Basics on Metabolic network analysis

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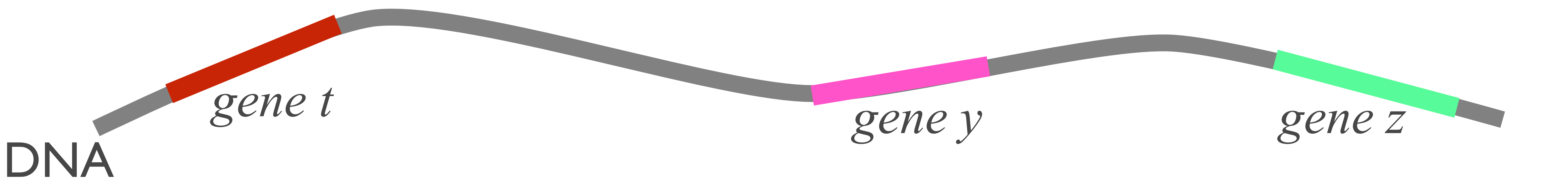
A simplistic illustration



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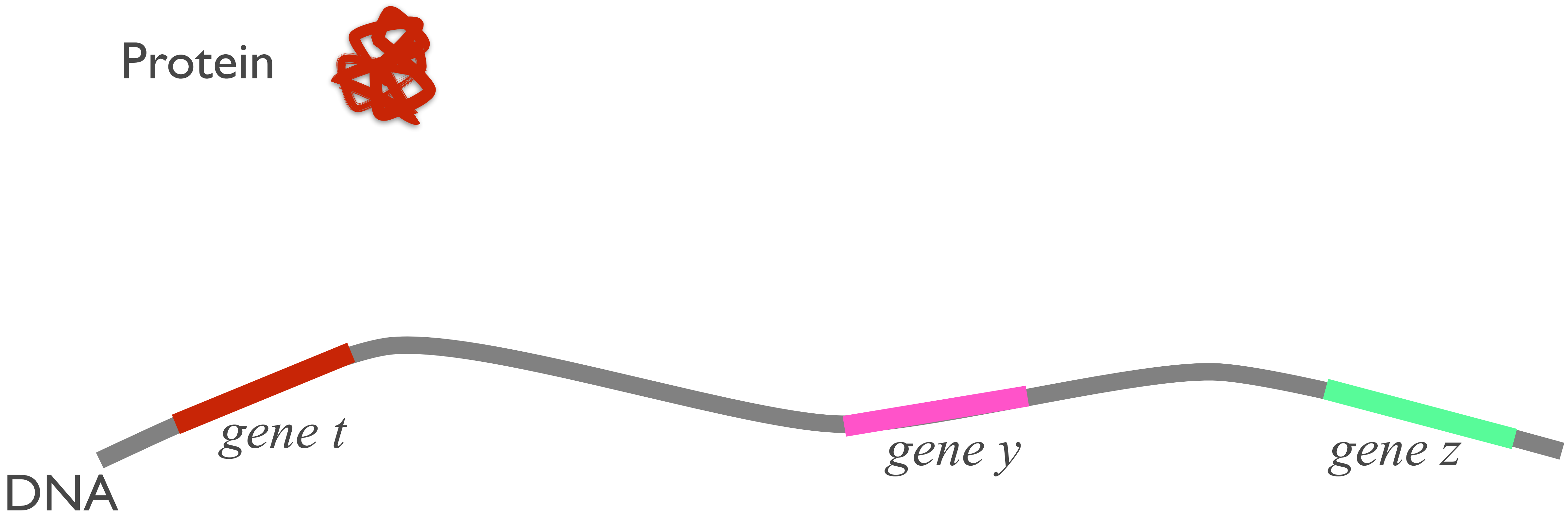
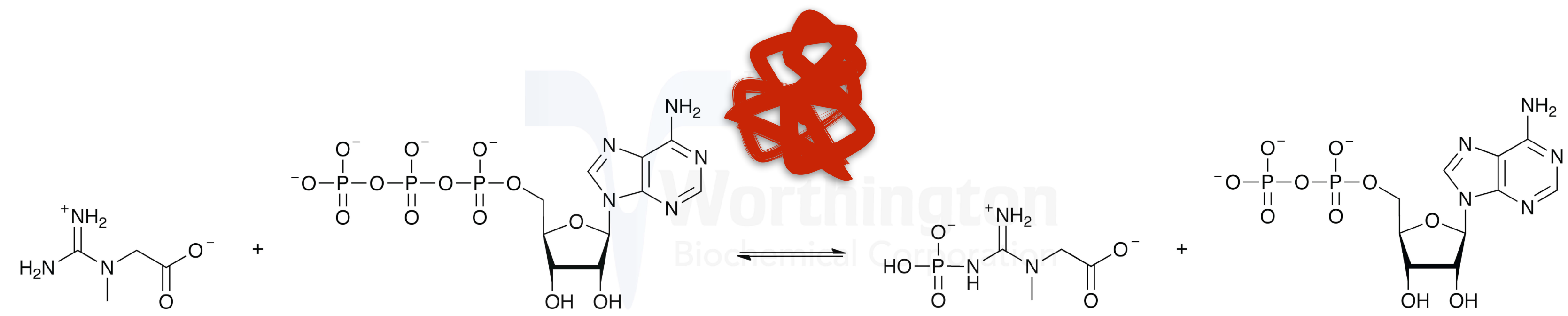


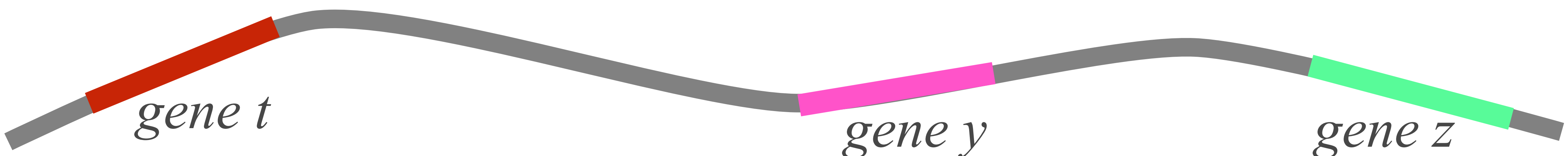
A simplistic illustration

Creatine kinase catabolyzes the chemical reaction

Protein



Creatine + ATP ⇌ Phosphocreatine + ADP



DNA

A simplistic illustration

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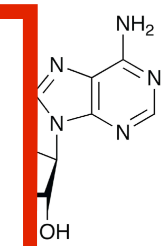


Major issue #3:

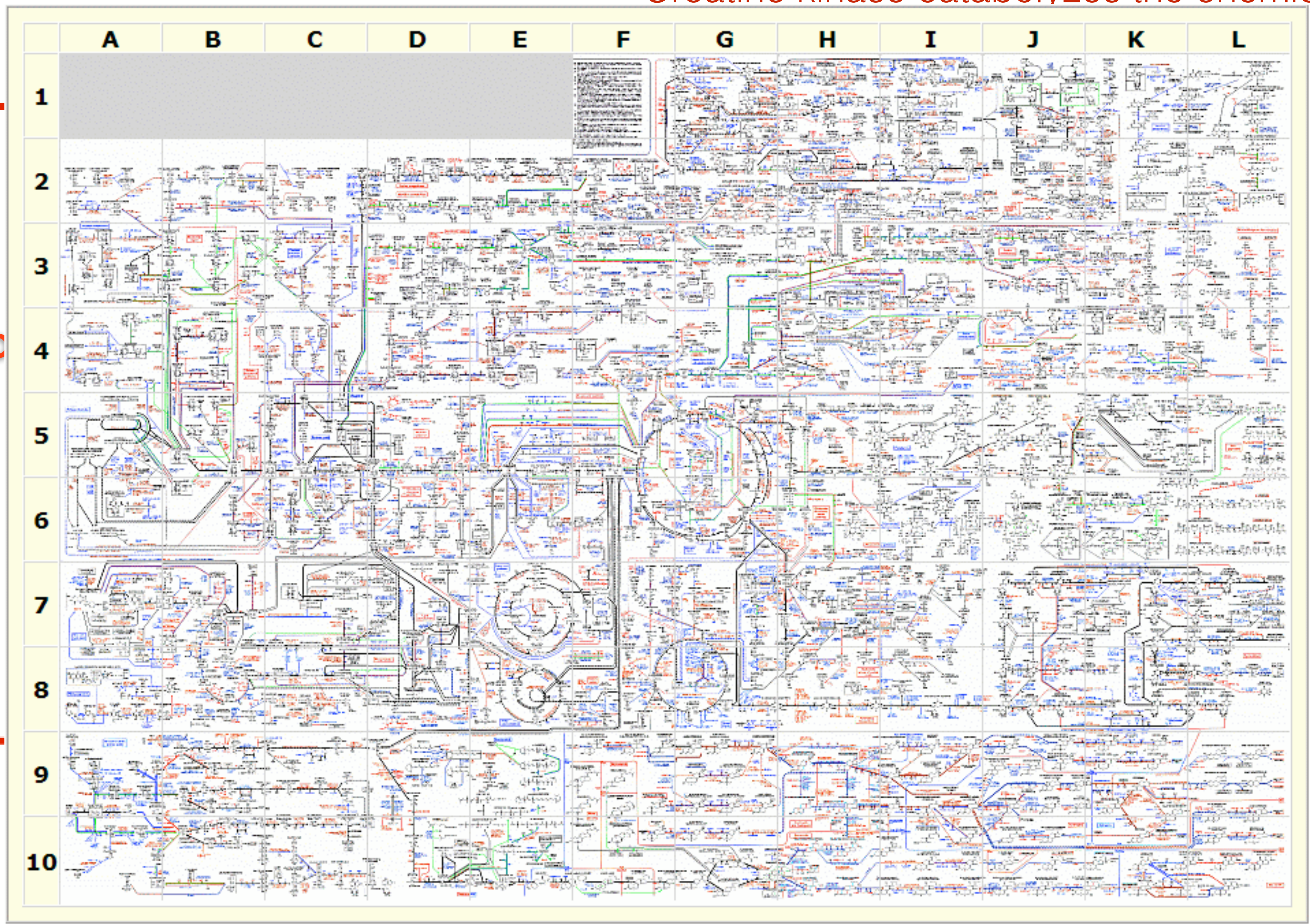
How to understand/predict/enhance the biochemical functioning/ productions of a cell/tissue/organism ?

Systems Biology : Metabolic network analysis

A simplistic illustration

Creatine kinase catabolyzes the chemical reaction

Ho



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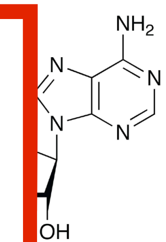

Mathematical modeling
a very simple task !

Hypothesis 0: from now, we consider the metabolic network composed by (and only by) the possible biochemical reactions (the enzyme is present or it is not required).

R1 : GLC + ATP <—> G6P
R2 : ATP + G6P —> 2 * G3P
R3 : ATP + GLC + G6P —> lactose
……

	R1	R2	R3
GLC	-1	0	-1
ATP	-1	-1	-1
G6P	+1	-1	-1
G3P	0	+2	0
lactose	0	0	+1

Stoichiometric matrix S

Mathematical modeling a very simple task !

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Stoichiometric matrix S

The evolution of G6P concentration can be deduced by the speeds of reactions (i.e., fluxes) R1, R2 and R3

$$d[G6P](t)/dt = +1 * V_{R1} -1 * V_{R2} -1 * V_{R3}$$

Hypothesis 1: The metabolites can't accumulate in the cell.

$$0 = d[G6P](t)/dt = +1 * V_{R1} -1 * V_{R2} -1 * V_{R3}$$

i.e.,: $V_{R1} = V_{R2} + V_{R3}$

Mathematical modeling
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Stoichiometric matrix S

The ev … ds of

Finding appropriate fluxes ≈ solving systems of linear equations !!!
—> quite easy !

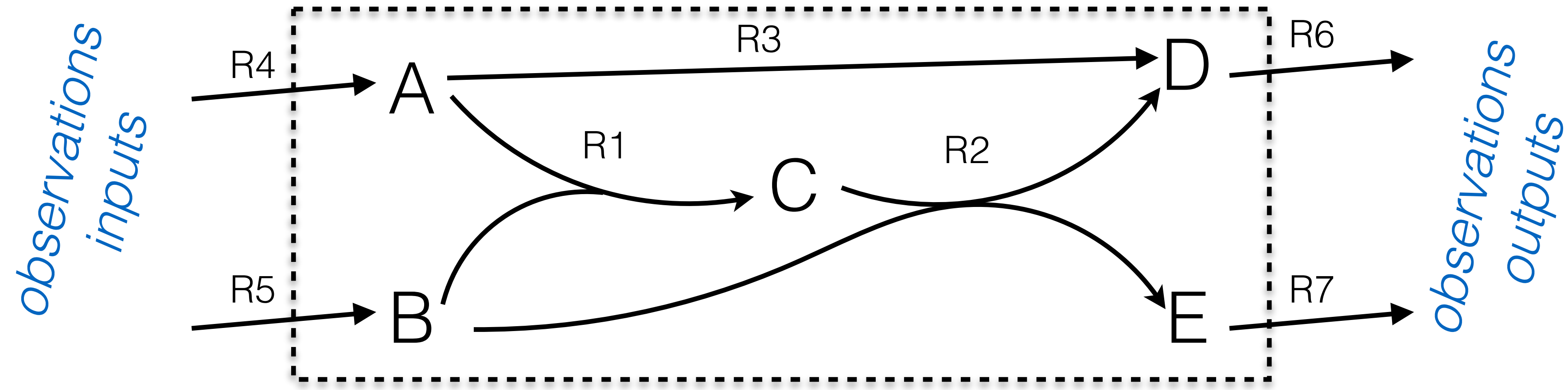
Hypothesis 1: The metabolites can't accumulate in the cell.

$$0 = d[G6P](t)/dt = +1 * V_{R1} - 1 * V_{R2} - 1 * V_{R3}$$

$$\text{i.e.,: } V_{R1} = V_{R2} + V_{R3}$$

Example

R1 : 2A + B —> C
R2 : B + C —> D + 2E
R3 : 4A —> D
R4 : —> A
R5 : —> B
R6 : D —>
R7 : E —>



Question 1 : Write the stoichiometric matrix
Question 2 : Write the linear system that has to be solved
Question 3 : Suppose that we observe V4 = 1 and V7 = 1 and solve the system
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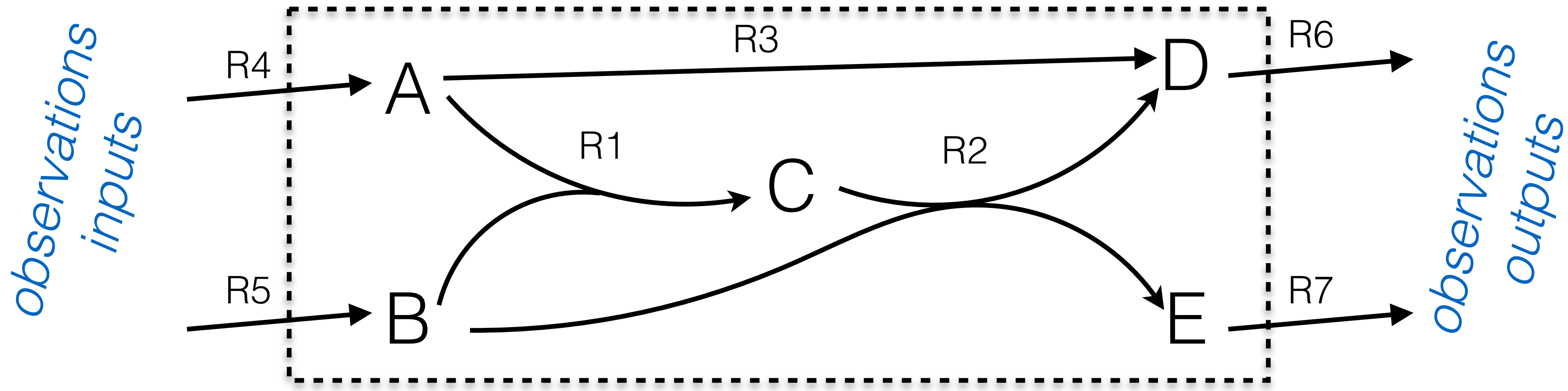

Question 1 : Write the stoichiometric matrix

	R1	R2	R3	R4	R5	R6	R7
A	-2	0	-4	1	0	0	0
B	-1	-1	0	0	1	0	0
C	+1	-1	0	0	0	0	0
D	0	+1	1	0	0	-1	0
E	0	+2	0	0	0	0	-1

	R1	R2	R3	R4	R5	R6	R7
A	-2	0	-4	1	0	0	0
B	-1	-1	0	0	1	0	0
C	+1	-1	0	0	0	0	0
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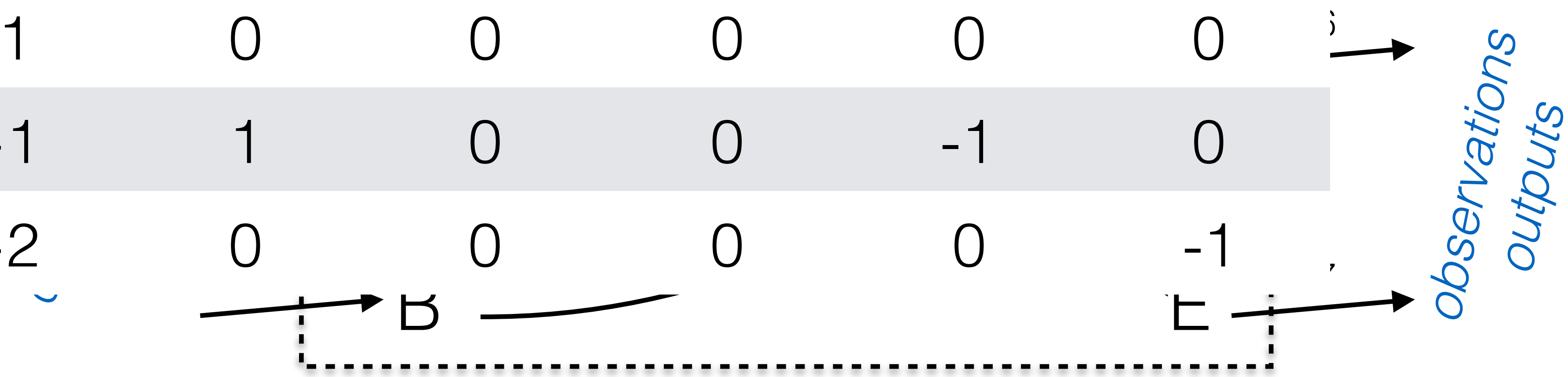

R6 : D —>
R7 : E —>

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	R1	R2	R3	R4	R5	R6	R7
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B	-1	-1	0	0	1	0	0
C	+1	-1	0	0	0	0	0
D	0	+1	1	0	0	-1	0
E	0	+2	0	0	0	0	-1

observations
outputs

R6 : D —>

for A : V4 = 2 V1 + 4 V3
for B : V5 = V1 + V2
for C : V1 = V2
for D : V2 + V3 = V6
for E : 2 V2 = V7

V1 = V2, V5 = V7 = 2 V2, V6 = V2 + V3 and V4 = 2 V2 +4 V3

only 2 unknowns but we must observe one of V4 or V6 and one of V5 or V7.

Example

R1 : 2A + B —> C
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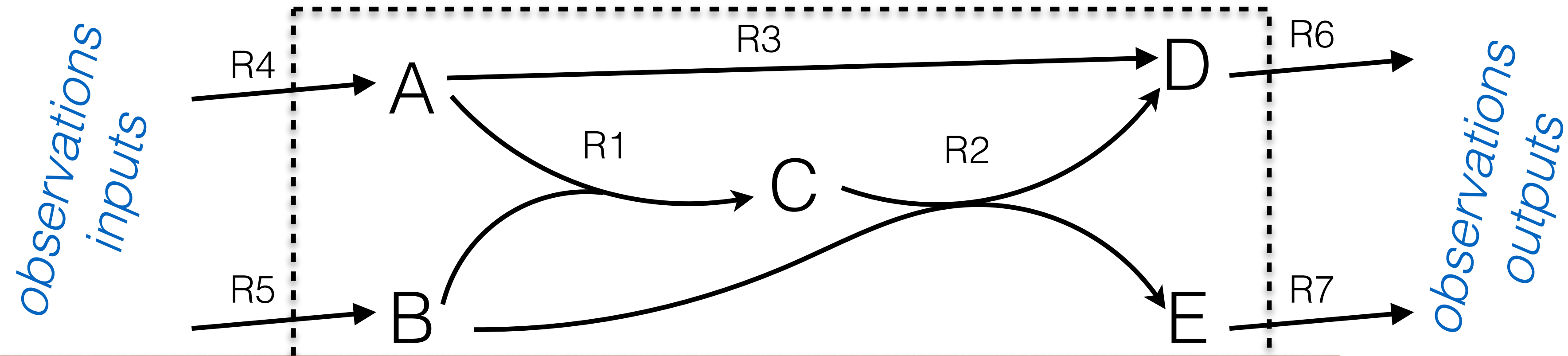
R3 : 4A —> D
R4 : —> A
R5 : —> B
R6 : D —>



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V1 = V2 = 0.5, V3 = 0, V4 = 1, V5 = 1, V6 = 0.5, V7 = 1

for A : V4 = 2 V1 + 4 V3
for B : V5 = V1 + V2
for C : V1 = V2
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V1 = V2 = 0.5, V3 = 0, V4 = 1, V5 = 1, V6 = 0.5, V7 = 1

V1 = V2 = 1, V3 = **-0.25**, V4 = 1, V5 = 2, V6 = 0.75, V7 = 1

The flux of an irreversible reaction is necessarily positive !!

V1 = V2, V5 = V7 = 2 V2, V6 = V2 + V3 and V4 = 2 V2 +4 V3

⇩ expresses by means of V4 and V7

V1 = V2=V7/2, V3=(V4-V7)/4, V5 = V7 and V6 = (V4 + V7)/4

1<V4<6, 1<V7<4 and V1,…,V6>0

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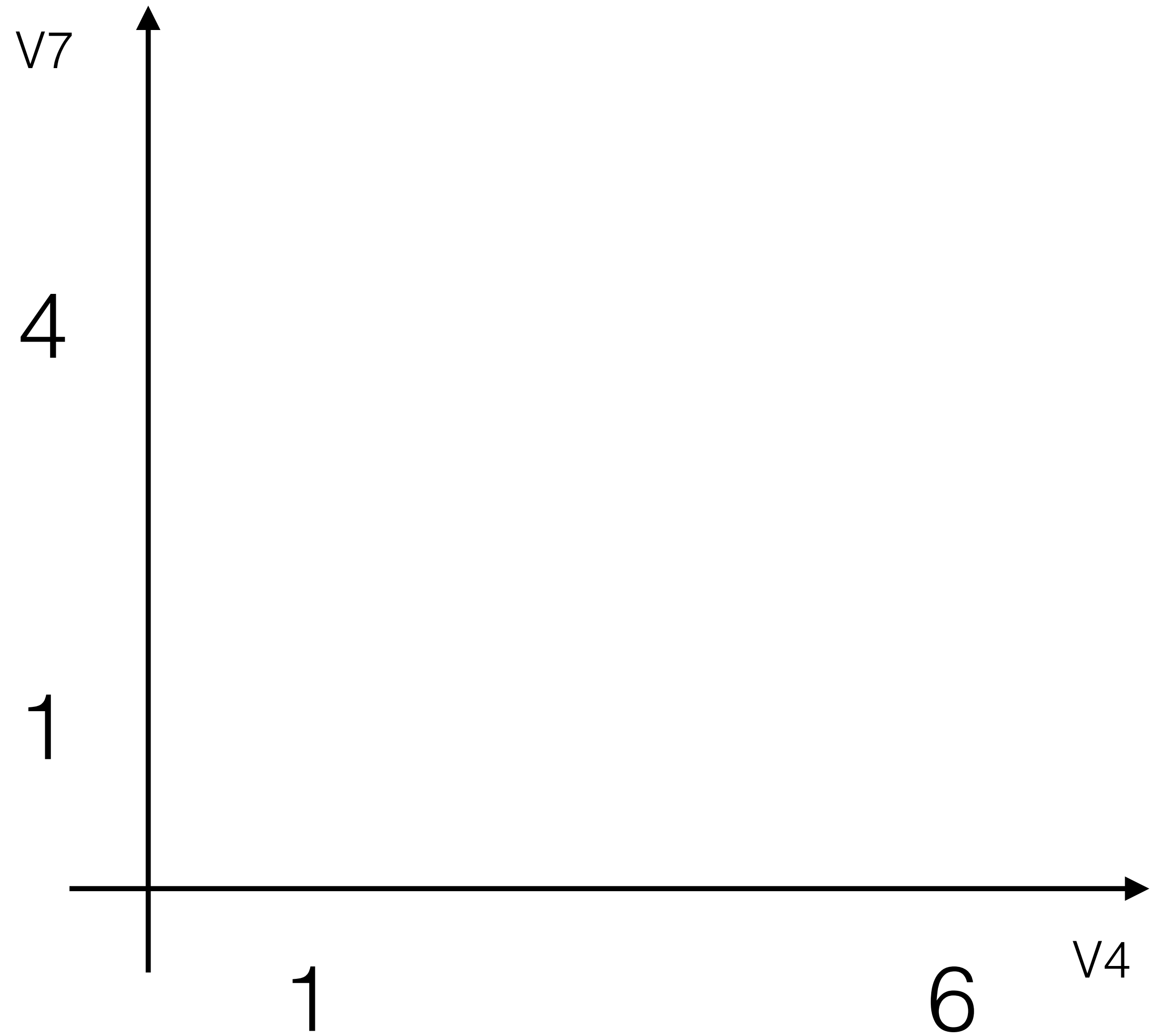

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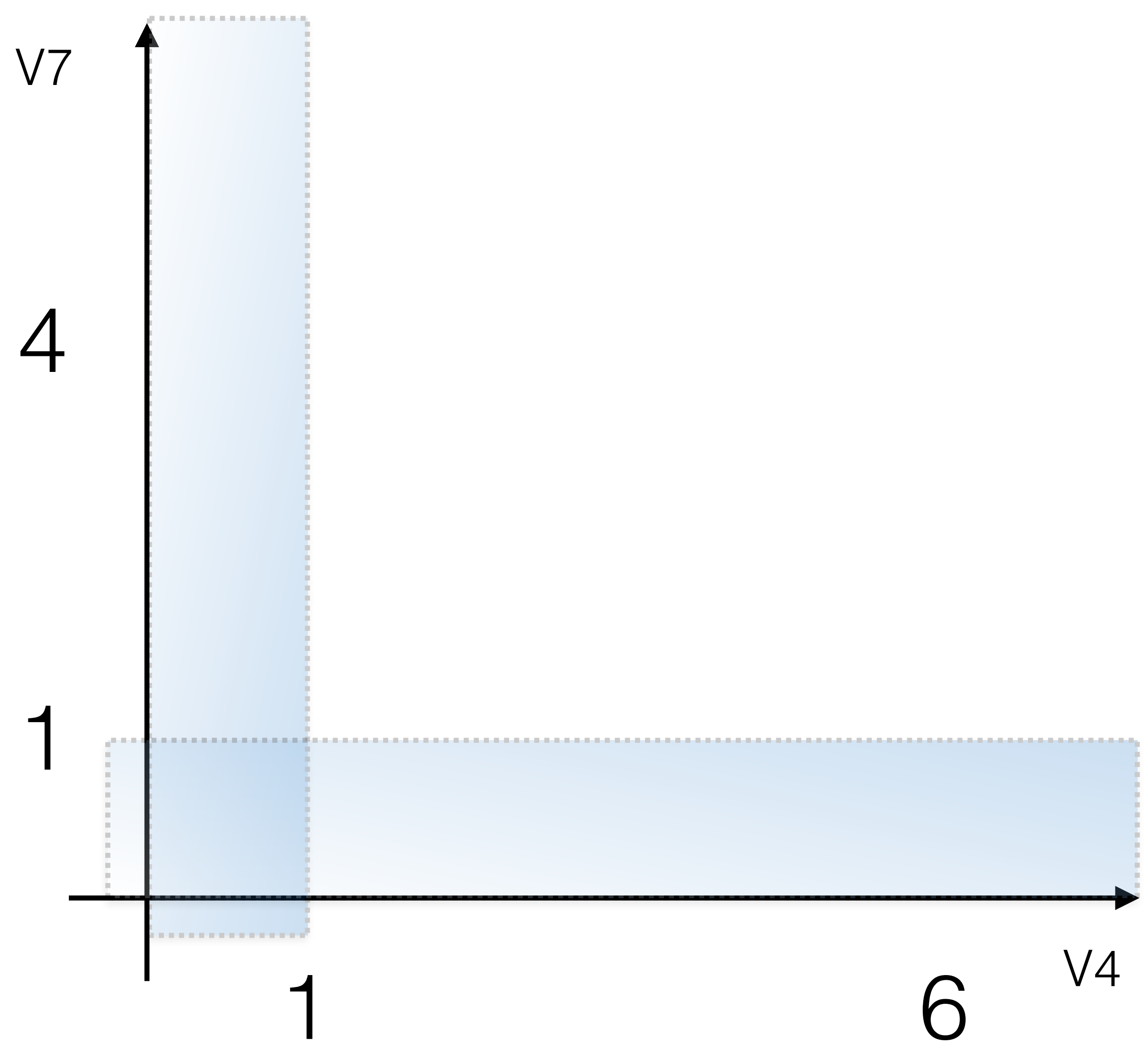

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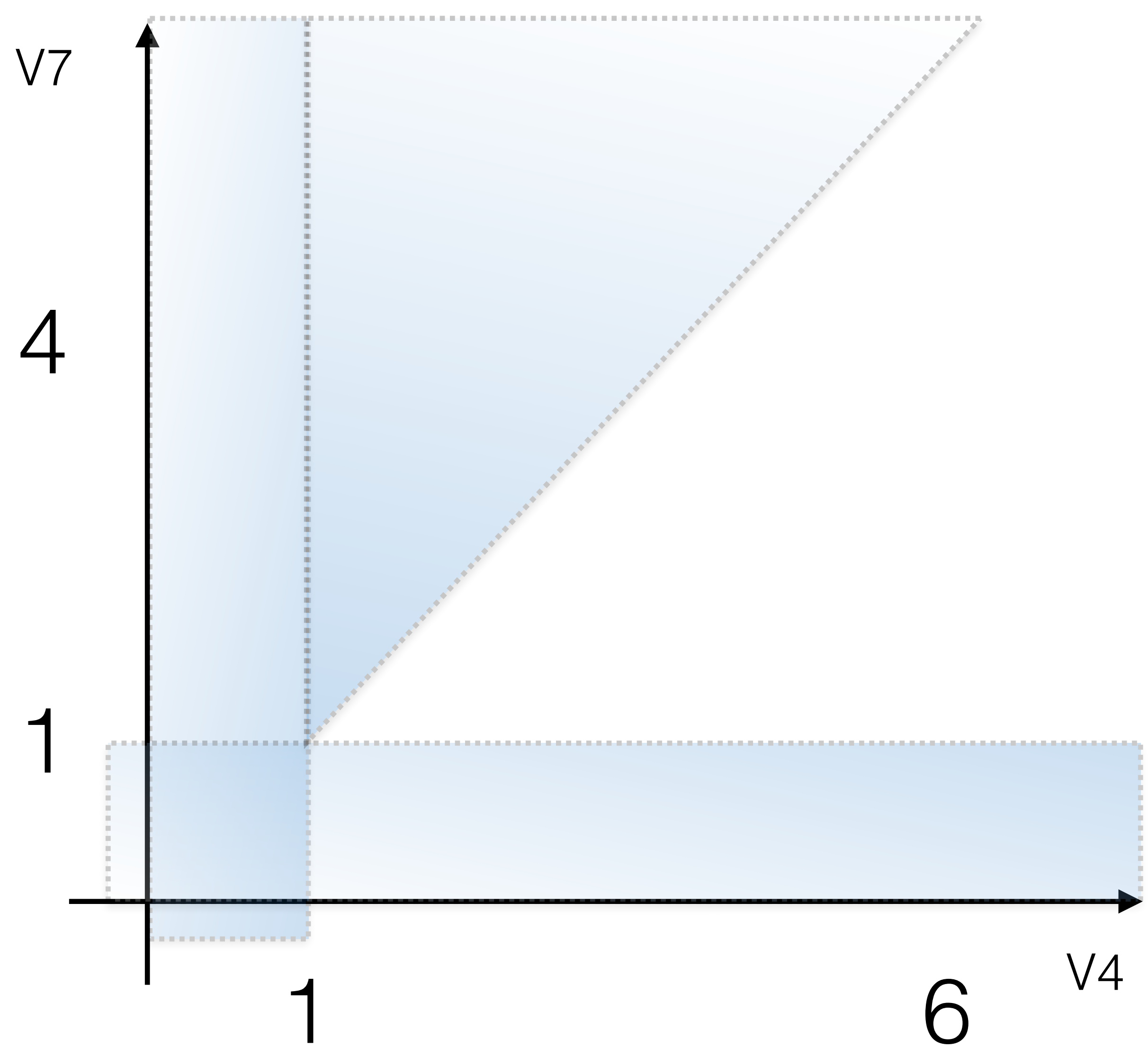

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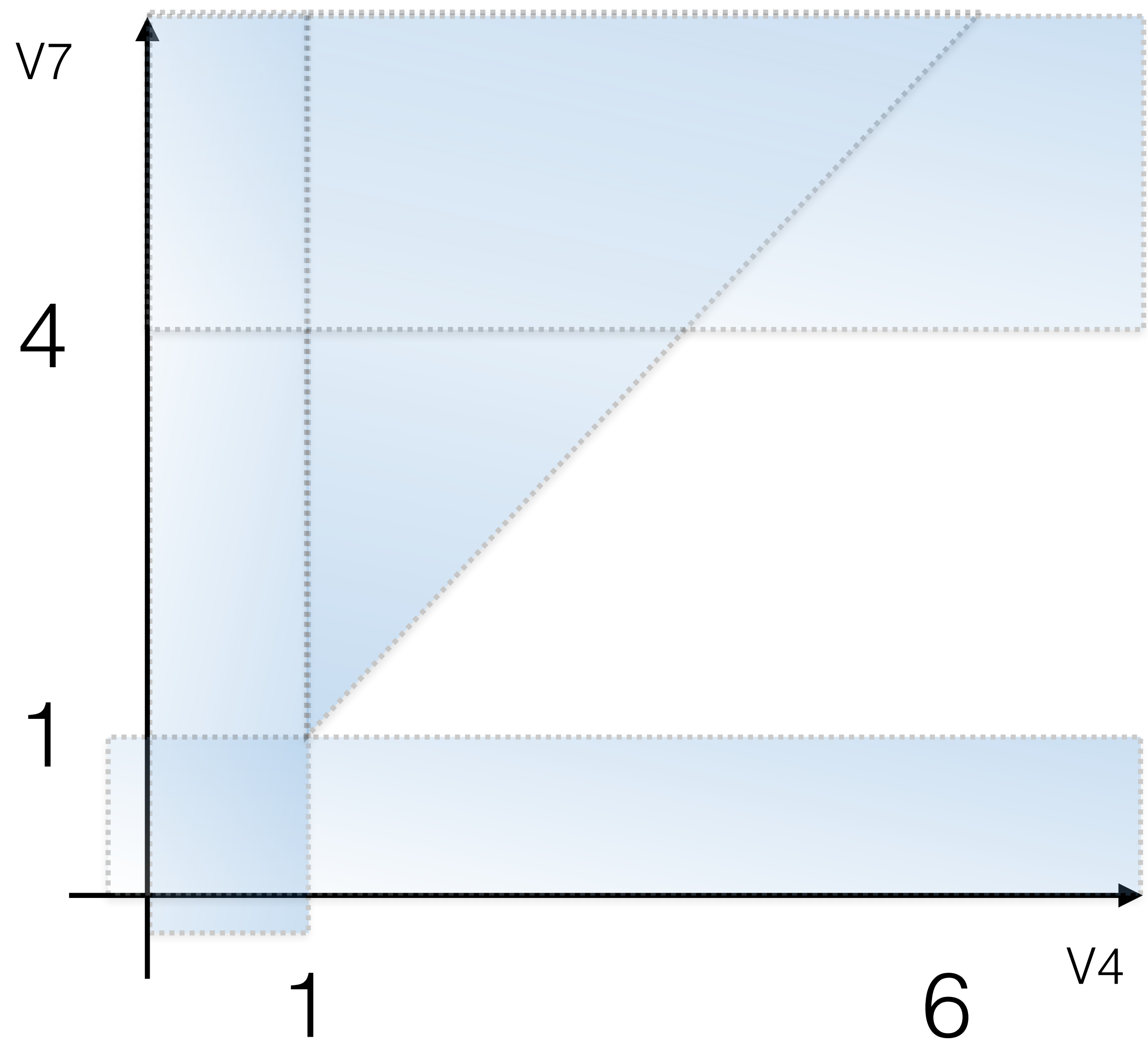

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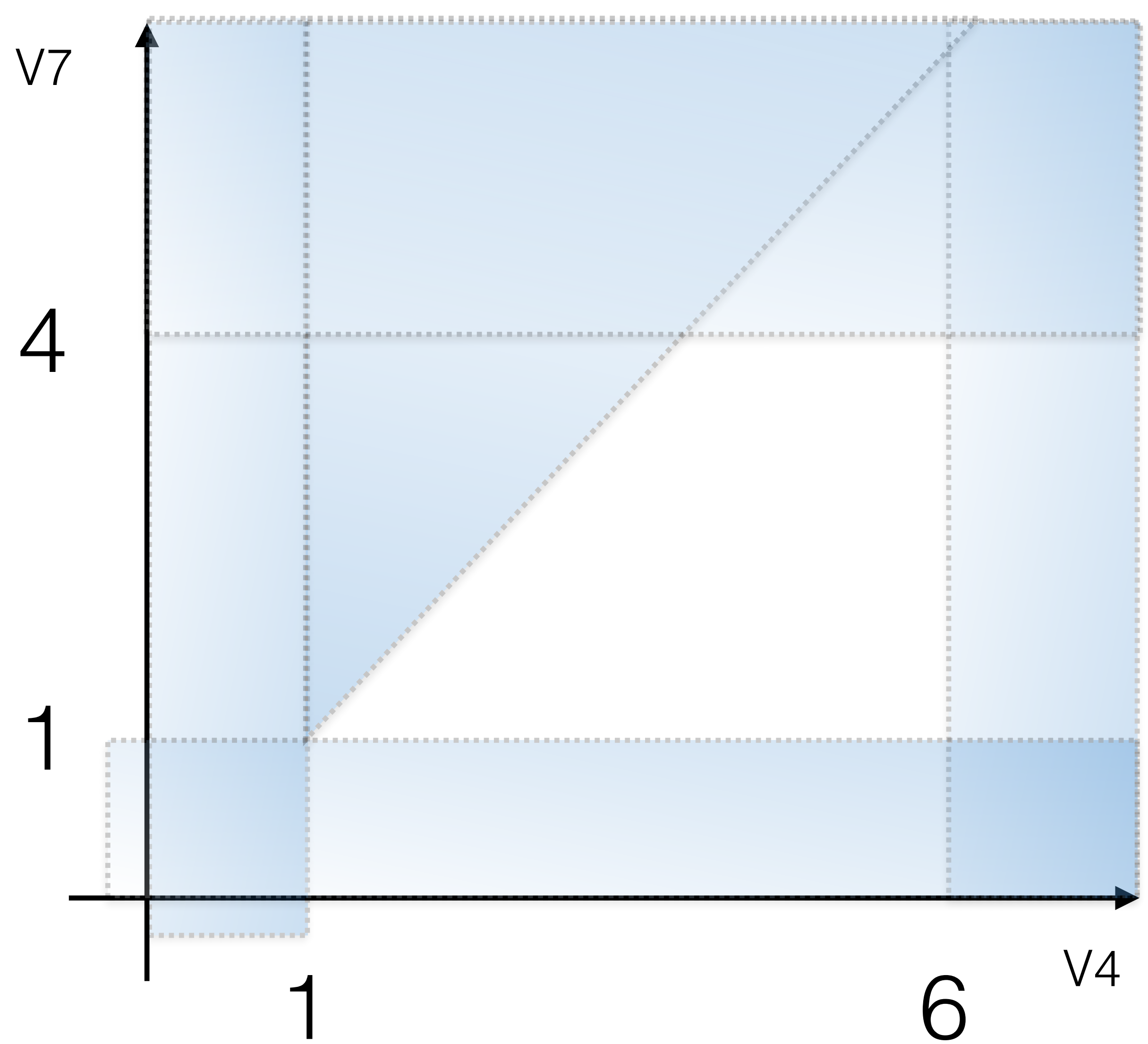

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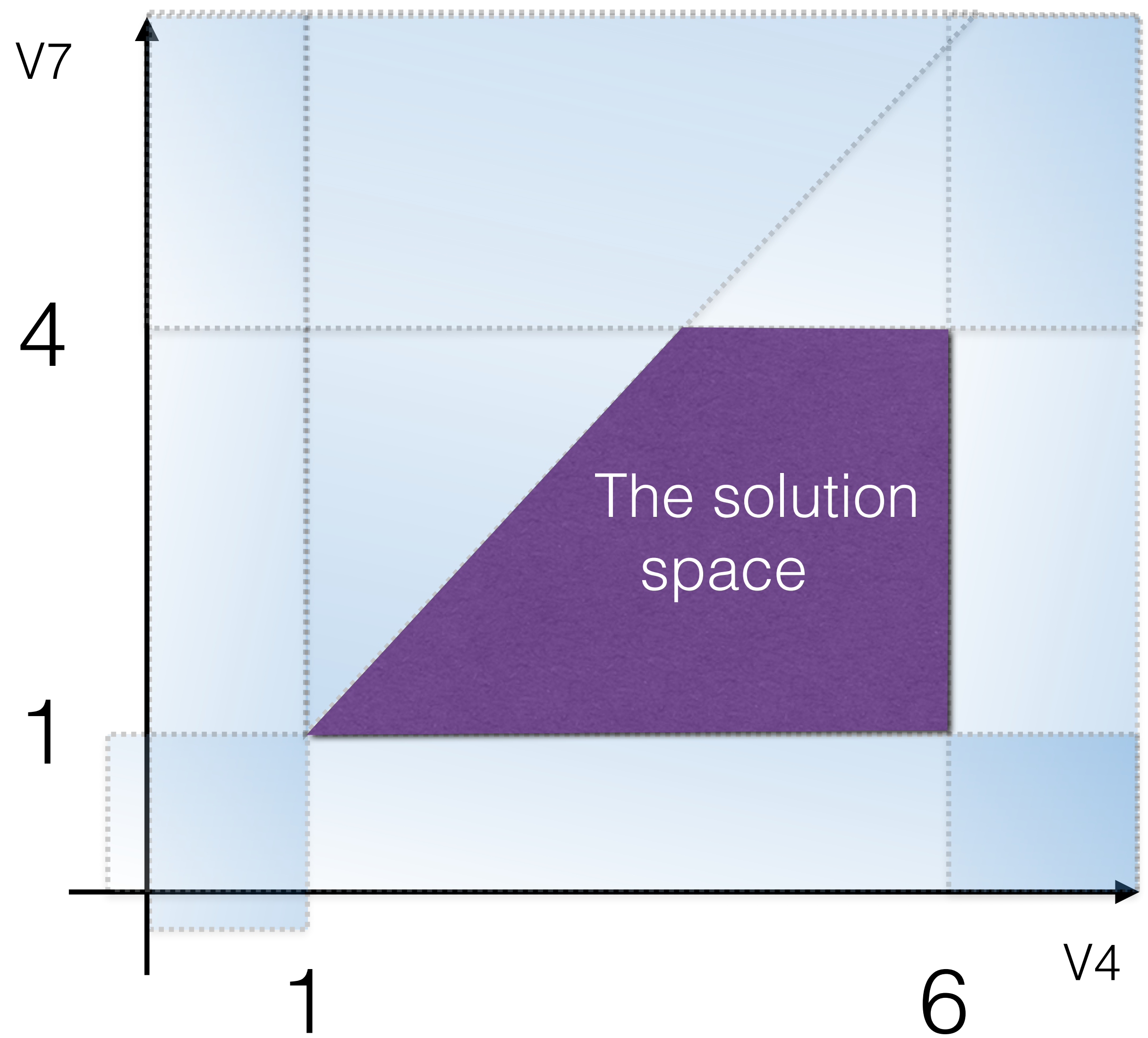

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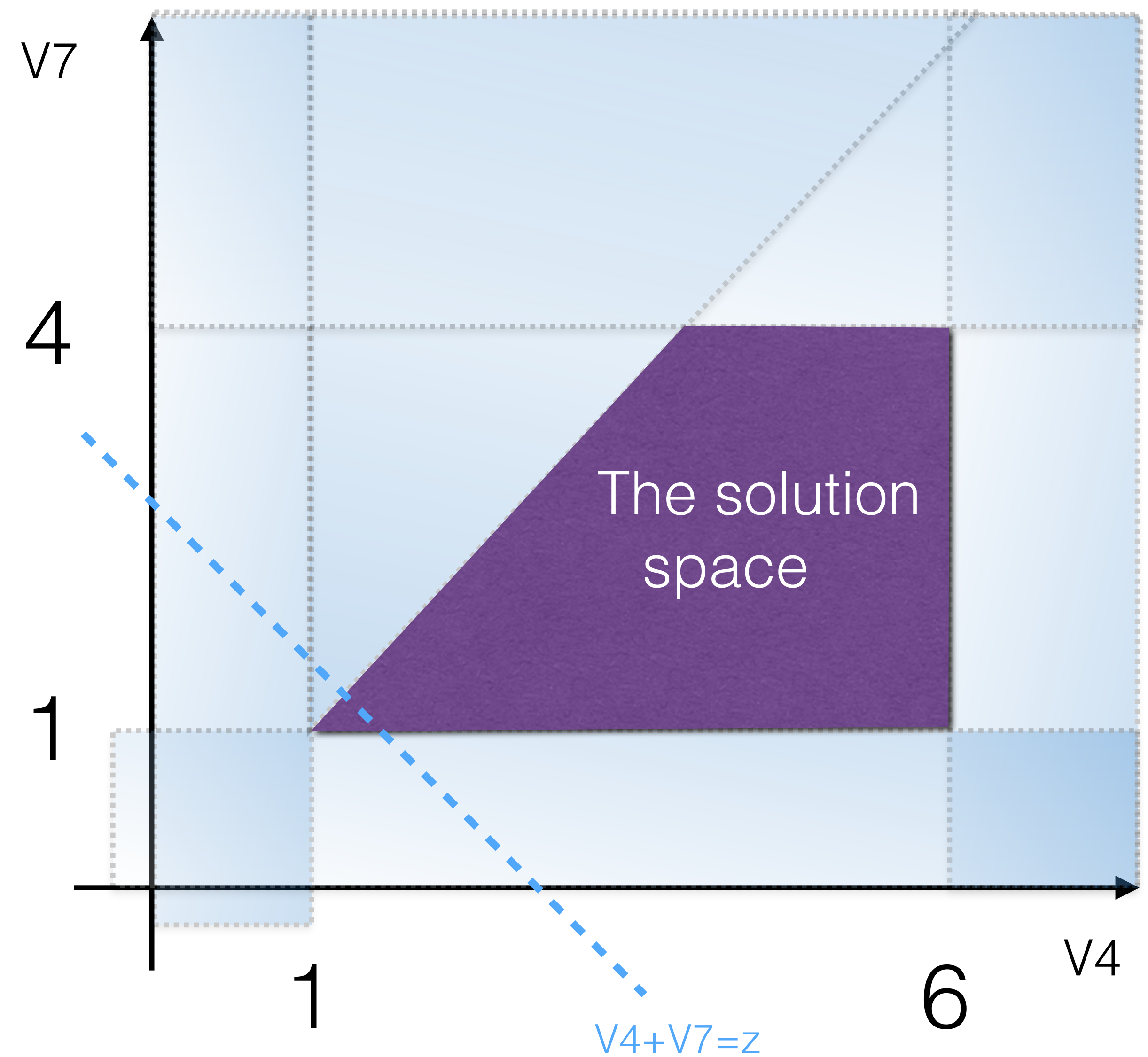

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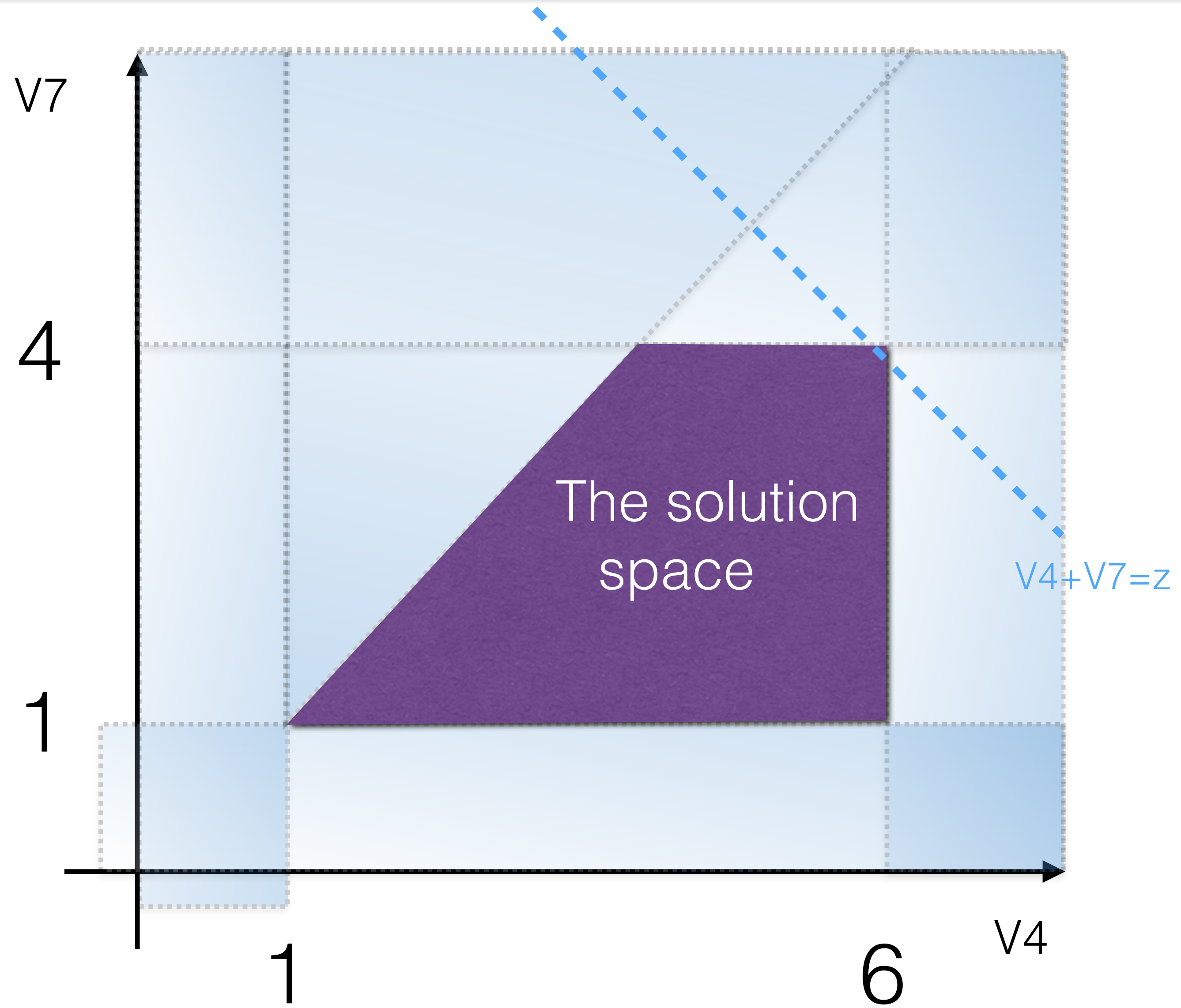

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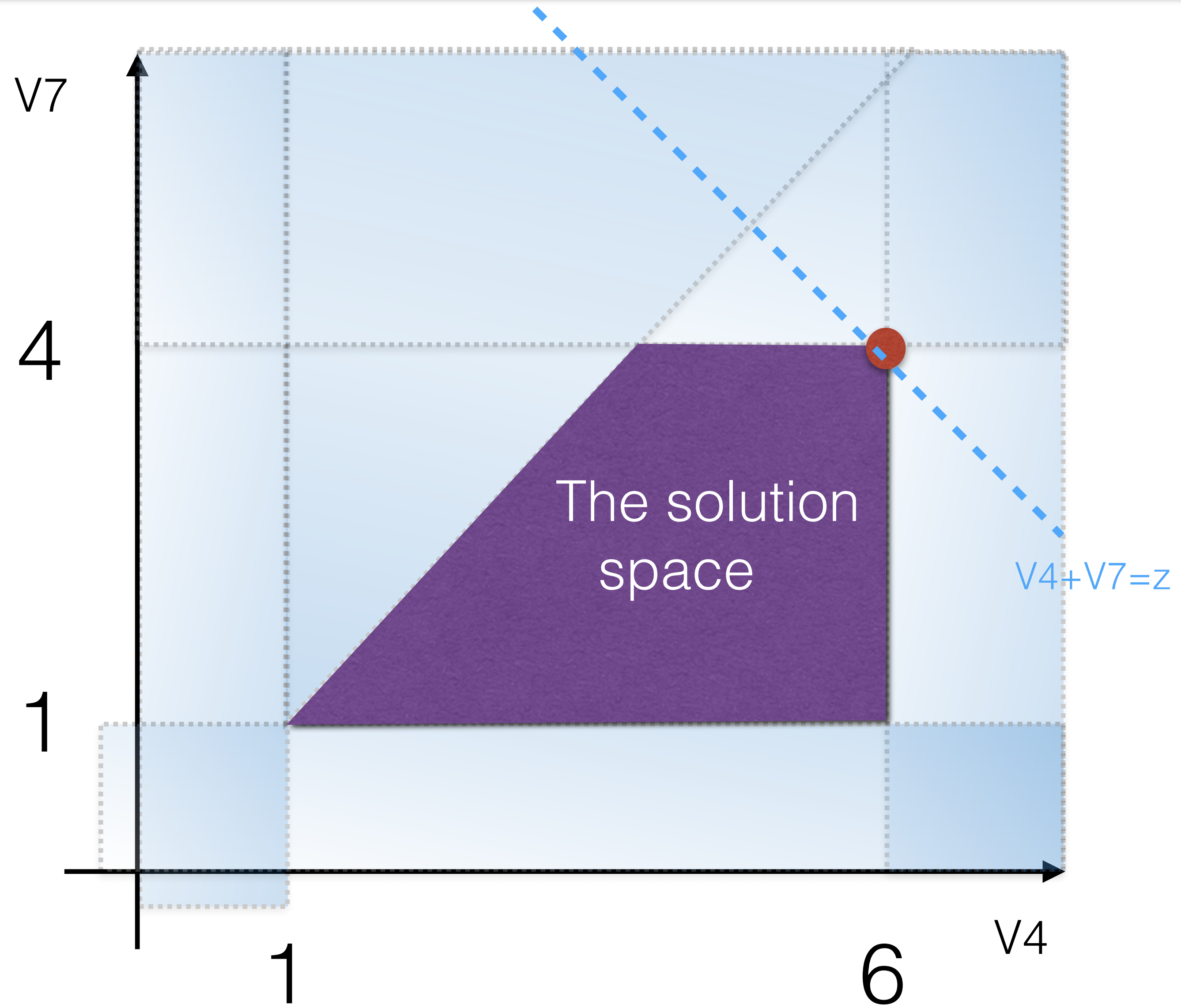

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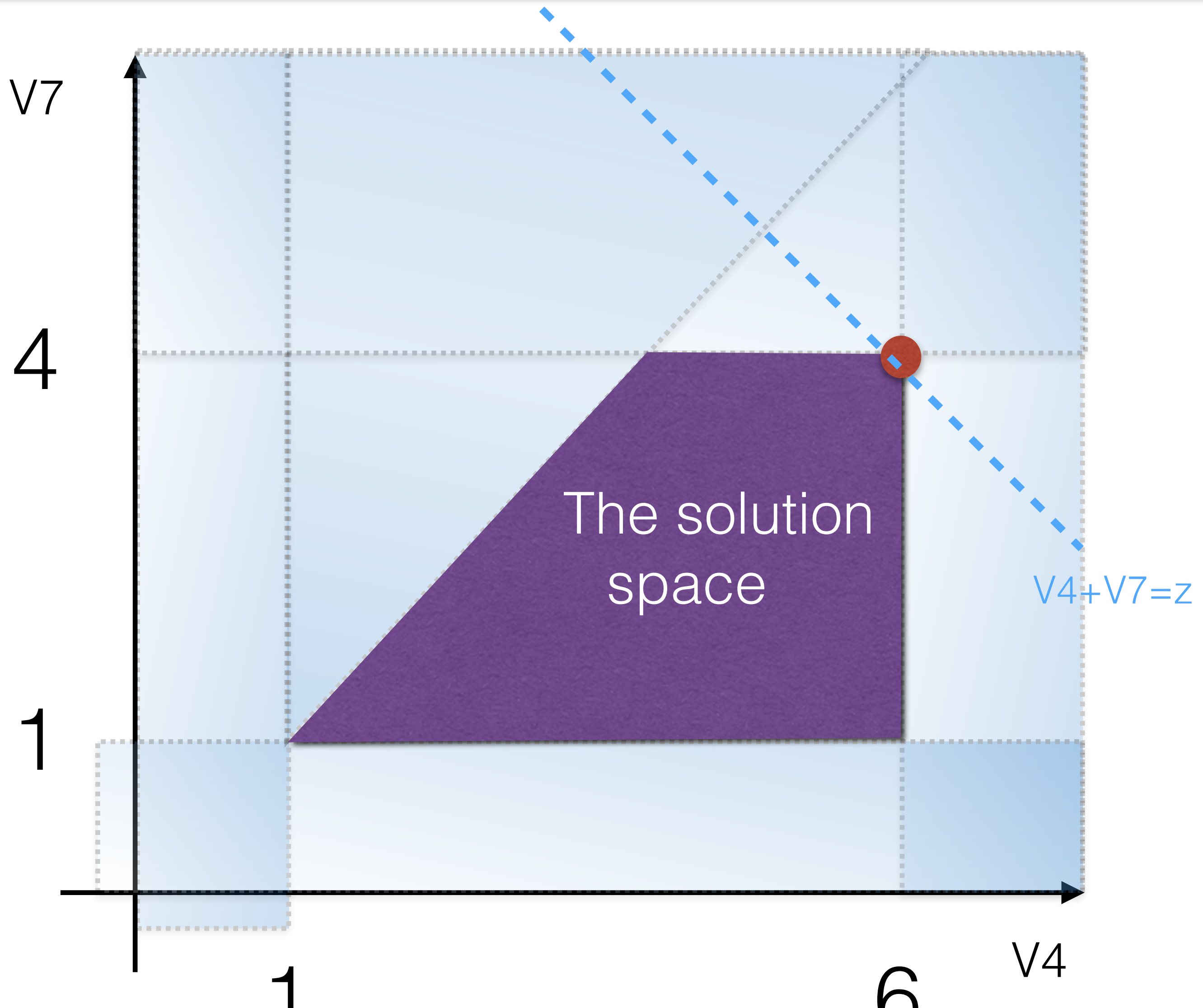

z is maximal when

V1=V2=2, V3=0.5, V4=4, V5=4, V6=2.5 and V7=6

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In higher dimensions,

1. The figure defined by inequalities on linear expressions is always convex (it is a convex polyedra also known as a simplex)

2. The optimal value of a linear expression is always on a vertex of the simplex (or on a face for very particular objectives)

3. Very efficient algorithms (such as the simplex algorithm) can find these optima

z is maximal when

V1=V2=2, V3=0.5, V4=4, V5=4, V6=2.5 and V7=6

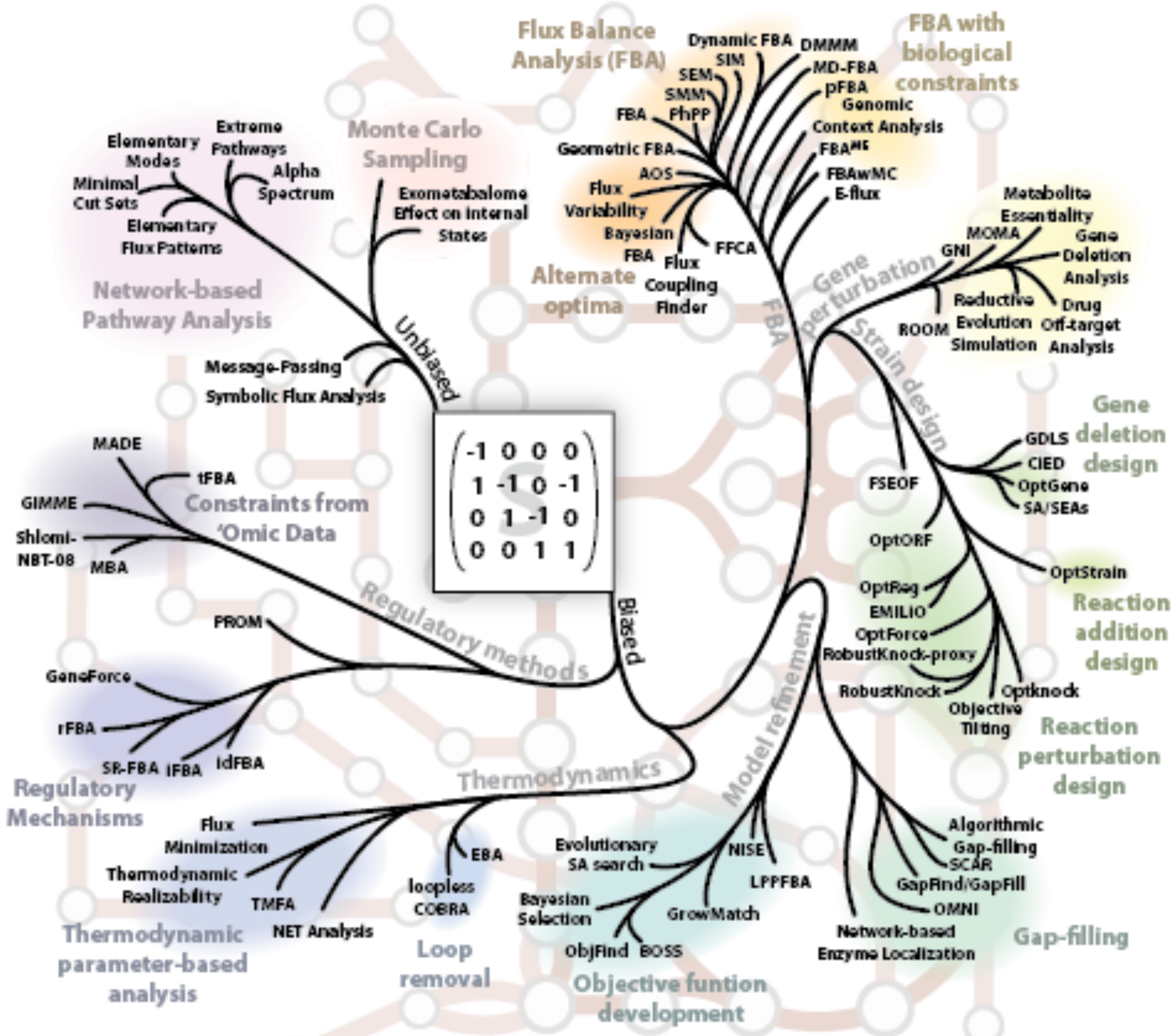
Why do we need a computer ?

- Current human metabolism has
  - 1,789 enzyme-encoding genes,
  - 7,440 reactions
  - 2,626 unique metabolites

- Study of the flux variations => 7440 * 2 * FBA
- Study of single gene knock out => 1789 * FBA
- Study of double gene knock out => 1789^2 * FBA

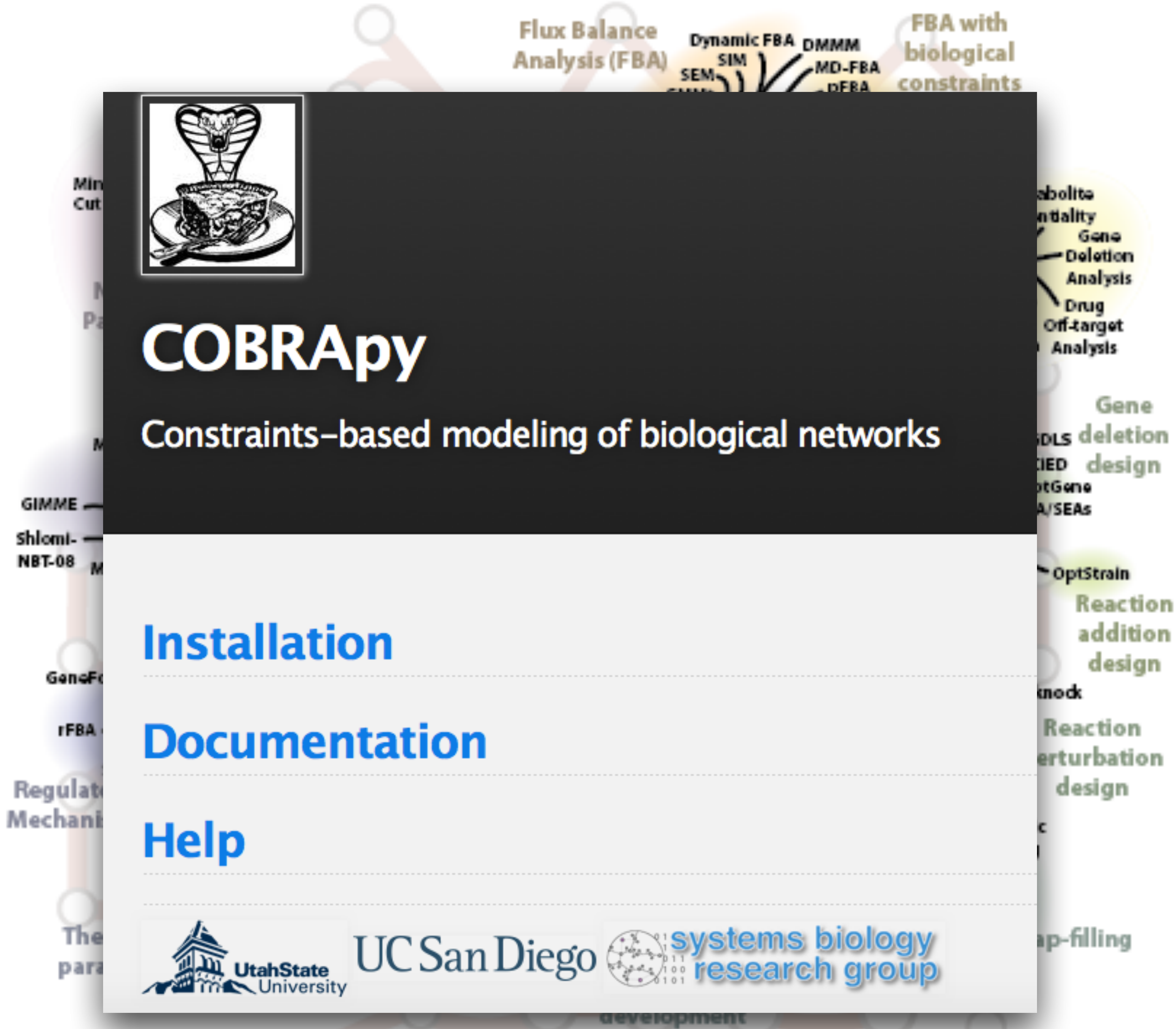
- Many other kind of analysis => A. Bockmayr talk !

Many tools



Flux Balance Analysis (FBA)
FBA with biological constraints
Dynamic FBA
DMMM
SIM
MD-FBA
SEM
pFBA
SMM
Genomic Context Analysis
FBA
PhPP
Geometric FBA
AOS
Flux Variability
Bayesian FBA
FFCA
Flux Coupling Finder
Alternate optima
FBAwMC
E-flux
Monte Carlo Sampling
Exometabolome Effect on internal States
Elementary Modes
Extreme Pathways
Alpha Spectrum
Minimal Cut Sets
Elementary Flux Patterns
Network-based Pathway Analysis
Message-Passing
Symbolic Flux Analysis
Unbiased
Biased
Metabolite Essentiality
MOMA
GNI
Gene Deletion Analysis
Reductive Evolution Simulation
ROOM
Drug Off-target Analysis
Gene perturbation
FBA
Strain design
Gene deletion design
GDLS
CIED
OptGene
SA/SEAs
FSEOF
OptORF
OptStrain
Reaction addition design
OptReg
EMILiO
OptForce
RobustKnock-proxy
RobustKnock
Optknock
Objective Tilting
Reaction perturbation design
MADE
tFBA
GIMME
Constraints from 'Omic Data
Shlomi-NBT-08
MBA
PROM
Regulatory methods
GeneForce
rFBA
SR-FBA
iFBA
idFBA
Regulatory Mechanisms
Thermodynamics
Model refinement
Flux Minimization
Thermodynamic Realizability
TMFA
NET Analysis
Thermodynamic parameter-based analysis
EBA
loopless COBRA
Loop removal
Evolutionary SA search
NISE
LPPFBA
Bayesian Selection
GrowMatch
ObjFind
BOSS
Objective funtion development
Algorithmic Gap-filling
SCAR
GapFind/GapFill
OMNI
Network-based Enzyme Localization
Gap-filling

Many tools



Flux Balance Analysis (FBA)
Dynamic FBA
SIM
SEM
DMMM
MD-FBA
FBA with biological constraints
COBRApy
Constraints-based modeling of biological networks
Installation
Documentation
Help
UtahState University
UC San Diego
systems biology research group
Gene Deletion Analysis
Drug Off-target Analysis
Gene deletion design
OptStrain
Reaction addition design
Reaction perturbation design
GIMME
Shlomi-NBT-08
rFBA