SMT Solving and modeling for biology

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GdT Plume
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Part 1

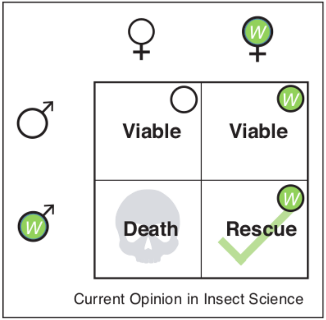
Wolbachia-induced infertility in mosquitoes

With
Sylvain Charlat, Alice Namias , Mathieu Sicard, Mylène Weill

LBBE LABORATOIRE DE BIOMÉTRIE ET BIOLOGIE ÉVOLUTIVE

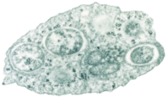
isem Institute of Evolutionary Science of Montpellier

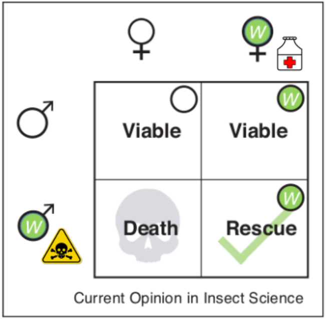
Cytoplasmic Incompatibility



Credit: [Namias et al 2022]

The toxin/antidote hypothesis





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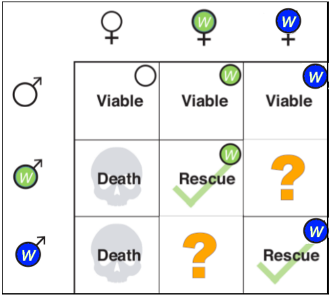
Different Wolbachia strains



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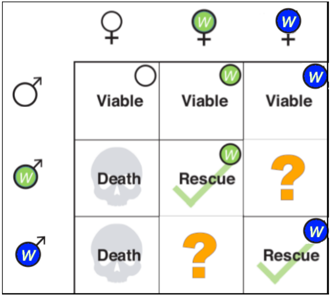
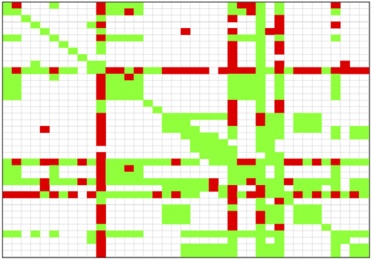


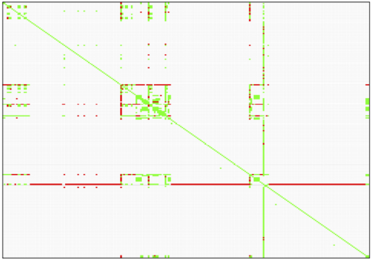
Hypothesis: each strain has its own cocktail.

The data

39 lines with phenotypic and molecular data



239 lines with phenotypic data



Optimizing the parameters

How many kind of toxins needed ?

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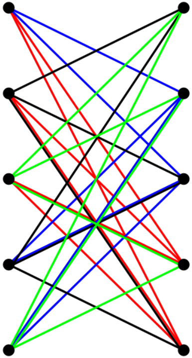
NP-complete [Nor et al 2012]:

biclique cover



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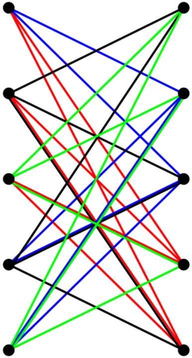

Variant: quantitative model

Using SAT/SMT Solver

Before SAT solving [Nor et al 2012]:

- ad-hoc heuristics for 19*19 matrix
- fill missing data manually
- approximate results

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With minisat/Z3 (this work):

- deal with 239*239 matrix
- robust to missing data
- explore various models and questions

Results

Boolean

Toxs per strain	Types
1	14
2	10
3	9

Quantitative

Levels	Types
1	14
2	7
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And more:

- test robustness
- predict missing data
- find cells discriminating models

Perspectives

- Confront predictions with new data
- Prescribe tests to discriminate models
- Find correlations with genetic data
- Evolutionary explanations

Part 2

Detection of autocatalytic cycles

With
Sylvain Charlat, Etienne Rajon, Nicolas Lartillot

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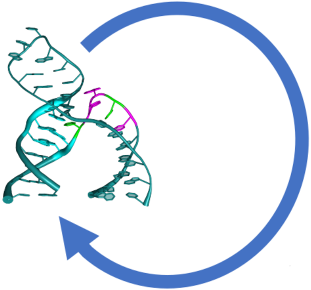
Origin of Life dichotomy

Replicator first



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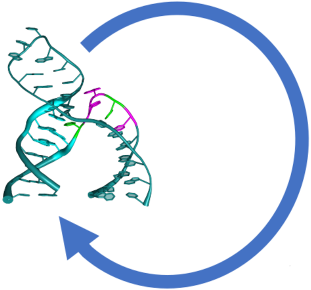
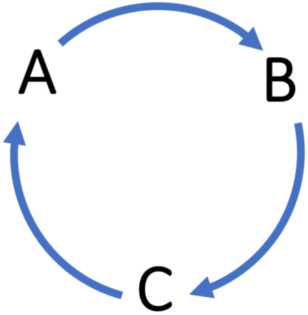
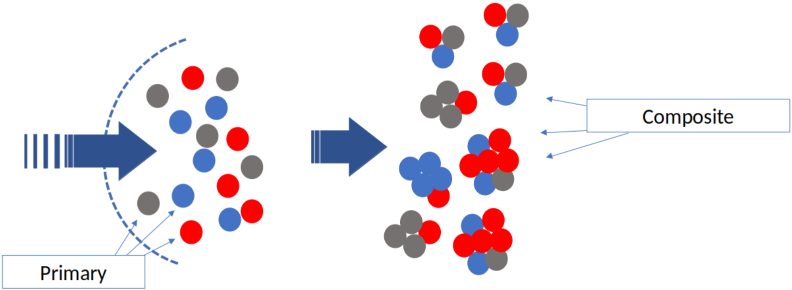


Metabolism first

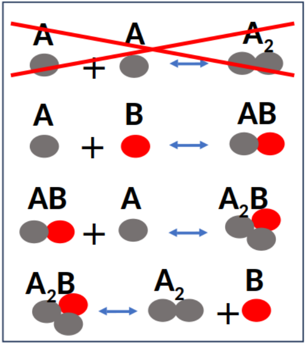


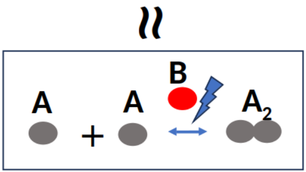
Soup of chemical reactions



Spontaneous (auto)catalysis

Catalysis





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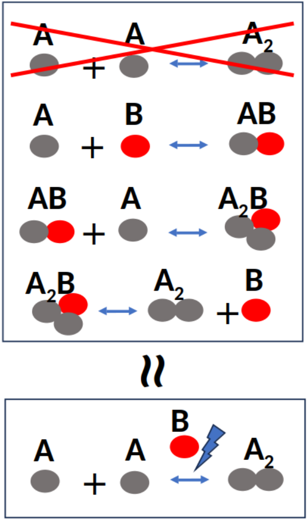
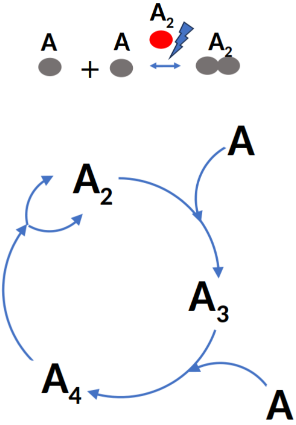


Autocatalysis



Reaction matrix

$$
\begin{array}{ll}
(R_1) & A + B \rightleftharpoons AB \\
(R_2) & A + A \rightleftharpoons AA
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	R_1	R_2
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$\vec{v} \in \mathbb{R}^2$ flow vector $\Rightarrow$ $M \cdot \vec{v}$ balance for each entity.

Autocatalysis via matrices

Autocatalytic core [Blockhuis et al 2022]:
Submatrix N of M such that

- each column and line contains coef< 0 and coef> 0
- $\exists \vec{v} \in \mathbb{R}^k$ such that $N \cdot \vec{v} \in (\mathbb{R}^{*+})^k$
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NP-complete ?

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$$A + B \rightleftharpoons AB$$

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Consistent core: Flow witness must be realistic

Concentration vector $\vec{u} \rightsquigarrow$ flow vector $\vec{v}$.

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Compatible cores: share the same witness

What we want

- design systems
- sample systems
- find autocatalytic cores
- mark consistent cores
- find sets of compatible cores

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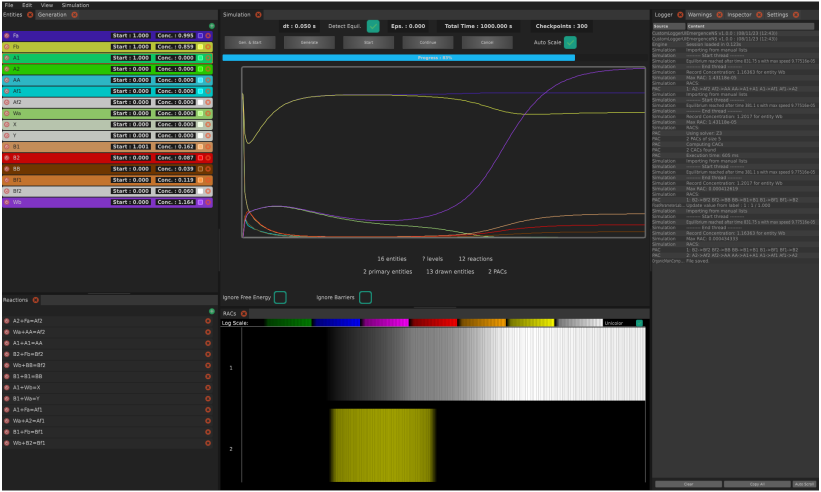
SMT Solver Z3

JUCE OrganicUI

The program


File
Edit
View
Simulation
Entities
Generation
Fa
Fb
A1
A2
AA
Af1
Af2
Wa
X
Y
B1
B2
BB
Bf1
Bf2
Wb
Start : 1.000
Conc. : 0.995
Conc. : 0.859
Start : 1.001
Conc. : 0.162
Conc. : 0.087
Conc. : 0.039
Conc. : 0.119
Conc. : 0.060
Conc. : 1.164
Reactions
A2+Fa=Af2
Wa+AA=Af2
A1+A1=AA
B2+Fb=Bf2
Wb+BB=Bf2
B1+B1=BB
A1+Wb=X
B1+Wa=Y
A1+Fa=Af1
Wa+A2=Af1
B1+Fb=Bf1
Wb+B2=Bf1
Simulation
dt : 0.050 s
Detect Equil.
Eps. : 0.000
Total Time : 1000.000 s
Checkpoints : 300
Auto Scale
16 entities
7 levels
12 reactions
2 primary entities
13 drawn entities
2 PACs
Ignore Free Energy
Ignore Barriers
RACs
Log Scale:
Unicolor
Logger
Warnings
Inspector
Settings

Perspectives

- Spectrum of interactions between cores
- Quantitative analysis (expectancy of autocatalysis,...)
- Links with multiplicity of equilibria
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Very long term goals:

- Quantify natural selection
- Criteria for life
- Possible build-up scenario

Thank you !