Ensemble Boolean modeling: example of a model of tumor invasion

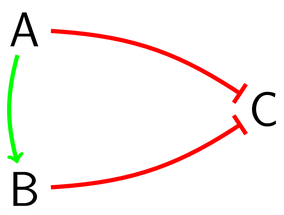
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Introduction

The construction of a mathematical model can give rise to a multitude of models, all in accordance with a set of constraints derived from experimental evidence. However, to simulate the behavior of these models, some choices have to be made, risking the introduction of some bias. We propose here a methodology that allows the simulation of sets of models without having to select one of them. We refer to it as ensemble boolean modeling.

Motivation



- A : *input*
- $B : A$
- $C : \begin{cases} !A \ \& \ !B \\ !A \mid !B \end{cases}$

There exist multiple models for a given regulatory graph (in the alongside example, there are already two possible models!). The classic approach would be to select one according to some criteria, at the risk of introducing a bias.

⇒Why not use all of the models, or, a least, a representative subset of them?

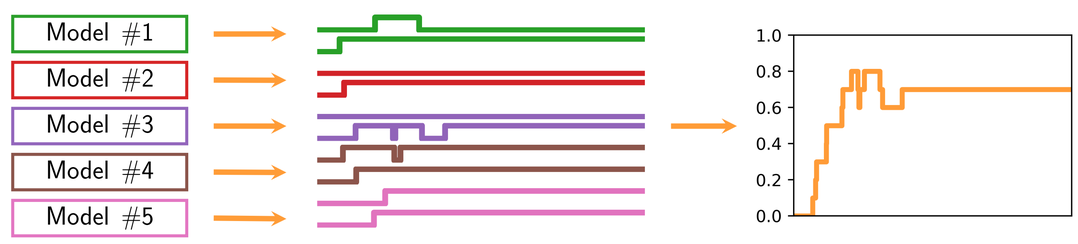
Building ensemble

We encode our knowledge of the biological system in the form of constraints, and use Answer-Set Programming (ASP) to produce models satisfying these constraints[1].

- Interaction signs between model components
- Fixpoints existence (and absence of others)
- Reachability or non-reachability of these fixpoints from a set of initial conditions

If the space of possible models is too large to be enumerated, we select a diverse subset, which should be representative of the whole ensemble.

Simulator

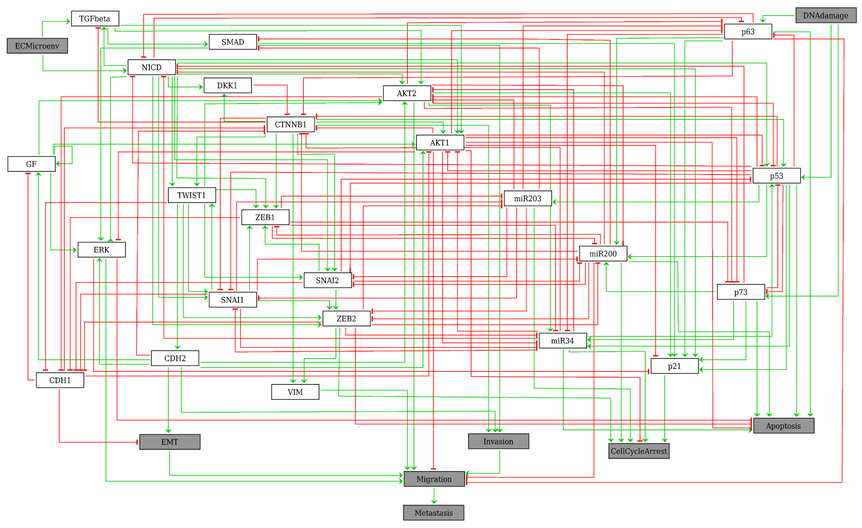


Using MaBoSS[2] (Markov Boolean Stochastic Simulator), we can simulate efficiently a large number of models. MaBoSS produces stochastic trajectories, from which we generate the dynamics of the network state probability distribution.

Example: Comparison with Cohen's tumor invasion model

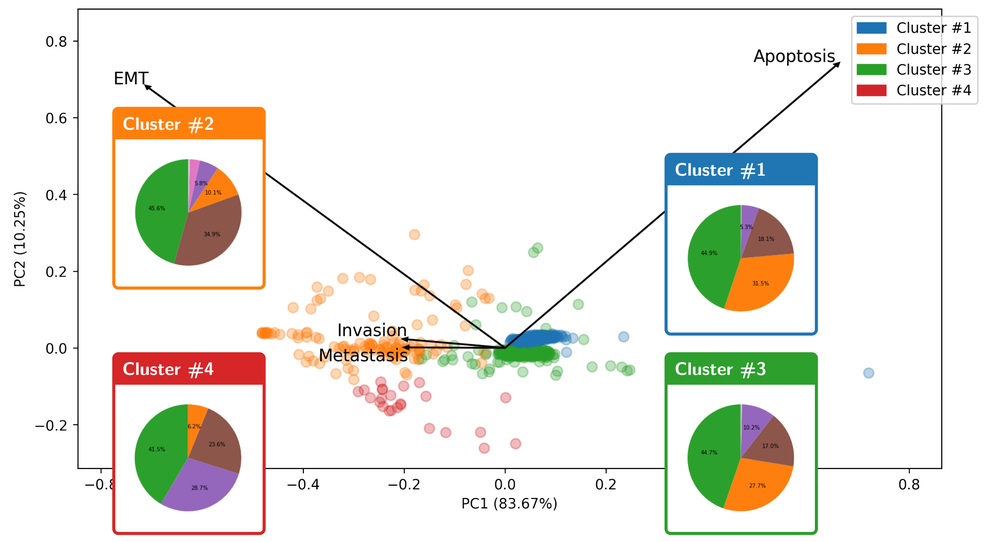
We build an ensemble of models based on a published model of tumor invasion (Cohen's model[3]): same interaction graph, same stable steady states.

Wild Type model



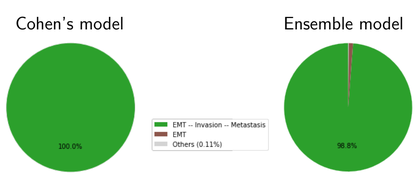
Despite not fitting the steady state probabilities, we obtain a similar distribution with slightly different proportions (more Metastasis, EMT and less Apoptosis).

Visualization of Wild Type solutions in PCA space



We visualize the phenotype probabilities, and identify clusters of models that behave similarly. We can thus remove models with aberrant phenotypes (e.g., Cluster #2 with Apoptosis - EMT concomitant phenotype, in pink).

Mutant analysis: Notch++/p53--



- Mutant conserves a vast majority of invasion phenotypes (98%)
- A small number of models (2%) stay stuck in EMT, highlighting that some rules are more stringent than others.

Conclusions

This methodology:

- Provides an efficient framework for fuzzy models
- Allows a cell-population interpretation
- Takes into account heterogeneity

References

1. Chevalier, Stéphanie et al. (2019), arXiv
2. Stoll, Gautier et al. (2017), Bioinformatics
3. Cohen, David PA, et al. (2015), PLoS computational biology

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