

Structural simplification of chemical reaction networks preserving deterministic semantics

Guillaume Madelaine

Cédric Lhoussaine

Joachim Niehren

Univ. Lille 1, CRIStAL, Biocomputing

Systems biology

- Mathematical and **computational modeling** of biological systems

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- **interdisciplinary** field

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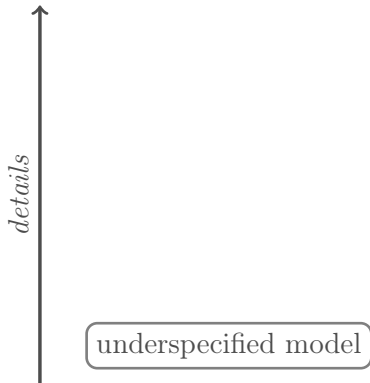
What is a **good** model?

- Mathematical and **computational modeling** of biological systems
- **interdisciplinary** field
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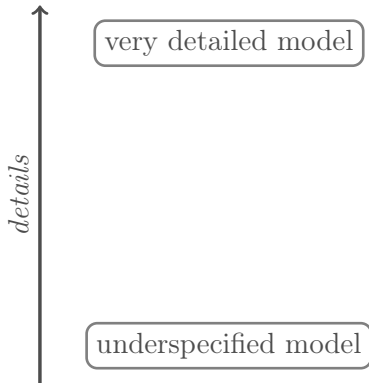
What is a **good** model?

A model that can be used to make **predictions**

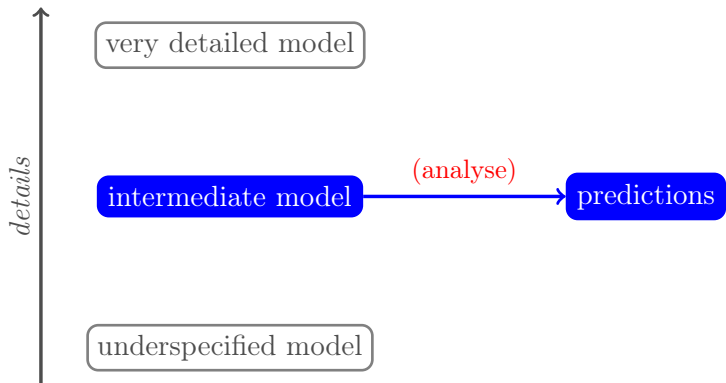
Model simplification



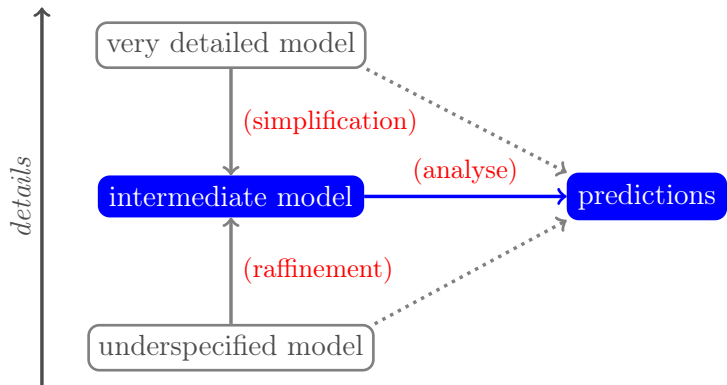
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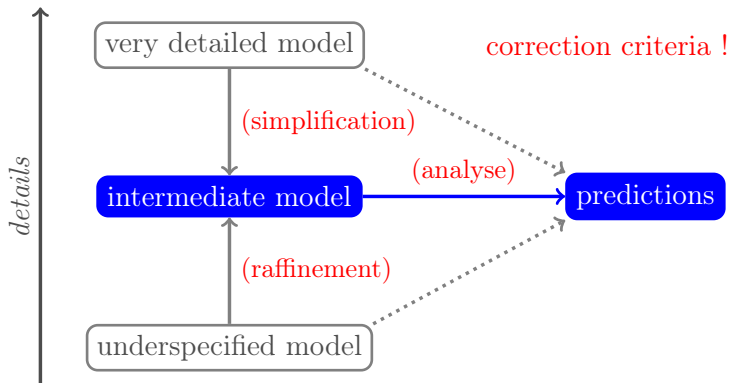
Model simplification



Model simplification



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Related work

Related work

Structural simplifications preserving qualitative semantics

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- Petri Nets [Berthelot et al. 1976, Murata et al. 1980, Haddad et al. 2006]

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Simplifications preserving deterministic semantics

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Simplifications preserving deterministic semantics

- Lie symmetries [Lemaire et al. 2008]

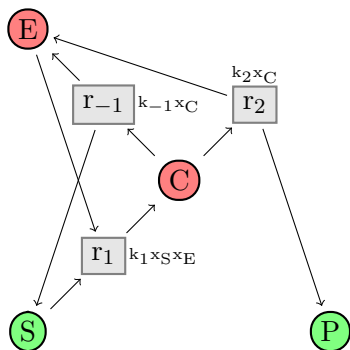
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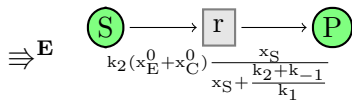
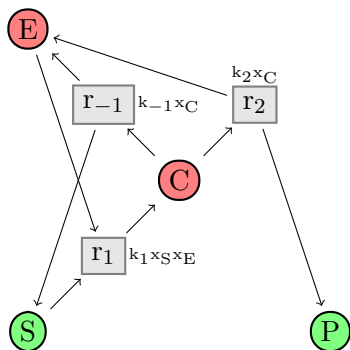
Simplifications preserving deterministic semantics

- Lie symmetries [Lemaire et al. 2008]
- Simplifications based on QE, QSSA, Tropical equilibration [King and Altman 1956, Gorban et al, Radulescu et al. 2013]

Michaelis-Menten



Michaelis-Menten



Our approach

- A **structural simplification**

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- Preserving the **deterministic semantics**

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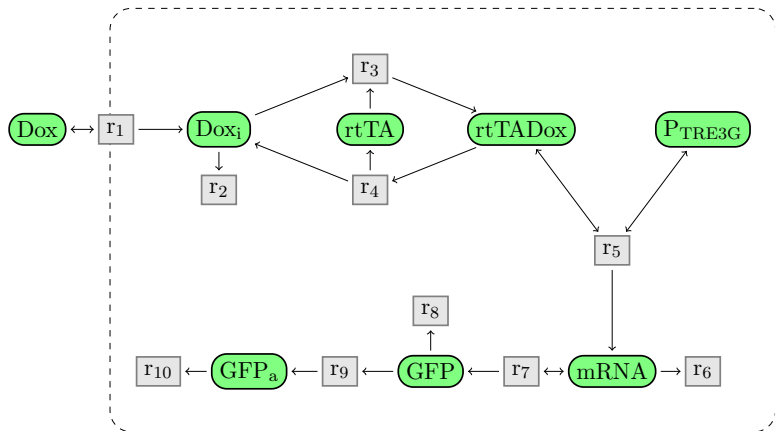
Our approach

- A **structural simplification**
- Preserving the **deterministic semantics** , under **partial equilibrium conditions**, and in every **compatible context**
- **Relevant for biological systems**

- 1 Introduction
- 2 Contextual equilibrium-equivalence
- 3 Simplification
- 4 Application
- 5 Conclusion

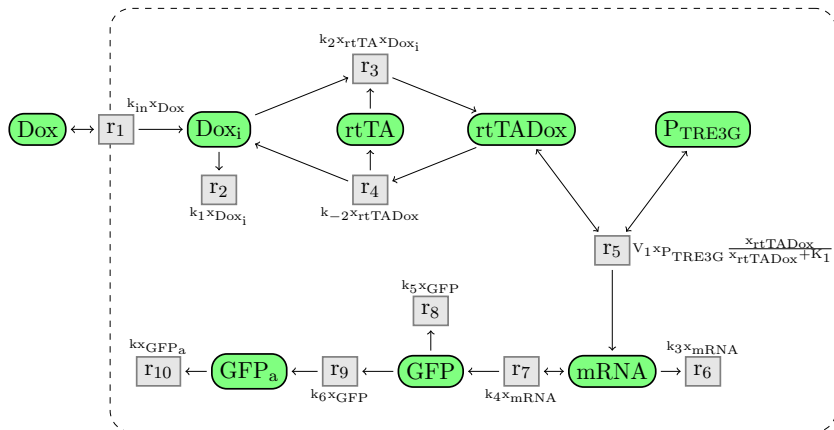
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Reaction networks



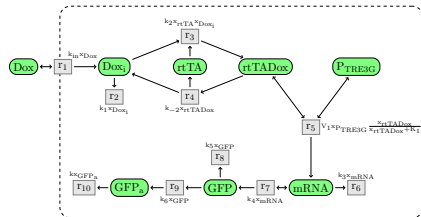
Tet-On reaction network [Huang et al., 2010]

Reaction networks

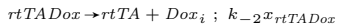
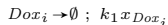
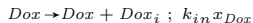


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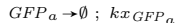
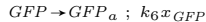
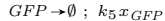
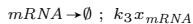
Reaction networks



Tet-On reaction network



$$V_1 x_{P_{TRE3G}} \frac{x_{rtTADox}}{x_{rtTADox} + K_1}$$



Tet-On reactions

Deterministic semantics

$$\begin{aligned}
 \frac{dx_{Dox}}{dt} &= 0 \\
 \frac{dx_{Dox_i}}{dt} &= k_{in}x_{Dox} - k_1x_{Dox_i} \\
 &\quad - k_2x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox} \\
 \frac{dx_{rtTA}}{dt} &= -k_2x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox} \\
 \frac{dx_{rtTADox}}{dt} &= k_2x_{rtTA}x_{Dox_i} - k_{-2}x_{rtTADox} \\
 \frac{dx_{PTRE3G}}{dt} &= 0 \\
 \frac{dx_{mRNA}}{dt} &= V_1x_{PTRE3G} \frac{x_{rtTADox}}{x_{rtTADox} + K_1} \\
 &\quad - k_3x_{mRNA} - k_4x_{mRNA} \\
 \frac{dx_{GFP}}{dt} &= k_4x_{mRNA} - k_5x_{GFP} - k_6x_{GFP} \\
 \frac{dx_{GFP_a}}{dt} &= k_6x_{GFP} - kx_{GFP_a}
 \end{aligned}
 \Leftrightarrow
 \begin{aligned}
 &Dox \rightarrow Dox + Dox_i ; k_{in}x_{Dox} \\
 &Dox_i \rightarrow \emptyset ; k_1x_{Dox_i} \\
 &rtTA + Dox_i \rightarrow rtTADox ; k_2x_{rtTA}x_{Dox_i} \\
 &rtTADox \rightarrow rtTA + Dox_i ; k_{-2}x_{rtTADox} \\
 &PTRE3G + rtTADox \rightarrow PTRE3G + rtTADox + mRNA ; \\
 &\quad V_1x_{PTRE3G} \frac{x_{rtTADox}}{x_{rtTADox} + K_1} \\
 &mRNA \rightarrow \emptyset ; k_3x_{mRNA} \\
 &mRNA \rightarrow mRNA + GFP ; k_4x_{mRNA} \\
 &GFP \rightarrow \emptyset ; k_5x_{GFP} \\
 &GFP \rightarrow GFP_a ; k_6x_{GFP} \\
 &GFP_a \rightarrow \emptyset ; kx_{GFP_a}
 \end{aligned}$$

Tet-On reactions

Tet-On ODE system

Deterministic semantics

$$\frac{dx_{Dox}}{dt} = 0$$

$$\frac{dx_{Dox_i}}{dt} = k_{in}x_{Dox} - k_1x_{Dox_i} - k_2x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox}$$

$$\frac{dx_{rtTA}}{dt} = -k_2x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox}$$

$$\frac{dx_{rtTADox}}{dt} = k_2x_{rtTA}x_{Dox_i} - k_{-2}x_{rtTADox}$$

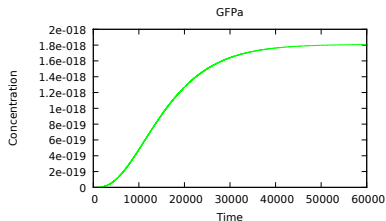
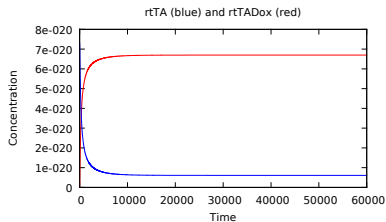
$$\frac{dx_{PTRE3G}}{dt} = 0$$

$$\frac{dx_{mRNA}}{dt} = V_1x_{PTRE3G} \frac{x_{rtTADox}}{x_{rtTADox} + K_1} - k_3x_{mRNA} - k_4x_{mRNA}$$

$$\frac{dx_{GFP}}{dt} = k_4x_{mRNA} - k_5x_{GFP} - k_6x_{GFP}$$

$$\frac{dx_{GFP_a}}{dt} = k_6x_{GFP} - kx_{GFP_a}$$

⇒



Tet-On ODE system

Tet-On solutions

Equilibrium

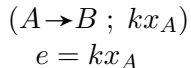
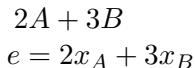
An **equilibrium condition** e is a kinetic expression.

A concentration **satisfies** e if $\frac{de}{dt} = 0$.

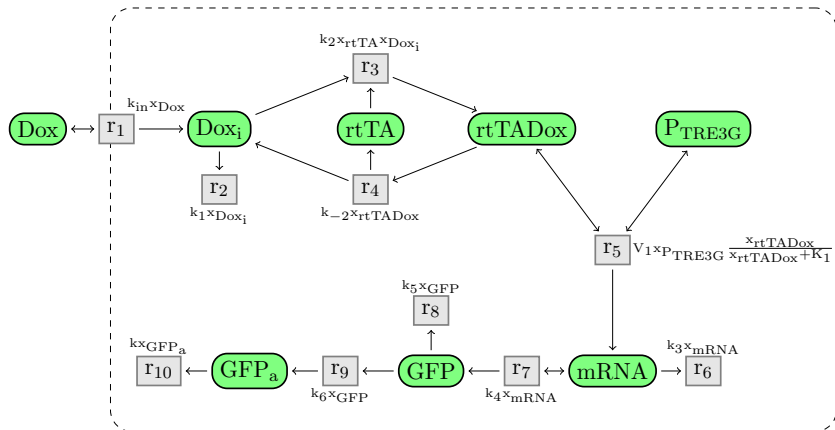
Equilibrium

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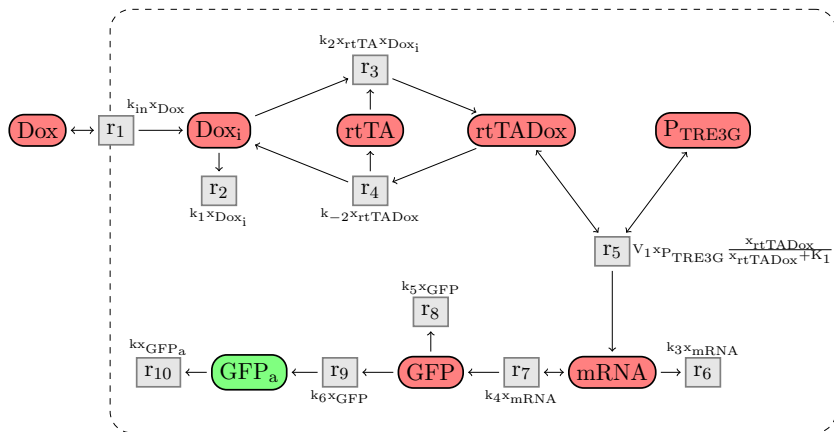
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Equilibrium



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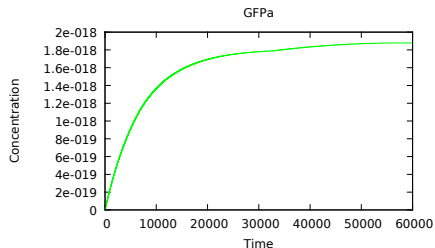
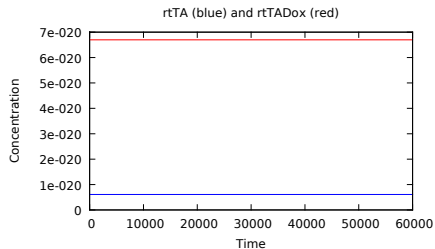
$$\mathbf{E} = \{x_{Dox}, x_{Dox_i}, x_{rtTA}, x_{rtTADox}, x_{P_{TRE3G}}, x_{mRNA}, x_{GFP}\}$$

Solutions

Given a network N and a set \mathbf{E} of equilibrium conditions, the **deterministic dynamics** of N that satisfies \mathbf{E} , denoted $sol(N, \mathbf{E}) = \{(\alpha_k, \alpha_0, \alpha)\}$, is the set of triplets of parameters values, initial concentrations and concentrations such that:

- α is a solution to the ODE system of N , with parameters α_k and initial concentration α_0
- α satisfies the equilibrium conditions \mathbf{E} , with parameters α_k and initial concentration α_0

Solutions



$$\mathbf{E} = \{x_{Dox}, x_{Dox_i}, x_{rtTA}, x_{rtTADox}, x_{P_{TRE3G}}, x_{mRNA}, x_{GFP}\}$$

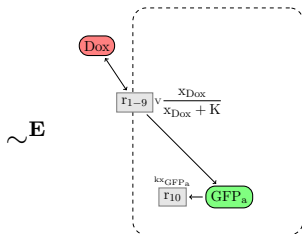
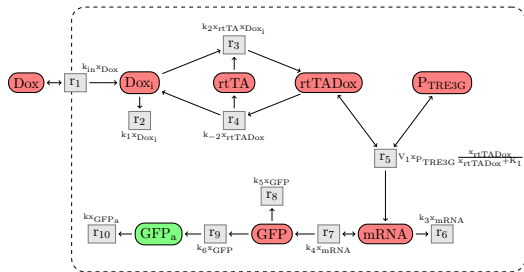
Weak equilibrium-equivalence

Weak equilibrium-equivalence

Two networks N and M are **weakly equilibrium-equivalent**, for a set of equilibrium conditions \mathbf{E} , if they have the same deterministic dynamics that satisfies \mathbf{E} :

$$N \sim^{\mathbf{E}} M \quad \text{iff} \quad \text{sol}(N, \mathbf{E}) = \text{sol}(M, \mathbf{E})$$

Weak equilibrium-equivalence

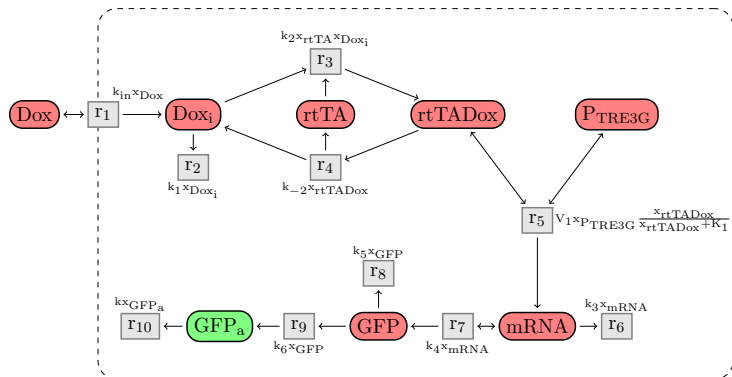


Context

A **context** is itself a reaction network.

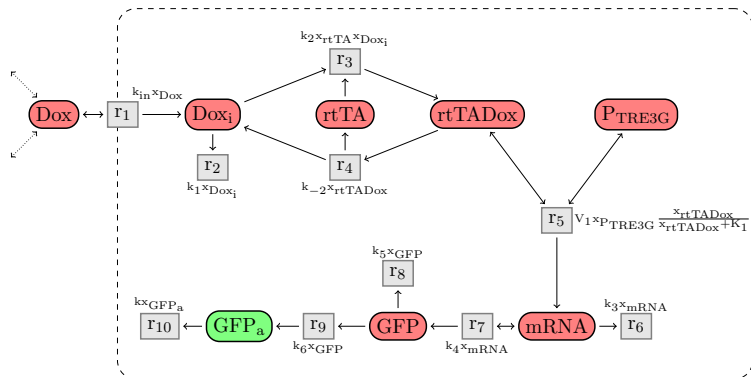
Given a set of **internal molecules** I , a context \mathcal{C} is **compatible** with I if $\mathcal{C} \cap I = \emptyset$.

Context



$$I = \{Dox_i, rtTA, rtTADox, P_{TRE3G}, mRNA, GFP, GFP_a\}$$

Context



$$I = \{Dox_i, rtTA, rtTADox, P_{TRE3G}, mRNA, GFP, GFP_a\}$$

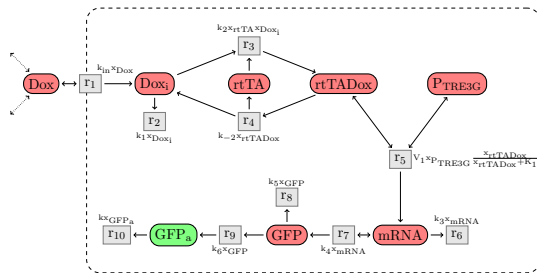
Contextual equilibrium-equivalence

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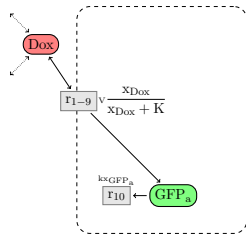
Two networks N and M are **contextually equilibrium-equivalent** for a set of equilibrium conditions \mathbf{E} if they are weakly equilibrium-equivalent in any context compatible with I :

$$N \equiv^{\mathbf{E}} M \quad \text{iff} \quad \forall \mathcal{C}. \mathcal{C}[N] \sim^{\mathbf{E}} \mathcal{C}[M]$$

Contextual equilibrium-equivalence

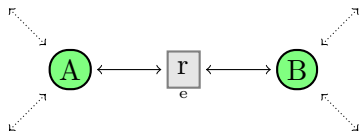


$\equiv \mathbf{E}$

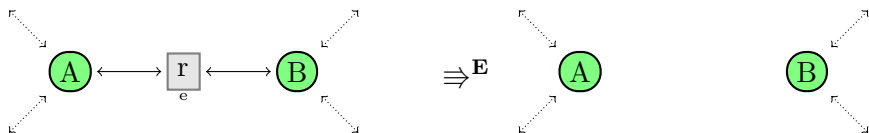


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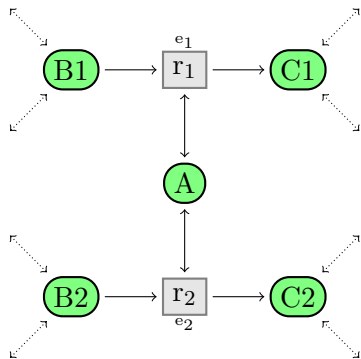
Useless reaction



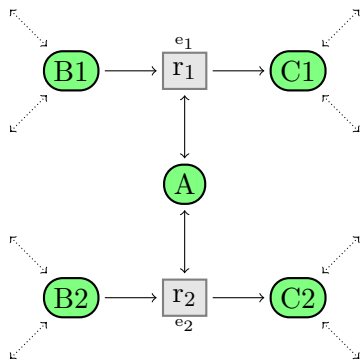
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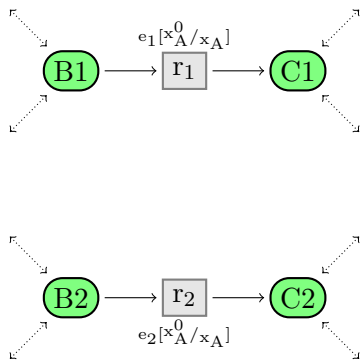
Activator



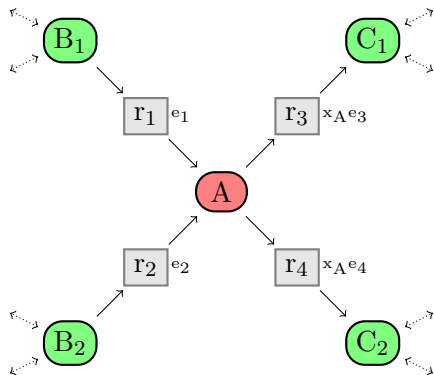
Activator



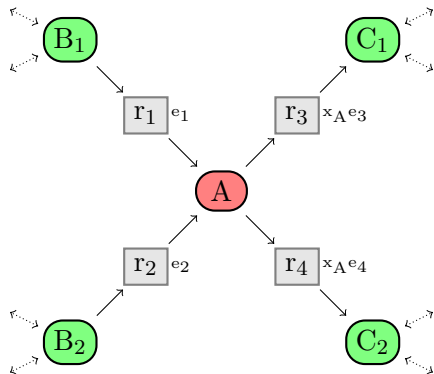
$\Rightarrow \mathbf{E}$



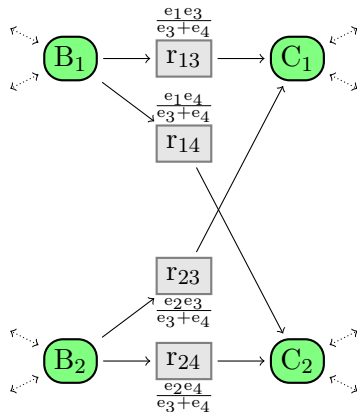
Intermediate molecule



Intermediate molecule



\Rightarrow **E**



Soundness

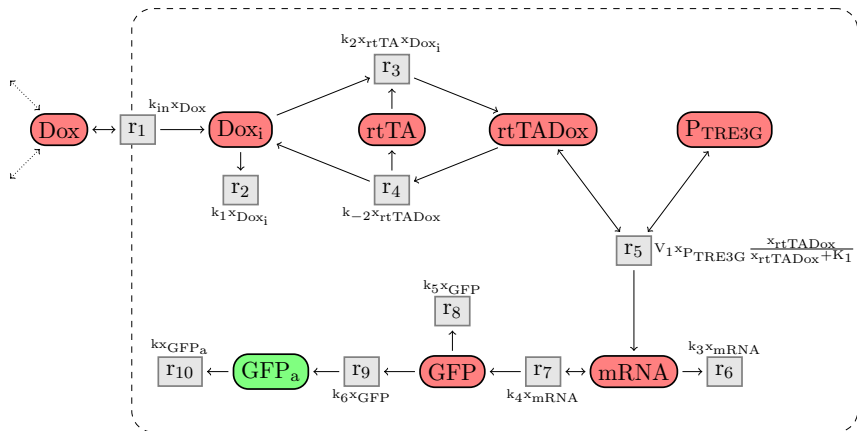
Theorem

The simplification axioms above are **sound** for the contextual equilibrium-equivalence:

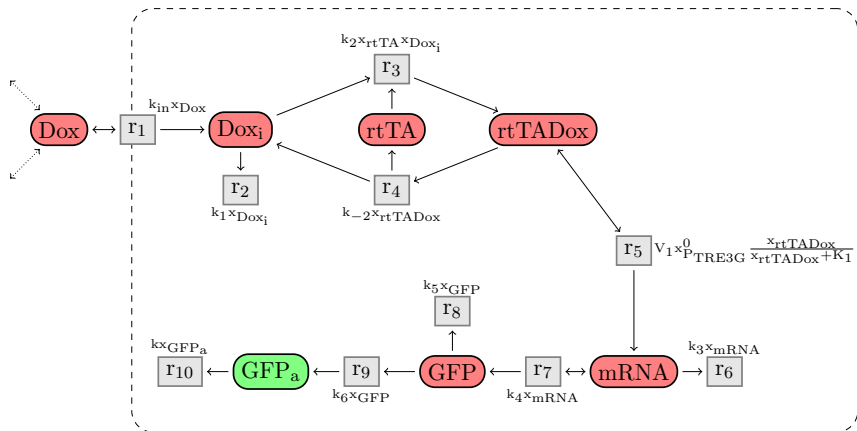
$$N \Rightarrow^{\mathbf{E}} M \quad \Rightarrow \quad N \equiv^{\mathbf{E}} M$$

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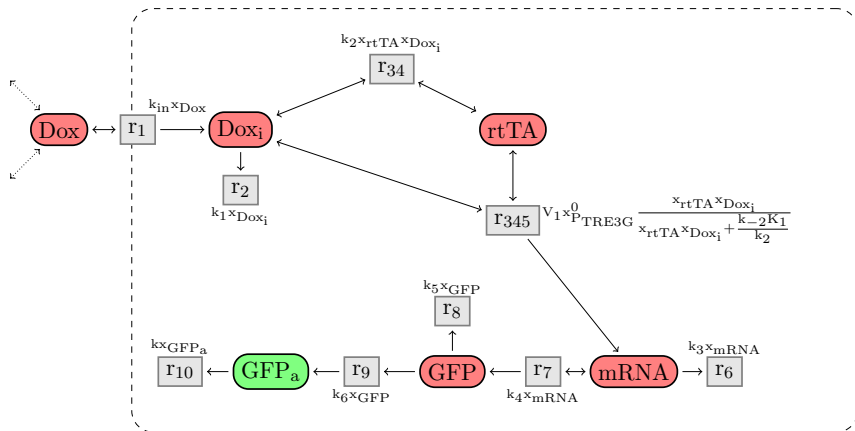
Tet-On simplification



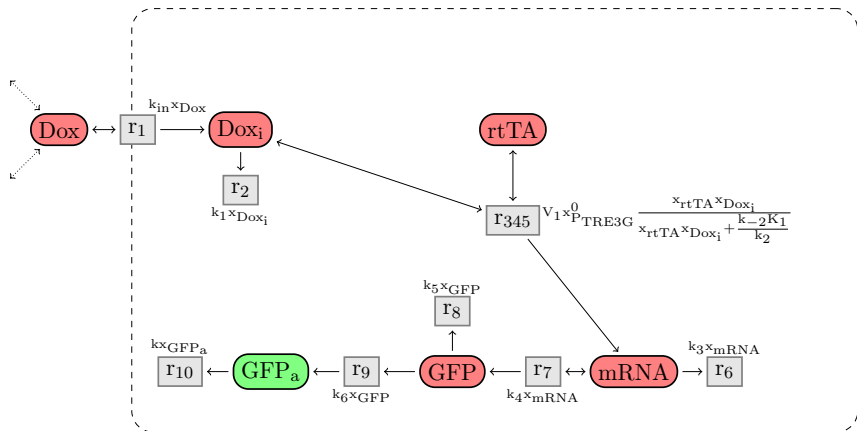
Tet-On simplification



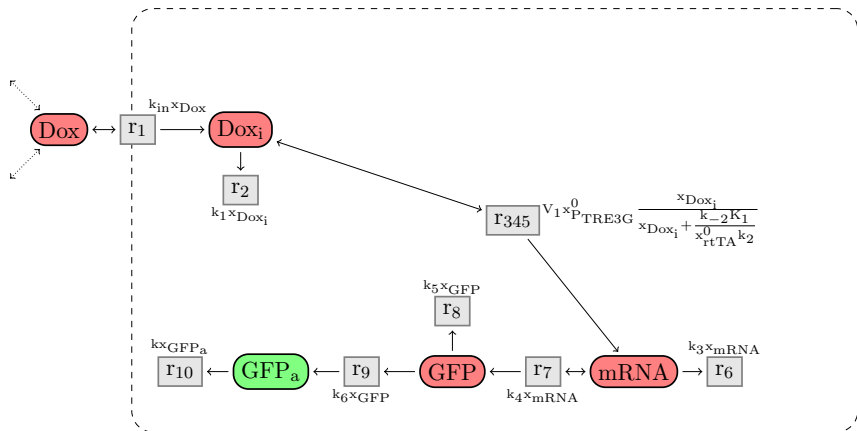
Tet-On simplification



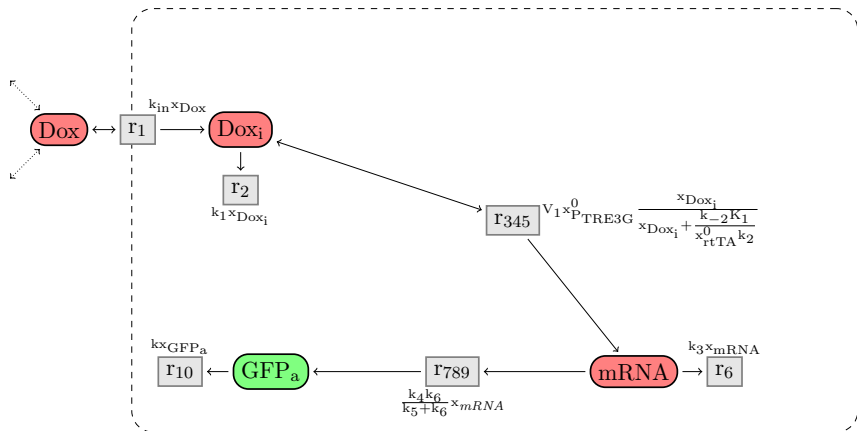
Tet-On simplification



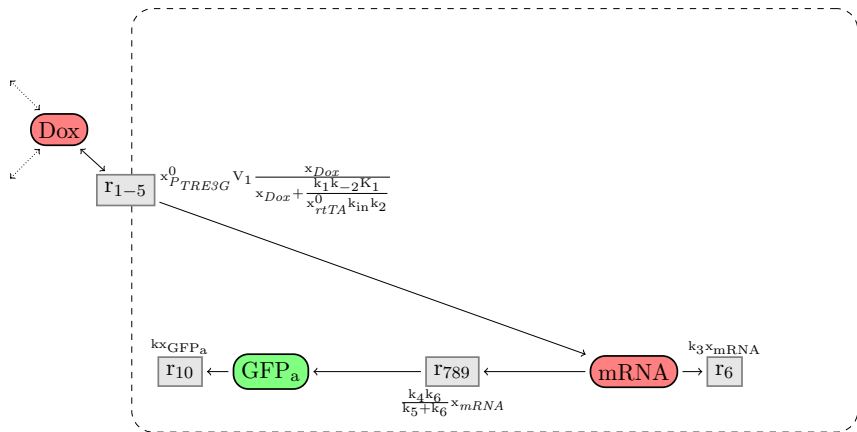
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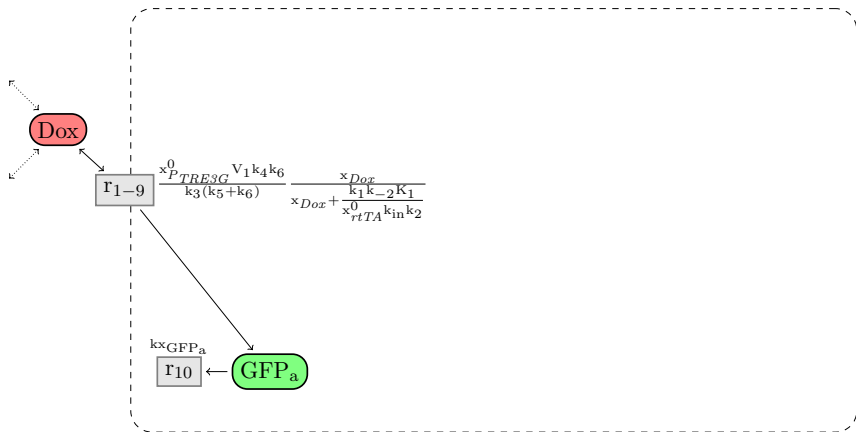
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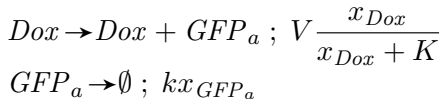
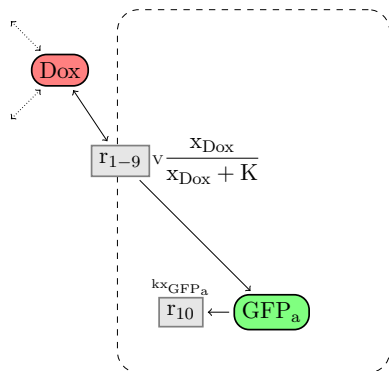
Tet-On simplification



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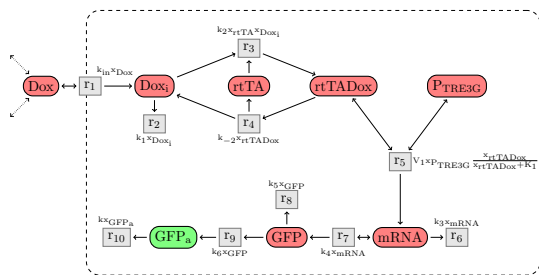
Tet-On simplified reaction network



$$V = \frac{x_{PTRE3G}^0 V_1 k_4 k_6}{k_3 (k_5 + k_6)}$$

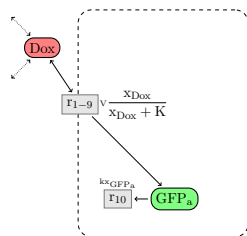
$$K = \frac{k_1 k_{-2} K_1}{x_{rtTA}^0 k_{in} k_2}$$

Tet-On simplification



8 molecules
10 reactions
11 parameters

\Rightarrow **E**



2 molecules
2 reactions
3 parameters

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Conclusion

- We propose a **structural simplification** of reaction network

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- The simplification preserves the **deterministic semantics**, in **every compatible context**

Conclusion

- We propose a **structural simplification** of reaction network
- The simplification preserves the **deterministic semantics**, in **every compatible context**
- We **apply** the simplification to a **concrete biological system**

Work in progress

- **Implementation** of the simplification
- Apply the simplification on **other biological systems**
- **Complete** the set of simplification axioms

Future work

- **Satisfiability** of equilibrium conditions
- **Approximated simplification**
- **Stochastic semantics**