Structural simplification of chemical reaction networks preserving deterministic semantics

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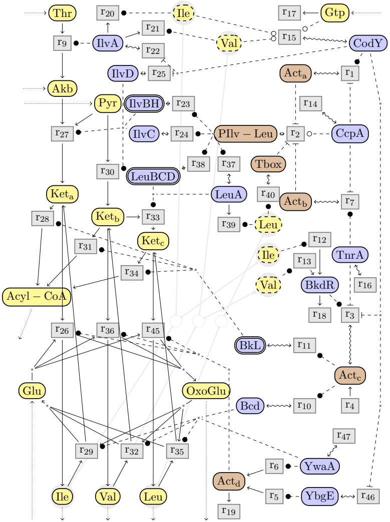
Systems biology



Leucine network [Coutte et al., 2015]

Model simplification

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Small models are beautiful!

Related work

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Structural simplifications preserving qualitative semantics

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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 [Gorban et al, Radulescu et al. 2013]

Our approach

- A **structural simplification**

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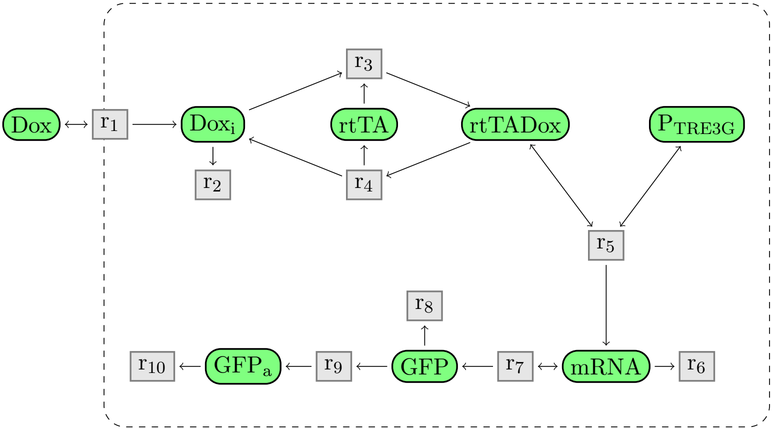
Our approach

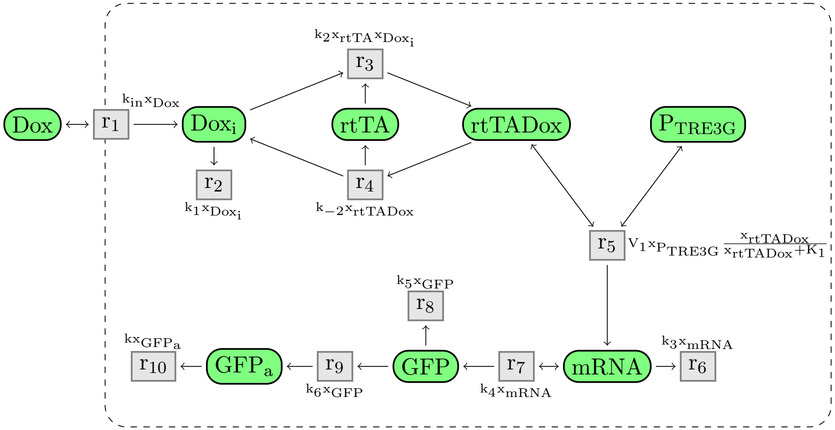
- A **structural simplification**
- Preserving the **deterministic semantics**, under **partial equilibrium conditions**, and in every **compatible context**
- **Relevant for biological systems**

Reaction networks



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

Reaction networks



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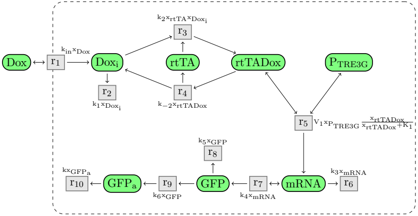

Tet-On reaction network

$$Dox \to Dox + Dox_i \;;\; k_{in} x_{Dox}$$

$$Dox_i \to \emptyset \;;\; k_1 x_{Dox_i}$$

$$rtTA + Dox_i \to rtTADox \;;\; k_2 x_{rtTA} x_{Dox_i}$$

$$rtTADox \to rtTA + Dox_i \;;\; k_{-2} x_{rtTADox}$$

$$P_{TRE3G} + rtTADox \to P_{TRE3G} + rtTADox + mRNA \;; \quad V_1 x_{P_{TRE3G}} \frac{x_{rtTADox}}{x_{rtTADox} + K_1}$$

$$mRNA \to \emptyset \;;\; k_3 x_{mRNA}$$

$$mRNA \to mRNA + GFP \;;\; k_4 x_{mRNA}$$

$$GFP \to \emptyset \;;\; k_5 x_{GFP}$$

$$GFP \to GFP_a \;;\; k_6 x_{GFP}$$

$$GFP_a \to \emptyset \;;\; k x_{GFP_a}$$

Tet-On reactions

Deterministic semantics

$$
\begin{aligned}
\frac{dx_{Dox}}{dt} &= 0 \\
\frac{dx_{Dox_i}}{dt} &= k_{in} x_{Dox} - k_1 x_{Dox_i} \\
&\quad - k_2 x_{rtTA} x_{Dox_i} + k_{-2} x_{rtTADox} \\
\frac{dx_{rtTA}}{dt} &= -k_2 x_{rtTA} x_{Dox_i} + k_{-2} x_{rtTADox} \\
\frac{dx_{rtTADox}}{dt} &= k_2 x_{rtTA} x_{Dox_i} - k_{-2} x_{rtTADox} \\
\frac{dx_{P_{TRE3G}}}{dt} &= 0 \\
\frac{dx_{mRNA}}{dt} &= V_1 x_{P_{TRE3G}} \frac{x_{rtTADox}}{x_{rtTADox} + K_1} \\
&\quad - k_3 x_{mRNA} - k_4 x_{mRNA} \\
\frac{dx_{GFP}}{dt} &= k_4 x_{mRNA} - k_5 x_{GFP} - k_6 x_{GFP} \\
\frac{dx_{GFP_a}}{dt} &= k_6 x_{GFP} - k x_{GFP_a}
\end{aligned}
$$

Tet-On ODE system

Deterministic semantics

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\begin{aligned}
\frac{dx_{Dox}}{dt} &= 0\\
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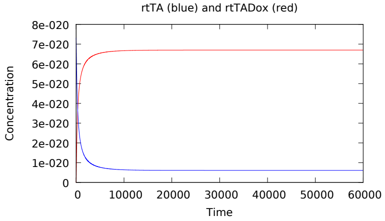
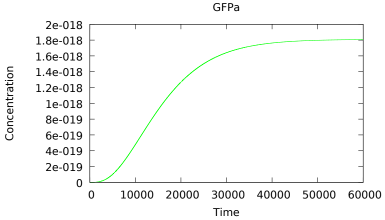
&\quad -k_2 x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox}\\
\frac{dx_{rtTA}}{dt} &= -k_2 x_{rtTA}x_{Dox_i} + k_{-2}x_{rtTADox}\\
\frac{dx_{rtTADox}}{dt} &= k_2 x_{rtTA}x_{Dox_i} - k_{-2}x_{rtTADox}\\
\frac{dx_{P_{TRE3G}}}{dt} &= 0\\
\frac{dx_{mRNA}}{dt} &= V_1 x_{P_{TRE3G}} \frac{x_{rtTADox}}{x_{rtTADox} + K_1}\\
&\quad -k_3 x_{mRNA} - k_4 x_{mRNA}\\
\frac{dx_{GFP}}{dt} &= k_4 x_{mRNA} - k_5 x_{GFP} - k_6 x_{GFP}\\
\frac{dx_{GFP_a}}{dt} &= k_6 x_{GFP} - k x_{GFP_a}
\end{aligned}
$$

Tet-On ODE system





Tet-On solutions

Equilibrium

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

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

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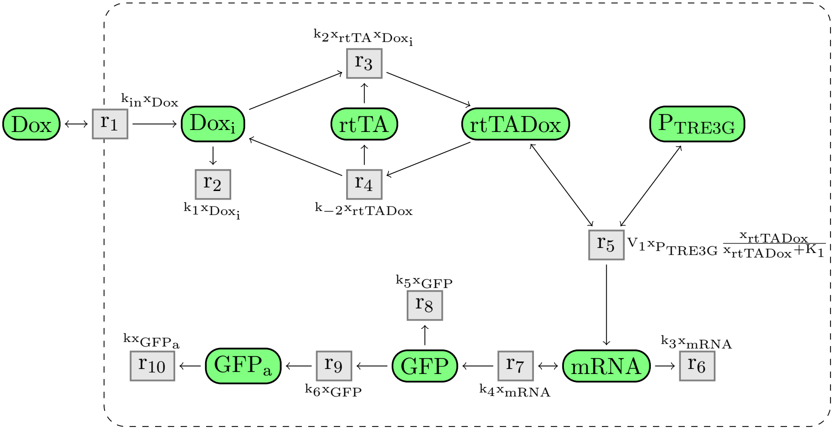
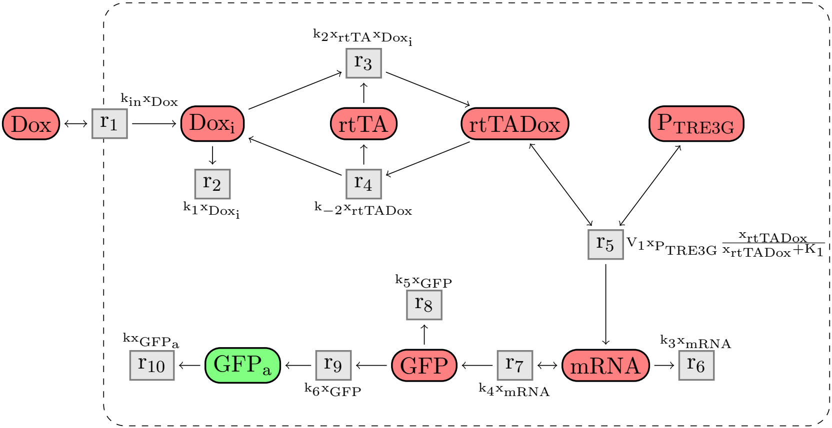
A concentration **satisfies** e if $\frac{de}{dt} = 0$.

A	$2A + 3B$	$(A \rightarrow B\ ;\ kx_A)$
$e = x_A$	$e = 2x_A + 3x_B$	$e = kx_A$

Equilibrium



Equilibrium



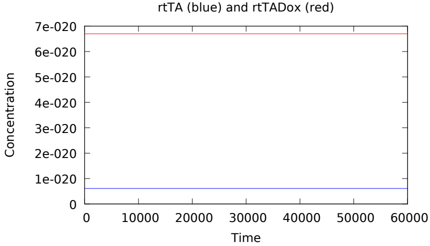
$$\mathbf{E} = \{x_{Dox}, x_{Dox_i}, x_{rtTA}, x_{rtTADox}, x_{P_{TRE3G}}, x_{mRNA}, x_{GFP}\}$$

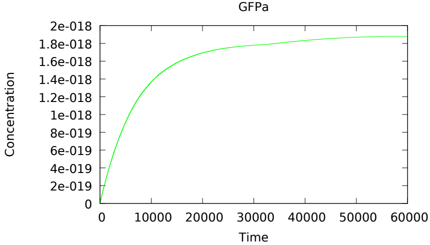
Solutions

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





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

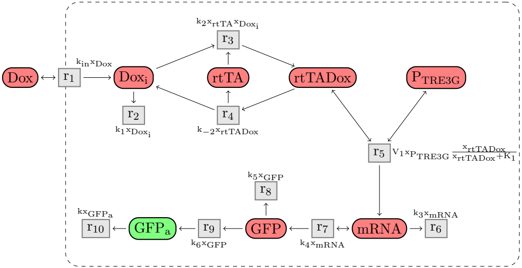
Weak equilibrium-equivalence

Weak equilibrium-equivalence

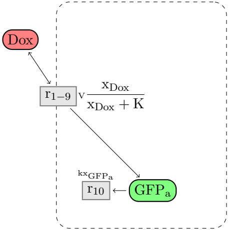
Two networks N and M are **weakly equilibrium-equivalent**, for a set of equilibrium conditions $\mathbf{E}$, if they have the same deterministic dynamics that satisfies $\mathbf{E}$:

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

Weak equilibrium-equivalence



$\sim^{\mathbf{E}}$

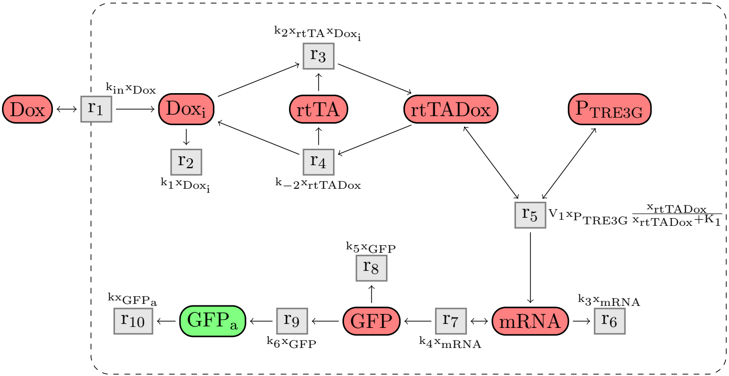


Context

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

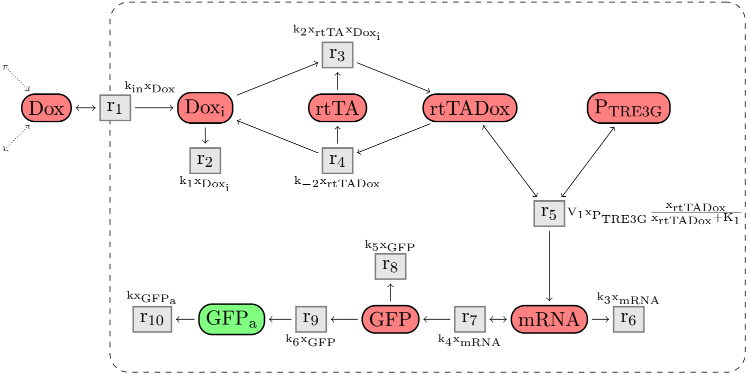
Given a set of **internal molecules** I, a context $\mathcal{C}$ is **compatible** with I if $\mathcal{C} \cap I = \emptyset$.

Context



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

Context



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

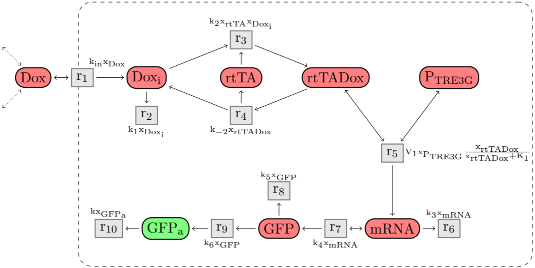
Contextual equilibrium-equivalence

Contextual equilibrium-equivalence

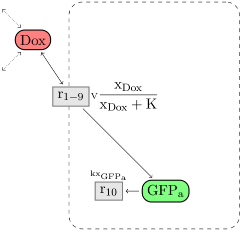
Two networks N and M are **contextually equilibrium-equivalent** for a set of equilibrium conditions $\mathbf{E}$ if they are weakly equilibrium-equivalent in any context compatible with I:

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

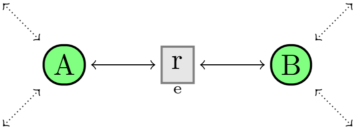
Contextual equilibrium-equivalence



$\equiv^{\mathbf{E}}$



Useless reaction



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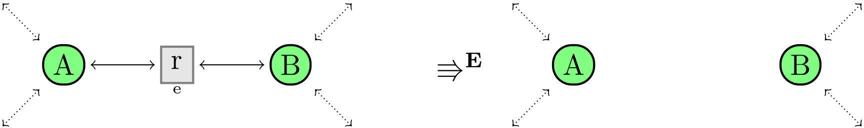
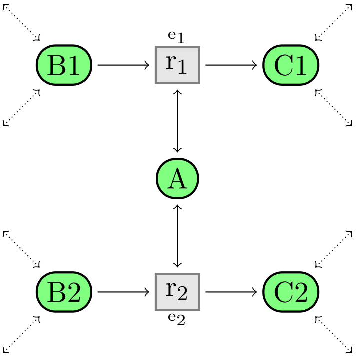


Activator



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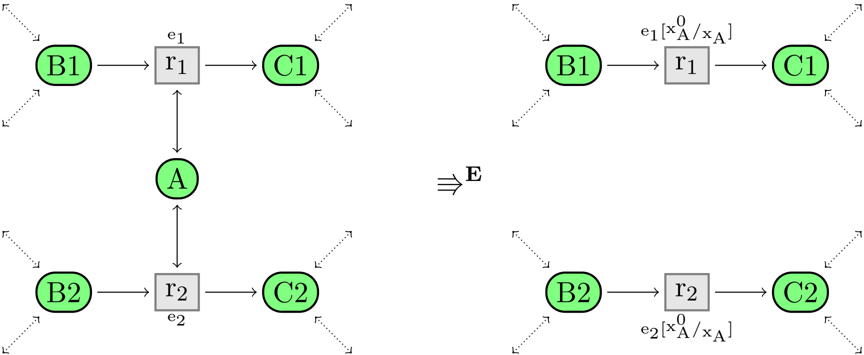
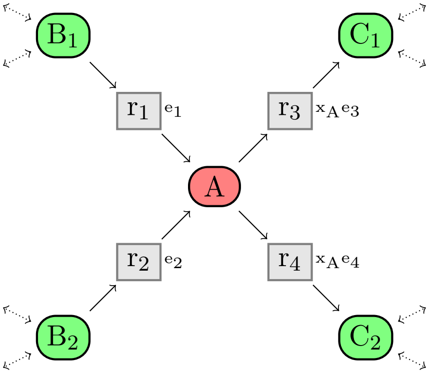


Intermediate axiom



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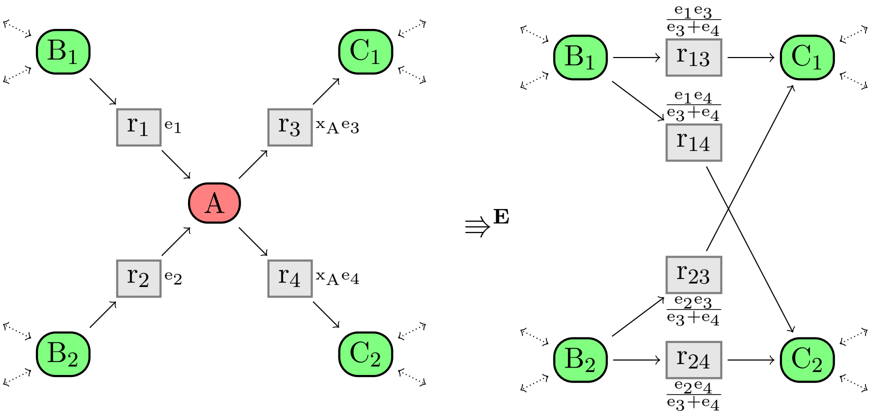


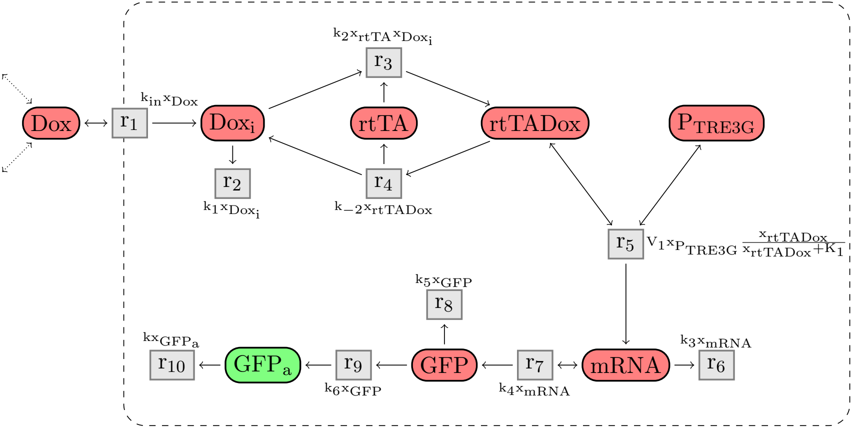
Soundness

Theorem

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

$$N \Rrightarrow^{\mathbf{E}} M \qquad \Rightarrow \qquad N \equiv^{\mathbf{E}} M$$

Tet-On simplification



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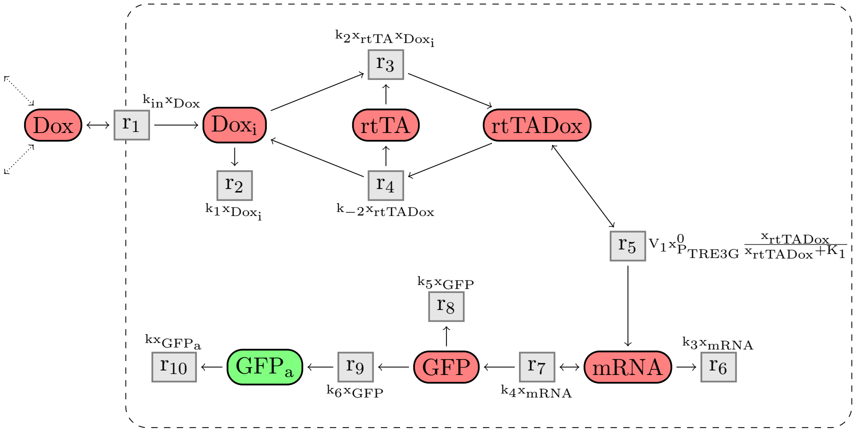

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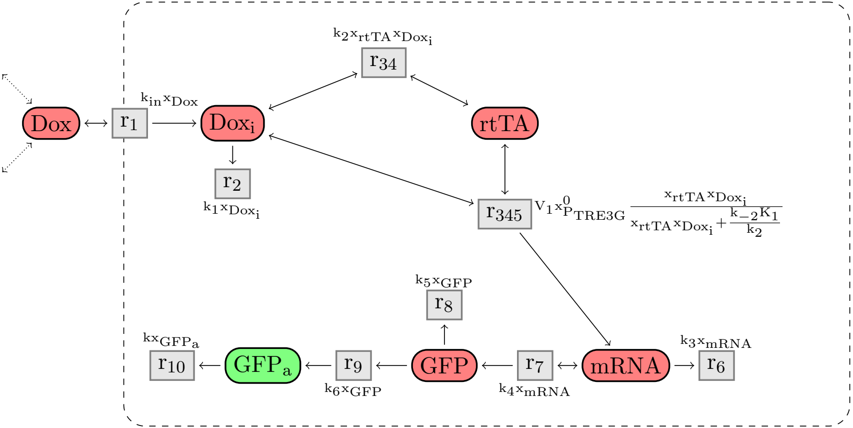

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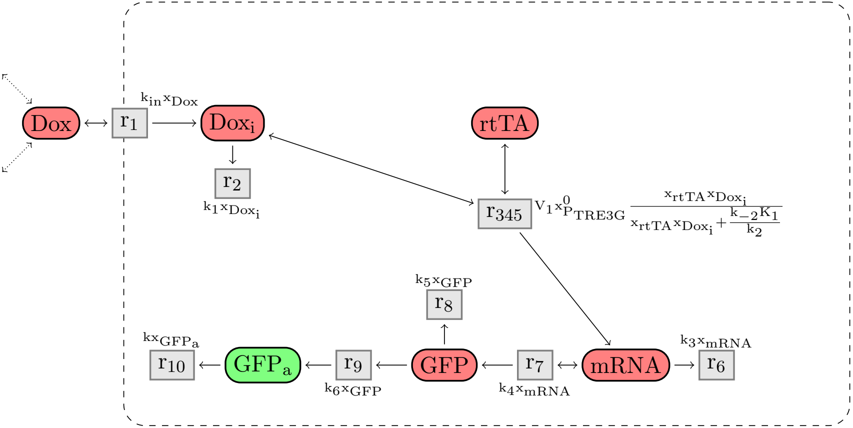

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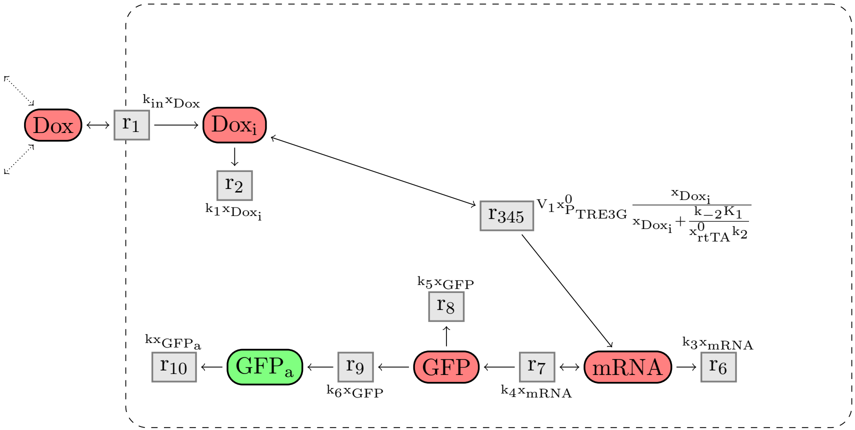

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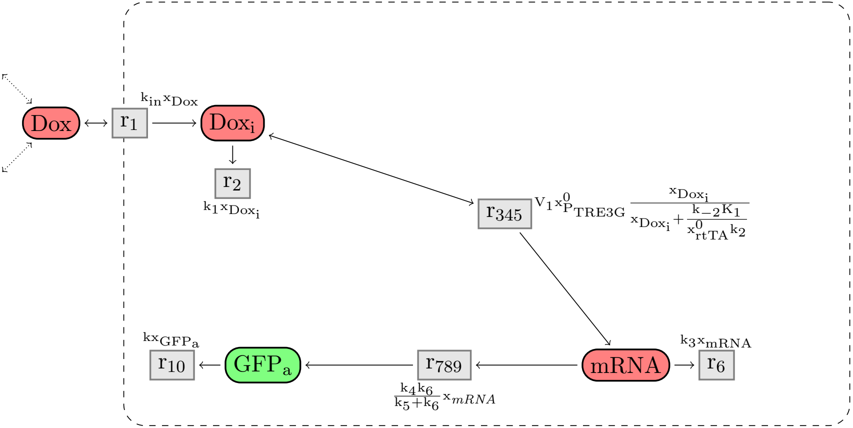

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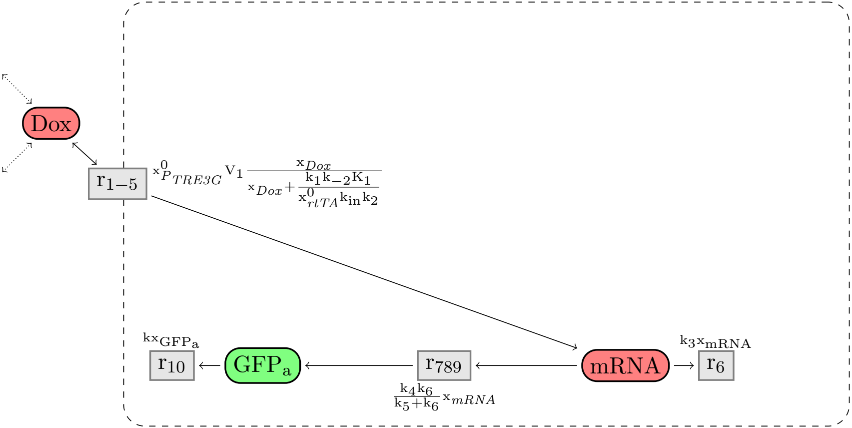

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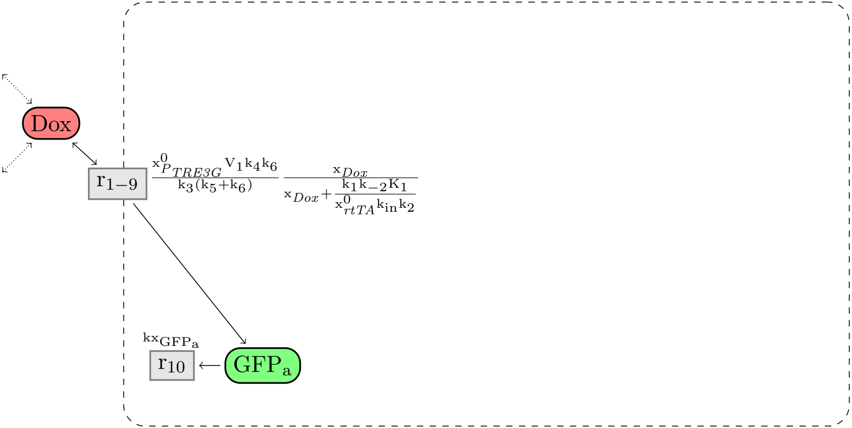
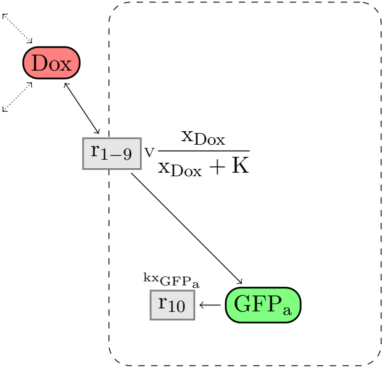


Tet-On simplified reaction network



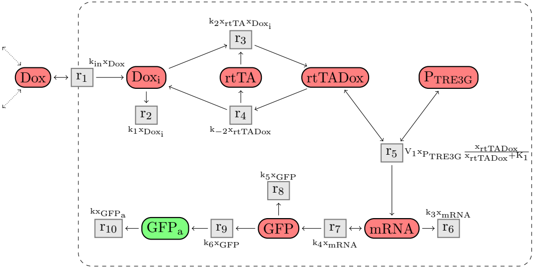
$$Dox \rightarrow Dox + GFP_a \; ; \; V\frac{x_{Dox}}{x_{Dox}+K}$$

$$GFP_a \rightarrow \emptyset \; ; \; kx_{GFP_a}$$

$$V = \frac{x^0_{P_{TRE3G}} V_1 k_4 k_6}{k_3(k_5 + k_6)}$$

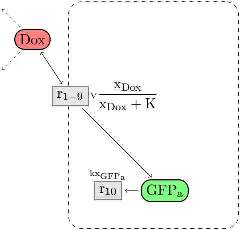
$$K = \frac{k_1 k_{-2} K_1}{x^0_{rtTA} k_{in} k_2}$$

Tet-On simplification



8 molecules
10 reactions
11 parameters

$\Rrightarrow^{\mathbf{E}}$



2 molecules
2 reactions
3 parameters

Conclusion

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- 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**