Gröbner bases in the study of chemical reaction networks

— What role can algebra play in the biochemistry of the future?

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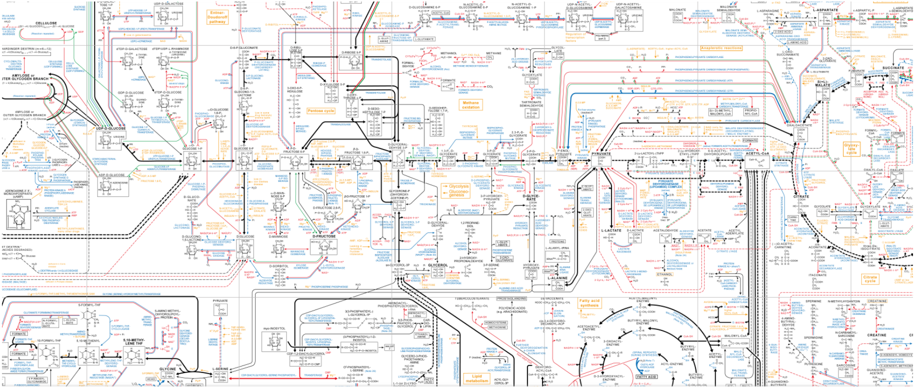

Screenshot from http://biochemical-pathways.com

Agenda

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1. Chemical reaction networks

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2. Gröbner bases

Agenda

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2. Gröbner bases
3. A promising example

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2. Gröbner bases
3. A promising example
4. Practical problems

What is a reaction network?

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\end{aligned}$$

Not just chemistry!

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Description	Reaction	Parameter value
Generation of new CD4+T cells	$\emptyset \xrightarrow{s_1} T$	10
Generation of new macrophages	$\emptyset \xrightarrow{s_2} M$	1.5×10^{-1}
Proliferation of T cells by presence of pathogen	$T + V \xrightarrow{k_1} (T+V) + T$	2×10^{-3}
Infection of T cells by HIV	$T + V \xrightarrow{k_2} T_i$	3×10^{-3}
Proliferation of M by presence of pathogen	$M + V \xrightarrow{k_3} (M+V) + M$	7.45×10^{-4}
Infection of M by HIV	$M + V \xrightarrow{k_4} M_i$	5.22×10^{-4}
Proliferation of HIV within CD4+T cell	$T_i \xrightarrow{k_5} V + T_i$	5.37×10^{-1}
Proliferation of HIV within macrophage	$M_i \xrightarrow{k_6} V + M_i$	2.85×10^{-1}
Natural death of CD4+T cells	$T \xrightarrow{\delta_1} \emptyset$	0.01
Natural death of infected T cells	$T_i \xrightarrow{\delta_2} \emptyset$	0.44
Natural death of macrophages	$M \xrightarrow{\delta_3} \emptyset$	6.6×10^{-3}
Natural death of infected macrophages	$M_i \xrightarrow{\delta_4} \emptyset$	6.6×10^{-3}
Natural death of HIV	$V \xrightarrow{\delta_5} \emptyset$	3

Gross, Davis, Ho, Bates & Harrington (2016)

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Natural death of HIV	$V \xrightarrow{\delta_5} \emptyset$	3

Gross, Davis, Ho, Bates & Harrington (2016)

$$
\begin{aligned}
[T]' &= s_1 + k_1[T][V] - k_2[T][V] - \delta_1[T] \\
[T_i]' &= k_2[T][V] - \delta_2[T_i] \\
[M]' &= s_2 + k_3[M][V] - k_4[M][V] - \delta_3[M] \\
[M_i]' &= k_4[M][V] - \delta_4[M_i] \\
[V]' &= k_5[T_i] + k_6[M_i] - \delta_5[V]
\end{aligned}
$$

An example from the news!

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$$\mathsf{A} + \mathsf{B} \xrightarrow{\beta} 2\,\mathsf{B}$$
$$\mathsf{B} \xrightarrow{\gamma} \mathsf{C}$$

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$$\mathrm{A} + \mathrm{B} \xrightarrow{\beta} 2\,\mathrm{B}$$
$$\mathrm{B} \xrightarrow{\gamma} \mathrm{C}$$

$$[\mathrm{A}]' = -\beta[\mathrm{A}][\mathrm{B}]$$
$$[\mathrm{B}]' = \beta[\mathrm{A}][\mathrm{B}] - \gamma[\mathrm{B}]$$
$$[\mathrm{C}]' = \gamma[\mathrm{B}]$$

An example from the news!

$$\mathsf{S} + \mathtt{I} \xrightarrow{\beta} 2\,\mathtt{I}$$
$$\mathtt{I} \xrightarrow{\gamma} \mathsf{R}$$

$$[\mathsf{S}]' = -\beta[\mathsf{S}][\mathtt{I}]$$
$$[\mathtt{I}]' = \beta[\mathsf{S}][\mathtt{I}] - \gamma[\mathtt{I}]$$
$$[\mathsf{R}]' = \gamma[\mathtt{I}]$$

The dynamics of reaction networks

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What happens when $t \to \infty$?

The Selkov model for glycolysis

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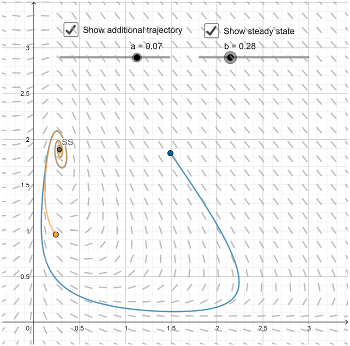
$$\mathsf{X} \xrightarrow{1} \varnothing$$
$$2\,\mathsf{X} + \mathsf{Y} \xrightarrow{1} 3\,\mathsf{X}$$
$$\varnothing \xrightarrow{b} \mathsf{Y} \xrightarrow{a} \mathsf{X}$$

The Selkov model for glycolysis

$$X \xrightarrow{1} \varnothing$$

$$2X + Y \xrightarrow{1} 3X$$

$$\varnothing \xrightarrow{b} Y \xrightarrow{a} X$$



The Selkov model for glycolysis

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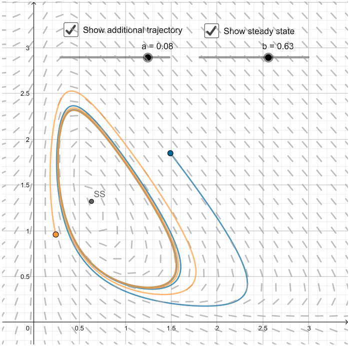


A network with multistability

A network with multistability

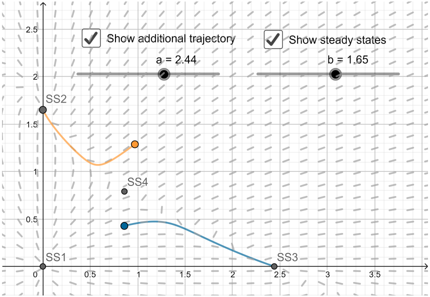
$$\mathsf{X} + \mathsf{Y} \xrightarrow{1} \mathsf{X} \underset{1}{\overset{a}{\rightleftharpoons}} 2\,\mathsf{X}$$

$$\mathsf{X} + \mathsf{Y} \xrightarrow{2} \mathsf{Y} \underset{1}{\overset{b}{\rightleftharpoons}} 2\,\mathsf{Y}$$

A network with multistability

$$X + Y \xrightarrow{1} X \underset{1}{\overset{a}{\rightleftharpoons}} 2X$$

$$X + Y \xrightarrow{2} Y \underset{1}{\overset{b}{\rightleftharpoons}} 2Y$$



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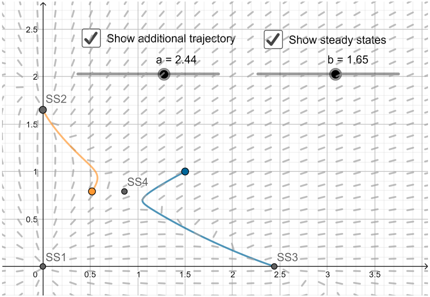

A network with multistability

$$X + Y \xrightarrow{1} X \underset{1}{\overset{a}{\rightleftharpoons}} 2X$$

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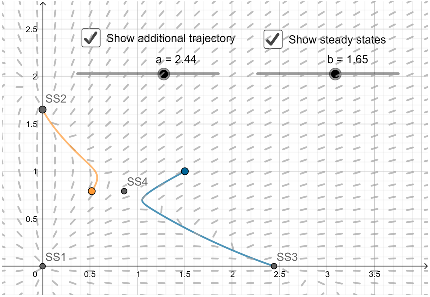

$$[X]' = a[X] - [X]^2 - 2[X][Y]$$

$$[Y]' = b[Y] - [Y]^2 - [X][Y]$$

A network with multistability

$$\mathrm{X} + \mathrm{Y} \xrightarrow{1} \mathrm{X} \underset{1}{\overset{a}{\rightleftharpoons}} 2\,\mathrm{X}$$

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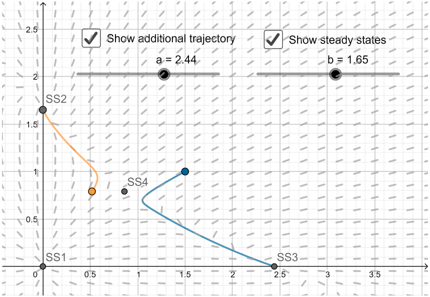

$$0 = a[X] - [X]^2 - 2[X][Y]$$
$$0 = b[Y] - [Y]^2 - [X][Y]$$

The long-term goal

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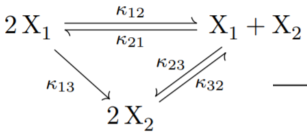
$$
\begin{tikzcd}
2\,X_1 \arrow[rr, shift left, "\kappa_{12}"] \arrow[dr, "\kappa_{13}"'] & & X_1 + X_2 \arrow[ll, shift left, "\kappa_{21}"] \arrow[dl, shift left, "\kappa_{23}"'] \\
& 2\,X_2 \arrow[ur, shift left, "\kappa_{32}"'] &
\end{tikzcd}
\longrightarrow
$$

$\longrightarrow$

Mathematical profile:

- Steady states
- Stability
- Oscilations
- Interesting regions of parameter space

The long-term goal



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Possible applications:

- Planning in synthetic biology

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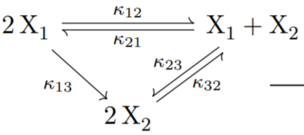

Mathematical profile:

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- Interesting regions of parameter space

Possible applications:

- Planning in synthetic biology
- Hypothesis testing in systems biology

The problem?

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Unknown rate constants!

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Forces us to work *algebraically* och *symbolically*.

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Gröbner bases:

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A method for rewriting a system of *polynomial* equations in a smart way

Gaussian elimination:

A method for rewriting a system of *linear* equations in a smart way

Example

$$x > y$$

$$\begin{aligned} 2x + 6y &= -6 \\ 5x + 2y &= 11 \end{aligned}$$

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$x > y$

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$$5 \cdot (2x + 6yy) = 5 \cdot (-6)$$
$$2 \cdot (5x + 2y) = 2 \cdot 11$$

Example

$$x > y$$

$$\begin{aligned} 2x + 6y &= -6 \\ 5x + 2y &= 11 \end{aligned}$$

$$\begin{aligned} 10x + 30y &= -30 \\ 10x + 4y &= 22 \end{aligned}$$

Example

$$x > y$$

$$\begin{aligned} 2x + 6y &= -6 \\ 5x + 2y &= 11 \end{aligned}$$

$$\begin{aligned} 10x + 30y &= -30 \\ -26y &= 52 \end{aligned}$$

Example

$$x > y$$

$$\begin{aligned} 2x + 6y &= -6 \\ 5x + 2y &= 11 \end{aligned}$$

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Example

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$$\begin{aligned} 10x - 60 &= -30 \\ y &= -2 \end{aligned}$$

Example

$x > y$

$$2x + 6y = -6$$
$$5x + 2y = 11$$

$$10x = 30$$
$$y = -2$$

Example

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$$\begin{aligned} 2x + 6y &= -6 \\ 5x + 2y &= 11 \end{aligned}$$

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Put differently: We knocked out the rows against each other!

$$S = 5 \cdot (2x + 6y + 6) - 2 \cdot (5x + 2y - 11) = 26y + 52$$

A polynomial example

$x > y$ (lex)

$$\begin{aligned} x^2 + 2xy^2 &= 0 \\ xy + 2y^3 - 1 &= 0 \end{aligned}$$

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$$S(f_2, f_3) = (xy + 2y^3 - 1) - {\color{red}y}x = 2y^3 - 1$$

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The Buchberger algorithm

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Input: $\mathcal{F} = \{f_1, \ldots, f_m\}$ och an "order of prioritization" for the variables.

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3. Identify the leading terms and "knock them out" by setting $S = \sigma p + \tau q$ for appropriate polynomials σ and τ.

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4. Reduce S with respect to the other elements in $\mathcal{G}$. If there is a remainder (i.e. S “contributes something new”), then add it to $\mathcal{G}$.

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6. Keep going until all possible pairs of polynomials in $\mathcal{G}$ (including newcommers) have been investigated.

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4. Reduce S with respect to the other elements in $\mathcal{G}$. If there is a remainder (i.e. S "contributes something new"), then add it to $\mathcal{G}$.
5. Go back to Step 2.
6. Keep going until all possible pairs of polynomials in $\mathcal{G}$ (including newcommers) have been investigated.
7. Clean up $\mathcal{G}$.

Example

$x > y > z$ (lex)

$$
\begin{aligned}
x^2 + y^2 + z^2 - 4 &= 0 \\
x^2 + 2y^2 - 5 &= 0 \\
xz - 1 &= 0
\end{aligned}
$$

Example

$$x > y > z \text{ (lex)}$$

$$\begin{aligned} x^2 + y^2 + z^2 - 4 &= 0 \\ x^2 + 2y^2 - 5 &= 0 \\ xz - 1 &= 0 \end{aligned}$$

$$\begin{aligned} x - 3z + 2z^3 &= 0 \\ y^2 - z^2 - 1 &= 0 \\ 2z^4 - 3z^2 + 1 &= 0 \end{aligned}$$

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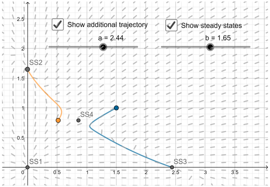
$$\begin{aligned} x - 3z + 2z^3 &= 0 \\ y^2 - z^2 - 1 &= 0 \\ 2z^4 - 3z^2 + 1 &= 0 \end{aligned}$$

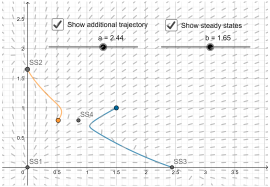
In total: 8 solutions!

Example



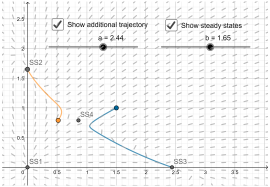
Show additional trajectory
Show steady states
a = 2.44
b = 1.65
SS1
SS2
SS3
SS4

Example



$$ax - x^2 - 2xy = 0$$
$$by - y^2 - xy = 0$$

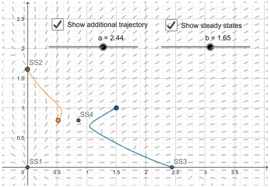
Example



$$ax - x^2 - 2xy = 0$$
$$by - y^2 - xy = 0$$

$$\begin{aligned} by + xy + y^2 &= 0 \\ -ax + 2by + x^2 - 2y^2 &= 0 \\ y^3 - ay^2 + (ab - b^2)y &= 0 \end{aligned}$$

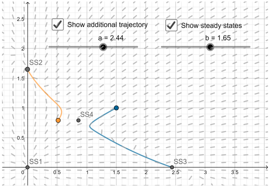
Example



$$ax - x^2 - 2xy = 0$$
$$by - y^2 - xy = 0$$

$$\begin{aligned} by + xy + y^2 &= 0 \\ -ax + 2by + x^2 - 2y^2 &= 0 \\ y(b-y)(-b+a-y) &= 0 \end{aligned}$$

Example



$$ax - x^2 - 2xy = 0$$
$$by - y^2 - xy = 0$$

$$by + xy + y^2 = 0$$
$$-ax + 2by + x^2 - 2y^2 = 0$$
$$y(b - y)(-b + a - y) = 0$$

Solutions: $(0, 0), (0, b), (a, 0), (-a + 2b, a - b)$.

A promising example from the literature:

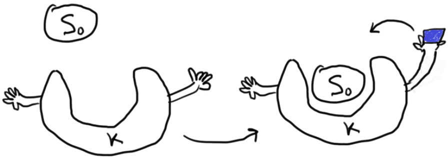
A promising example from the literature:

Biochemical hypothesis testing

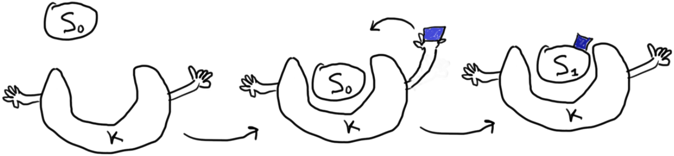
Phosphorylation/dephosphorylation

Phosphorylation/dephosphorylation

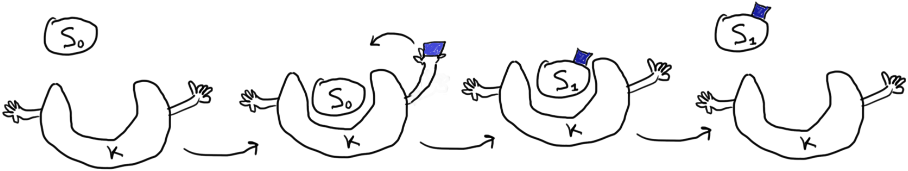
Phosphorylation/dephosphorylation



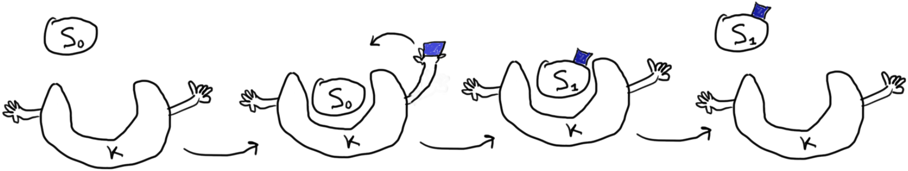
Phosphorylation/dephosphorylation



Phosphorylation/dephosphorylation

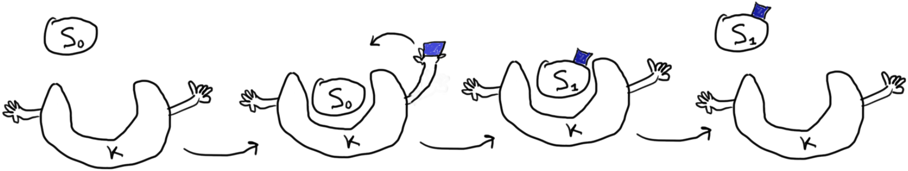


Phosphorylation/dephosphorylation



$$K + S_0 \underset{b}{\overset{a}{\rightleftharpoons}} KS_0 \xrightarrow{c} K + S_1$$

Phosphorylation/dephosphorylation



$$K + S_0 \underset{b}{\overset{a}{\rightleftharpoons}} KS_0 \xrightarrow{c} K + S_1$$

$$F + S_1 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} FS_1 \xrightarrow{\gamma} F + S_0$$

Double phosphorylation

Double phosphorylation

$$\mathsf{K} + \mathsf{S}_{00} \underset{b_{00}}{\overset{a_{00}}{\rightleftharpoons}} \mathsf{KS}_{00} \begin{cases} \xrightarrow{c_{00,01}} \mathsf{K} + \mathsf{S}_{01} \\ \xrightarrow{c_{00,10}} \mathsf{K} + \mathsf{S}_{10} \\ \\ \end{cases}$$

Double phosphorylation

$$\mathrm{K} + \mathrm{S}_{00} \underset{b_{00}}{\overset{a_{00}}{\rightleftharpoons}} \mathrm{KS}_{00} \begin{cases} \xrightarrow{c_{00,01}} \mathrm{K} + \mathrm{S}_{01} \\ \xrightarrow{c_{00,10}} \mathrm{K} + \mathrm{S}_{10} \\ \end{cases}$$

$$\mathrm{K} + \mathrm{S}_{01} \underset{b_{01}}{\overset{a_{01}}{\rightleftharpoons}} \mathrm{KS}_{01} \xrightarrow{c_{01,11}} \mathrm{K} + \mathrm{S}_{11}$$

Double phosphorylation

$$\mathsf{K}+\mathsf{S}_{00} \underset{b_{00}}{\overset{a_{00}}{\rightleftharpoons}} \mathsf{KS}_{00} \begin{cases} \xrightarrow{c_{00,01}} \mathsf{K}+\mathsf{S}_{01} \\ \xrightarrow{c_{00,10}} \mathsf{K}+\mathsf{S}_{10} \\ \end{cases}$$

$$\mathsf{K}+\mathsf{S}_{01} \underset{b_{01}}{\overset{a_{01}}{\rightleftharpoons}} \mathsf{KS}_{01} \xrightarrow{c_{01,11}} \mathsf{K}+\mathsf{S}_{11}$$

$$\mathsf{K}+\mathsf{S}_{10} \underset{b_{10}}{\overset{a_{10}}{\rightleftharpoons}} \mathsf{KS}_{10} \xrightarrow{c_{10,11}} \mathsf{K}+\mathsf{S}_{11}$$

Double phosphorylation

$$K + S_{00} \underset{b_{00}}{\overset{a_{00}}{\rightleftharpoons}} KS_{00} \begin{cases} \xrightarrow{c_{00,01}} K + S_{01} \\ \xrightarrow{c_{00,10}} K + S_{10} \end{cases}$$

$$K + S_{01} \underset{b_{01}}{\overset{a_{01}}{\rightleftharpoons}} KS_{01} \xrightarrow{c_{01,11}} K + S_{11}$$

$$K + S_{10} \underset{b_{10}}{\overset{a_{10}}{\rightleftharpoons}} KS_{10} \xrightarrow{c_{10,11}} K + S_{11}$$

$$F + S_{01} \underset{\beta_{01}}{\overset{\alpha_{01}}{\rightleftharpoons}} FS_{01} \xrightarrow{\gamma_{01,00}} F + S_{00}$$

$$F + S_{10} \underset{\beta_{10}}{\overset{\alpha_{10}}{\rightleftharpoons}} FS_{10} \xrightarrow{\gamma_{10,00}} F + S_{00}$$

$$F + S_{11} \underset{\beta_{11}}{\overset{\alpha_{11}}{\rightleftharpoons}} FS_{11} \begin{cases} \xrightarrow{\gamma_{11,01}} F + S_{01} \\ \xrightarrow{\gamma_{11,10}} F + S_{10} \end{cases}$$

Double phosphorylation

$$\mathrm{K} + \mathrm{S}_{00} \underset{b_{00}}{\overset{a_{00}}{\rightleftharpoons}} \mathrm{KS}_{00} \begin{cases} \xrightarrow{c_{00,01}} \mathrm{K} + \mathrm{S}_{01} \\ \xrightarrow{c_{00,10}} \mathrm{K} + \mathrm{S}_{10} \\ \xrightarrow{c_{00,11}} \mathrm{K} + \mathrm{S}_{11} \end{cases}$$

$$\mathrm{K} + \mathrm{S}_{01} \underset{b_{01}}{\overset{a_{01}}{\rightleftharpoons}} \mathrm{KS}_{01} \xrightarrow{c_{01,11}} \mathrm{K} + \mathrm{S}_{11}$$

$$\mathrm{K} + \mathrm{S}_{10} \underset{b_{10}}{\overset{a_{10}}{\rightleftharpoons}} \mathrm{KS}_{10} \xrightarrow{c_{10,11}} \mathrm{K} + \mathrm{S}_{11}$$

$$\mathrm{F} + \mathrm{S}_{01} \underset{\beta_{01}}{\overset{\alpha_{01}}{\rightleftharpoons}} \mathrm{FS}_{01} \xrightarrow{\gamma_{01,00}} \mathrm{F} + \mathrm{S}_{00}$$

$$\mathrm{F} + \mathrm{S}_{10} \underset{\beta_{10}}{\overset{\alpha_{10}}{\rightleftharpoons}} \mathrm{FS}_{10} \xrightarrow{\gamma_{10,00}} \mathrm{F} + \mathrm{S}_{00}$$

$$\mathrm{F} + \mathrm{S}_{11} \underset{\beta_{11}}{\overset{\alpha_{11}}{\rightleftharpoons}} \mathrm{FS}_{11} \begin{cases} \xrightarrow{\gamma_{11,01}} \mathrm{F} + \mathrm{S}_{01} \\ \xrightarrow{\gamma_{11,10}} \mathrm{F} + \mathrm{S}_{10} \end{cases}$$

Differential equations

```
dK/dt =
-a00*K*S00 + b00*KS00 + c0001*KS00 +
c0010*KS00 -a01*K*S01 + b01*KS01 + c0111*KS01
-a10*K*S10 + b10*KS10 + c1011*KS10
+ c0011*KS00

dF/dt =
-alpha01*F*S01 + beta01*FS01 + gamma0100*FS01
-alpha10*F*S10 + beta10*FS10 + gamma1000*FS10
-alpha11*F*S11 + beta11*FS11 + gamma1101*FS11
+ gamma1110*FS11

dS00/dt =
-a00*K*S00 + b00*KS00 + gamma0100*FS01 +
gamma1000*FS10

dS01/dt =
-a01*K*S01 + b01*KS01 - alpha01*F*S01 +
beta01*FS01 + c0001*KS00 + gamma1101*FS11

dS10/dt =
-a10*K*S10 + b10*KS10 - alpha10*F*S10 +
beta10*FS10 + c0010*KS00 + gamma1110*FS11

dS11/dt =
-alpha11*F*S11 + beta11*FS11 + c0111*KS01 +
c1011*KS10 + c0011*KS00

dKS00/dt =
a00*K*S00 - b00*KS00 - c0001*KS00 - c0010*KS00
- c0011*KS00

dKS01/dt =
a01*K*S01 - b01*KS01 - c0111*KS01

dKS10/dt =
a10*K*S10 - b10*KS10 - c1011*KS10

dFS01/dt =
alpha01*F*S01 - beta01*FS01 - gamma0100*FS01

dFS10/dt =
alpha10*F*S10 - beta10*FS10 - gamma1000*FS10

dFS11/dt =
alpha11*F*S11 - beta11*FS11 - gamma1101*FS11 -
gamma1110*FS11
```

Steady state equations

```
0 =
-a00*K*S00 + b00*KS00 + c0001*KS00 +
c0010*KS00 -a01*K*S01 + b01*KS01 + c0111*KS01
-a10*K*S10 + b10*KS10 + c1011*KS10
+ c0011*KS00

0 =
-alpha01*F*S01 + beta01*FS01 + gamma0100*FS01
-alpha10*F*S10 + beta10*FS10 + gamma1000*FS10
-alpha11*F*S11 + beta11*FS11 + gamma1101*FS11
+ gamma1110*FS11

0 =
-a00*K*S00 + b00*KS00 + gamma0100*FS01 +
gamma1000*FS10

0 =
-a01*K*S01 + b01*KS01 - alpha01*F*S01 +
beta01*FS01 + c0001*KS00 + gamma1101*FS11

0 =
-a10*K*S10 + b10*KS10 - alpha10*F*S10 +
beta10*FS10 + c0010*KS00 + gamma1110*FS11

0 =
-alpha11*F*S11 + beta11*FS11 + c0111*KS01 +
c1011*KS10 + c0011*KS00

0 =
a00*K*S00 - b00*KS00 - c0001*KS00 - c0010*KS00
- c0011*KS00

0 =
a01*K*S01 - b01*KS01 - c0111*KS01

0 =
a10*K*S10 - b10*KS10 - c1011*KS10

0 =
alpha01*F*S01 - beta01*FS01 - gamma0100*FS01

0 =
alpha10*F*S10 - beta10*FS10 - gamma1000*FS10

0 =
alpha11*F*S11 - beta11*FS11 - gamma1101*FS11 -
gamma1110*FS11
```

Steady state equations

```
0 =
-a00*K*S00 + b00*KS00 + c0001*KS00 +
c0010*KS00 -a01*K*S01 + b01*KS01 + c0111*KS01
-a10*K*S10 + b10*KS10 + c1011*KS10
+ c0011*KS00

0 =
-alpha01*F*S01 + beta01*FS01 + gamma0100*FS01
-alpha10*F*S10 + beta10*FS10 + gamma1000*FS10
-alpha11*F*S11 + beta11*FS11 + gamma1101*FS11
+ gamma1110*FS11

0 =
-a00*K*S00 + b00*KS00 + gamma0100*FS01 +
gamma1000*FS10

0 =
-a01*K*S01 + b01*KS01 - alpha01*F*S01 +
beta01*FS01 + c0001*KS00 + gamma1101*FS11

0 =
-a10*K*S10 + b10*KS10 - alpha10*F*S10 +
beta10*FS10 + c0010*KS00 + gamma1110*FS11

0 =
-alpha11*F*S11 + beta11*FS11 + c0111*KS01 +
c1011*KS10 + c0011*KS00

0 =
a00*K*S00 - b00*KS00 - c0001*KS00 - c0010*KS00
- c0011*KS00

0 =
a01*K*S01 - b01*KS01 - c0111*KS01

0 =
a10*K*S10 - b10*KS10 - c1011*KS10

0 =
alpha01*F*S01 - beta01*FS01 - gamma0100*FS01

0 =
alpha10*F*S10 - beta10*FS10 - gamma1000*FS10

0 =
alpha11*F*S11 - beta11*FS11 - gamma1101*FS11 -
gamma1110*FS11
```

Problem: We can only measure $[S_{00}]$, $[S_{01}]$, $[S_{10}]$ och $[S_{11}]$.

Steady state equations

```
0 =
-a00*K*S00 + b00*KS00 + c0001*KS00 +
c0010*KS00 -a01*K*S01 + b01*KS01 + c0111*KS01
-a10*K*S10 + b10*KS10 + c1011*KS10
+ c0011*KS00

0 =
-alpha01*F*S01 + beta01*FS01 + gamma0100*FS01
-alpha10*F*S10 + beta10*FS10 + gamma1000*FS10
-alpha11*F*S11 + beta11*FS11 + gamma1101*FS11
+ gamma1110*FS11

0 =
-a00*K*S00 + b00*KS00 + gamma0100*FS01 +
gamma1000*FS10

0 =
-a01*K*S01 + b01*KS01 - alpha01*F*S01 +
beta01*FS01 + c0001*KS00 + gamma1101*FS11

0 =
-a10*K*S10 + b10*KS10 - alpha10*F*S10 +
beta10*FS10 + c0010*KS00 + gamma1110*FS11

0 =
-alpha11*F*S11 + beta11*FS11 + c0111*KS01 +
c1011*KS10 + c0011*KS00

0 =
a00*K*S00 - b00*KS00 - c0001*KS00 - c0010*KS00
- c0011*KS00

0 =
a01*K*S01 - b01*KS01 - c0111*KS01

0 =
a10*K*S10 - b10*KS10 - c1011*KS10

0 =
alpha01*F*S01 - beta01*FS01 - gamma0100*FS01

0 =
alpha10*F*S10 - beta10*FS10 - gamma1000*FS10

0 =
alpha11*F*S11 - beta11*FS11 - gamma1101*FS11 -
gamma1110*FS11
```

Problem: We can only measure $[S_{00}]$, $[S_{01}]$, $[S_{10}]$ och $[S_{11}]$.

Idea: Compute a Gröbner basis that eliminates variables!

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

In [1]:
```
A.<a00,a01,a10,b00,b01,b10,c0001,c0010,c0111,c1011,c0011,alpha01,alpha10,alpha11,beta01,beta10,beta11,gamma0100,gamma1000,gamma1
F = A.fraction_field()
R.<KS00,KS01,KS10,FS01,FS10,FS11,K,F,S00,S01,S10,S11> = PolynomialRing(F, 12, order='lex')
```

In [2]:
```
I = Ideal([-a00*K*S00 + b00*KS00 + c0001*KS00 + c0010*KS00 + c0011*KS00 -a01*K*S01 + b01*KS01 + c0111*KS01-a10*K*S10 + b10*KS10 
-alpha01*F*S01 + beta01*FS01 + gamma0100*FS01-alpha10*F*S10 + beta10*FS10 + gamma1000*FS10-alpha11*F*S11 + beta11*FS11 + gamma11
-a00*K*S00 + b00*KS00 + gamma0100*FS01 + gamma1000*FS10,
-a01*K*S01 + b01*KS01 - alpha01*F*S01 + beta01*FS01 + c0001*KS00 + gamma1101*FS11,
-a10*K*S10 + b10*KS10 - alpha10*F*S10 + beta10*FS10 + c0010*KS00 + gamma1110*FS11,
-alpha11*F*S11 + beta11*FS11 + c0111*KS01 + c1011*KS10 + c0011*KS00,
a00*K*S00 - b00*KS00 - c0001*KS00 - c0010*KS00 - c0011*KS00,
a01*K*S01 - b01*KS01 - c0111*KS01,
a10*K*S10 - b10*KS10 - c1011*KS10,
alpha01*F*S01 - beta01*FS01 - gamma0100*FS01,
alpha10*F*S10 - beta10*FS10 - gamma1000*FS10,
alpha11*F*S11  - beta11*FS11 - gamma1101*FS11 - gamma1110*FS11]
)
```

In [3]:
```
G = I.groebner_basis()
```

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

```
In [4]: G[-1]

Out[4]: F*S01^2 + ((a10*b01*c0010*c1011*alpha01*beta10*gamma0100 + a10*c0010*c0111*c1011*alpha01*beta10*gamma0100 + a10*b01*c1011*c0011
*alpha01*beta10*gamma0100 + a10*c0111*c1011*c0011*alpha01*beta10*gamma0100 - a01*b10*c0001*c0111*alpha10*beta01*gamma1000 - a01
*c0001*c0111*c1011*alpha10*beta01*gamma1000 - a01*b10*c0111*c0011*alpha10*beta01*gamma1000 - a01*c0111*c1011*c0011*alpha10*beta
01*gamma1000 + a10*b01*c0010*c1011*alpha01*gamma0100*gamma1000 + a10*c0010*c0111*c1011*alpha01*gamma0100*gamma1000 + a10*b01*c1
011*c0011*alpha01*gamma0100*gamma1000 + a10*c0111*c1011*c0011*alpha01*gamma0100*gamma1000 - a01*b10*c0001*c0111*alpha10*gamma01
00*gamma1000 - a01*c0001*c0111*c1011*alpha10*gamma0100*gamma1000 - a01*b10*c0111*c0011*alpha10*gamma0100*gamma1000 - a01*c0111*
c1011*c0011*alpha10*gamma0100*gamma1000)/(a01*b10*c0010*c0111*alpha01*beta10*gamma0100 + a01*c0010*c0111*c1011*alpha01*beta10*g
amma0100 + a01*b10*c0010*c0111*alpha01*gamma0100*gamma1000 + a01*c0010*c0111*c1011*alpha01*gamma0100*gamma1000))*F*S01*S10 +
((c0001*alpha11*beta01*gamma1110 + c0010*alpha11*beta01*gamma1110 + c0011*alpha11*beta01*gamma1110 + c0001*alpha11*gamma0100*ga
mma1110 + c0010*alpha11*gamma0100*gamma1110 + c0011*alpha11*gamma0100*gamma1110)/(c0010*alpha01*beta11*gamma0100 + c0010*alpha0
1*gamma0100*gamma1101 + c0010*alpha01*gamma0100*gamma1110))*F*S01*S11 + ((-a10*b01*c0001*c1011*alpha10*beta01*gamma1000 - a10*c
0001*c0111*c1011*alpha10*beta01*gamma1000 - a10*b01*c0001*c1011*alpha10*gamma0100*gamma1000 - a10*c0001*c0111*c1011*alpha10*gam
ma0100*gamma1000)/(a01*b10*c0010*c0111*alpha01*beta10*gamma0100 + a01*c0010*c0111*c1011*alpha01*beta10*gamma0100 + a01*b10*c001
0*c0111*alpha01*gamma0100*gamma1000 + a01*c0010*c0111*c1011*alpha01*gamma0100*gamma1000))*F*S10^2 + ((-a10*b01*c0001*c1011*alph
a11*beta01*gamma1101 - a10*b01*c0010*c1011*alpha11*beta01*gamma1101 - a10*c0001*c0111*c1011*alpha11*beta01*gamma1101 - a10*c001
0*c0111*c1011*alpha11*beta01*gamma1101 - a10*b01*c1011*c0011*alpha11*beta01*gamma1101 - a10*c0111*c1011*c0011*alpha11*beta01*ga
mma1101 - a10*b01*c0001*c1011*alpha11*gamma0100*gamma1101 - a10*b01*c0010*c1011*alpha11*gamma0100*gamma1101 - a10*c0001*c0111*c
1011*alpha11*gamma0100*gamma1101 - a10*c0010*c0111*c1011*alpha11*gamma0100*gamma1101 - a10*b01*c1011*c0011*alpha11*gamma0100*ga
mma1101 - a10*c0111*c1011*c0011*alpha11*gamma0100*gamma1101)/(a01*b10*c0010*c0111*alpha01*beta11*gamma0100 + a01*c0010*c0111*c1
011*alpha01*beta11*gamma0100 + a01*b10*c0010*c0111*alpha01*gamma0100*gamma1101 + a01*c0010*c0111*c1011*alpha01*gamma0100*gamma1
101 + a01*b10*c0010*c0111*alpha01*gamma0100*gamma1110 + a01*c0010*c0111*c1011*alpha01*gamma0100*gamma1110))*F*S10*S11
```

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

```
In [5]: G[-2]

Out[5]: F*S00*S10 + ((-c0010*alpha11*beta10*gamma1101 - c0010*alpha11*gamma1000*gamma1101 - c0010*alpha11*beta10*gamma1110 - c0011*alph
        a11*beta10*gamma1110 - c0010*alpha11*gamma1000*gamma1110 - c0011*alpha11*gamma1000*gamma1110)/(c0011*alpha10*beta11*gamma1000 +
        c0011*alpha10*gamma1000*gamma1101 + c0011*alpha10*gamma1000*gamma1110))*F*S00*S11 + ((a01*b00*c0111 + a01*c0001*c0111 + a01*c00
        10*c0111 + a01*c0111*c0011)/(a00*b01*c0011 + a00*c0111*c0011))*F*S01*S10 + ((-a01*b00*c0111*alpha11*beta10*gamma1110 - a01*c000
        1*c0111*alpha11*beta10*gamma1110 - a01*c0010*c0111*alpha11*beta10*gamma1110 - a01*c0111*c0011*alpha11*beta10*gamma1110 - a01*b0
        0*c0111*alpha11*gamma1000*gamma1110 - a01*c0001*c0111*alpha11*gamma1000*gamma1110 - a01*c0010*c0111*alpha11*gamma1000*gamma1110
        - a01*c0111*c0011*alpha11*gamma1000*gamma1110)/(a00*b01*c0011*alpha10*beta11*gamma1000 + a00*c0111*c0011*alpha10*beta11*gamma10
        00 + a00*b01*c0011*alpha10*gamma1000*gamma1101 + a00*c0111*c0011*alpha10*gamma1000*gamma1101 + a00*b01*c0011*alpha10*gamma1000*
        gamma1110 + a00*c0111*c0011*alpha10*gamma1000*gamma1110))*F*S01*S11 + ((a10*b00*c1011 + a10*c0001*c1011 + a10*c0010*c1011 + a10
        *c1011*c0011)/(a00*b10*c0011 + a00*c1011*c0011))*F*S10^2 + ((a10*b00*c1011*alpha11*beta10*gamma1101 + a10*c0001*c1011*alpha11*b
        eta10*gamma1101 + a10*c0010*c1011*alpha11*beta10*gamma1101 + a10*c1011*c0011*alpha11*beta10*gamma1101 + a10*b00*c1011*alpha11*g
        amma1000*gamma1101 + a10*c0001*c1011*alpha11*gamma1000*gamma1101 + a10*c0010*c1011*alpha11*gamma1000*gamma1101 + a10*c1011*c001
        1*alpha11*gamma1000*gamma1101)/(a00*b10*c0011*alpha10*beta11*gamma1000 + a00*c1011*c0011*alpha10*beta11*gamma1000 + a00*b10*c00
        11*alpha10*gamma1000*gamma1101 + a00*c1011*c0011*alpha10*gamma1000*gamma1101 + a00*b10*c0011*alpha10*gamma1000*gamma1110 + a00*
        c1011*c0011*alpha10*gamma1000*gamma1110))*F*S10*S11
```

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

```
F*S00*S11 +

((-a01*b00*c0111*alpha10*beta11*gamma1000 - a01*c0001*c0111*alpha10*beta11*gamma1000 - a01*c0010*c0111*alpha10*beta11*gamma1000 -
a01*b00*c0111*alpha10*gamma1000*gamma1101 - a01*c0001*c0111*alpha10*gamma1000*gamma1101 - a01*c0010*c0111*alpha10*gamma1000*gamma1101 -
a01*b00*c0111*alpha10*gamma1000*gamma1110 - a01*c0001*c0111*alpha10*gamma1000*gamma1110 - a01*c0010*c0111*alpha10*gamma1000*gamma1110)/
(a00*b01*c0010*alpha11*beta10*gamma1101 + a00*c0010*c0111*alpha11*beta10*gamma1101 + a00*b01*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c0111*alpha11*gamma1000*gamma1101 + a00*b01*c0010*alpha11*beta10*gamma1110 + a00*c0010*c0111*alpha11*beta10*gamma1110 +
a00*b01*c0010*alpha11*gamma1000*gamma1110 + a00*c0010*c0111*alpha11*gamma1000*gamma1110))*F*S01*S10 +

((a01*b00*c0111*gamma1110 + a01*c0001*c0111*gamma1110 + a01*c0010*c0111*gamma1110)/(a00*b01*c0010*gamma1101 + a00*c0010*c0111*gamma1101 +
a00*b01*c0010*gamma1110 + a00*c0010*c0111*gamma1110))*F*S01*S11

+ ((-a10*b00*c1011*alpha10*beta11*gamma1000 - a10*c0001*c1011*alpha10*beta11*gamma1000 - a10*c0010*c1011*alpha10*beta11*gamma1000 -
a10*b00*c1011*alpha10*gamma1000*gamma1101 - a10*c0001*c1011*alpha10*gamma1000*gamma1101 - a10*c0010*c1011*alpha10*gamma1000*gamma1101 -
a10*b00*c1011*alpha10*gamma1000*gamma1110 - a10*c0001*c1011*alpha10*gamma1000*gamma1110 - a10*c0010*c1011*alpha10*gamma1000*gamma1110)/
(a00*b10*c0010*alpha11*beta10*gamma1101 + a00*c0010*c1011*alpha11*beta10*gamma1101 + a00*b10*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c1011*alpha11*gamma1000*gamma1101 + a00*b10*c0010*alpha11*beta10*gamma1110 + a00*c0010*c1011*alpha11*beta10*gamma1110 +
a00*b10*c0010*alpha11*gamma1000*gamma1110 + a00*c0010*c1011*alpha11*gamma1000*gamma1110))*F*S10^2

+ ((-a10*b00*c1011*gamma1101 - a10*c0001*c1011*gamma1101 - a10*c0010*c1011*gamma1101)/(a00*b10*c0010*gamma1101 + a00*c0010*c1011*gamma1101 +
a00*b10*c0010*gamma1110 + a00*c0010*c1011*gamma1110))*F*S10*S11
```

Gröbner basis computation

(Model without simultaneous double phosphorylation.)

```
F*S00*S11 +

((-a01*b00*c0111*alpha10*beta11*gamma1000 - a01*c0001*c0111*alpha10*beta11*gamma1000 - a01*c0010*c0111*alpha10*beta11*gamma1000 -
a01*b00*c0111*alpha10*gamma1000*gamma1101 - a01*c0001*c0111*alpha10*gamma1000*gamma1101 - a01*c0010*c0111*alpha10*gamma1000*gamma1101 -
a01*b00*c0111*alpha10*gamma1000*gamma1110 - a01*c0001*c0111*alpha10*gamma1000*gamma1110 - a01*c0010*c0111*alpha10*gamma1000*gamma1110)/
(a00*b01*c0010*alpha11*beta10*gamma1101 + a00*c0010*c0111*alpha11*beta10*gamma1101 + a00*b01*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c0111*alpha11*gamma1000*gamma1101 + a00*b01*c0010*alpha11*beta10*gamma1110 + a00*c0010*c0111*alpha11*beta10*gamma1110 +
a00*b01*c0010*alpha11*gamma1000*gamma1110 + a00*c0010*c0111*alpha11*gamma1000*gamma1110))*F*S01*S10 +

((a01*b00*c0111*gamma1110 + a01*c0001*c0111*gamma1110 + a01*c0010*c0111*gamma1110)/(a00*b01*c0010*gamma1101 + a00*c0010*c0111*gamma1101 +
a00*b01*c0010*gamma1110 + a00*c0010*c0111*gamma1110))*F*S01*S11

+ ((-a10*b00*c1011*alpha10*beta11*gamma1000 - a10*c0001*c1011*alpha10*beta11*gamma1000 - a10*c0010*c1011*alpha10*beta11*gamma1000 -
a10*b00*c1011*alpha10*gamma1000*gamma1101 - a10*c0001*c1011*alpha10*gamma1000*gamma1101 - a10*c0010*c1011*alpha10*gamma1000*gamma1101 -
a10*b00*c1011*alpha10*gamma1000*gamma1110 - a10*c0001*c1011*alpha10*gamma1000*gamma1110 - a10*c0010*c1011*alpha10*gamma1000*gamma1110)/
(a00*b10*c0010*alpha11*beta10*gamma1101 + a00*c0010*c1011*alpha11*beta10*gamma1101 + a00*b10*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c1011*alpha11*gamma1000*gamma1101 + a00*b10*c0010*alpha11*beta10*gamma1110 + a00*c0010*c1011*alpha11*beta10*gamma1110 +
a00*b10*c0010*alpha11*gamma1000*gamma1110 + a00*c0010*c1011*alpha11*gamma1000*gamma1110))*F*S10^2

+ ((-a10*b00*c1011*gamma1101 - a10*c0001*c1011*gamma1101 - a10*c0010*c1011*gamma1101)/(a00*b10*c0010*gamma1101 + a00*c0010*c1011*gamma1101 +
a00*b10*c0010*gamma1110 + a00*c0010*c1011*gamma1110))*F*S10*S11
```

$$\mu_1[\mathrm{S}_{00}][\mathrm{S}_{11}] + \mu_2[\mathrm{S}_{01}][\mathrm{S}_{10}] + \mu_3[\mathrm{S}_{01}][\mathrm{S}_{11}] + \mu_4[\mathrm{S}_{10}]^2 + \mu_5[\mathrm{S}_{10}][\mathrm{S}_{11}] = 0$$

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```
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((-a01*b00*c0111*alpha10*beta11*gamma1000 - a01*c0001*c0111*alpha10*beta11*gamma1000 - a01*c0010*c0111*alpha10*beta11*gamma1000 -
a01*b00*c0111*alpha10*gamma1000*gamma1101 - a01*c0001*c0111*alpha10*gamma1000*gamma1101 - a01*c0010*c0111*alpha10*gamma1000*gamma1101 -
a01*b00*c0111*alpha10*gamma1000*gamma1110 - a01*c0001*c0111*alpha10*gamma1000*gamma1110 - a01*c0010*c0111*alpha10*gamma1000*gamma1110)/
(a00*b01*c0010*alpha11*beta10*gamma1101 + a00*c0010*c0111*alpha11*beta10*gamma1101 + a00*b01*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c0111*alpha11*gamma1000*gamma1101 + a00*b01*c0010*alpha11*beta10*gamma1110 + a00*c0010*c0111*alpha11*beta10*gamma1110 +
a00*b01*c0010*alpha11*gamma1000*gamma1110 + a00*c0010*c0111*alpha11*gamma1000*gamma1110))*F*S01*S10 +

((a01*b00*c0111*gamma1110 + a01*c0001*c0111*gamma1110 + a01*c0010*c0111*gamma1110)/(a00*b01*c0010*gamma1101 + a00*c0010*c0111*gamma1101 +
a00*b01*c0010*gamma1110 + a00*c0010*c0111*gamma1110))*F*S01*S11

+ ((-a10*b00*c1011*alpha10*beta11*gamma1000 - a10*c0001*c1011*alpha10*beta11*gamma1000 - a10*c0010*c1011*alpha10*beta11*gamma1000 -
a10*b00*c1011*alpha10*gamma1000*gamma1101 - a10*c0001*c1011*alpha10*gamma1000*gamma1101 - a10*c0010*c1011*alpha10*gamma1000*gamma1101 -
a10*b00*c1011*alpha10*gamma1000*gamma1110 - a10*c0001*c1011*alpha10*gamma1000*gamma1110 - a10*c0010*c1011*alpha10*gamma1000*gamma1110)/
(a00*b10*c0010*alpha11*beta10*gamma1101 + a00*c0010*c1011*alpha11*beta10*gamma1101 + a00*b10*c0010*alpha11*gamma1000*gamma1101 +
a00*c0010*c1011*alpha11*gamma1000*gamma1101 + a00*b10*c0010*alpha11*beta10*gamma1110 + a00*c0010*c1011*alpha11*beta10*gamma1110 +
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```

$$\mu_1[S_{00}][S_{11}] + \mu_2[S_{01}][S_{10}] + \mu_3[S_{01}][S_{11}] + \mu_4[S_{10}]^2 + \mu_5[S_{10}][S_{11}] = 0$$

Conclusion: If the model without simultaneous double phosphorylation is correct, then an equation on this form will hold for all steady states (independently of total concentrations).

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Sample	$[S_{00}]$	$[S_{01}]$	$[S_{10}]$	$[S_{11}]$	$([S_{00}][S_{11}], [S_{01}][S_{10}], [S_{01}][S_{11}], [S_{10}]^2, [S_{10}][S_{11}])$
#1	0.44	0.18	0.96	0.19	(0.10, 0.04, 0.18, 0.02, 0.04, 0.10)
#2	0.74	0.58	0.43	0.10	(0.05, 0.04, 0.25, 0.03, 0.01, 0.02)
#3	0.25	0.13	0.26	0.94	(0.42, 0.11, 0.03, 0.05, 0.89, 0.11)
#4	0.20	0.43	0.17	0.11	(0.31, 0.06, 0.07, 0.13, 0.01, 0.05)
#5	0.22	0.65	0.14	0.26	(0.39, 0.09, 0.09, 0.26, 0.07, 0.05)
#6	0.31	0.66	0.76	0.32	(0.39, 0.12, 0.50, 0.26, 0.10, 0.30)
#7	0.25	0.47	0.24	0.53	(0.86, 0.21, 0.11, 0.40, 0.28, 0.21)
#8	0.17	0.72	0.51	0.01	(0.29, 0.05, 0.37, 0.21, 0.00, 0.15)
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- No, $\sigma_{\min} = 0.062 \gg 0$. Hence, the hypothesis is falsified!

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- Gröbner bases for systems with many variables take a long time to compute.
- The last few years, new methods for computing Gröbner bases for reaction networks have been proposed, that make use of *intermediates* to reduce the computation times:

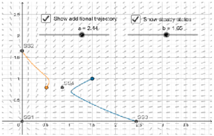
  A. Sadeghimanesh and E. Feliu, *Gröbner Bases of Reaction Networks with Intermediate Species*, Adv. Appl. Math. **107** (2019): 74–101.

Summary

$$\mathrm{X} + \mathrm{Y} \xrightarrow{1} \mathrm{X} \underset{1}{\overset{a}{\rightleftharpoons}} 2\,\mathrm{X}$$

$$\mathrm{X} + \mathrm{Y} \xrightarrow{2} \mathrm{Y} \underset{1}{\overset{b}{\rightleftharpoons}} 2\,\mathrm{Y}$$

$$[X]' = a[X] - [X]^2 - 2[X][Y]$$
$$[Y]' = b[Y] - [Y]^2 - [X][Y]$$



Reaction network → Differential equations → Interesting dynamics

Interesting dynamics ↔ Steady states

Differential equations ↓

$$0 = ax - x^2 - 2xy$$
$$0 = by - y^2 - xy$$

Polynomial equations → Steady states

Polynomial equations → Equations at the steady states

Equations at the steady states → Reaction network

Model differentiation

References

Reaction network theory:

- J. Gunawardena, *Modeling of interaction networks in the cell: theory and mathematical methods*, Comp. Biophys. **9** (2012).
- M. Feinberg, *Foundations of Chemical Reaction Network Theory*, Springer, 2019.
- D. Cox: *The Classical Theory of Reaction Networks:* `https://youtu.be/Z1TwOeHNGgo`.
- A. Dickenstein, *Biochemical reaction networks: an invitation for algebraic geometers*: `http://mate.dm.uba.ar/~alidick/papers/MCA0215.pdf`

Gröbner bases:

- D.A. Cox, J. Little, and D. O'Shea, *Ideals, Varieties, and Algorithms*, Undergraduate Texts in Mathematics, Springer, 2015.
- B. Sturmfels: *Introduction to Gröbner Bases:* `https://youtu.be/TNO5WuxuNak`.

Model discrimination:

- H.A. Harrington, K.L. Ho, T. Thorne, M.P.H. Stumpf, *Parameter-free model discrimination*, PNAS **109** (2012): 15746–15751.

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Example:
$$\begin{tikzcd} \mathrm{T}+\mathrm{M} \arrow[r, shift left, "k_1"] & \mathrm{C} \arrow[l, shift left, "k_4"] \arrow[r, "k_2"] & \mathrm{A} \arrow[ll, bend left, "k_3"] \end{tikzcd}$$
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Recent paper about the interpretation of δ: `arxiv.org/abs/2008.11468`.

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But – there might be relations that can't be be obtained in this way!

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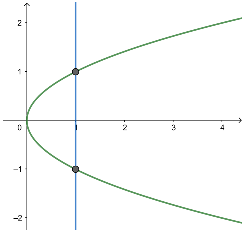

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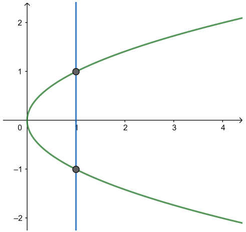

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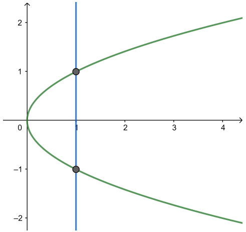

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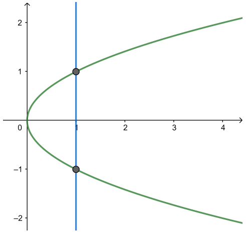

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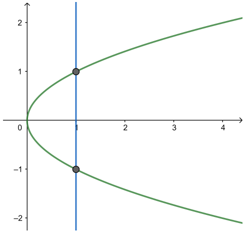

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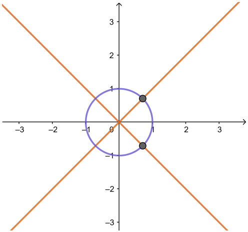

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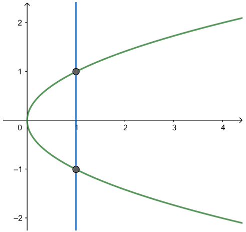

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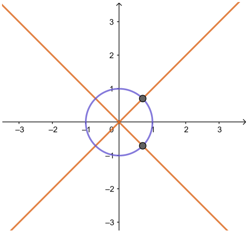

The relation $x - \sqrt{2} = 0$ is not detected!