Applying Mixed Integer Linear Programming in the Biomedical Sciences

1st MMS Days, Berlin, January 2016

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Example for linear programming

Let‘s assume the following problem:

Minimize

$$x_1 + x_2 \quad (= \text{error})$$

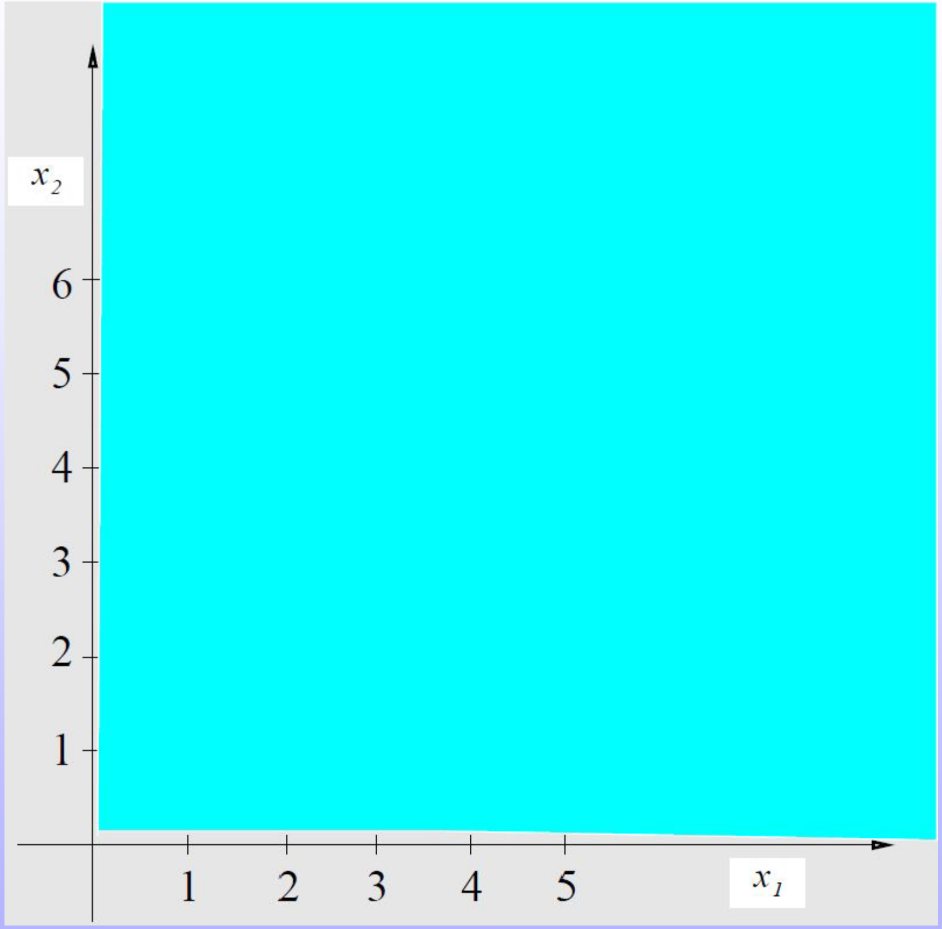
Subject to

$$4x_1 + x_2 \geq 4$$
$$x_1 + 2x_2 \geq 3$$

Example for linear programming

Min $x_1 + x_2$

Let's assume $x_1, x_2 \geq 0$



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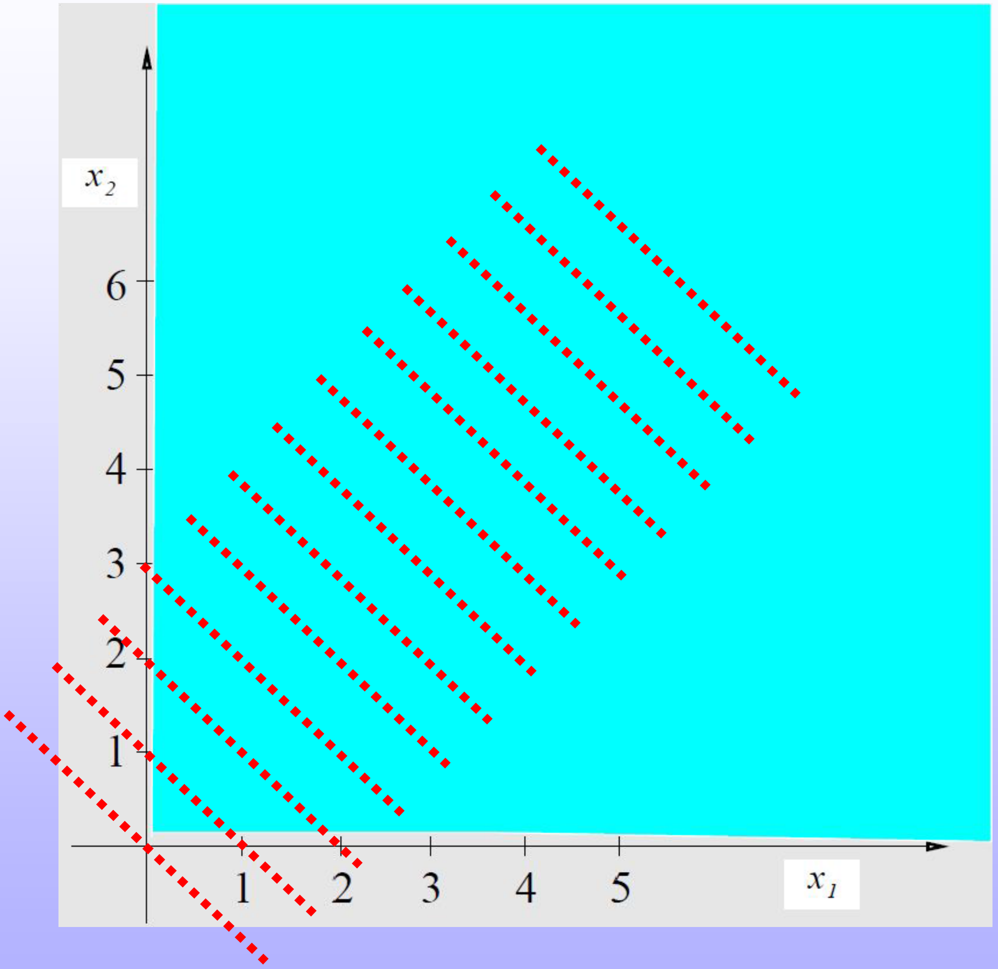

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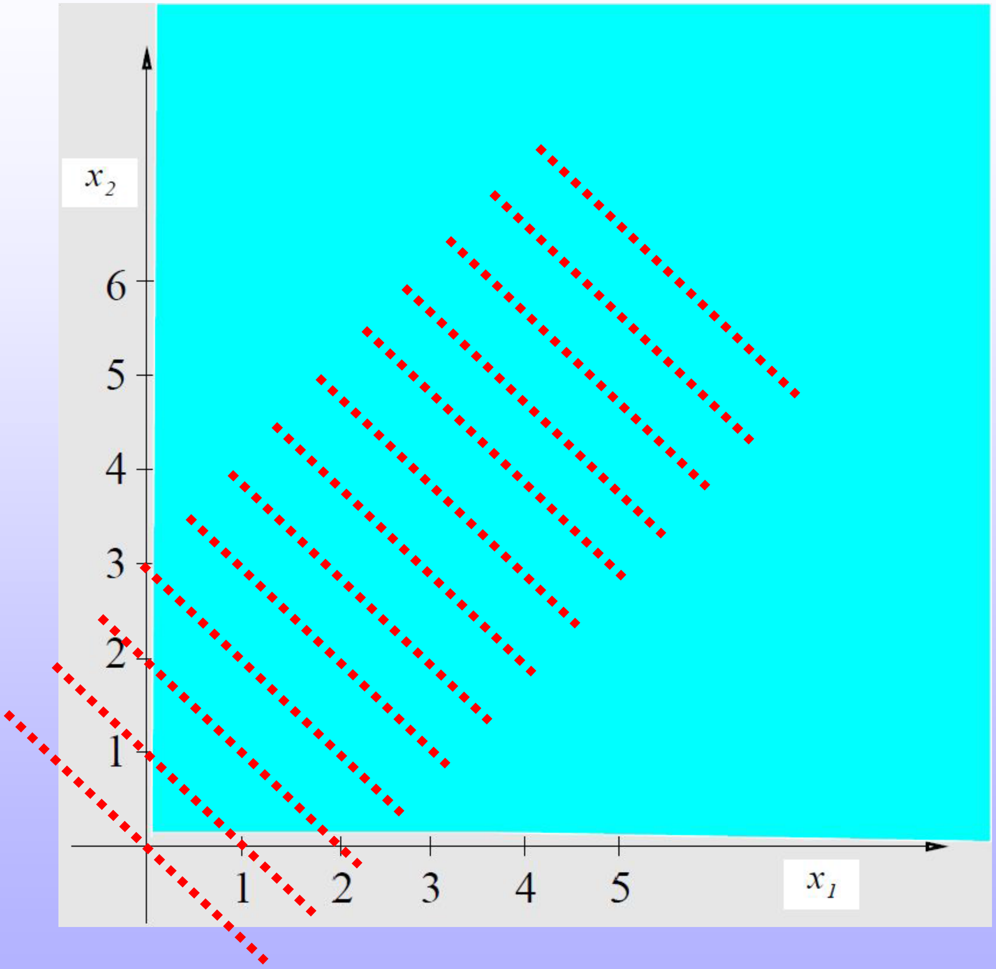

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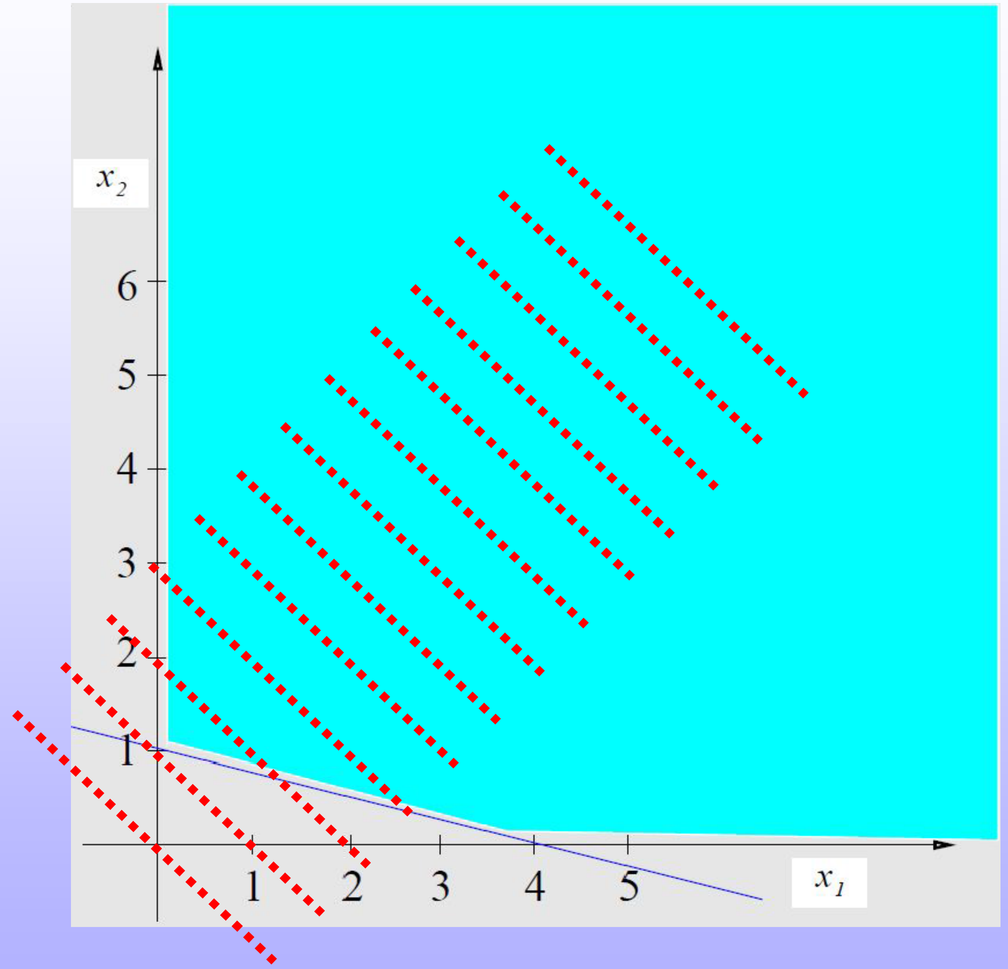

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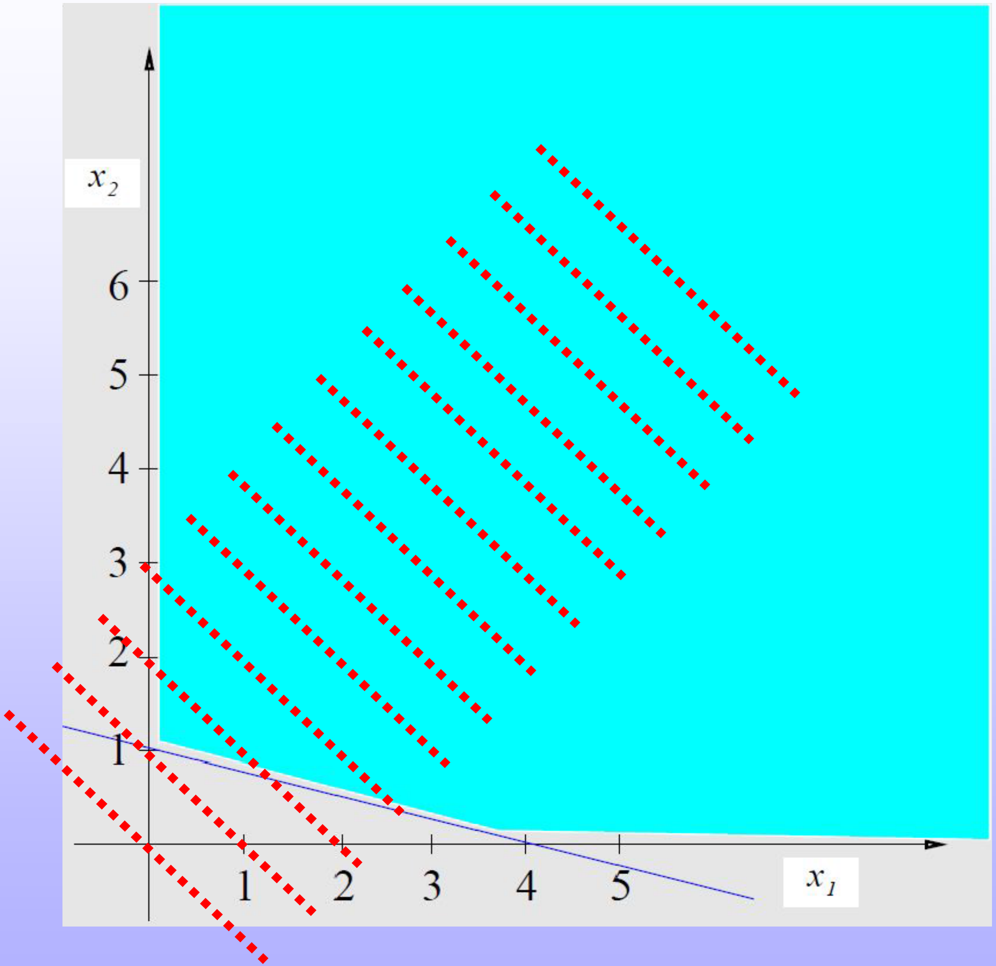

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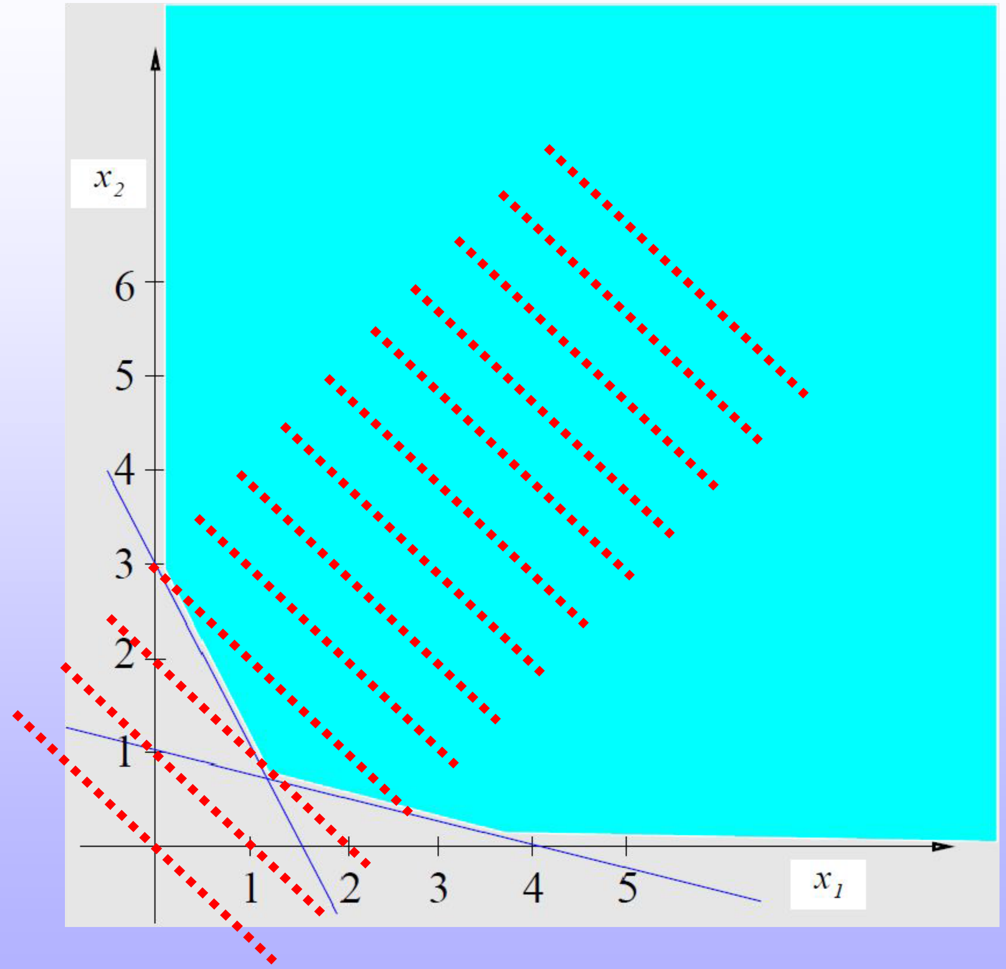

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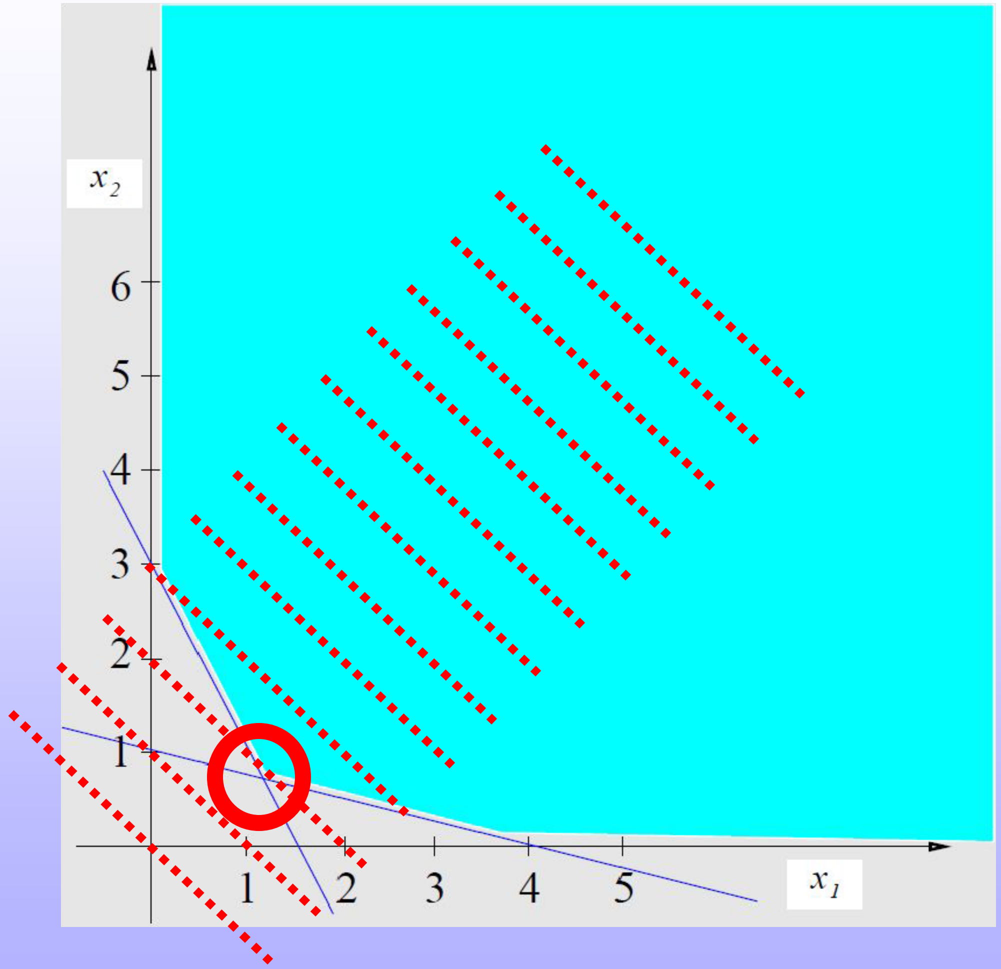
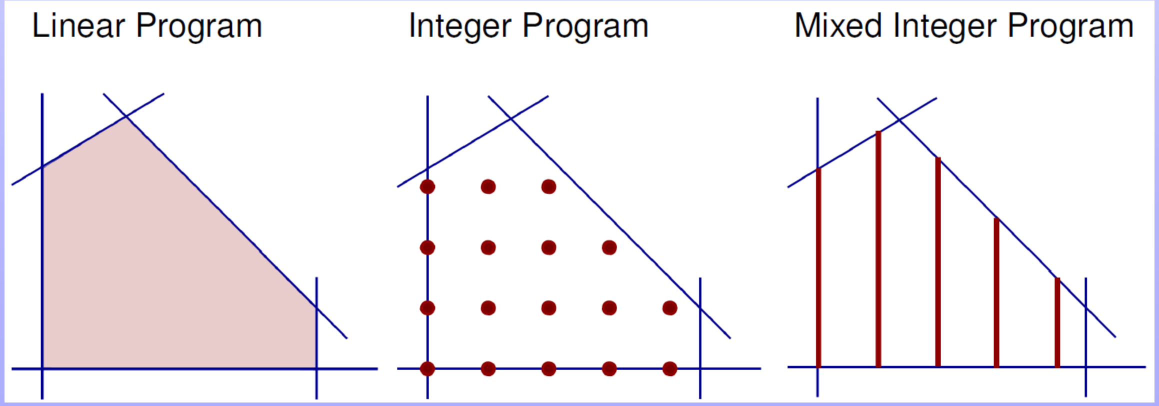


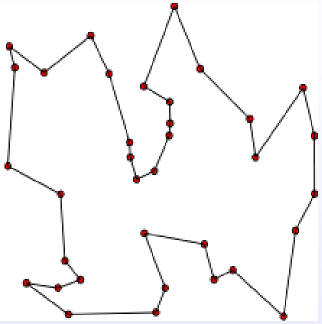
Resume, and from linear to Mixed Integer programming

Resume
- Putting up an optimization criterion
- Adding linear constraints
- the solution space can be continuous or discrete (Mixed Integer Linear Programming)
- MILP: binary and continuous variables can be multiplied



Applications

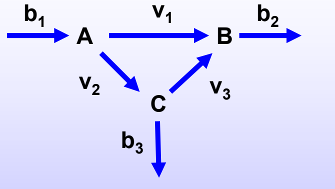
- Time table optimization (school, train, public transport)
- Traveling salesman problem (record: n=85,900 cities, $\frac{n^2-n}{2}$ variables, $\frac{(n-1)!}{2}$ solutions)



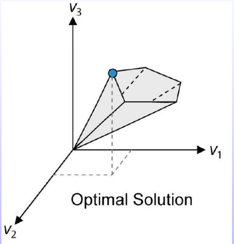
Bioinformatics:

Analysis of cellular **networks (graphs)**:

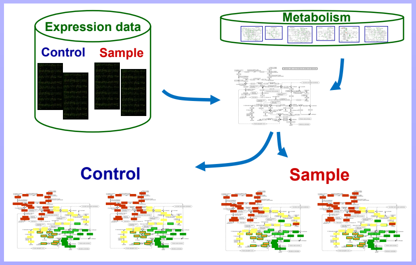
- Metabolism: Flux Balance Analysis
- Gene regulation: Linear models
- Signal transduction: Finding discriminative modules in protein interaction networks
- Pattern recognition on networks (PathWave) (Schramm et al, 2010, Bioinformatics)

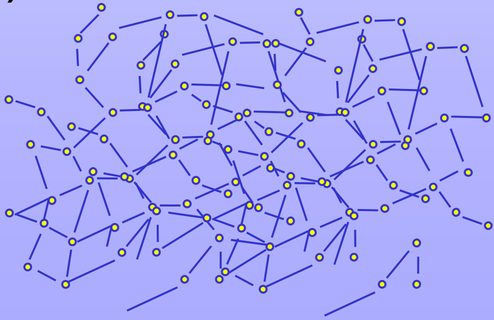


$$\frac{dA}{dt} = -v_1 - v_2 + b_1$$
$$\frac{dB}{dt} = +v_1 + v_3 - b_2$$
$$\frac{dC}{dt} = +v_2 - v_3 - b_3$$



$$\begin{aligned} \max \quad & c^T v \\ \text{s.t.} \quad & Sv = 0 \\ & \text{lb}_i \leq v_i \leq \text{ub}_i \end{aligned}$$

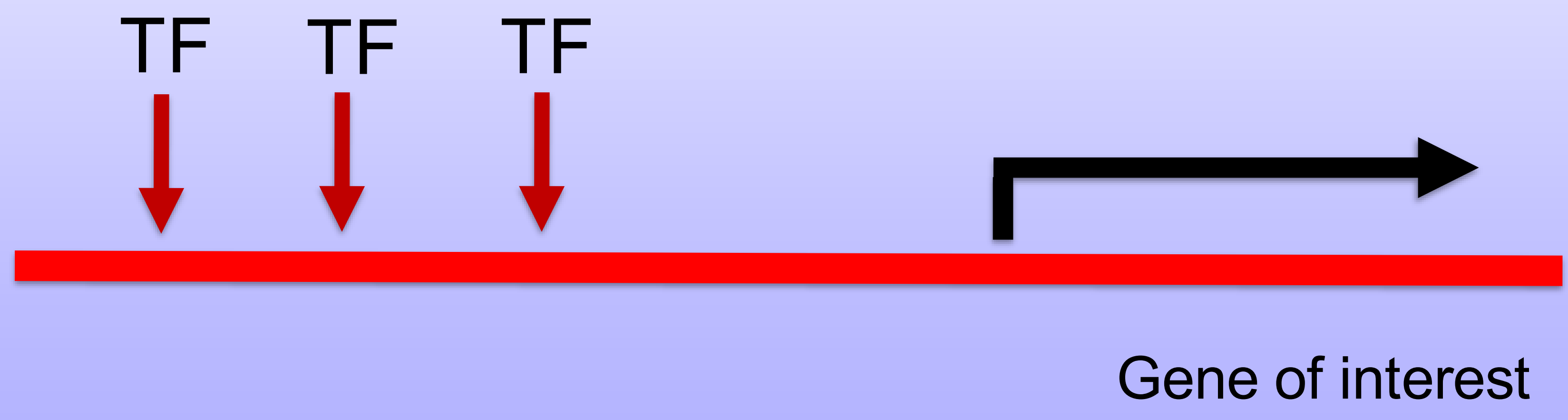




Identifying the regulation of genes

Which effectors are responsible for the transcript level of a certain gene within a specific cellular context?

Constructing models to infer regulation by transcription factors



Putting up the linear model

The model

$$\tilde{g}_j = \beta_0 + \sum_{t=1}^{T} \beta_t \cdot eff_{t,j}$$

j=sample
t=TF

Optimization min

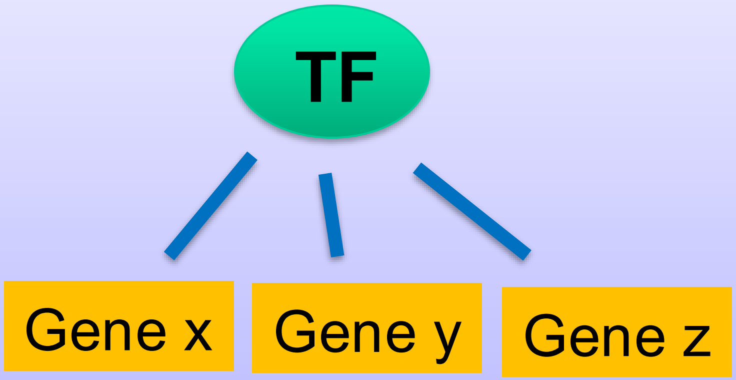
$$\min \sum_{j=1}^{l} \left| g_j - \tilde{g}_j \right|$$

(Schacht et al., 2014, Bioinformatics)

Estimating the effect of a transcription factor

a) By the gene expression of the TF itself
b) By our new definition of the **activity**

$eff_{t,j} = act_{t,j}$ = sum of z-scores of the TF's target genes



c) "Switch" approach, a combination of a) and b)

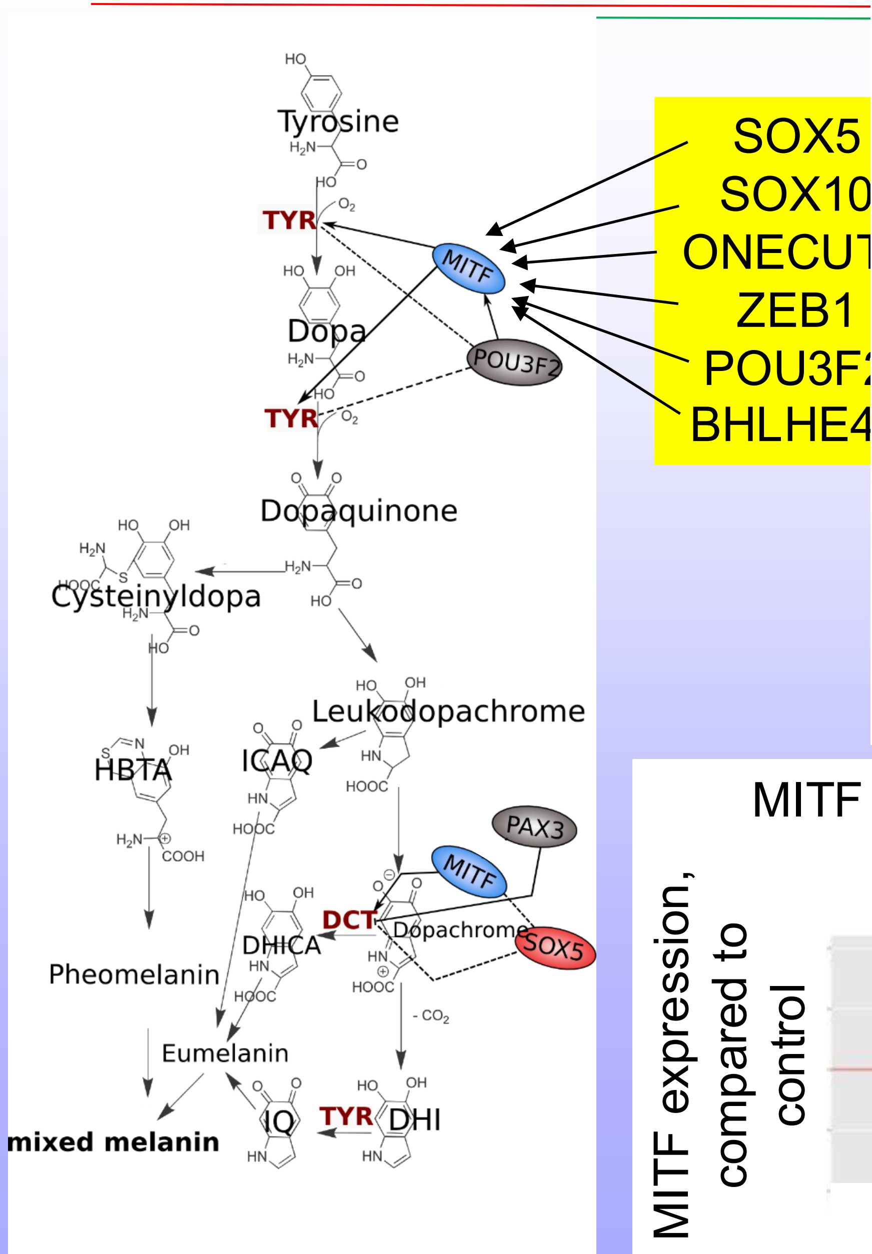
(Schacht et al., 2014, Bioinformatics)

Advantages using MILP

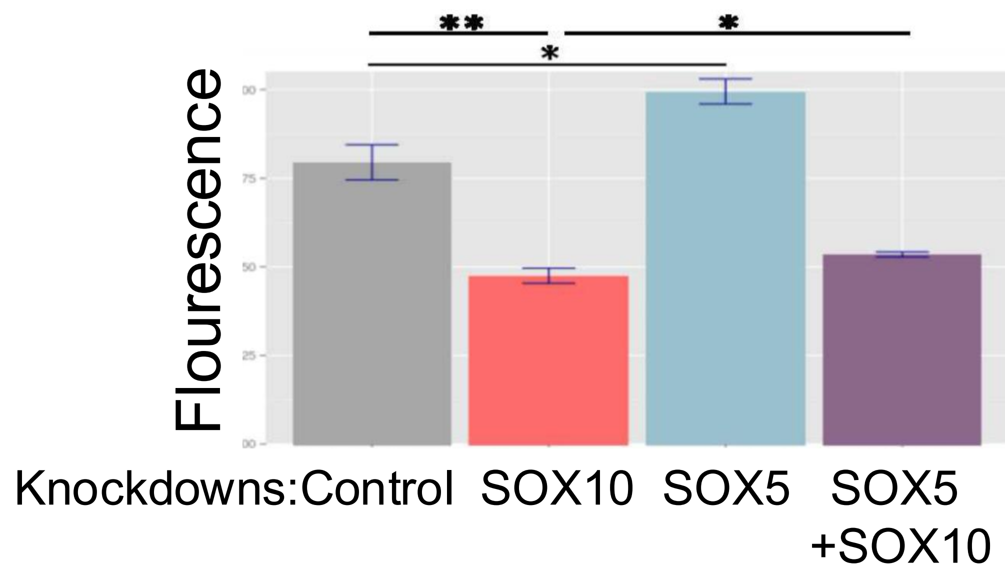
- The algorithm can choose which model fits best to the given problem (for each gene independently)

- Preselection of the exact number of parameters

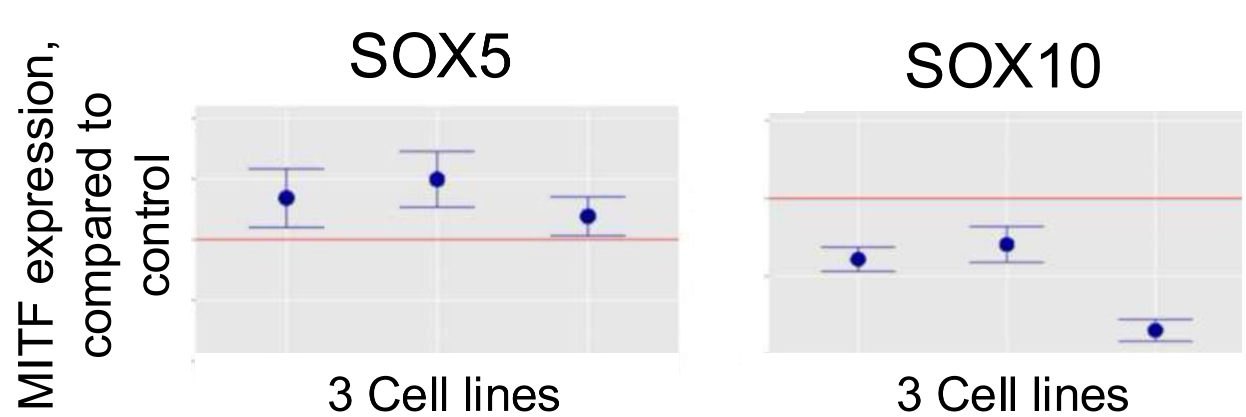
Regulation of melanogenesis



Signal of the reporter gene with MITF promoter



MITF expression after SOX5 and SOX10 knockdown



Discussion

Mixed Integer Linear Programming has a large variety of applications in bioinformatics, mostly for analyzing cellular networks/graphs

We applied MILP to infer cell context specific regulators of transcription by

- linear models and
- estimating the activity of a TF by expression of its target genes

MILP allowed us to use switches which gives the search space a non-linear topology, this compares to biological systems (cell death, immortalization)

Melanogenesis: SOX5 is a newly identified regulator of MITF in human melanomas seit 1558

Center for Sepsis Control & Care

Acknowledgements

Universitätsklinikum Jena

Theresa Schacht
Vijay Muley
Marcus Oswald
Ashwin Sharma
Volker Ast
Anna Dieckmann
Antje Biering
Joao Saraiva
Alexandra Poos
Franziska Hörhold
Amol Kolte

Gunnar Schramm
Rosario Piro
Moritz Aschoff

University Hospital Jena
Michael Bauer

Hans-Knöll-Institute Jena
Axel Brakhage

Theoretical Bioinformatics, DKFZ: Benedikt Brors
Roland Eils

Discrete and Combinatorical Optimization, University of Heidelberg: Stefan Wiesberg, Gerhard Reinelt

Theoretical Systemsbiology DKFZ: Frank Westermann

DKFZ Core Facility
Stefan Wiemann, Ulrike Korf, Nicolle Diessl

Bundesministerium für Bildung und Forschung

HELMHOLTZ | ASSOCIATION

Leibniz-Gemeinschaft

Network Modelling

Hans-Knöll-Institut