University of Milan
Department of Physics

Overshoot of cancer stem cell population

A theoretical model via rate eq. and stochastic simulations

21th October 2016

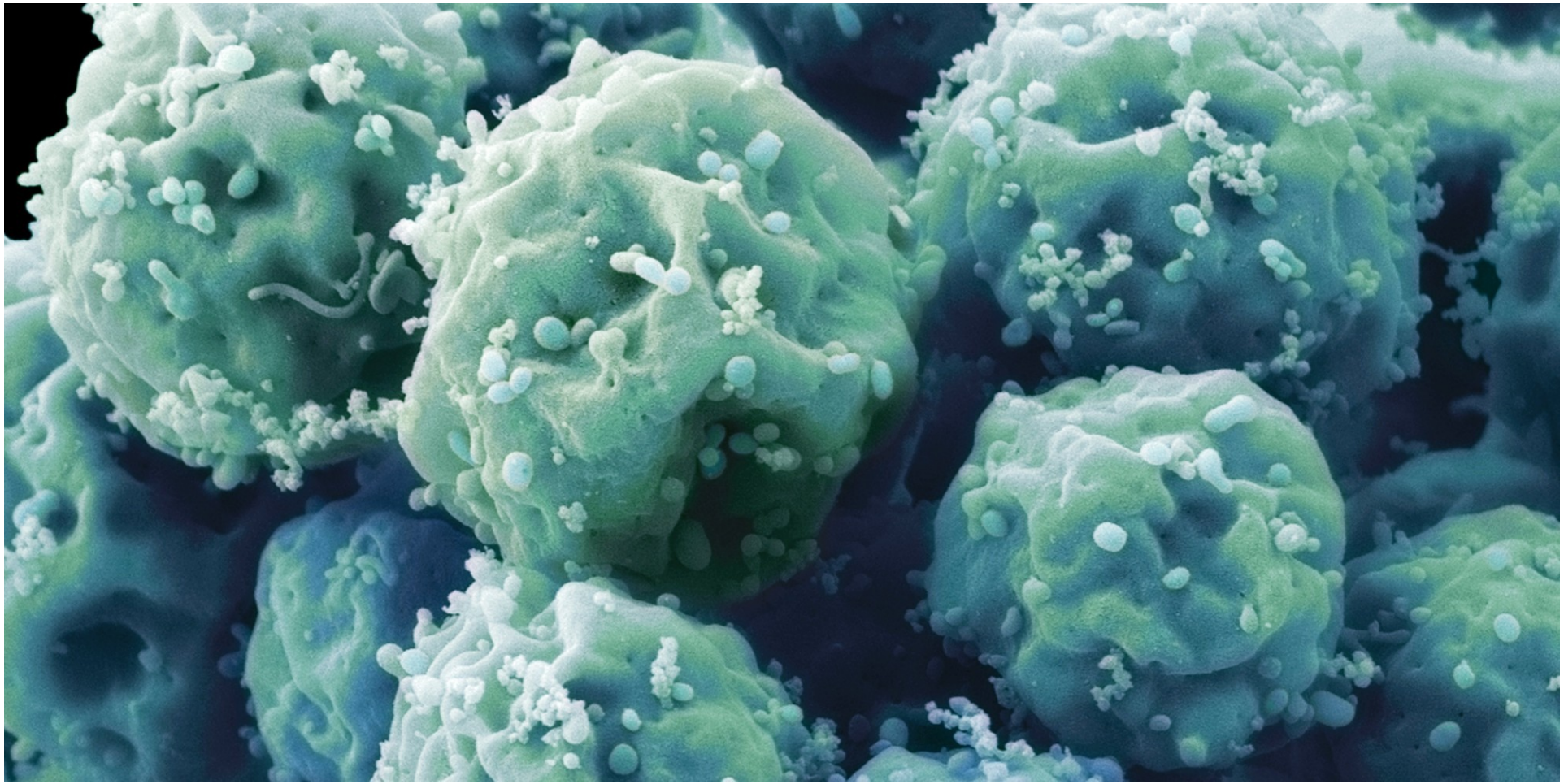
-Milan

Filippo Cola

WWW.COMPLEXITY.UNIMI.IT

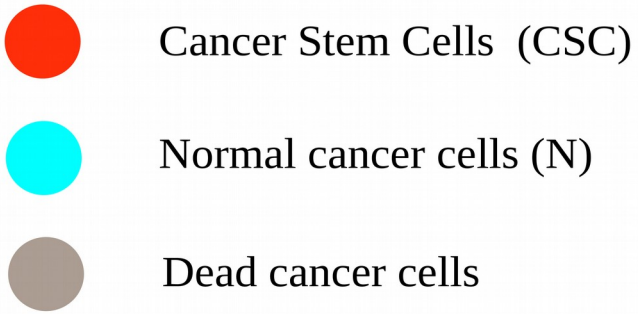
Unusually for physicists, the main protagonist of our talk shall be biological cells… in particular

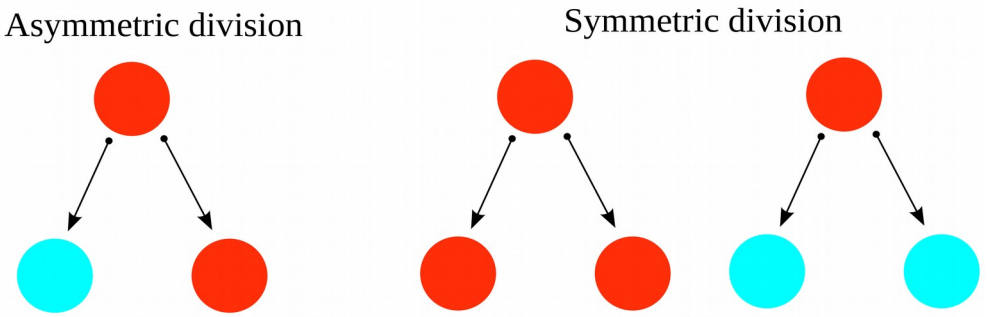
CANCER STEM CELLS (CSC)

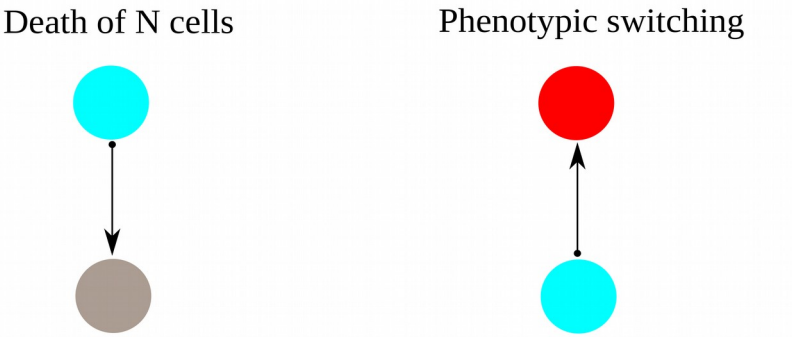


The Bayer Scientific Magazine

Aberrant CSC Hierarchy Theory for Tumor Growth







- only small fraction of malignant cells drives tumor growth (stem cell like);

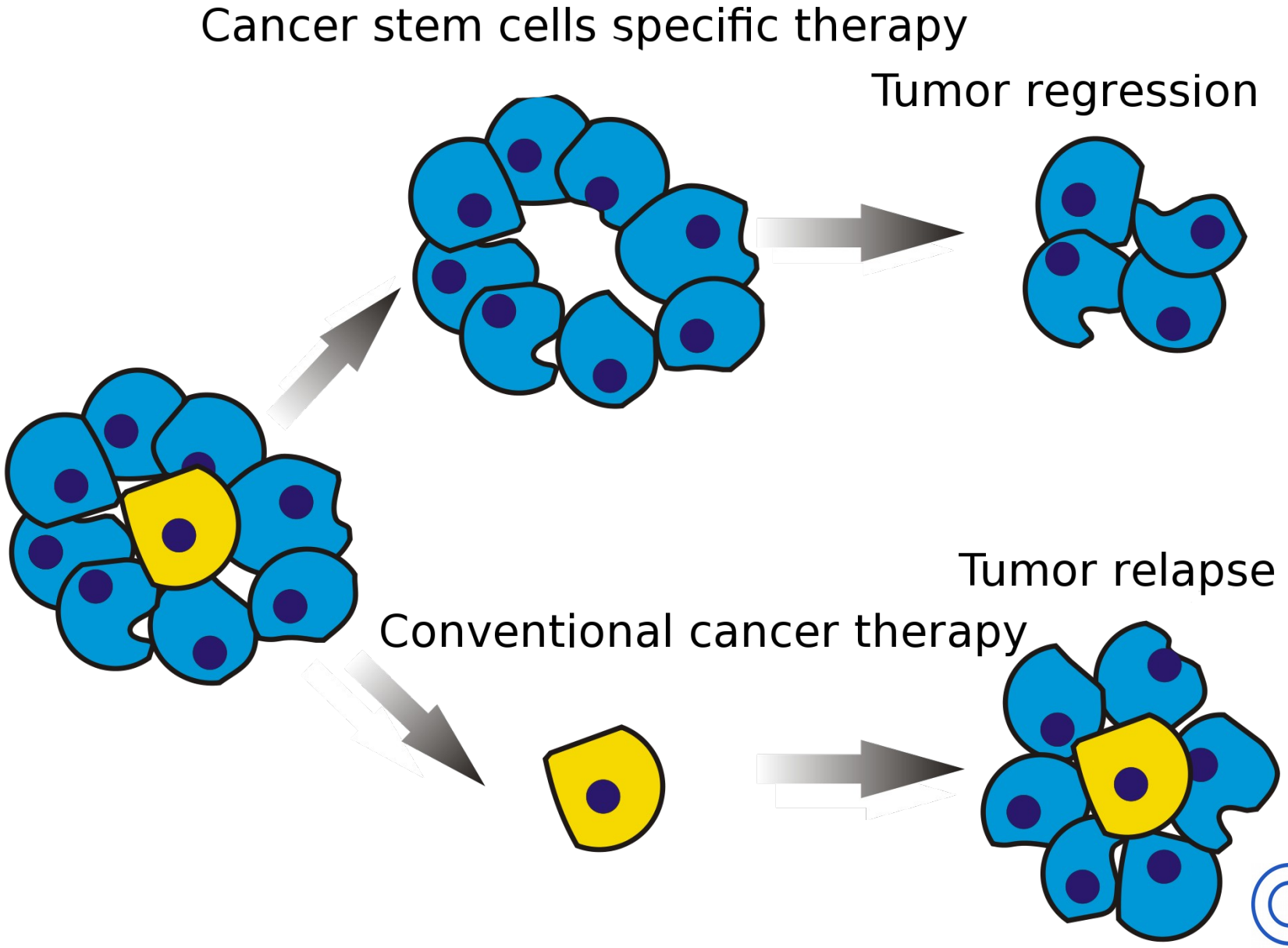
- CSC prop.: self-renewal, differentiation into multiple cell types, longer life span;

- origin not clear;

- first identified in leukemia, then also in brain, breast, colon, pancreas cancers and melanoma.

CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

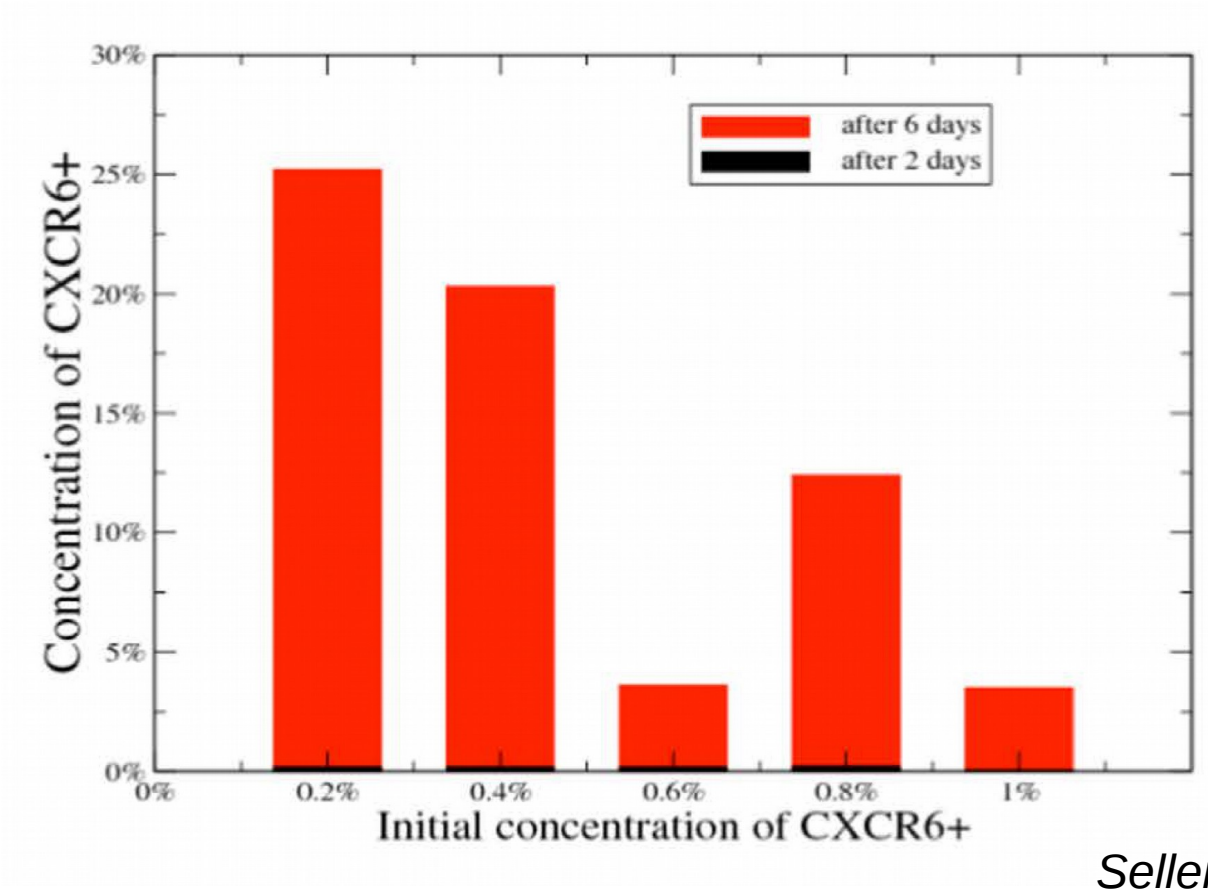
The hierarchy model suggests a specific therapy to eradicate CSC population



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

Howewer, experiments performed by La Porta's Group in the Department of Biosciences suggest this may not always be the case

Observed Overshoot of CSC Population in a Melanoma (initially reduced under 1% of total)

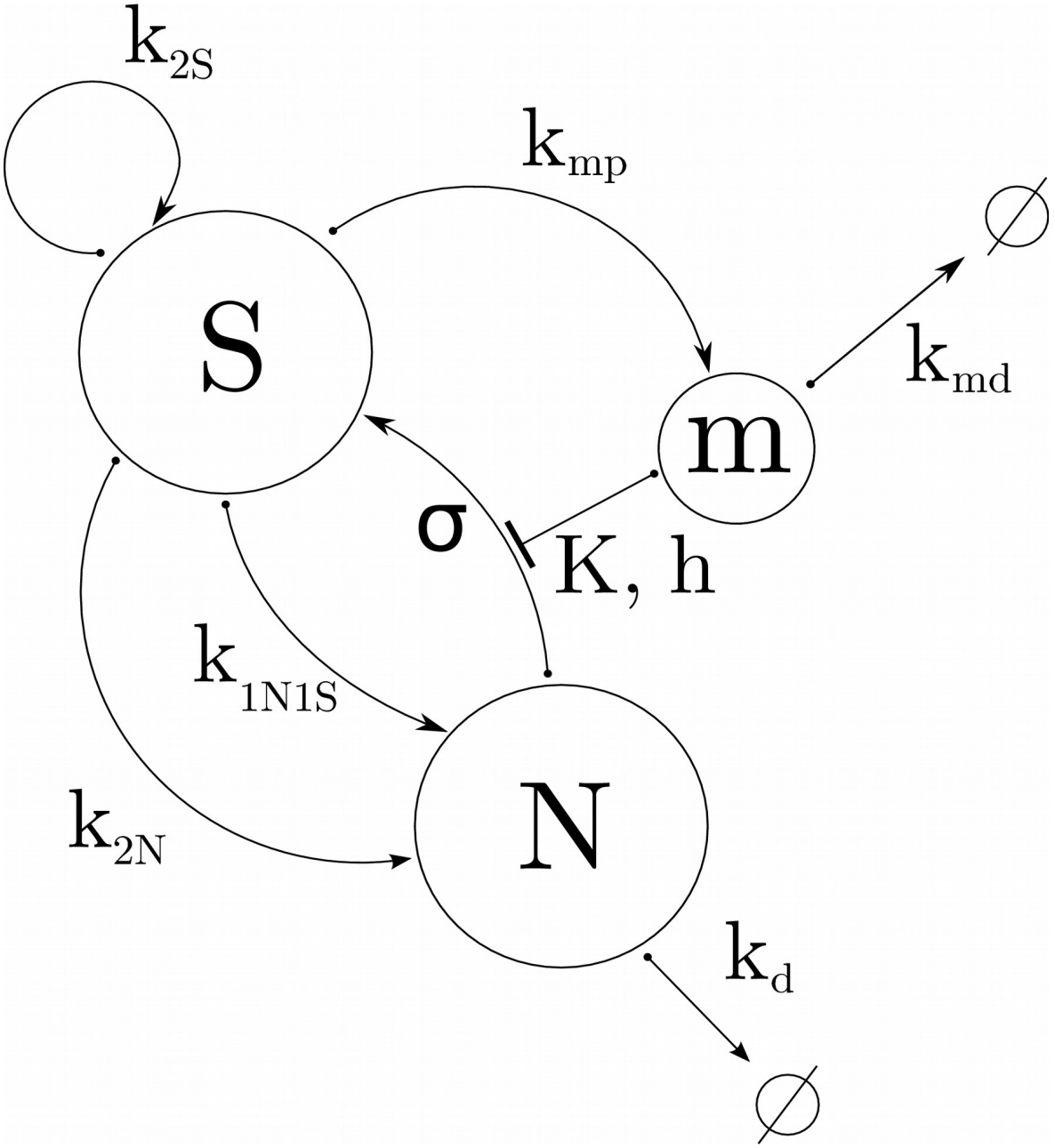


Sellerio et al., Sci. Rep., 2015

The fraction of CSC grows from less than 1% of total cells to a maximum of 25% after some days and then decreases to a steady value.

CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Reaction Network of the model



CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Model 1: Rate Equations

Initial Values: $m(0) = m_0$, $S(0) = S_0$, $N(0) = N_0$.

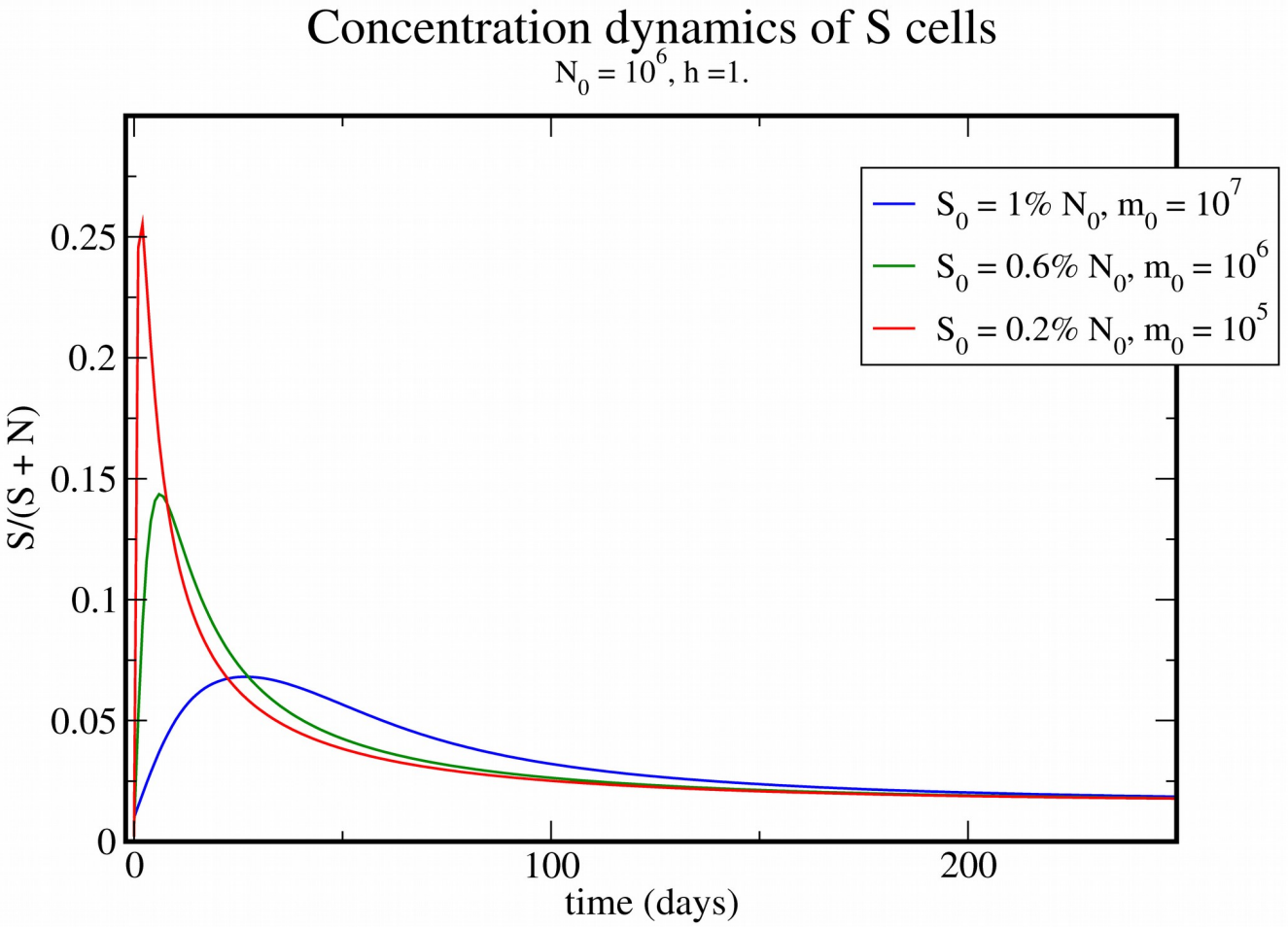
$$\begin{cases} \dot{m} = k_{np}S - k_{nm}m \\ \dot{S} = (k_{2S} - k_{2N})S + \sigma N\left(1 - \frac{m^h}{k^h + m^h}\right) \\ \dot{N} = (2k_{2N} + k_{1N1S})S - \left(k_d + \sigma\left(1 - \frac{m^h}{k^h + m^h}\right)\right)N \end{cases}$$

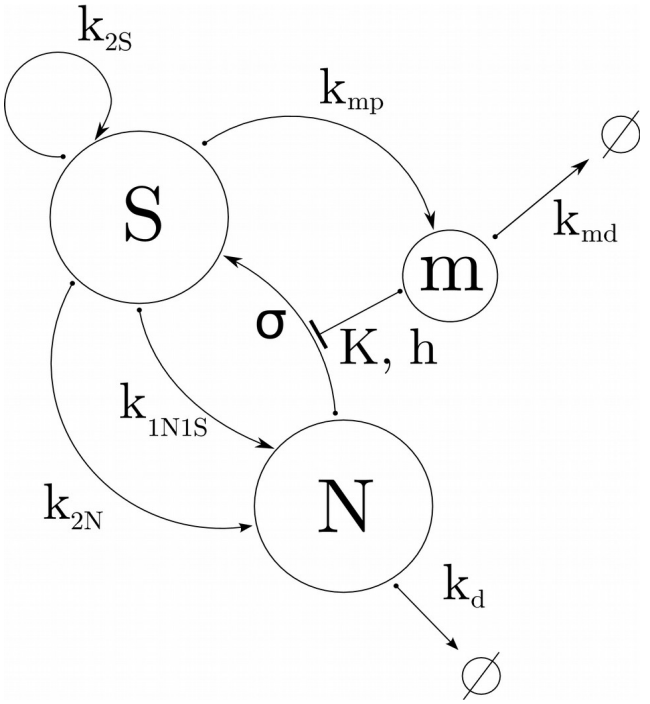
- Simple model;
- presence of many unknown parameters.

CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Model 1: Rate Eq. Output

We are interested in the dynamics of $\frac{S}{S+N}$

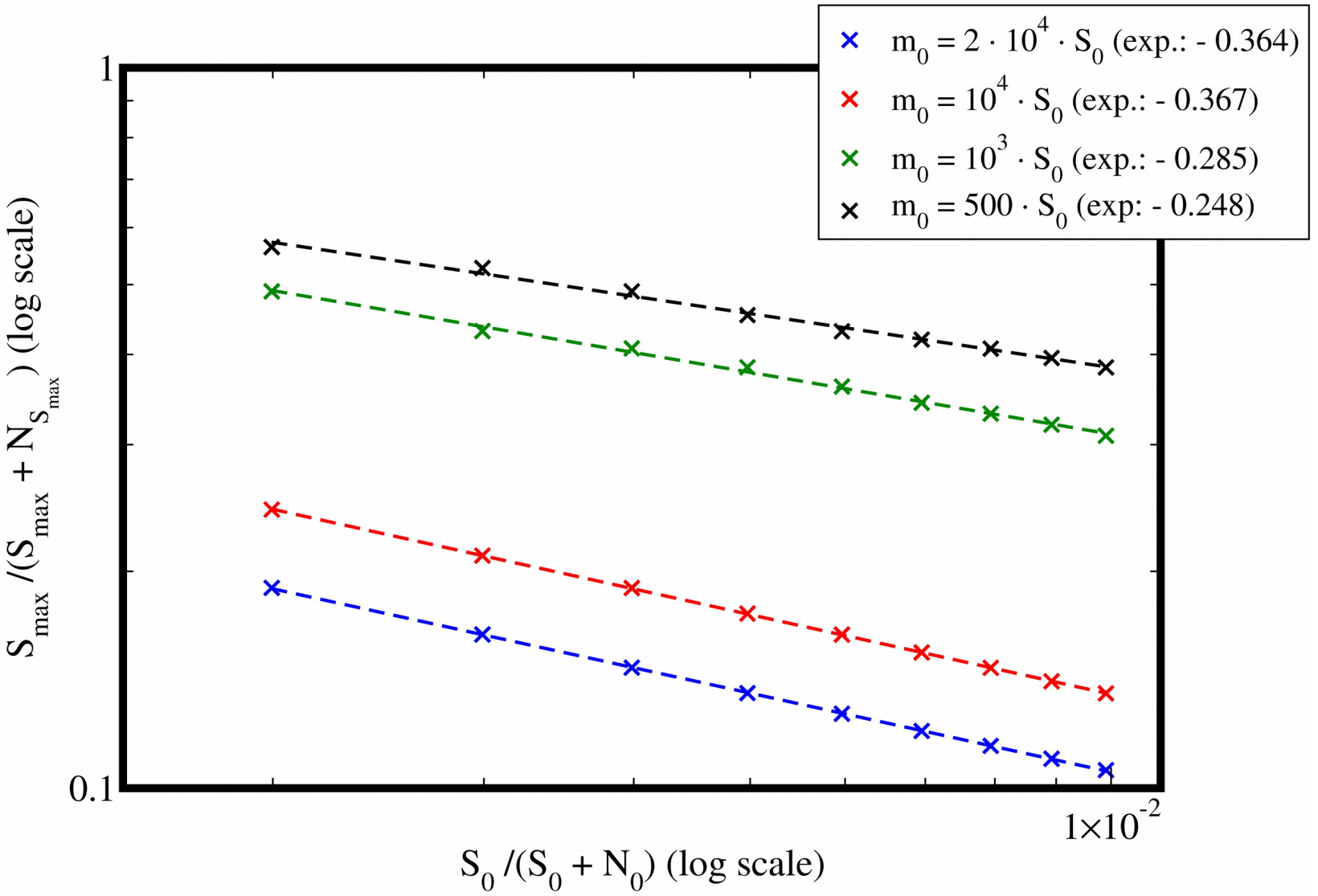




Additional hyphothesis:
removal of S cells causes a removal of a certain amount of *m*

CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Power law for maxima of concentration of S cells with respect to initial concentration (for different ratios S_0/m_0)



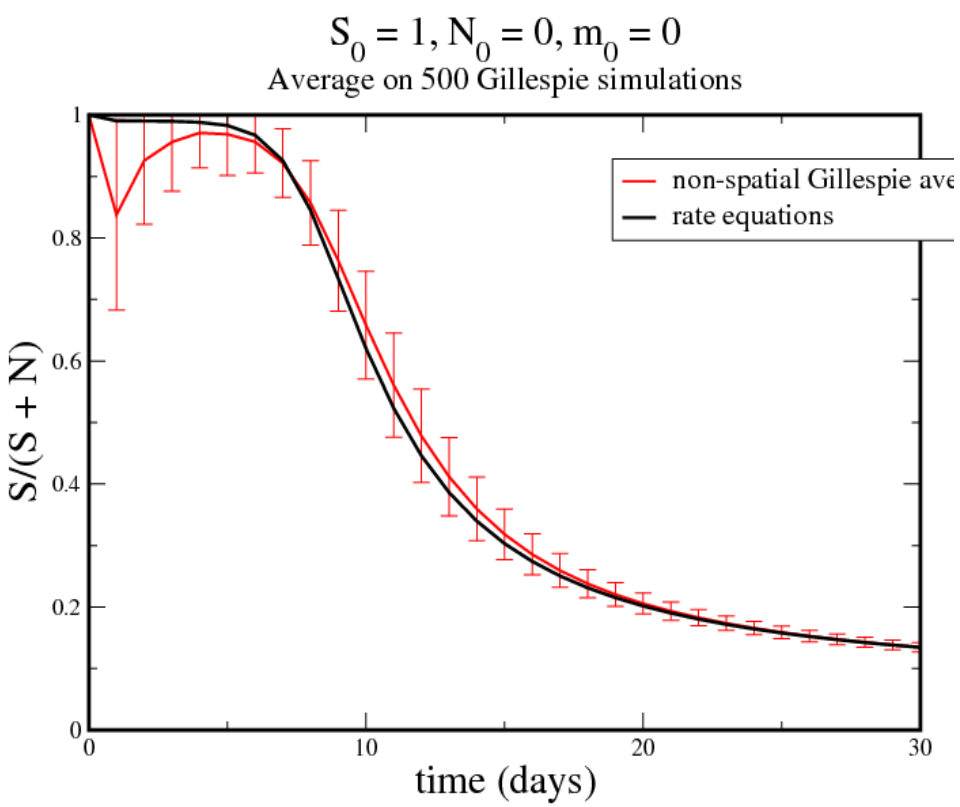
CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

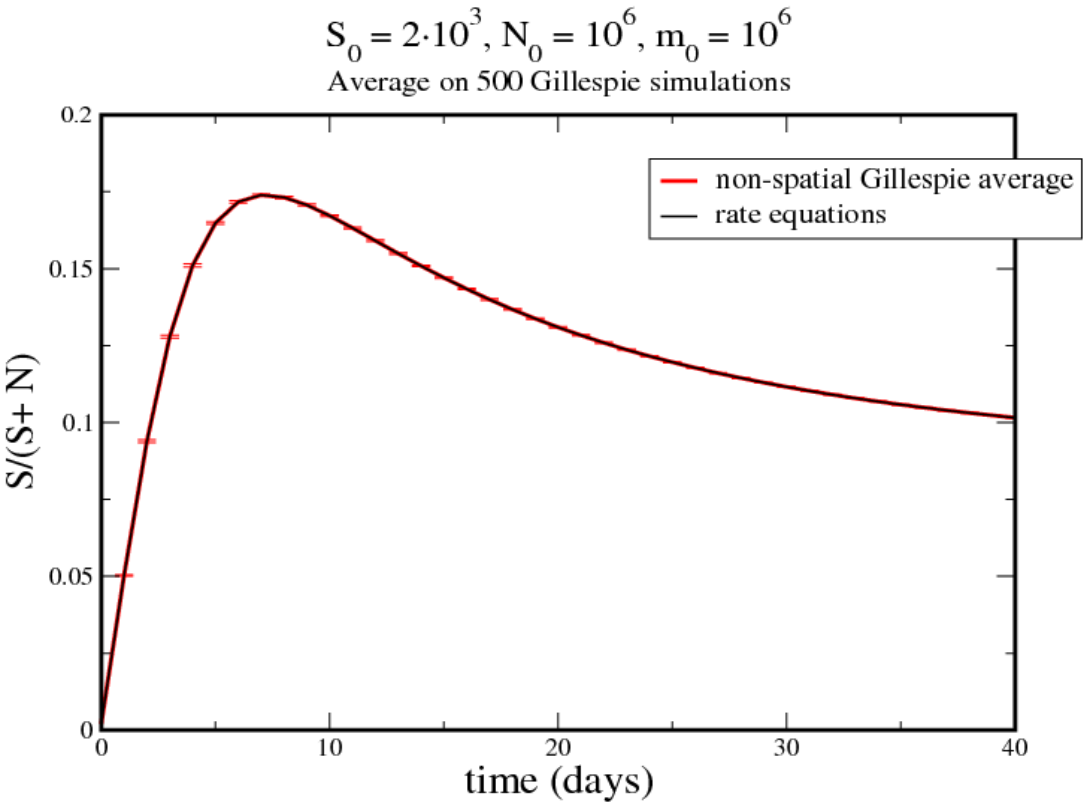
To improve our model, consider as a first step:

- the discrete nature of cells and molecules;
- possibility of reactions with low number of cells and molecules involved (failure of well-mixed system hyphothesis in most biochemical systems);
- stochastic noise in biochemical reactions.

This lead to modeling the proposed reaction network via the non-spatial Gillespie algorithm (computational consistent solution of the chemical master equations).

Model 2: Gillespie average vs rate equations

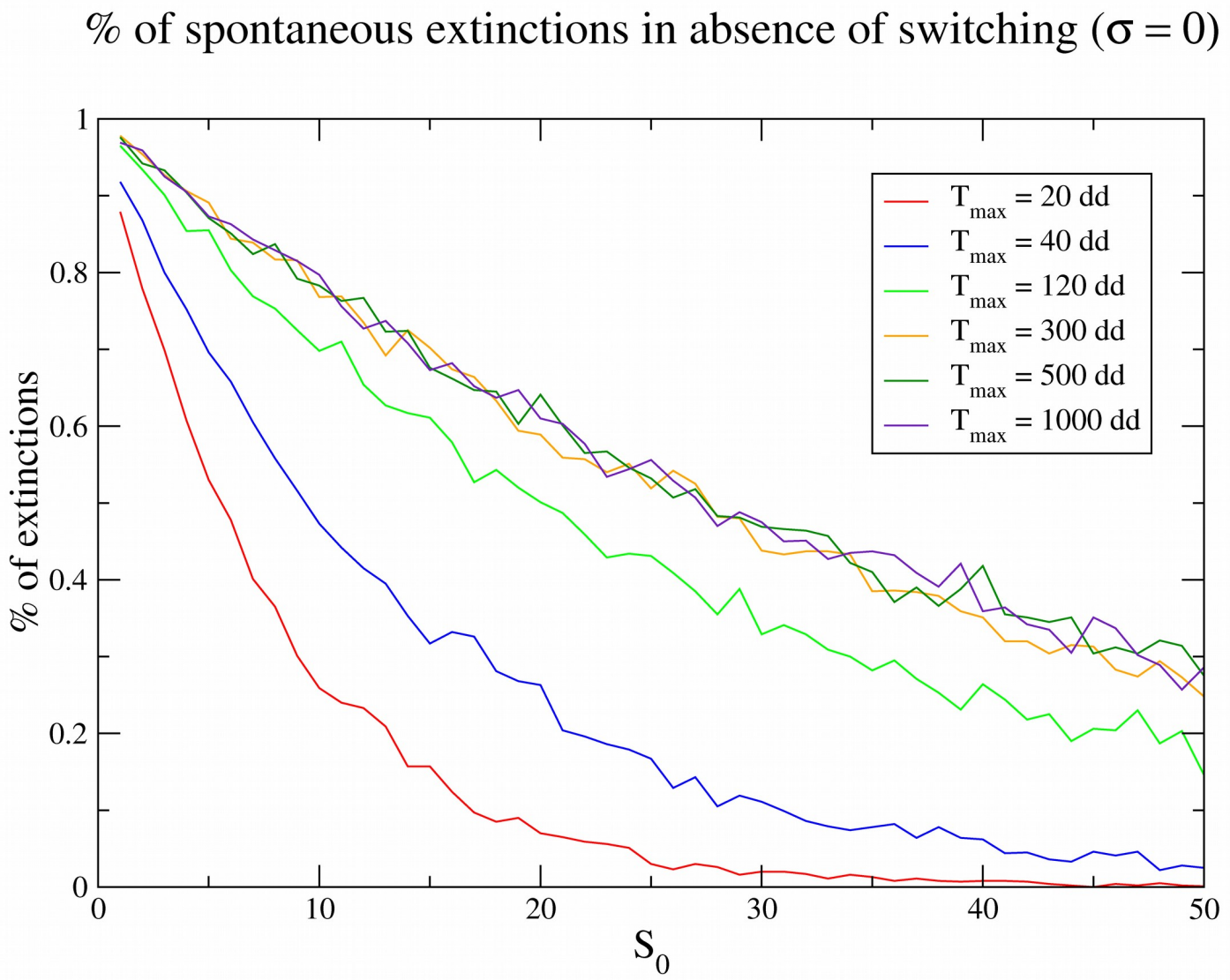




For high rates of spontaneous extinction of S cells dynamics, averages shall not match rate equations (intrinsic stochastic nature of the system).

C&B CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Spontaneous extinction of tumor dynamics in absence of switch (small $\varepsilon = k_{2S} - k_{2N}$)



CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Next step: modeling in space

– Phenotypic switch dependent on local cell--molecule interactions;

– molecule *m* are produced in S cells sites and then diffuse;

– Effects of crowded environment on cell division rates.

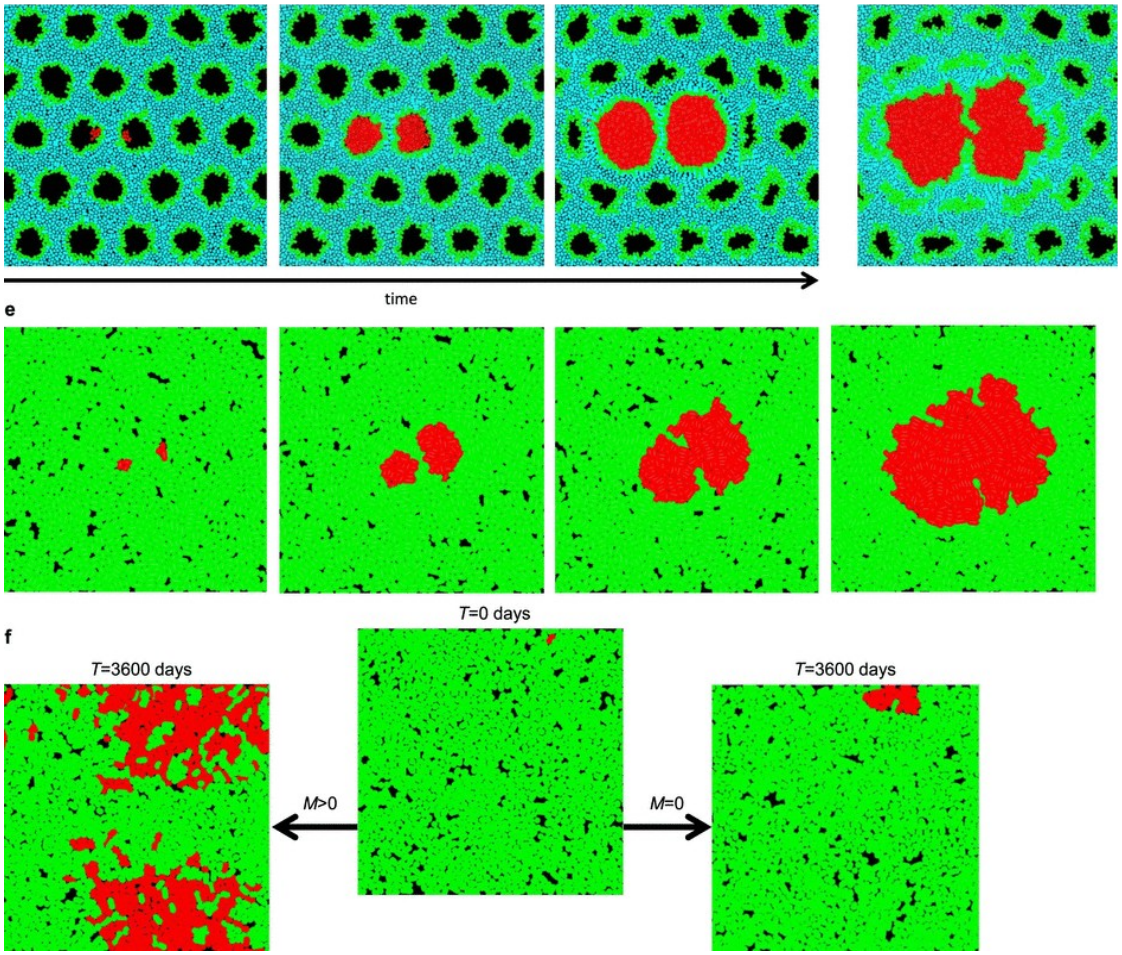
C&B CENTER FOR COMPLEXITY & BIOSYSTEMS
University of Milan

Future Developments: Spatial Gillespie (2d and 3d)

– Role of diffusion of molecule *m;*

– Stochastic fluctuations in space;

– Detection of spatial patterns to match images observed at the microscope.



Waclaw et al., Nature, 2015.