents**) that move in space, interact and change their internal state according to a set of rules.
- ABMs are capable of re-creating macro-level phenomena by the actions and interactions of microlevel individual agents (**emergence**).



Cellular Systems

Molecular Systems/Pathways

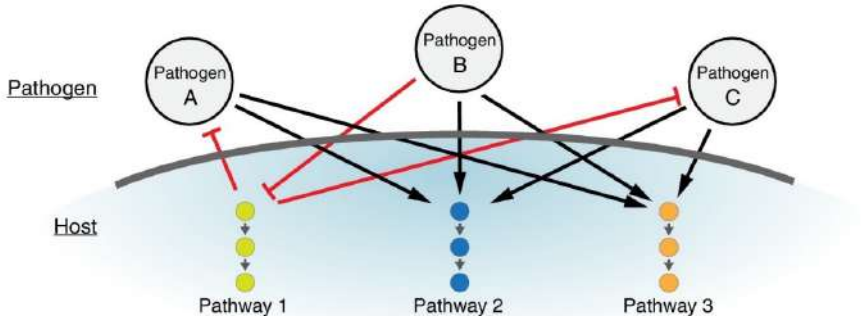


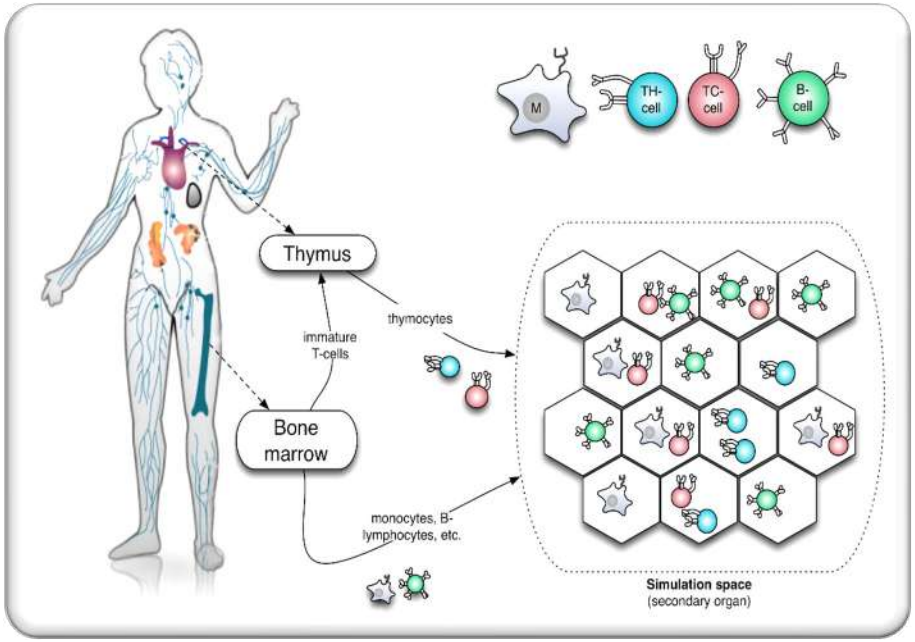
Agent-based Modeling

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.



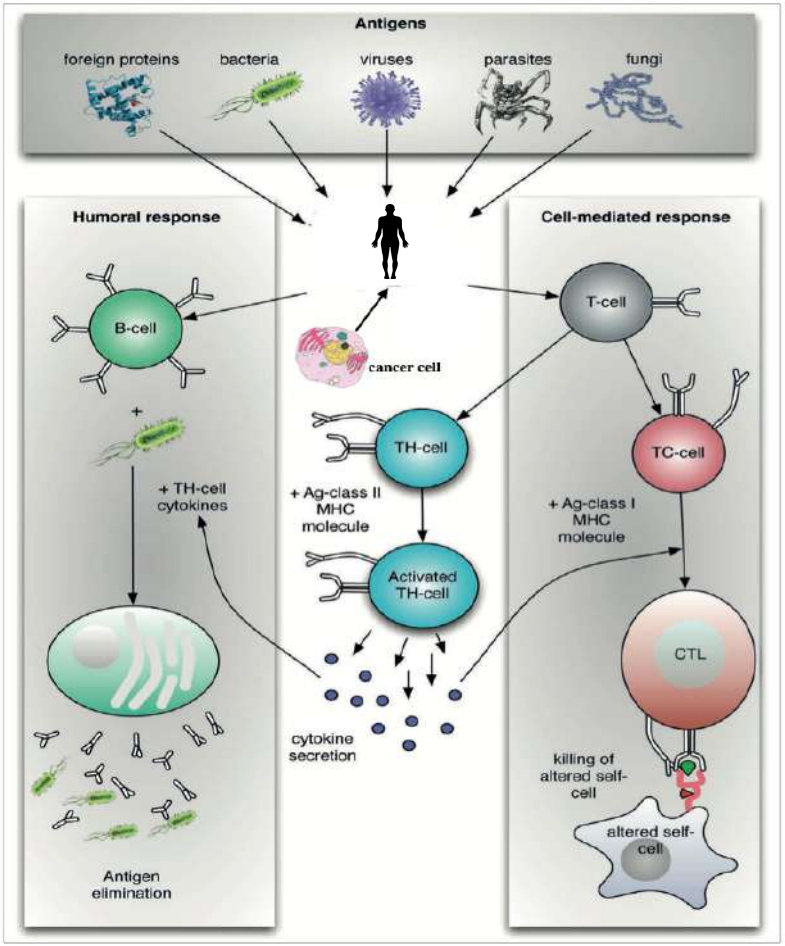


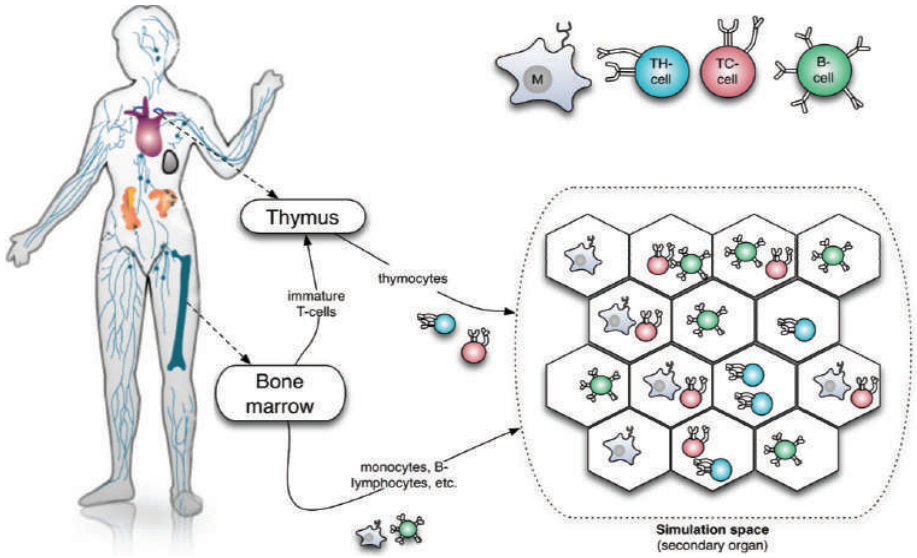
UISS KEYpoints

- 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

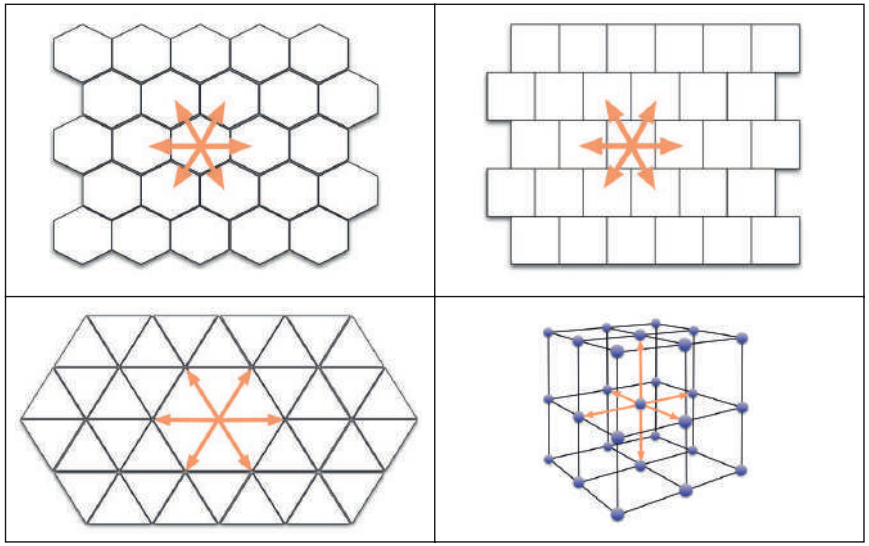
UISS: the big picture

- 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.



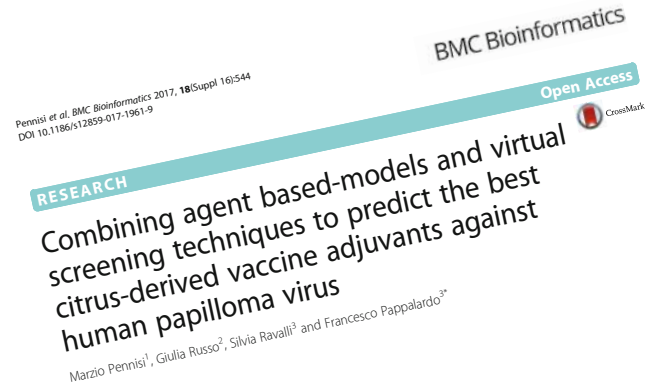


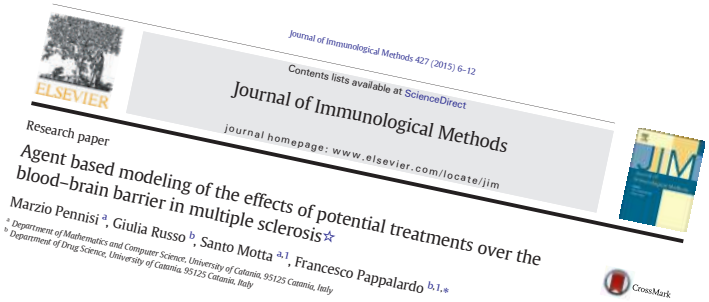
The three anatomical compartments modelled in UISS are the thymus, the bone marrow and a portion of a generic secondary organ.

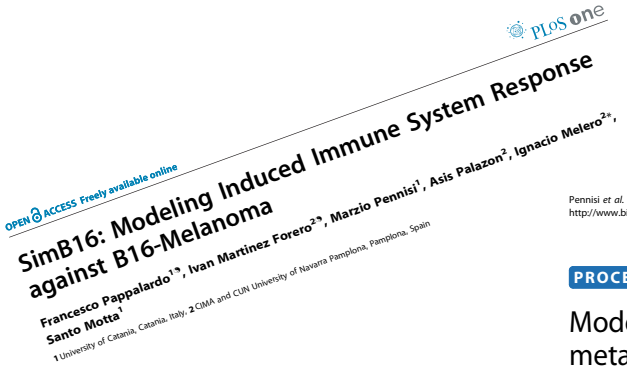


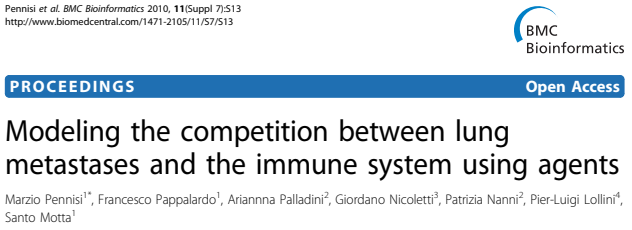
The space is discrete. UISS grid is a **hexagonal lattice** (top, left) or square-shifted (top, right). This is equivalent to the triangular lattice if you look at the edges instead of the nodes (bottom-left). For specific purposes, three-dimensional version could be implemented. In this case, the space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

UISS


BMC Bioinformatics
Pennisi et al. BMC Bioinformatics 2017, 18(Suppl 16):544
DOI 10.1186/s12859-017-1961-9
Open Access
RESEARCH
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*], Ivan Martinez Forero[2*], 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

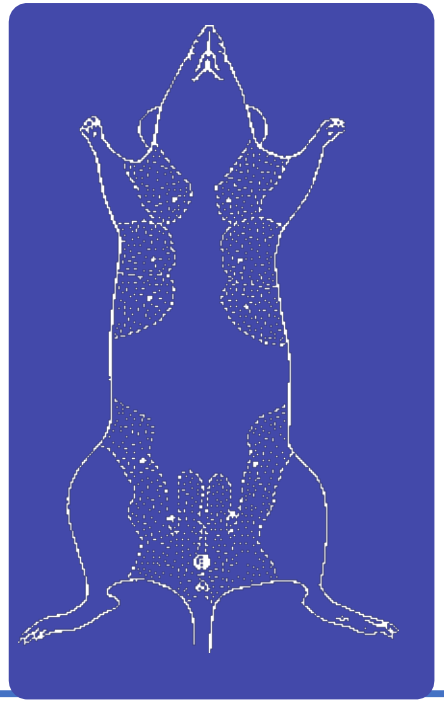
UISS-MC: efficacy prediction and optimization of vaccines against mammary carcinoma

Joint work with Prof. Lollini group, University of Bologna, Italy

June 21th 2024 - Università degli Studi Mediterranea

Immunoprevention of breast cancer: animal model

Mammary areas



HER-2/neu TRANSGENIC MICE: BALBneuT

Transgenic mice for the **rat-activated HER-2/neu oncogene.**

Female mice develop multifocal mammary carcinoma with a short latency, about 20 weeks of age.

At 33 weeks, lobular carcinomas are palpable in all 10 mammary glands

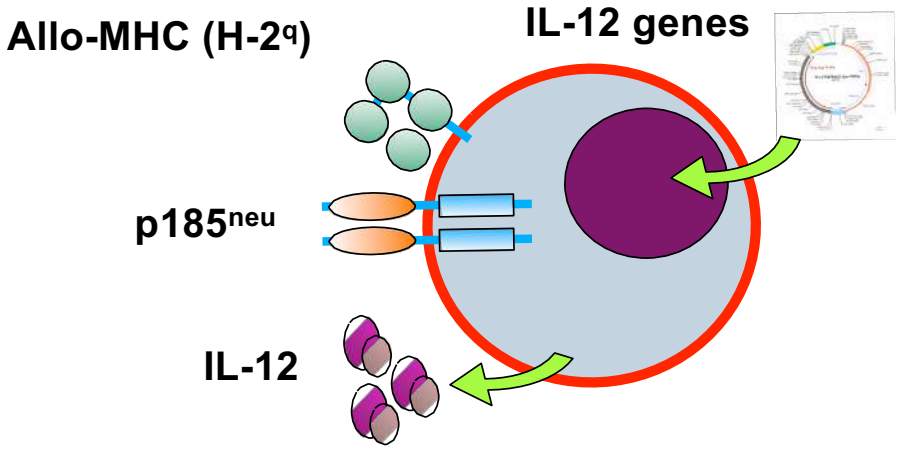
J. Exp. Med. 188: 589 (1998)

Biotechnology: TRIPLEX VACCINE

Triplex is a cellular vaccine based on murine mammary carcinoma cells.

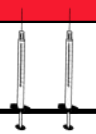
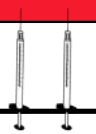
Triplex combines three stimuli:

- ✓ **p185^{neu} antigen** (the product of rat HER-2/neu oncogene)
- ✓ **Allogeneic MHC** (major histocompatibility complex), haplotype H-2^{q}
- ✓ **Interleukin (IL-12)**



J. Exp. Med. 194:1195 (2001)
Cancer Res. 1, 64: 4001 (2004)

In vivo experiments: chronic protocol

1st wk	2nd wk	3rd wk	4th wk
		REST	REST

4-WEEK CYCLE

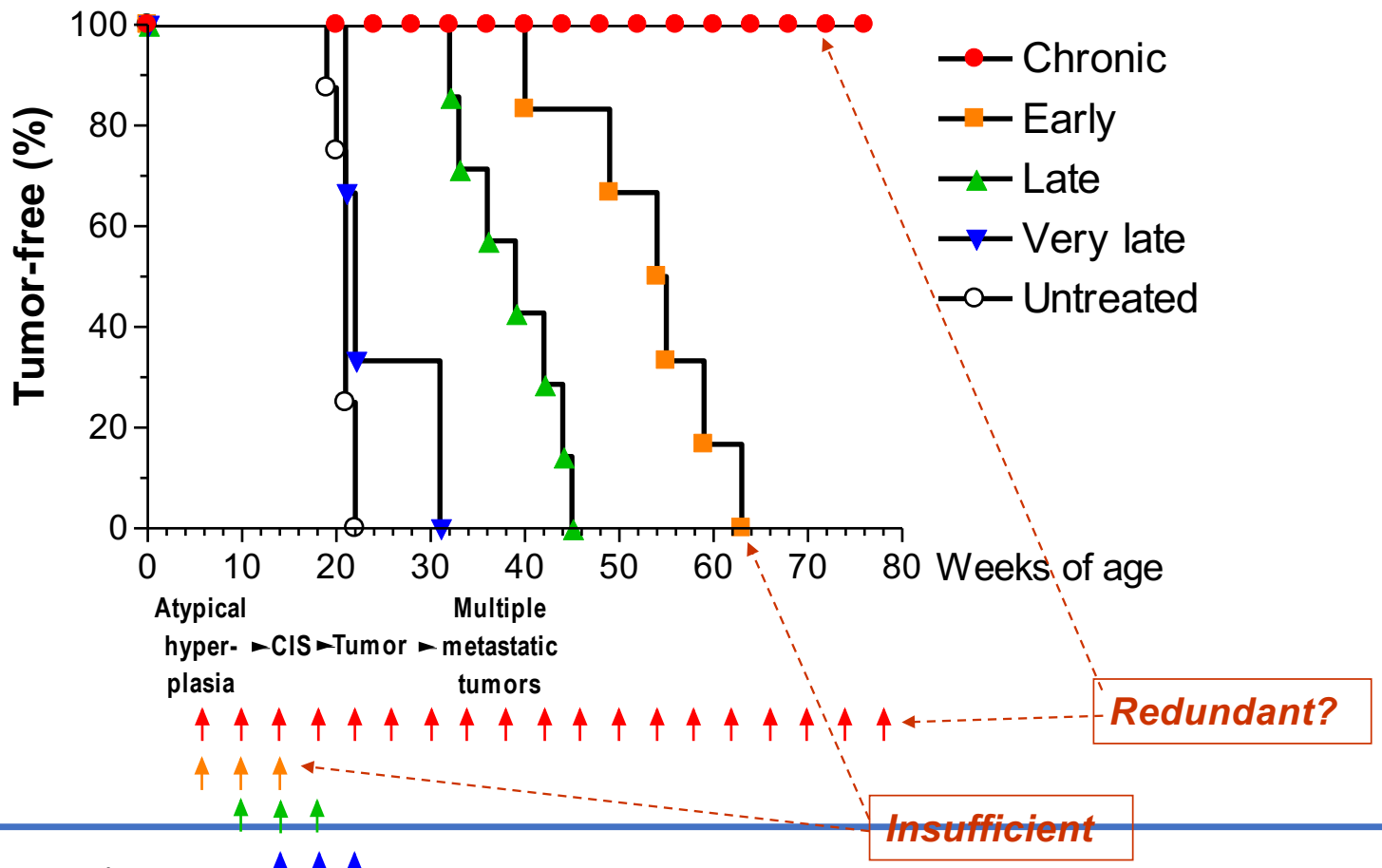
CHRONIC protocol was based on 4-week cycles:

in the first 2 weeks, mice received four twice-weekly intraperitoneal vaccinations with $2x10^6$ proliferation-blocked vaccine cells, followed by two weeks of rest.

Vaccination was started at 6 weeks of age, between 35 and 42 days of age, and the four-week vaccination cycle was repeated for 1-year, at least.

J. Exp. Med. 194:1195 (2001)
Cancer Res. 1, 64: 4001 (2004)

The problem: finding the optimal/minimal vaccination schedule



Future Oncol. Feb 1: 57 (2005)

Exhaustive search?

- The length of the experiment is 400 days;
- in this timespan roughly 100 days are available for vaccine administrations;
- it follows that the number of possible different schedules is 2^{100} i.e. about 10^{30}.

Then

- A biological exhaustive search is simply impossible
- Even a virtual exhaustive search is impossible as a single run of the simulator takes about 30 seconds. The analysis of all the possible different schedules will be require about $3x10^{31}$ secs i.e. 10^{24} yrs.

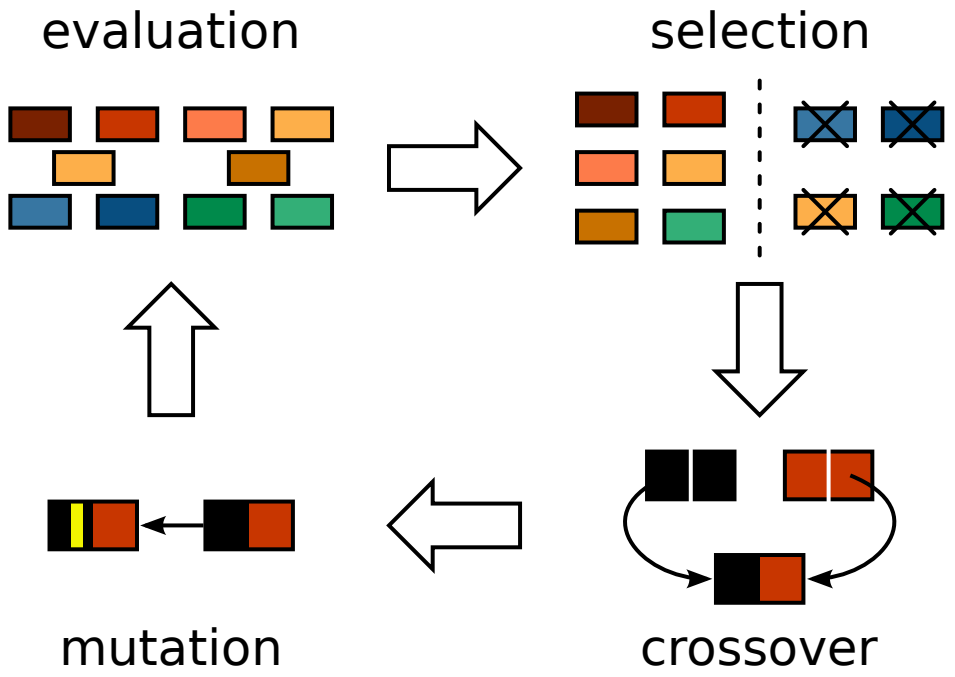
Hence:

- Apply UISS to reproduce *in silico* the wet-lab experiments
- Find optimal schedule using artificial intelligence methodology (**genetic algorithms**)
- Test the *in silico* results *in vivo*

A sketch of what genetic algorithms are

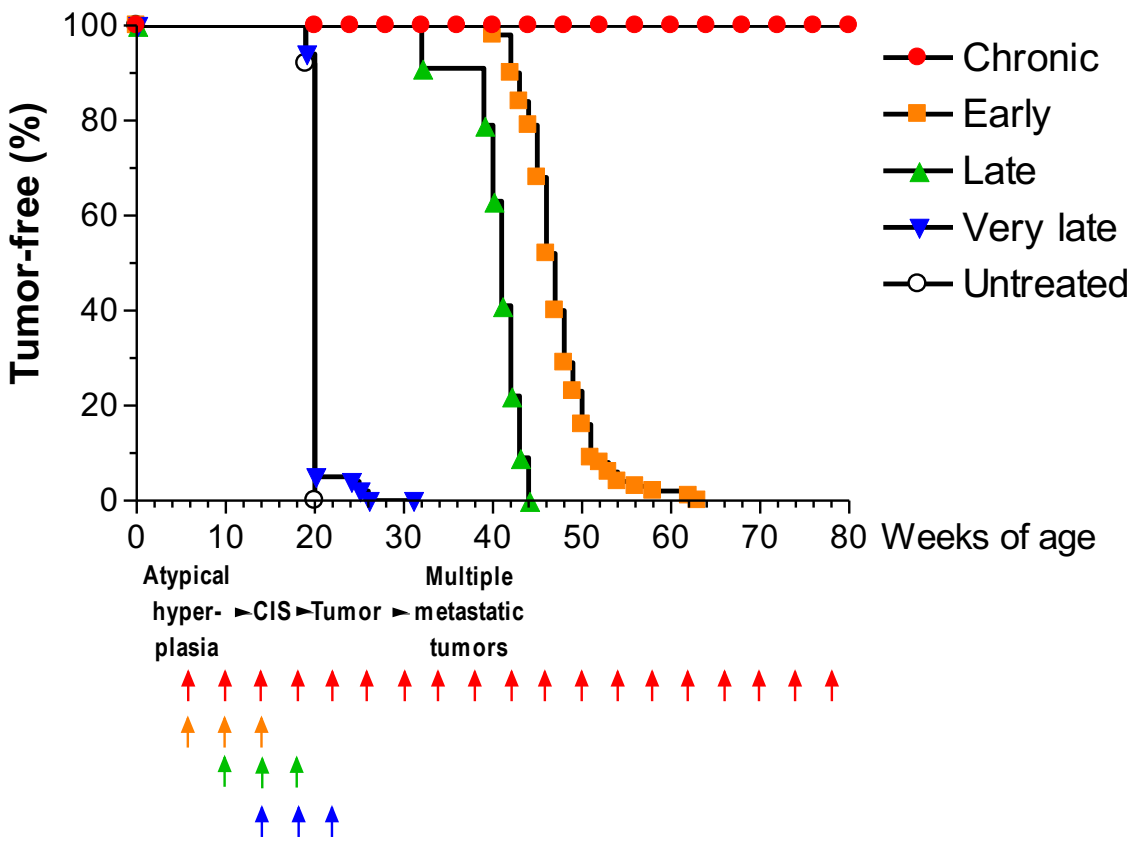
- **Genetic Algorithms:** a stochastic optimization technique that takes inspiration from the biological evolution of living systems

- A population of candidate solutions (called individuals, or chromosomes) evolved toward better solutions using bio-inspired operators.

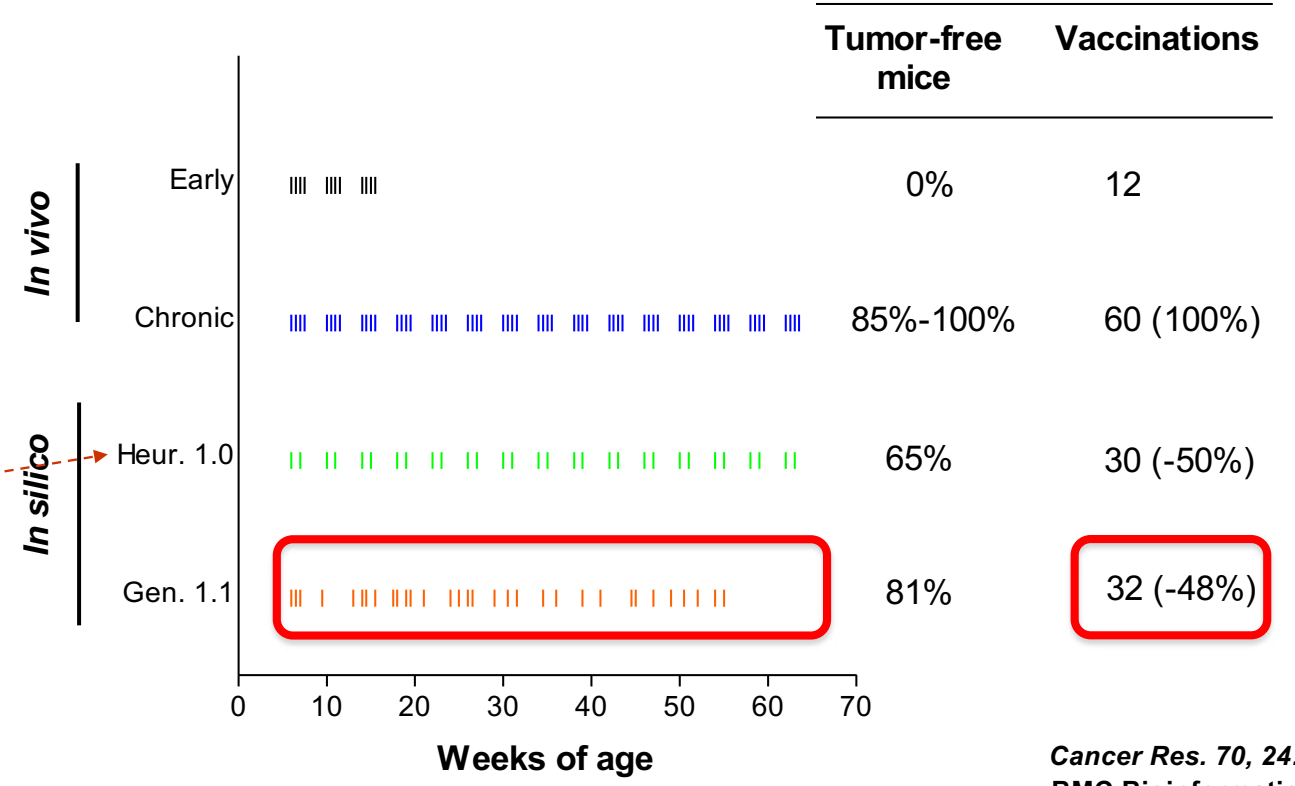


UISS-MC reproduced in vivo experiments

In silico results (100 virtual mice vs 8 in the in vivo experiment)



UISS-MC: prediction of the best dosage



	Tumor-free mice	Vaccinations
Early	0%	12
Chronic	85%-100%	60 (100%)
Heur. 1.0	65%	30 (-50%)
Gen. 1.1	81%	32 (-48%)

Heuristic protocol is a periodic vaccination protocol using the same number of vaccine administration of the genetic optimal protocol (**from an immunologist point of view**).

Cancer Res. 70, 24: 7755 (2010)
BMC Bioinformatics 7:352 (2006)

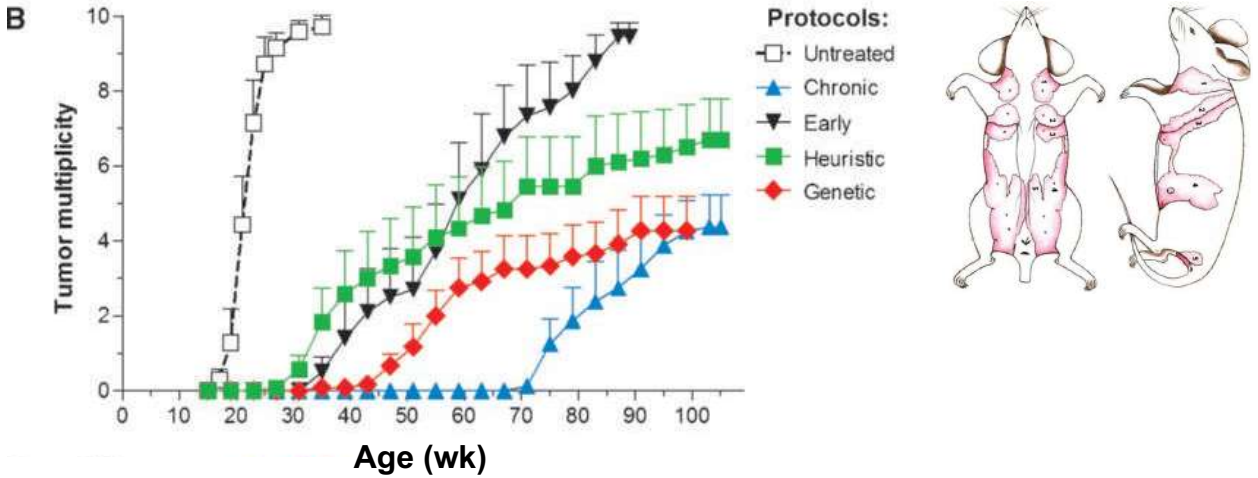
The validation experiment

- The experiment was performed using five groups of mice.
- The number of mice in each experimental group was untreated, 7; Chronic protocol, 11; Early protocol, 10; Heuristic protocol, 13; Genetic protocol, 12.
- After the appearance of the first tumor mass (> 3mm) vaccination was continued up to the end of the protocol to measure the tumor multiplicity in all mammary glands. Mice with extended tumors were killed according to ethical rules.

The validation experiment (CONTD)

TUMOR MULTIPLICITY:

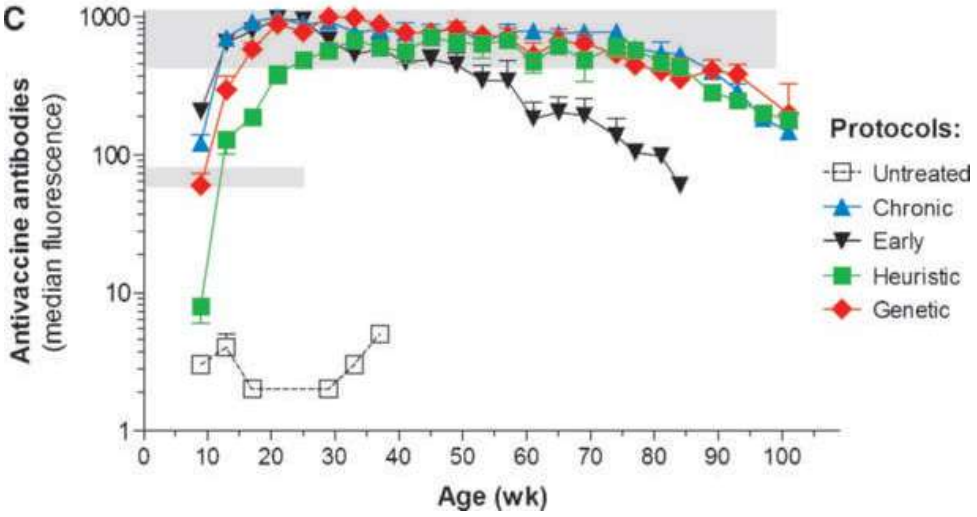
number of tumors subsequently appearing in each mouse.



- ✓ Genetic, Heuristic and Early schedules: significantly different at various time points
- ✓ Genetic better than Heuristic better than Early
- ✓ The number of prevented tumors is similar for Chronic and Genetic protocols

Cancer Res. 70, 24: 7753 (2010)

The validation experiment: immune mechanisms



Chronic protocol:

- ✓ Early vaccination elicited a rapid increase in antibody titers.
- ✓ High and steady antibody level.
- ✓ After the and of vaccination gradual decrease in antibody titers.

Early protocol:

- ✓ Antibody levels decrease precede the onset of mammary carcinoma.

Heuristic protocol:

- ✓ Reached the plateu several weeks later.

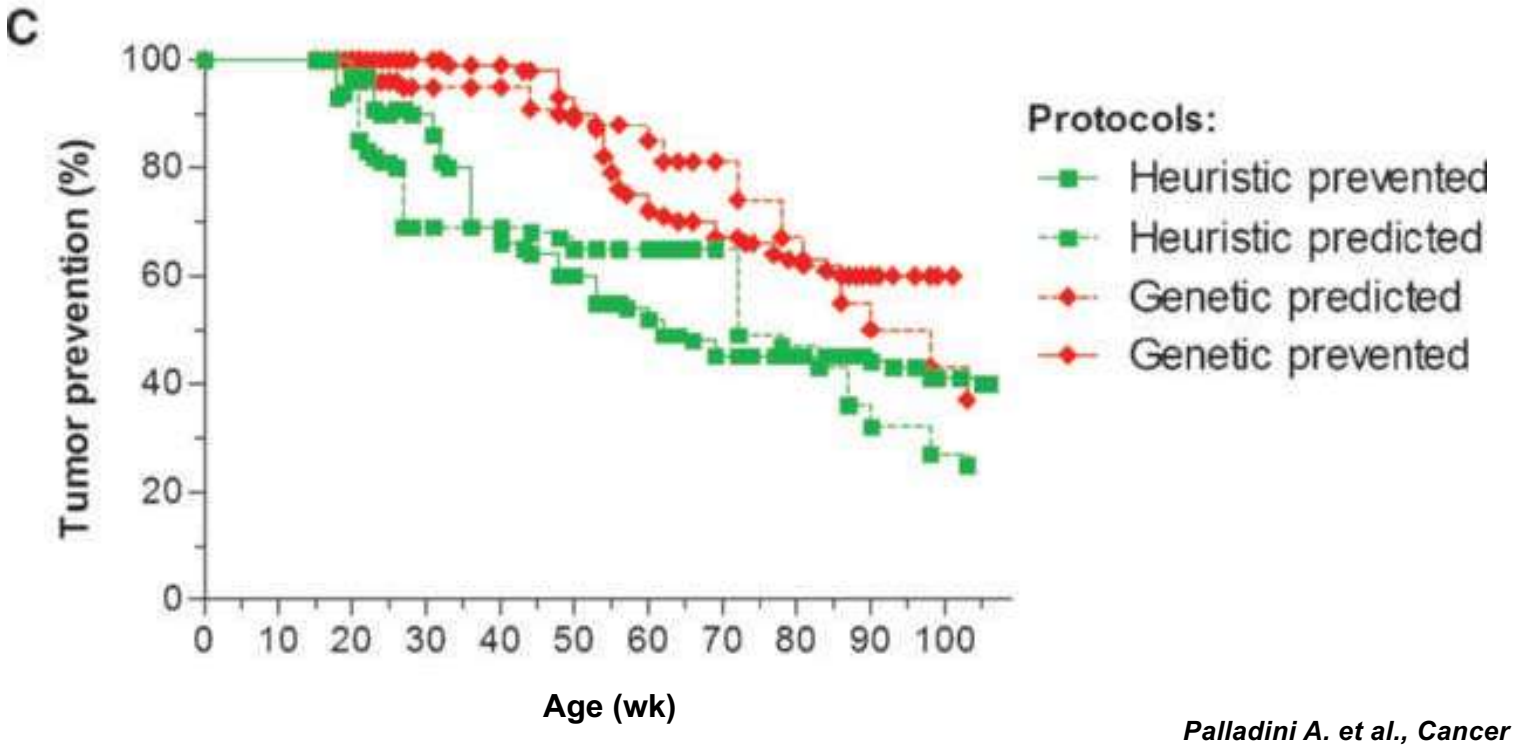
Genetic protocol:

- ✓ Comparable with Chronic but induced a less efficient early antibody response.

Cancer Res. 70, 24: 7755 (2010)

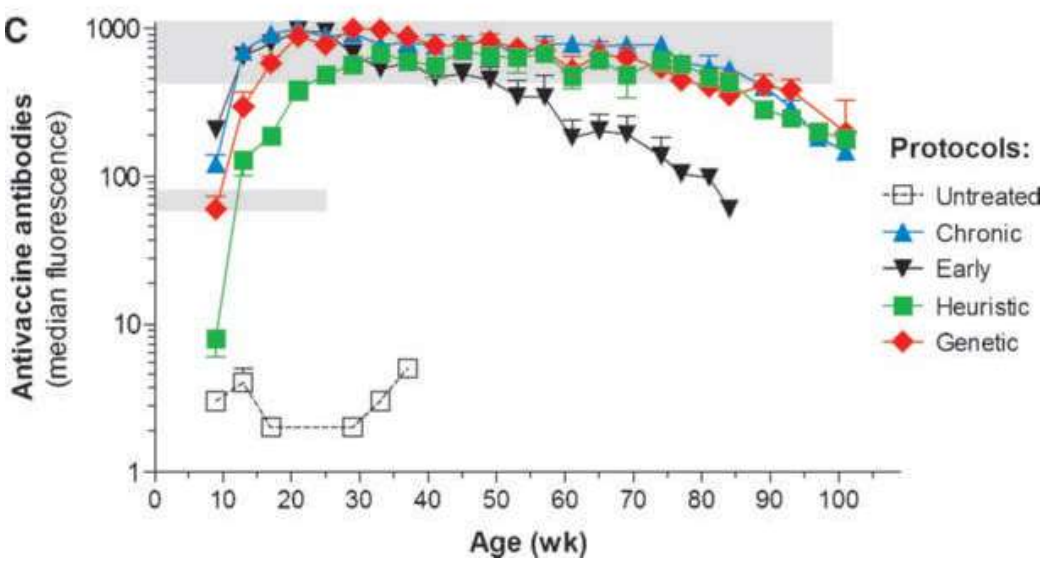
The validation experiment: prediction of prevented tumors

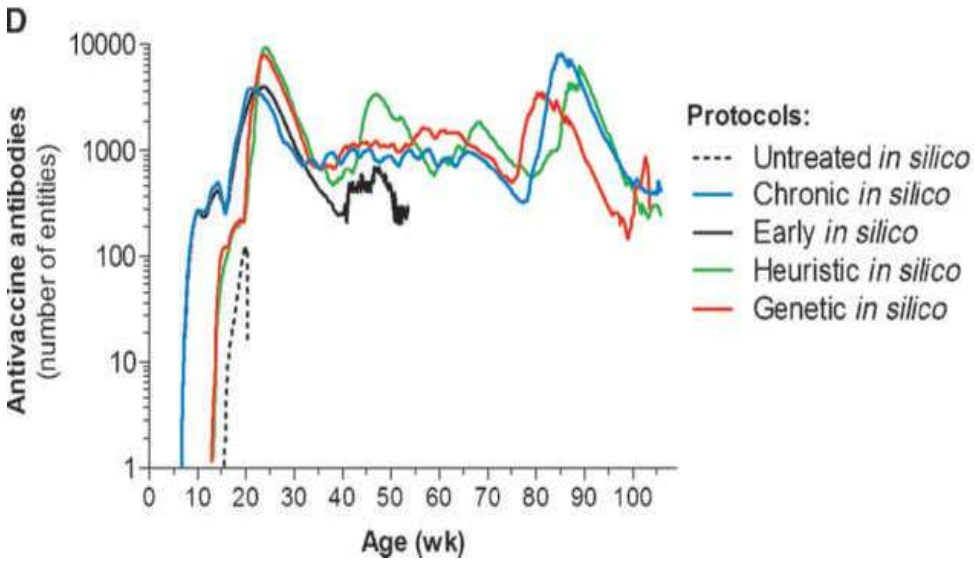
The kinetics of prevented tumors was in good agreement with the predicted efficacy



Palladini A. et al., Cancer Res. 70, 24: 7755 (2010)

The validation experiment: prediction of antibodies levels





Long-term decrease in antibody levels *in vivo* **was mirrored** by that predicted by the simulator.

Cancer Res. 70, 24: 7755 (2010)

The validation experiment: conclusions

- **Vaccine efficacy**: periodicity not required, temporal distribution key role. Intensified vaccination protocols with more vaccine administrations in the initial phases.

- Use of antibody titers to seek a better correlation with the corresponding *in vivo* results and with predicted tumor-free survival.

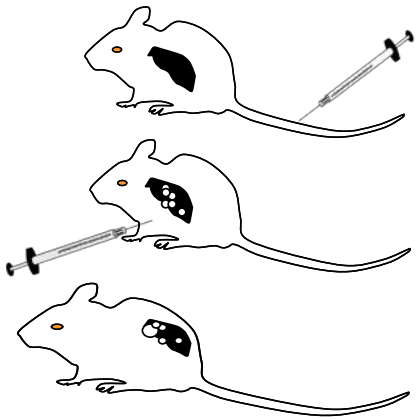
- Correlation between early antibody response and long-term tumor-free survival: shorter *in vivo* experiments to test new vaccination schedules in just 3 to 4 months.

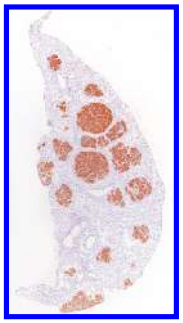
NOT ONLY PRIMARY TUMORS: VACCINE AGAINST MICROMETASTASES

Syngeneic tumor cells i.v. — Day 0

Triplex vaccine i.p. — From Day +1/+7

Evaluation of lung metastases — Day +33





Untreated **Vaccinated**

Nanni et al., Cancer Research 2007

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]

BMC Bioinformatics. 2022 Nov 16;22(Suppl 14):631. doi: 10.1186/s12859-022-05038-6.

Evaluation of word embedding models to extract and predict surgical data in breast cancer

Giuseppe Sgroi [1], Giulia Russo [2], Anna Maglia [3], Giuseppe Catanuto [3 4], Peter Barry [3], Andreas Karakatsanis [3], Nicola Rocco [3]; ETHOS Working Group; Francesco Pappalardo [5]

Affiliations + expand

PMID: 36384559 PMCID: PMC9667561 DOI: 10.1186/s12859-022-05038-6

Free PMC article

The proposed methodology has increased the usefulness of Delphi surveys favoring the extraction of keywords that can represent a specific clinical context. It permits the characterization of the clinical context suggesting words for the evaluation process of the data.

Breast. 2016 Oct;29:74-81. doi: 10.1016/j.breast.2016.06.004. Epub 2016 Jul 28.

Formal analysis of the surgical pathway and development of a new software tool to assist surgeons in the decision making in primary breast surgery

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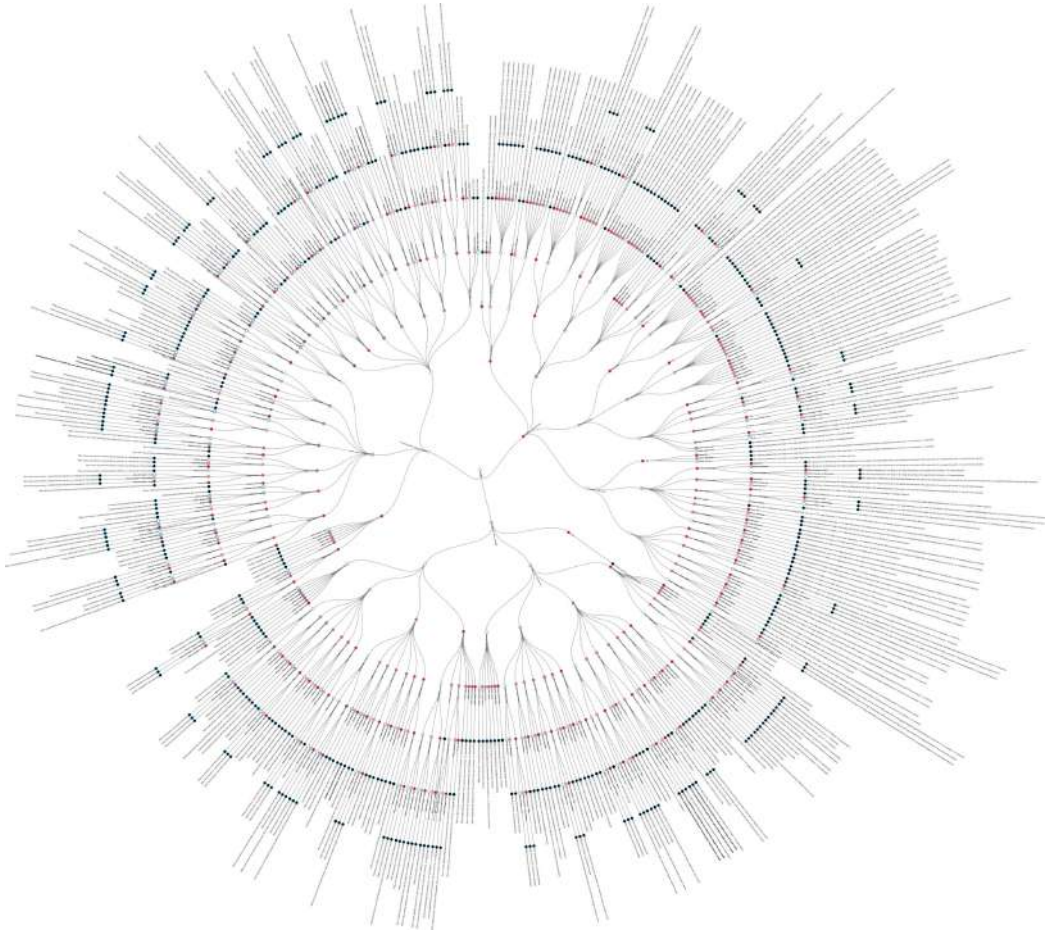

The complexity flower!