Stochastic Simulation of Biological Systems

G. Caravagna
Department of Computer Science
University of Pisa

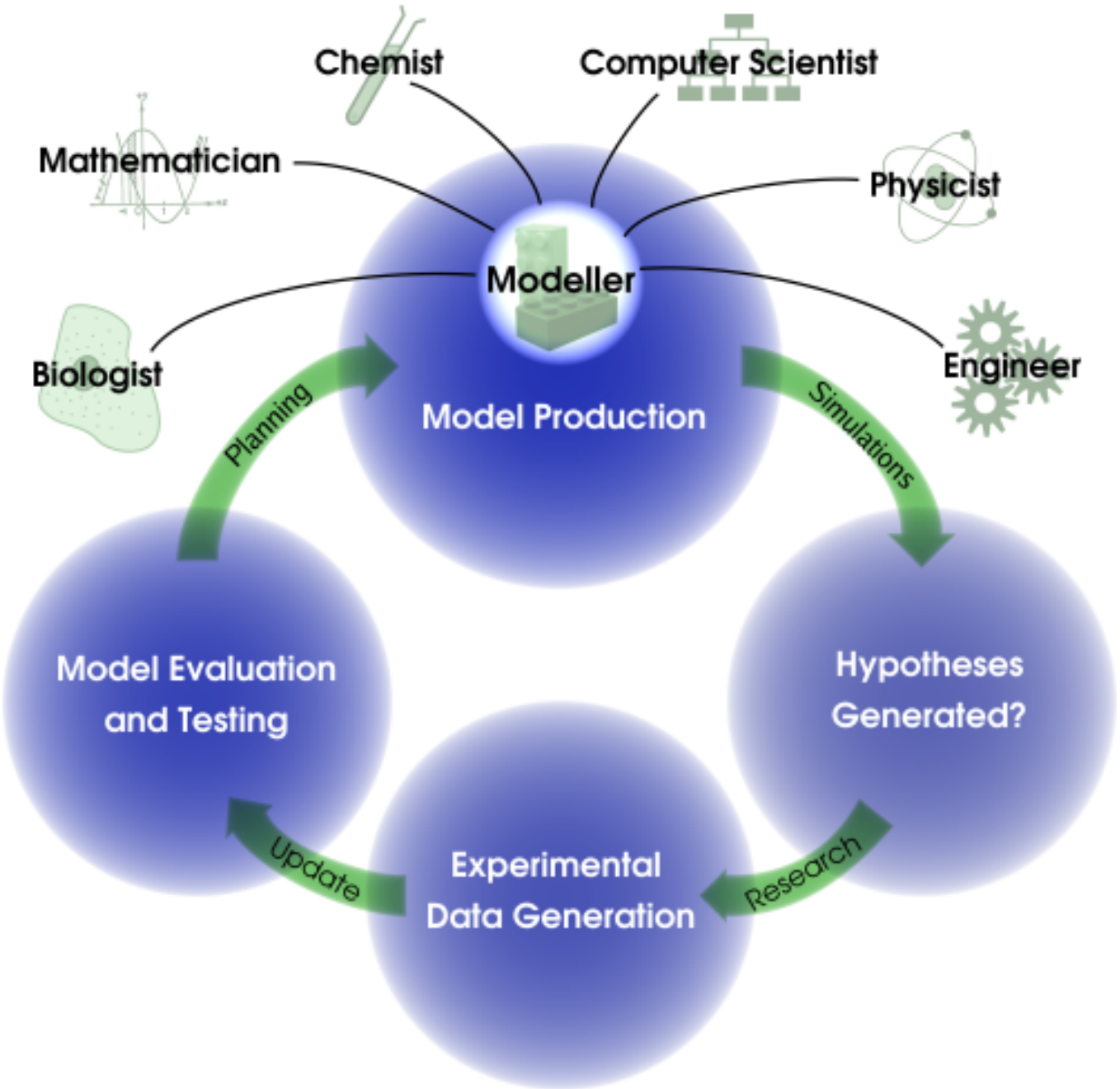
Joint Workshop IEO–University of Pisa
Milan, 2009

Some "Spontaneous" Questions

1. Why simulations?
2. What is a stochastic simulation?
3. Which are the dis/advantages of this approach?

Question ♯1

Why simulations?


Chemist
Computer Scientist
Mathematician
Physicist
Modeller
Biologist
Engineer
Planning
Model Production
Simulations
Model Evaluation and Testing
Hypotheses Generated?
Update
Experimental Data Generation
Research

Methods from Mathematics

Deterministic Models as *differential equations*:

- describe the variations of *concentrations*;
- the terms of the equations *model* the observed events.

Advantages:

- well–founded theory (since Newton, Leibiniz);
- many analysis techniques;

Disadvantages:

- a continuous approach (concentrations) which is not suitable for systems dealing with small concentrations.

Question ♯2

What is a Stochastic Simulation ?

The Gillespie Stochastic Simulation Algorithm (1970)

Given a model composed by:

- some *species* (i.e. molecules, cells, pop. individuals, ..)
- some *reaction channels* (i.e. chem. reactions, intra-cellular events, ..):
- a clock;

repeat:

1. compute the probability of each reaction;
2. choose the stochastic time instant for the next reaction;
3. choose the the next reaction that will happen;
4. update the model (clock and species).

Question ♯3

Why a Stochastic Simulation ?

Stochastic Simulation: motivations

Advantages:

- is *exact* (number of molecules)
- under *reasonable* conditions
  - "small" number of molecules;
  - oscillating behaviours;

  stochastic models exhibit behaviors observable in the real biological systems but not in the deterministic counterpart.

Disadvantages:

- as it is exact the simulation is slower than the deterministic one;

Your Question

Some Examples ?

Tumor–Immune System interaction (with A.D'Onofrio)

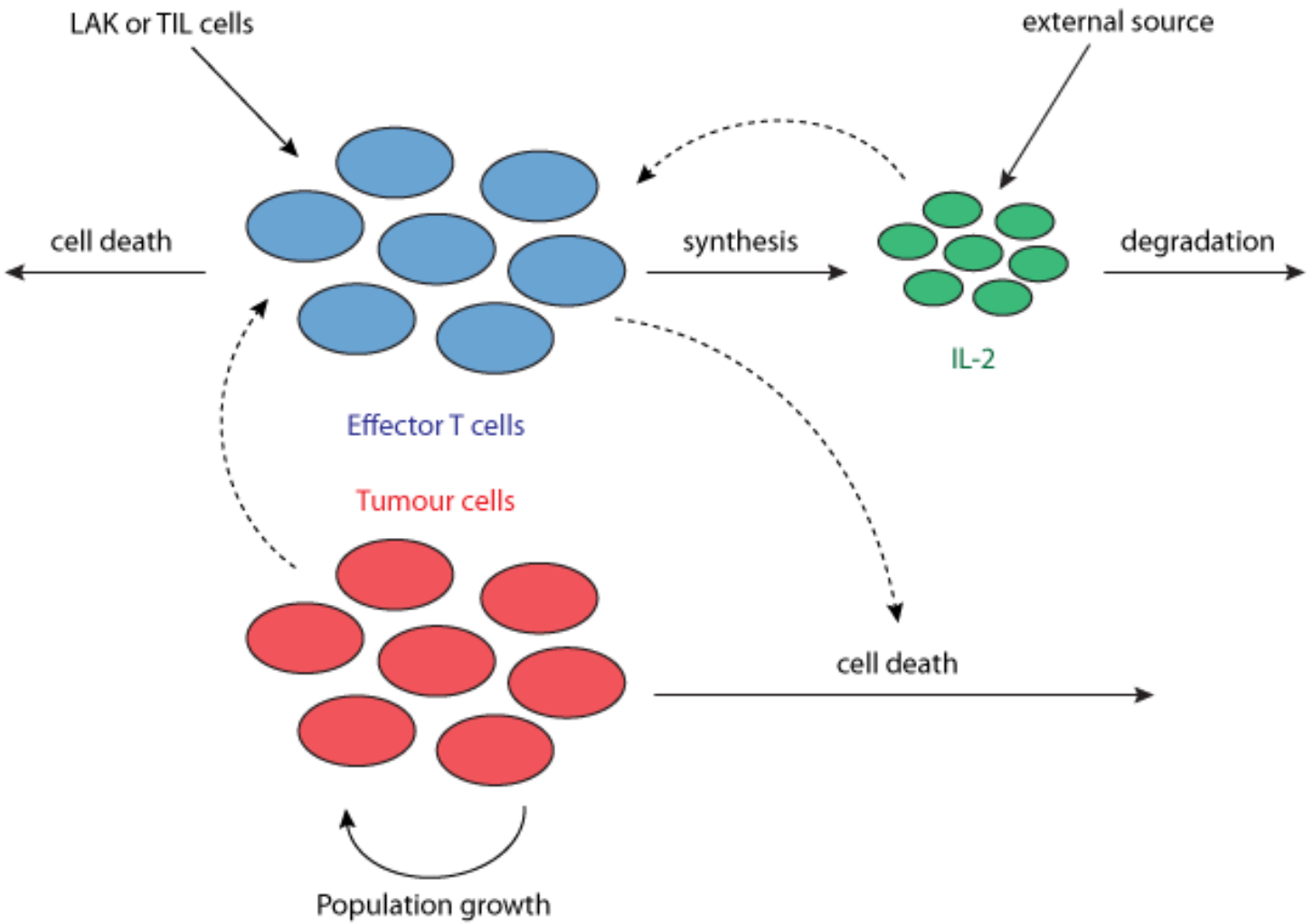
Three populations:

- activated immune–system cells (*effectors*);
- *tumor* cells;
- interleukine IL-2.

Expected behavior for tumor cells:

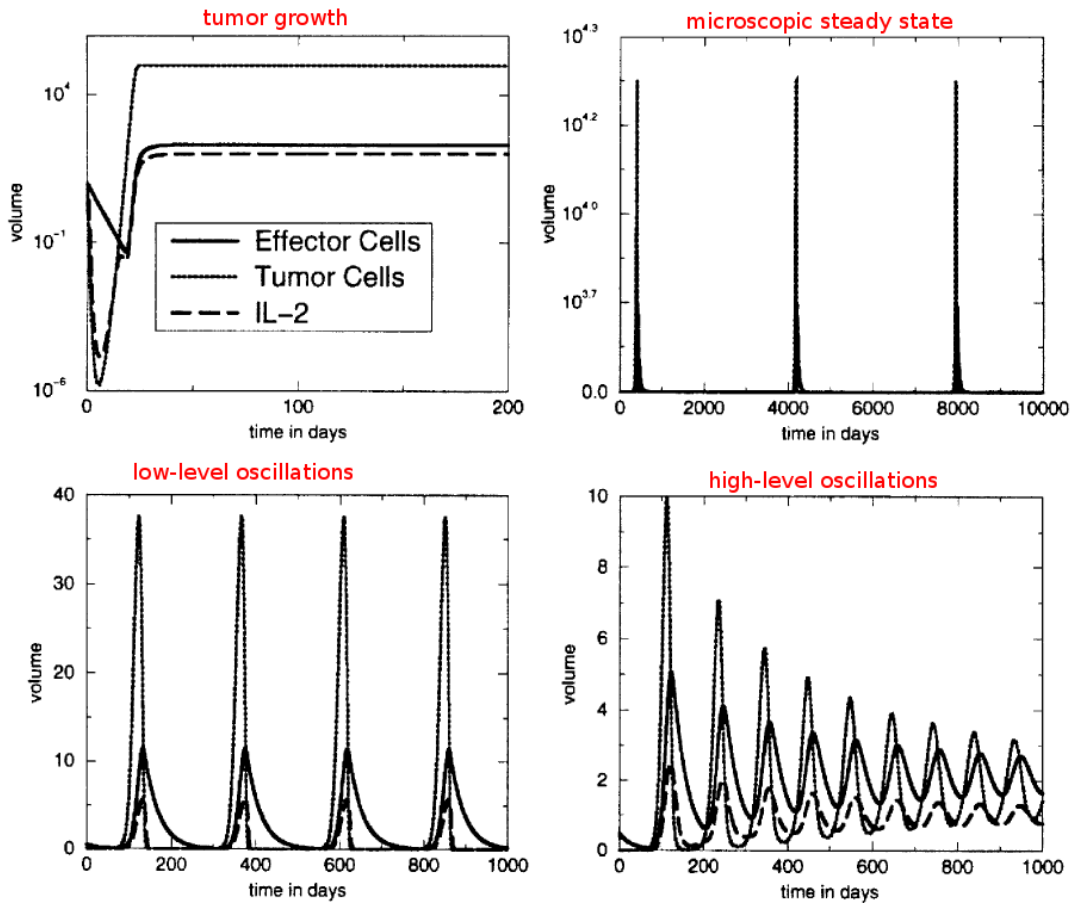
- bounded growth;
- microscopic steady state with sudden re–growth;
- alternation of dormiant/re–growth (oscillations);
- suppression by the IS.

Tumor–Immune System interaction (with A.D'Onofrio)



Tumor–Immune System interaction (with A.D'Onofrio)

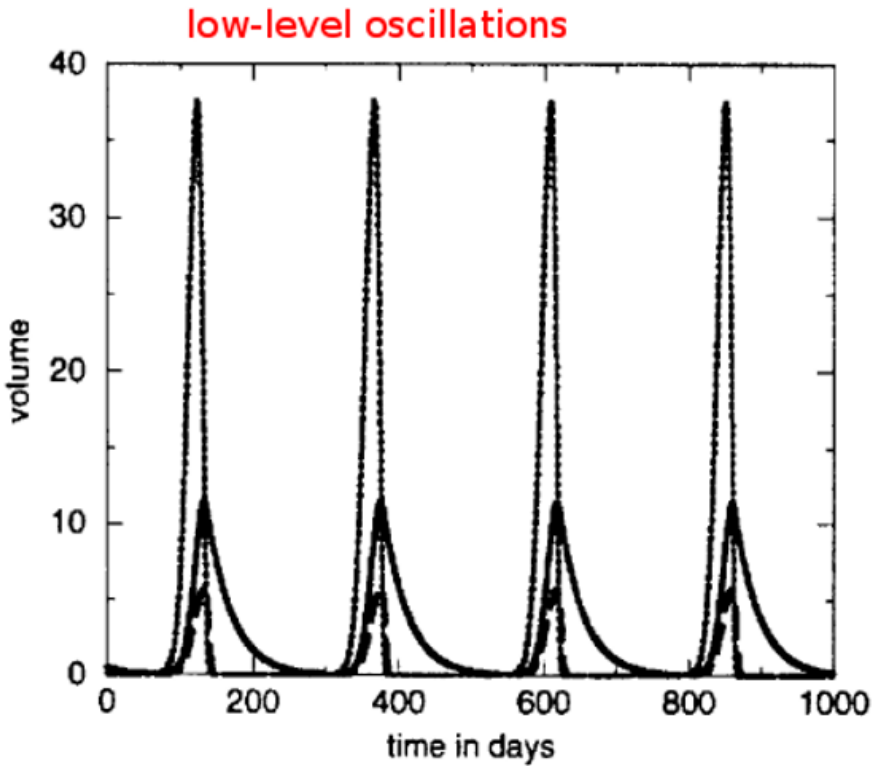
Deterministic model (Panetta–Kirschner, 1998) with variation of IS response

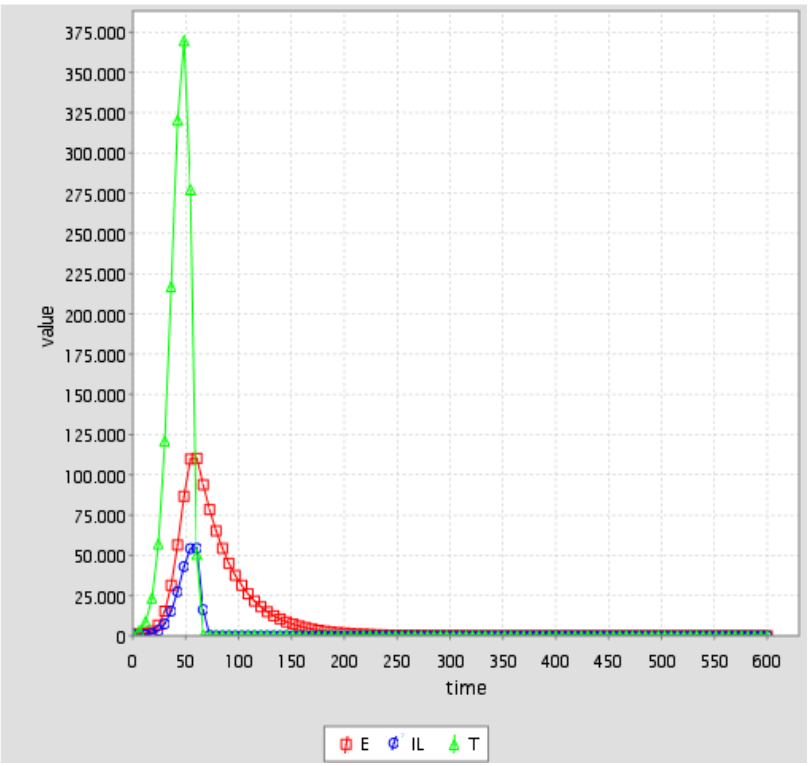


shows no tumor suppression.

Tumor–Immune System interaction (with A.D'Onofrio)

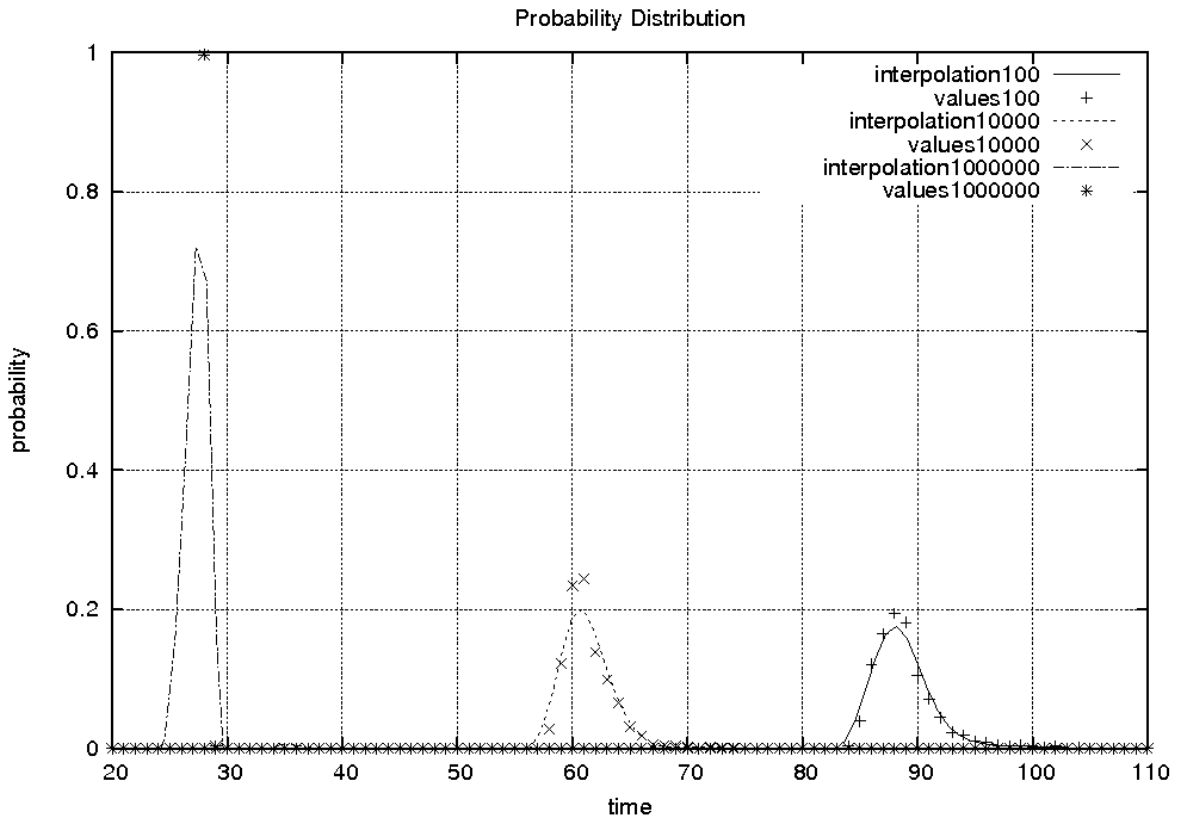
Our stochastic model shows always the same behavior but in this scenario (oscillations approaching 0) shows tumor suppression!





Tumor–Immune System interaction (with A.D'Onofrio)

Sample analysis: in that scenario, given different number of intial effectors, which is the probability observing the suppression at a given day?



A few more words on the modelling

One key problem in defining models is that exact simulation requires a *complete* knowledge of *all* the dynamics.

For instance, in the modeling of biochemical systems:

- reactants/products of each reaction;
- exact kinetic constants;

Unfortunately, not all this data is always avalaible.

Sometimes, it is possible to observe a minimum time quantity such that an event completes.

A complex dynamics (i.e. cell cycle) too hard to be exactly modeled can be *abstracted* with its duration.

Partially overcome the incompleteness data:

- more complex simulation techniques;
- as before, both deterministic and stochastic models.