Basics on Metabolic network analysis

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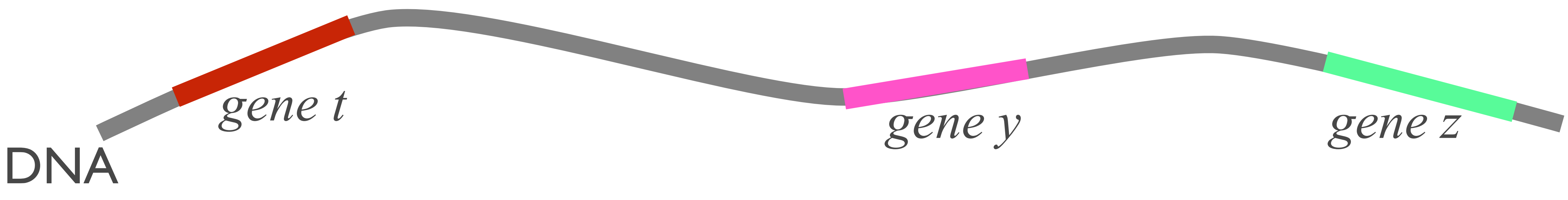
A simplistic illustration



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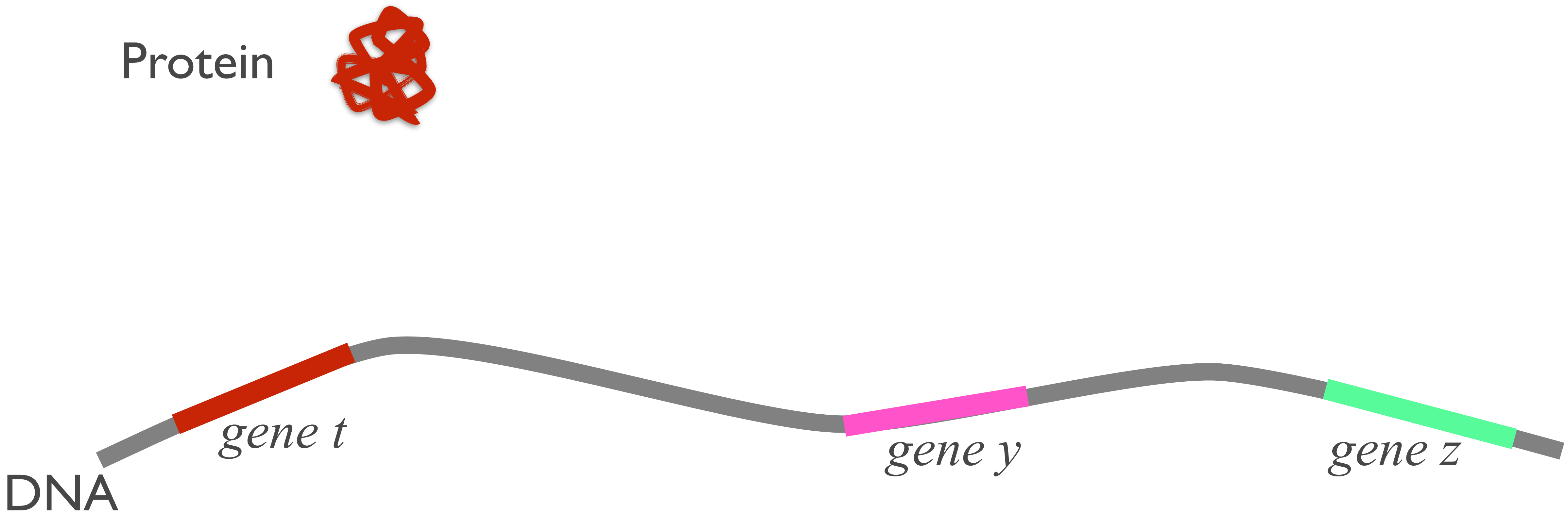
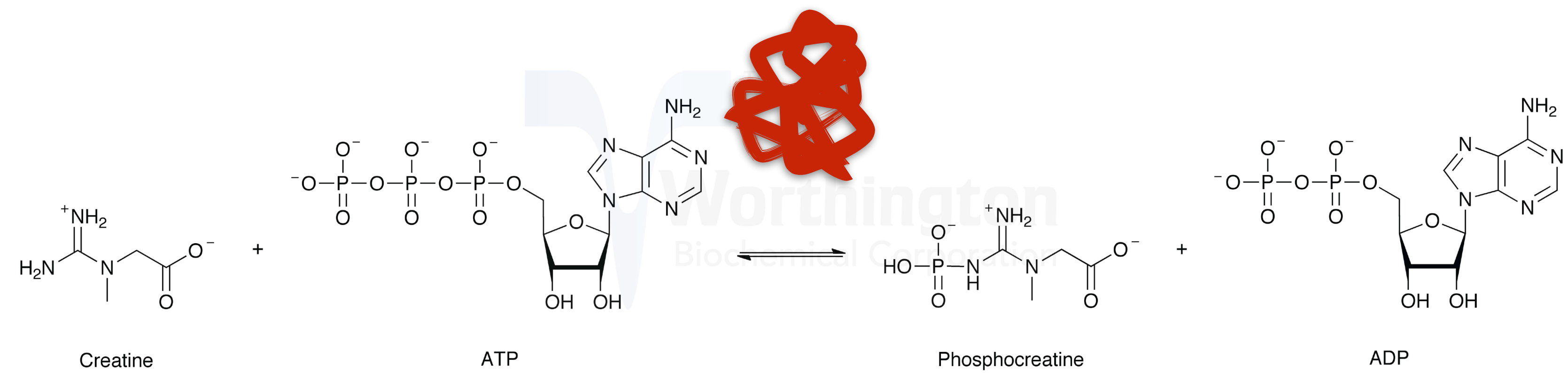


A simplistic illustration

Creatine kinase catabolyzes the chemical reaction

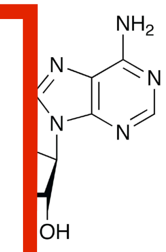
Protein



DNA

A simplistic illustration

Creatine kinase catabolyzes the chemical reaction



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

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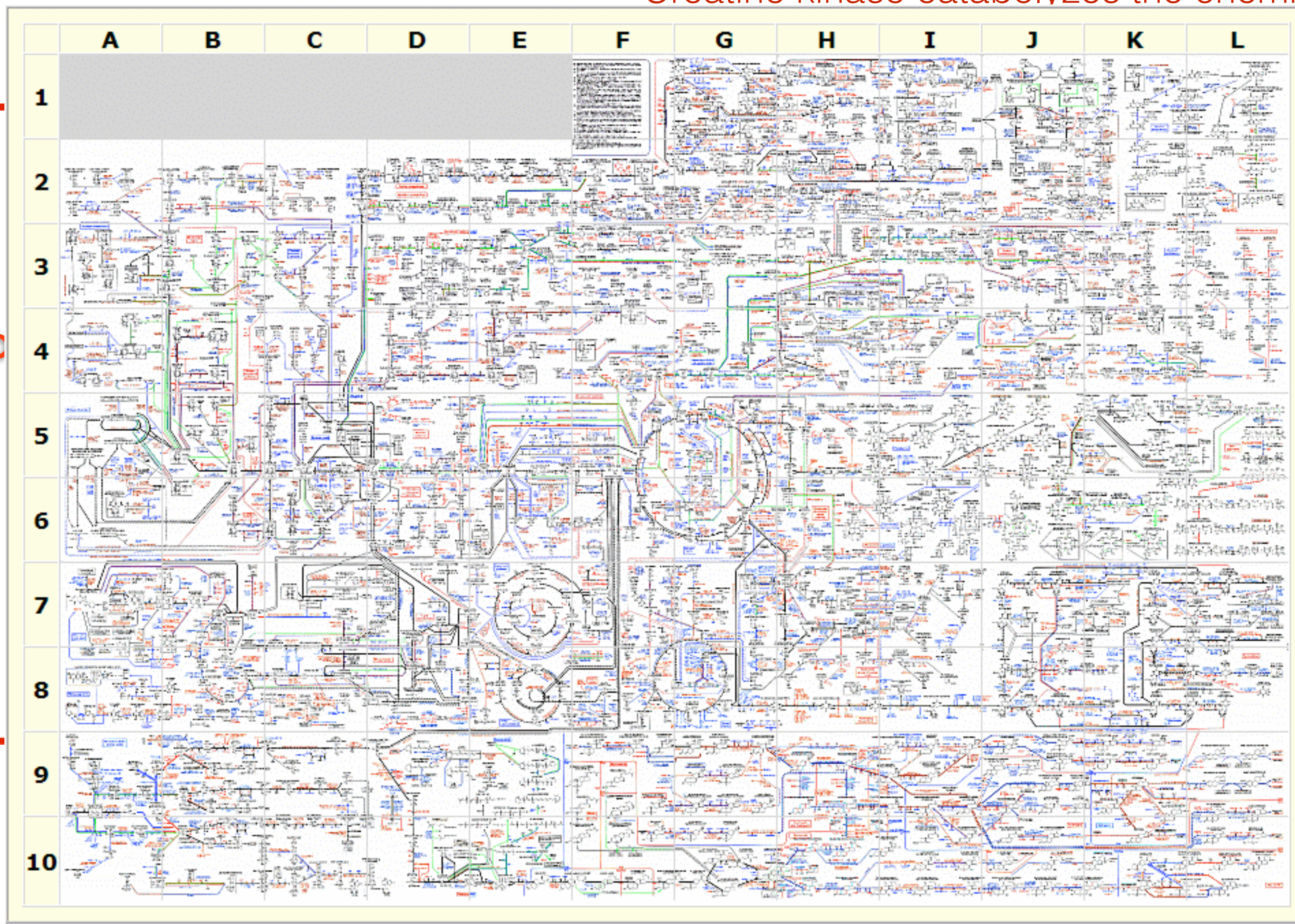

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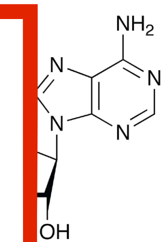
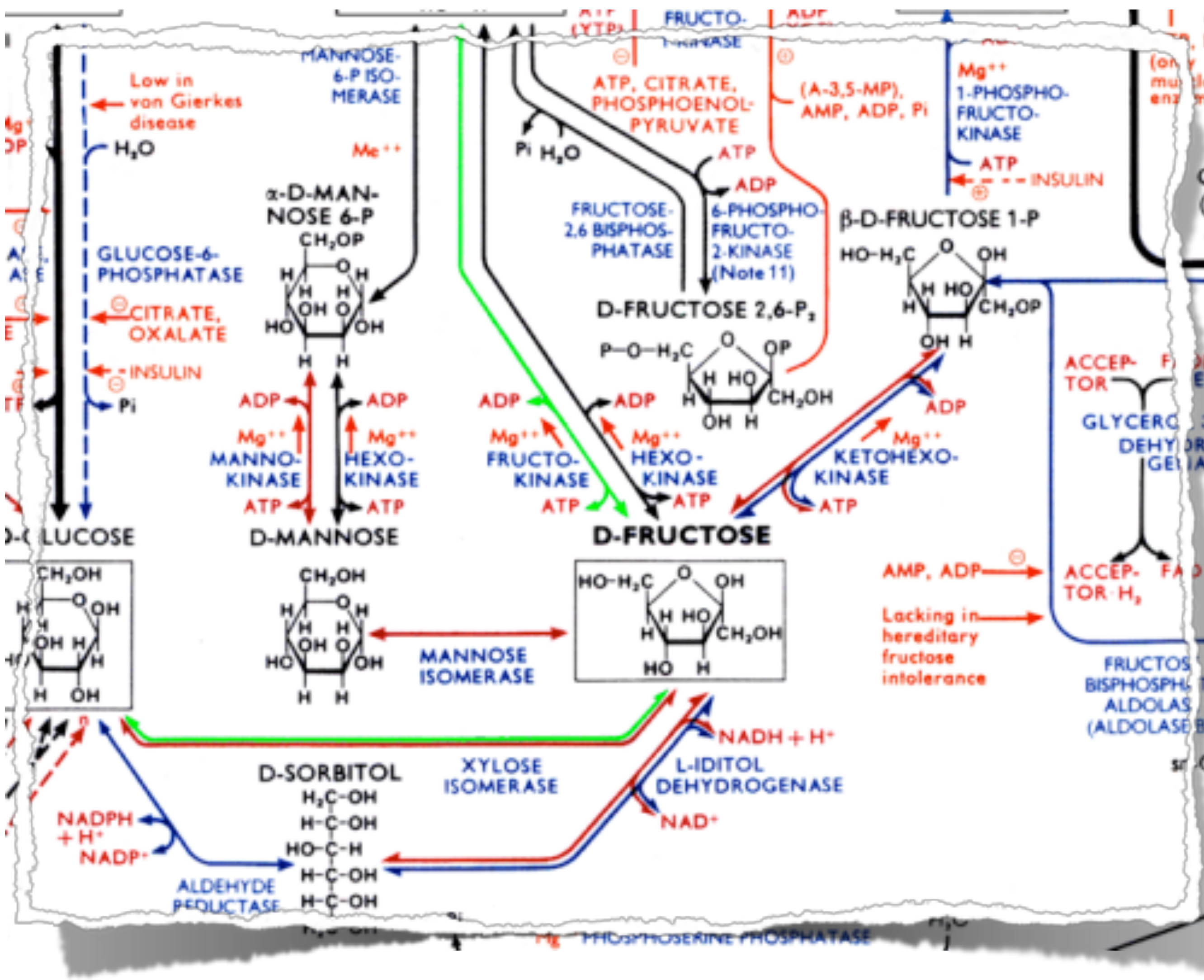


A few words on metabolism

- Bio-chemical network = set of (bio)-chemical reactions that can appear in a living system.
- Some of these reactions can be catabolized by enzymes.
- Metabolism = biological process that we aim at modelling (sub-set of bio-chemical reactions dealing with metabolites (CO_2, O_2, Glucose,….))
- Metabolic Network = incomplete mathematical abstraction of the metabolism.

A few words on metabolism



- f (bio)-chemical reactions
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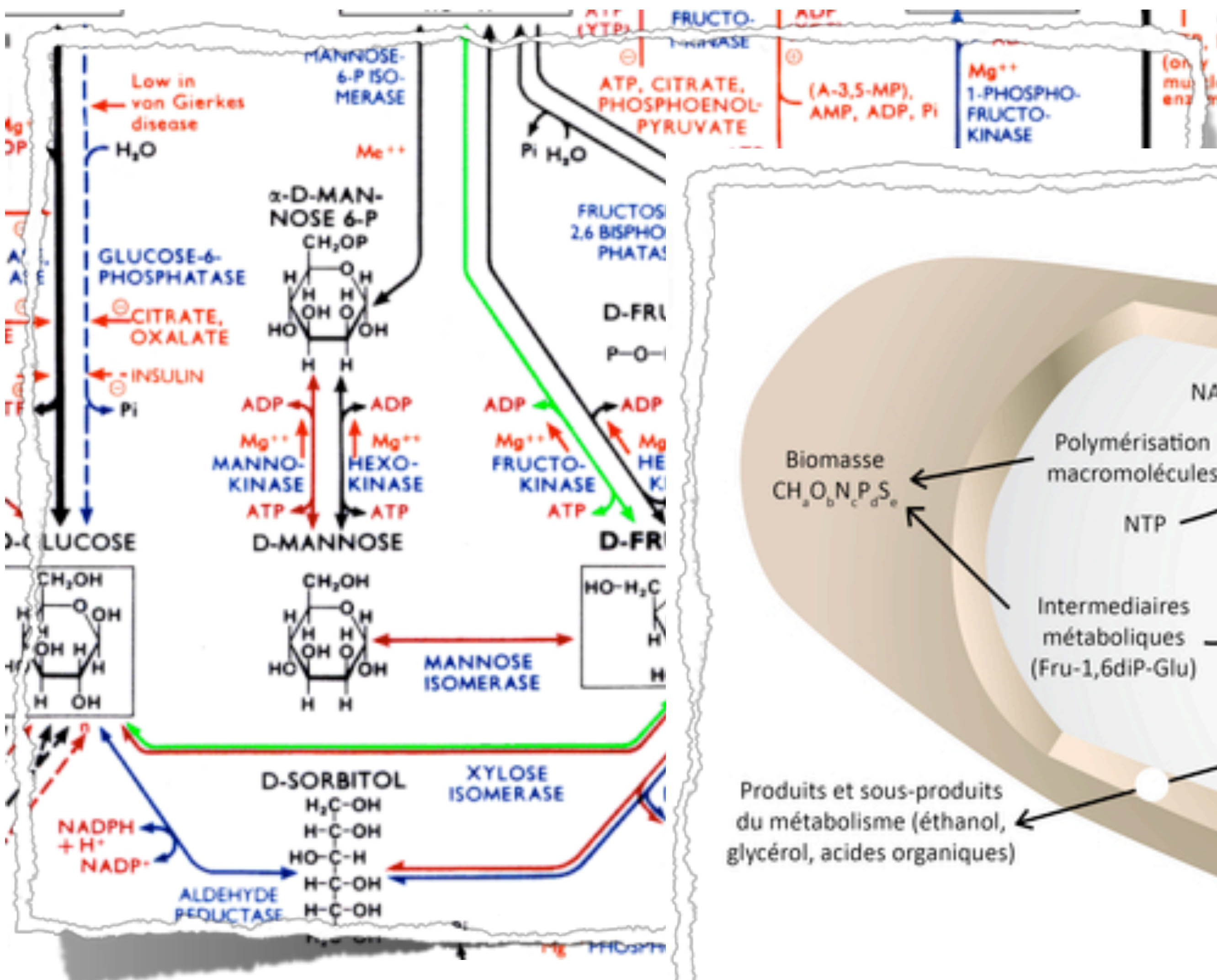

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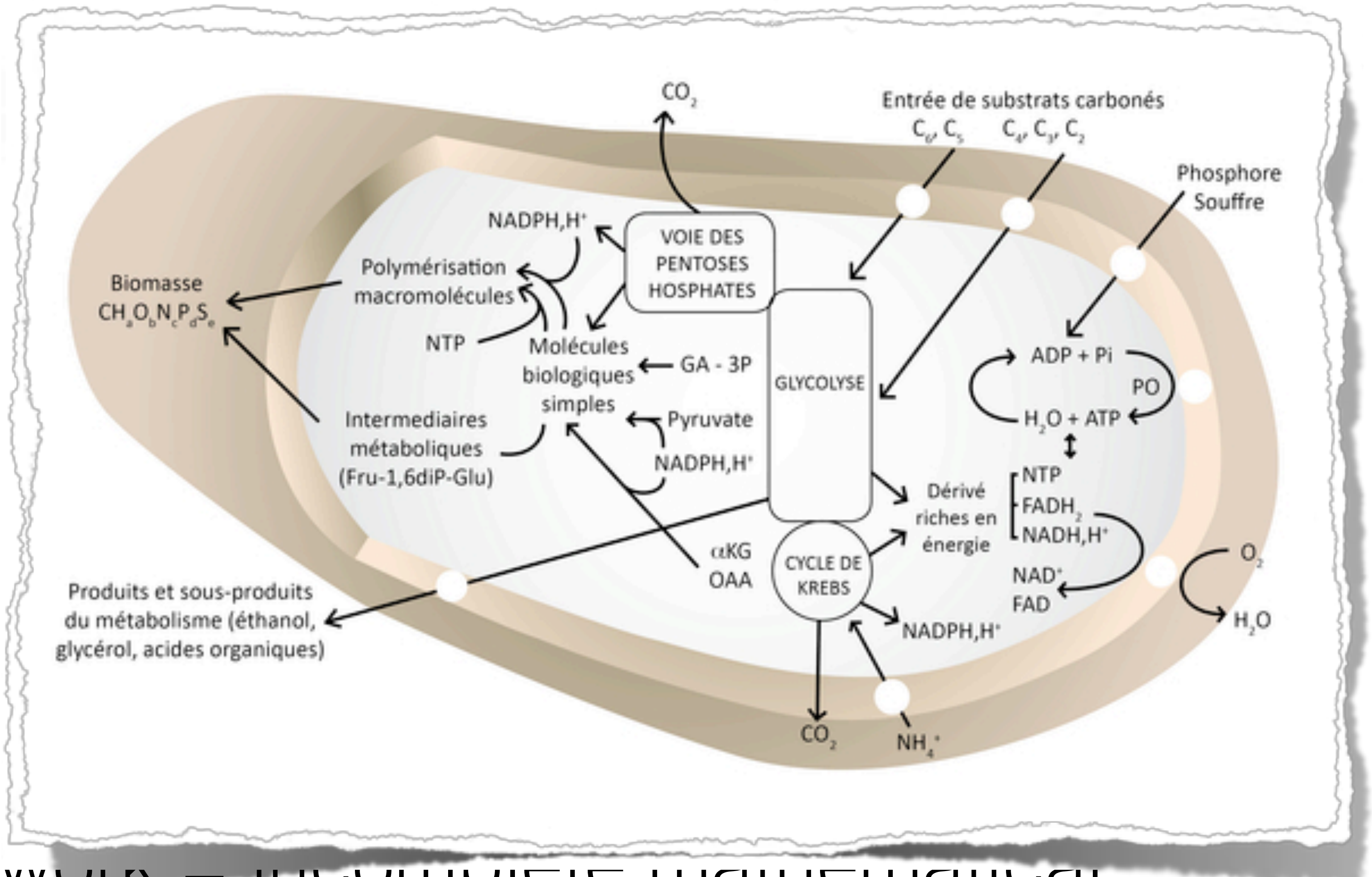

- Metabolic Network – incomplete mathematical abstraction of the metabolism.

A few words on metabolism

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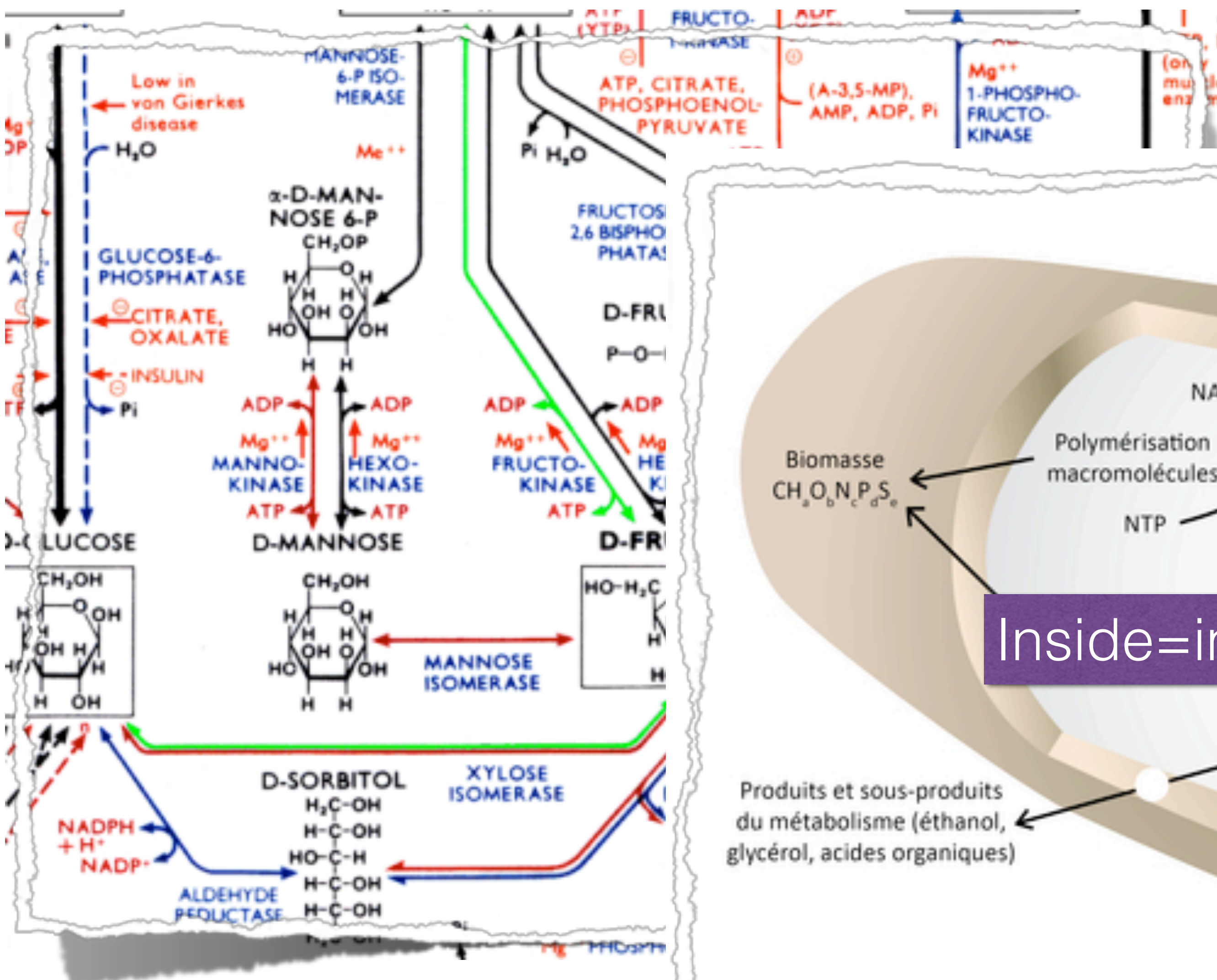

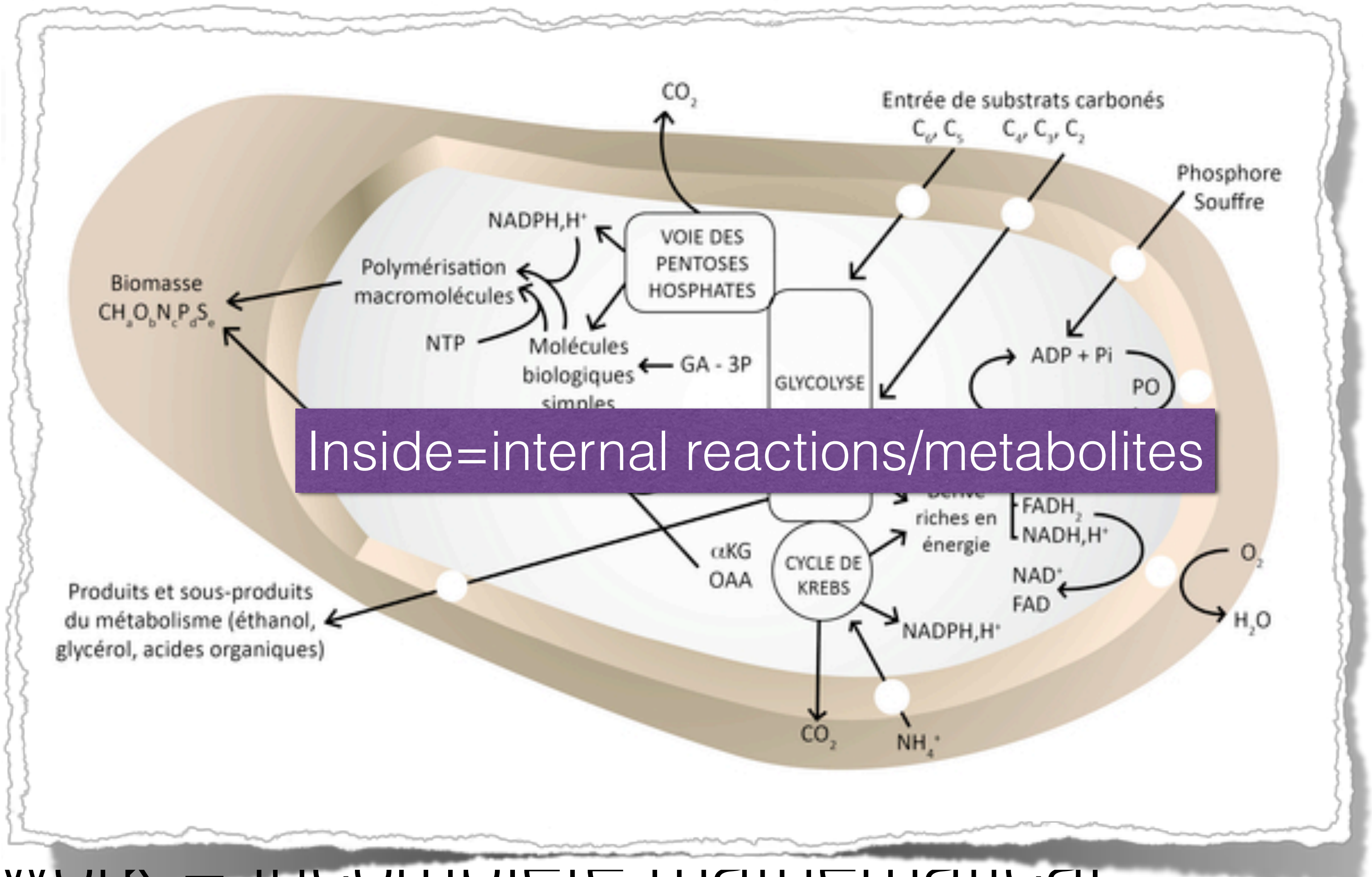

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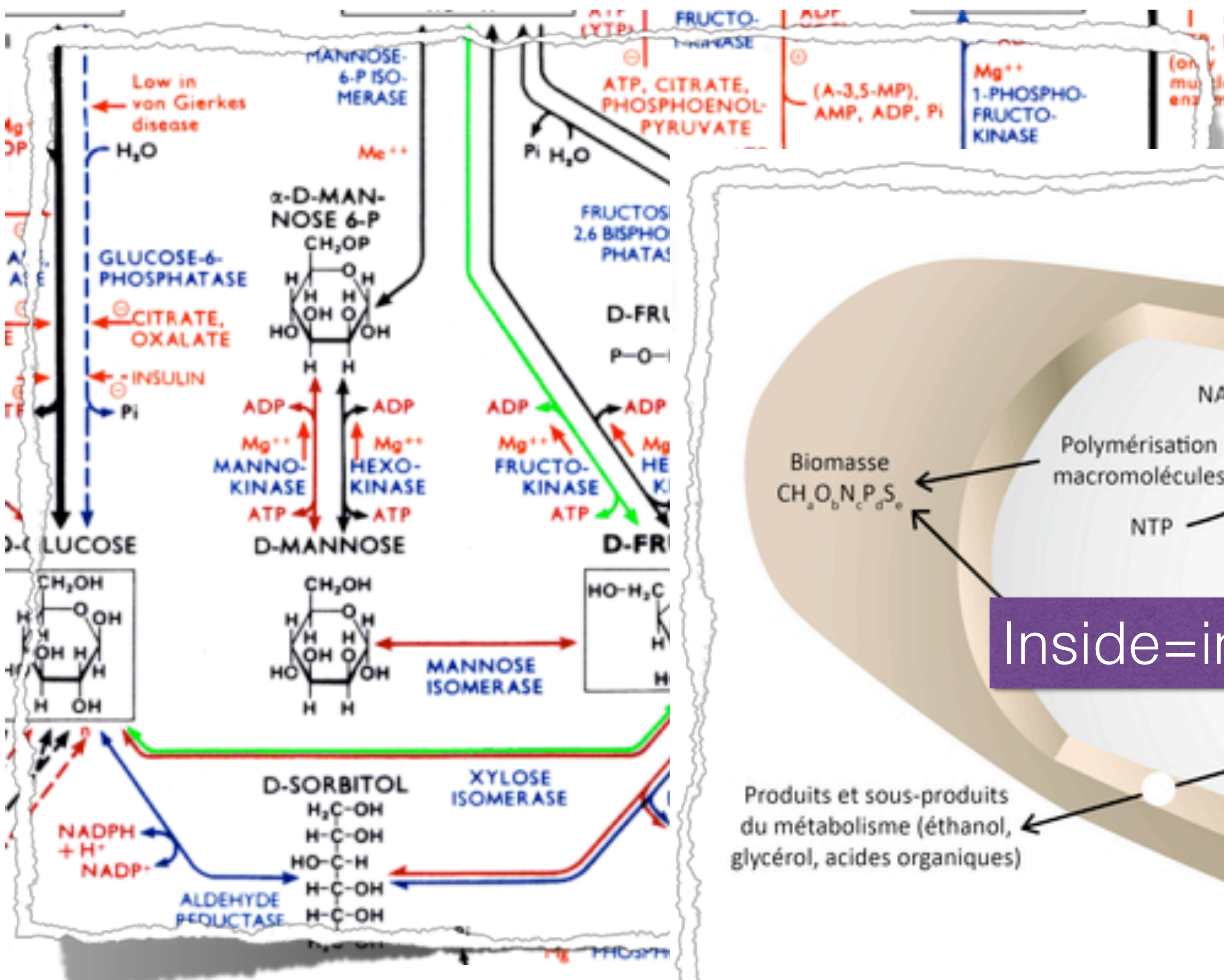

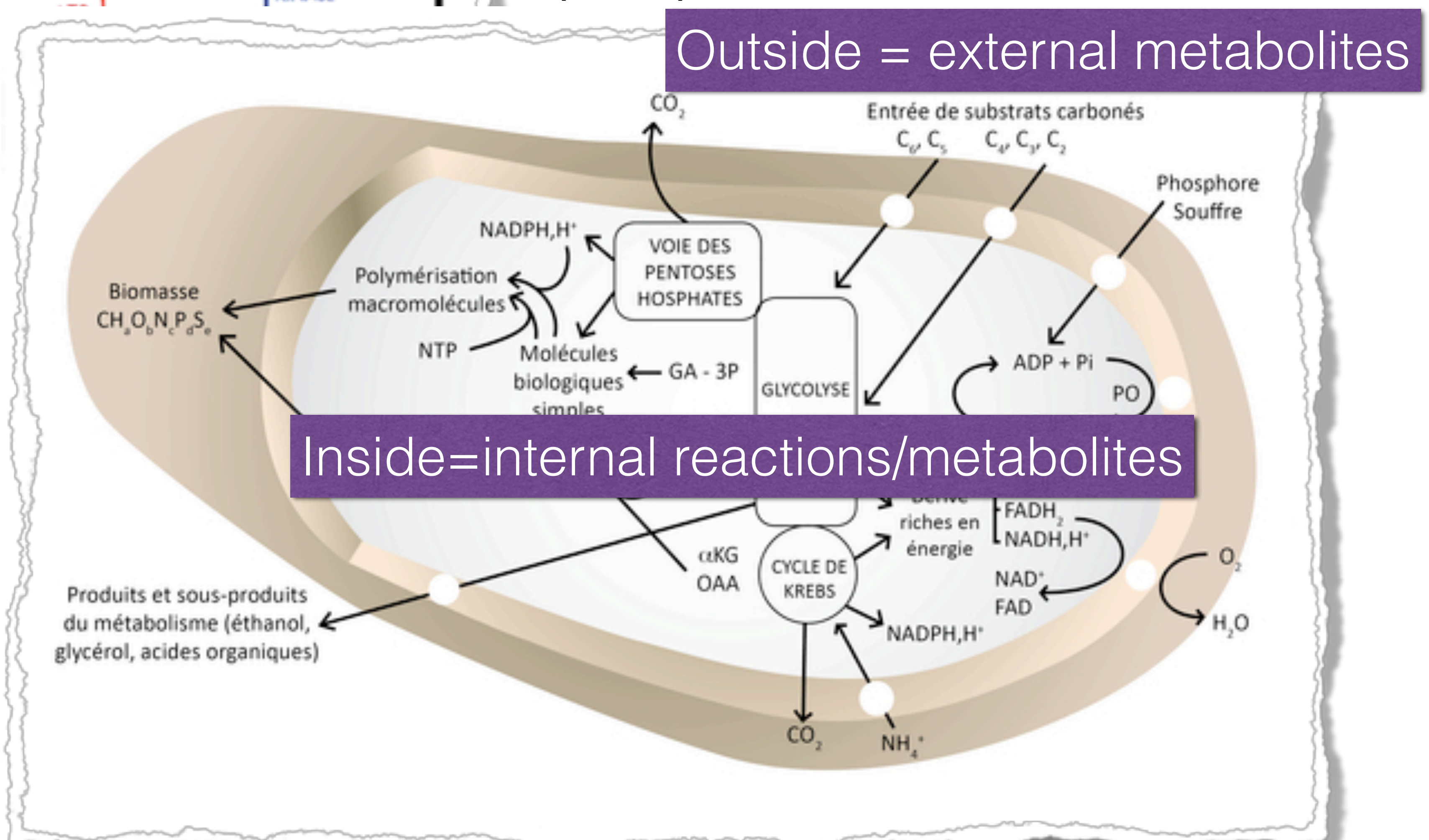

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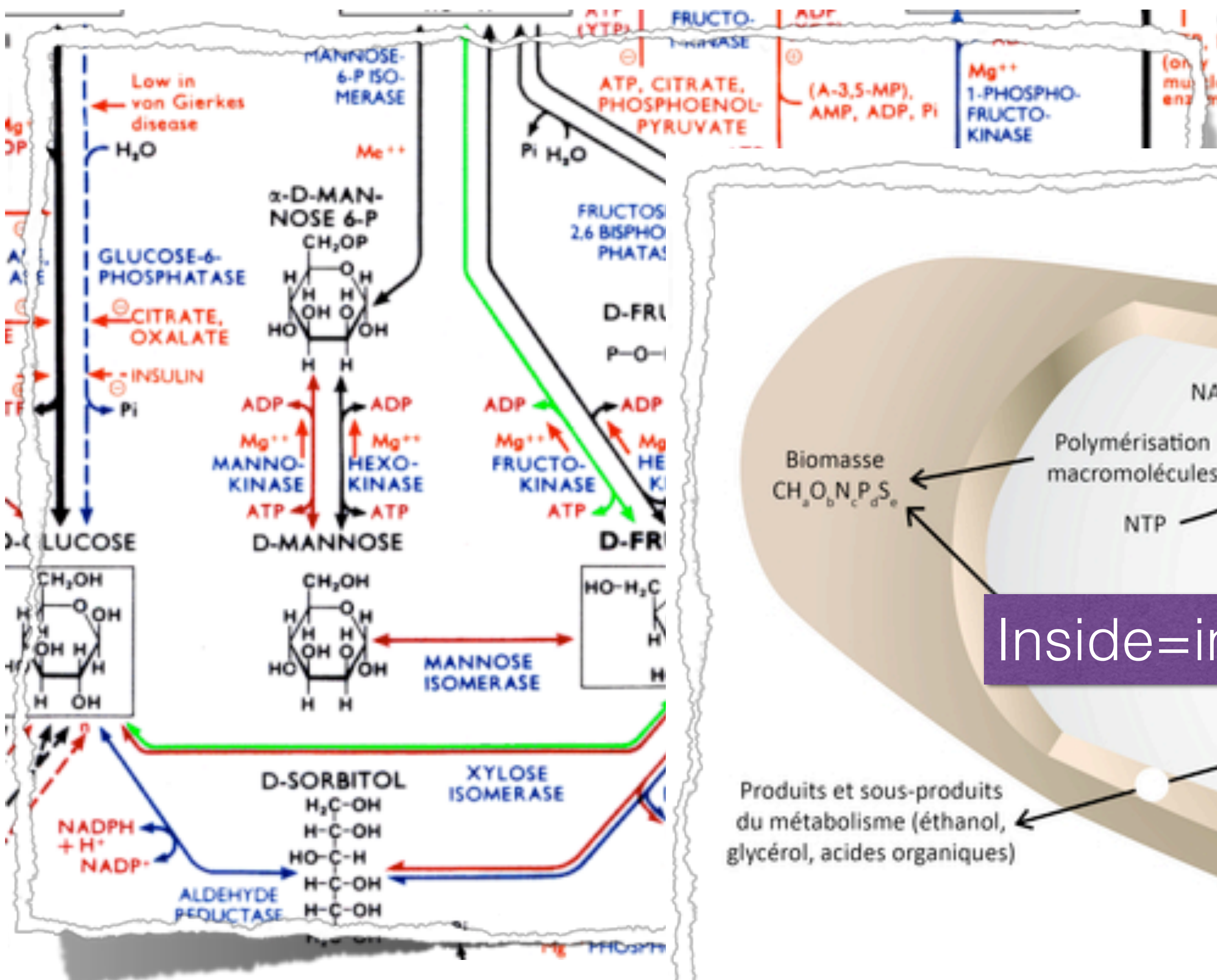

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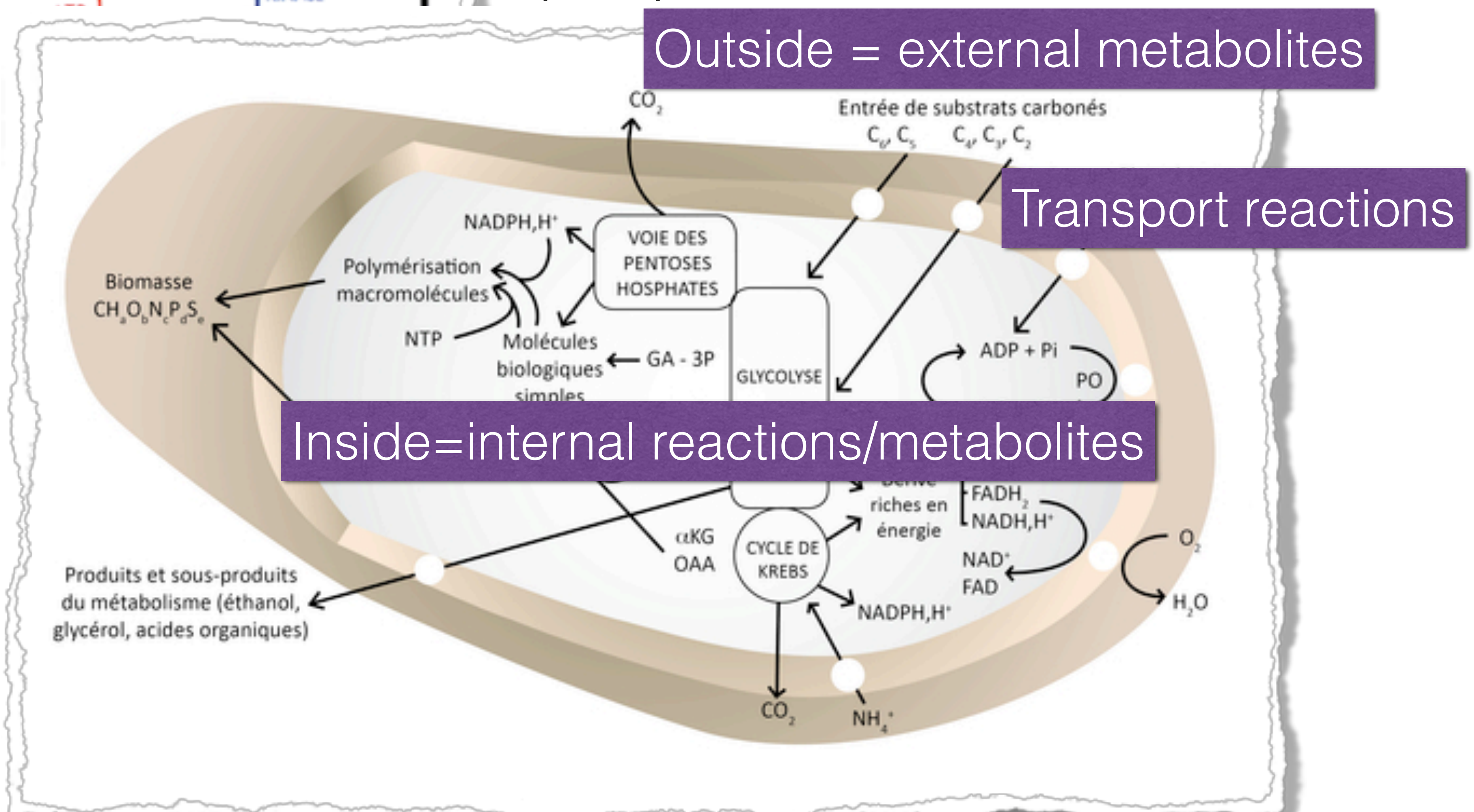

- Metabolic Network = incomplete mathematical abstraction of the metabolism.

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

NB : in a matrix notation, it rewrites as S.v = 0 !

Mathematical modeling
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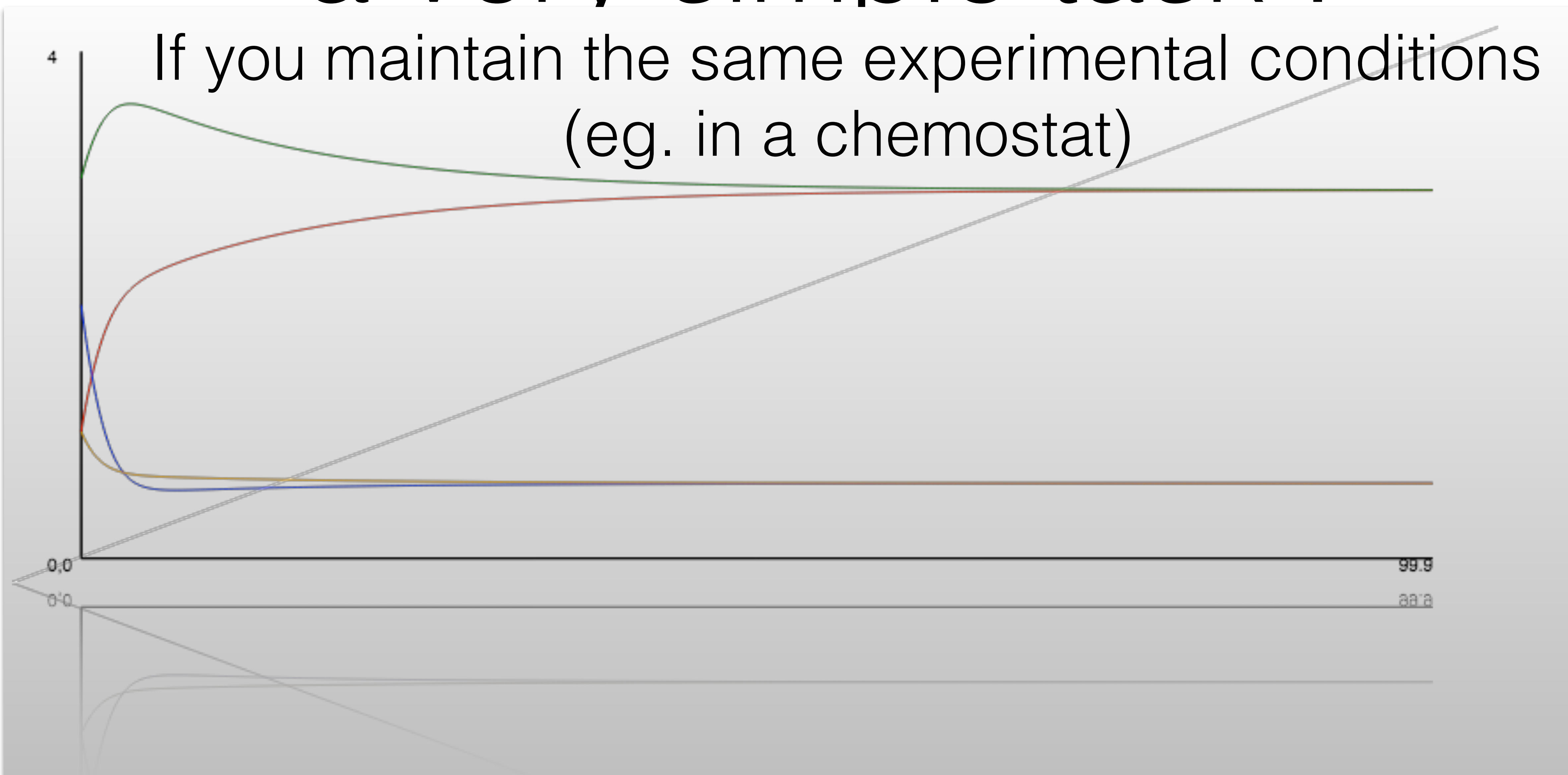
If you maintain the same experimental conditions
(eg. in a chemostat)



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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.

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

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

NB : in a matrix notation, it rewrites as S.v = 0 !

Mathematical modeling a very simple task !

Hypothesis 2 : There exists some thermodynamical constraints on the fluxes that imposes the reaction to be oriented (i.e., $V_R \geq 0$)
Hypothesis 2' : There exists some constraints due to the availability of the metabolic nutrient in the growth media (translates as $V_R \geq$ constante where R is a transport reaction)
Hypothesis 2'' : There exists some constraints the cell cannot be of infinite size…. (translates as $V_R \leq$ constante)

The metabolic network is then described properly by giving its stoichiometric matrix S and some lower bound (lb) and upper bound (ub) such that lb $\leq$ v $\leq$ ub.

$V_{R1} = V_{R2} + V_{R3}$
$V_{R4} = V_{R2}$
$V_{R3} = V_{R4} - V_{R1}$
$V_{R2} = V_{R1} + 2V_{R3}$
…..

The set of possible fluxes is a convex polyhedron !

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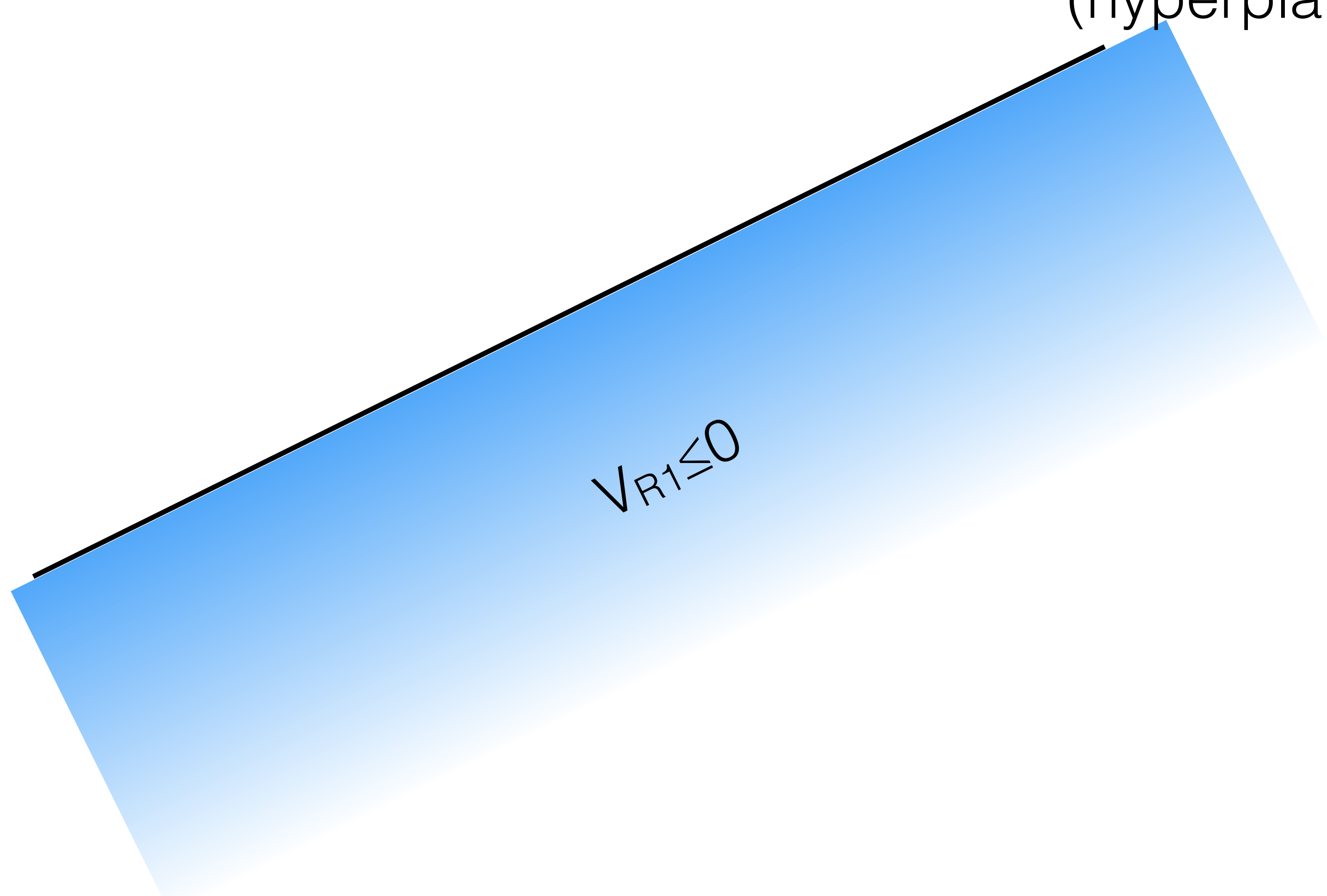
(hyperplane) $0 = V_{R1} = V_{R2} + V_{R3}$



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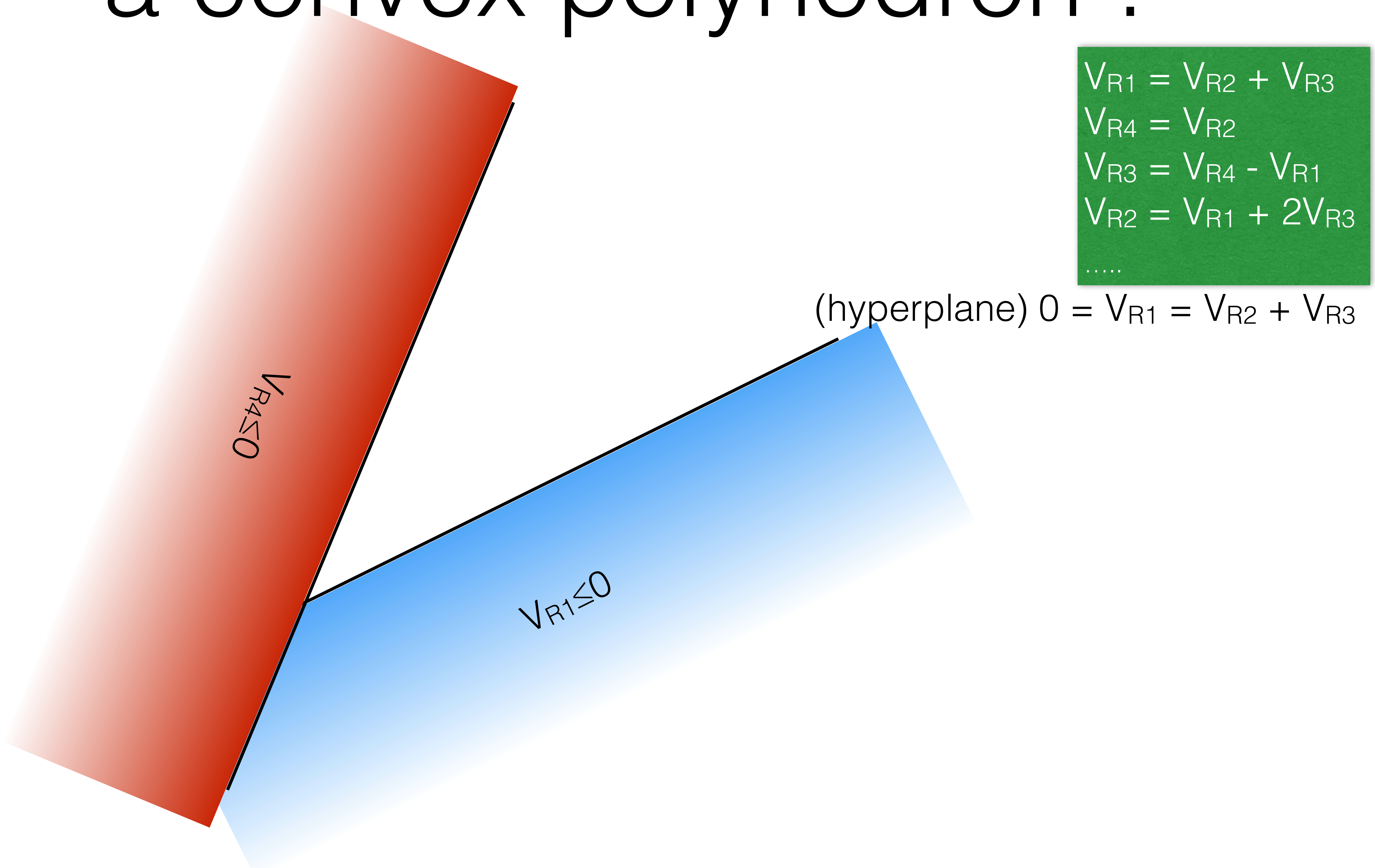

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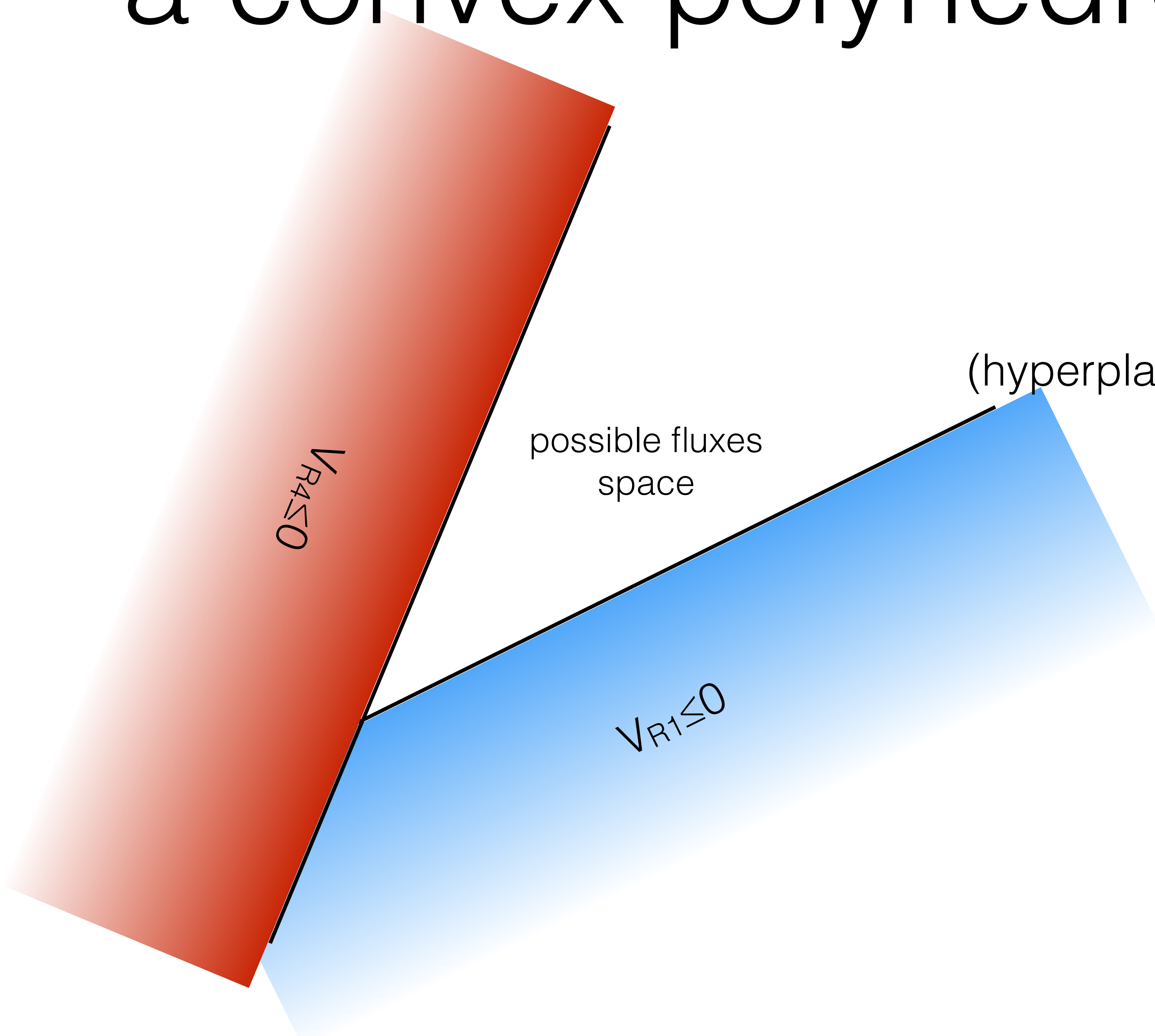

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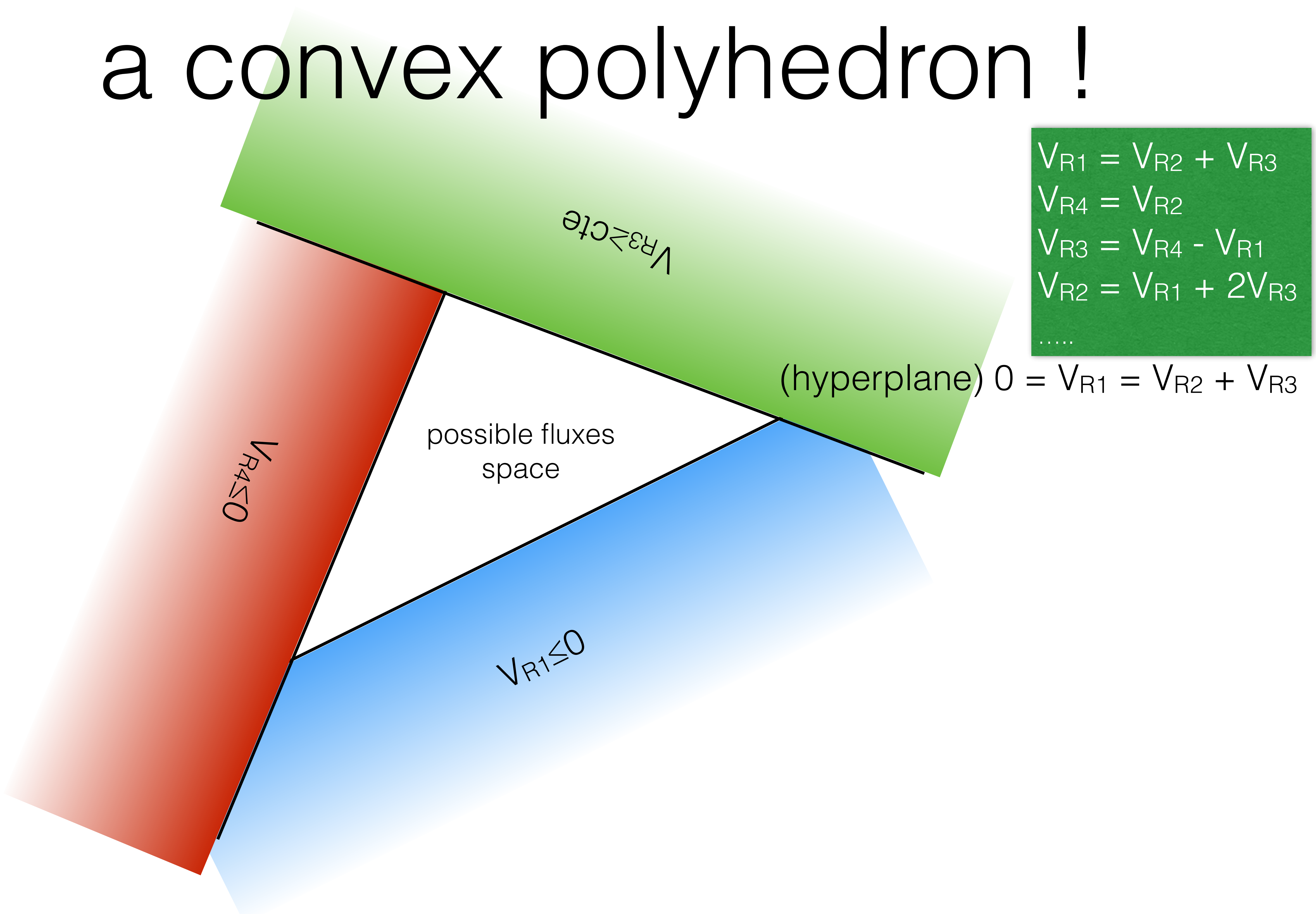

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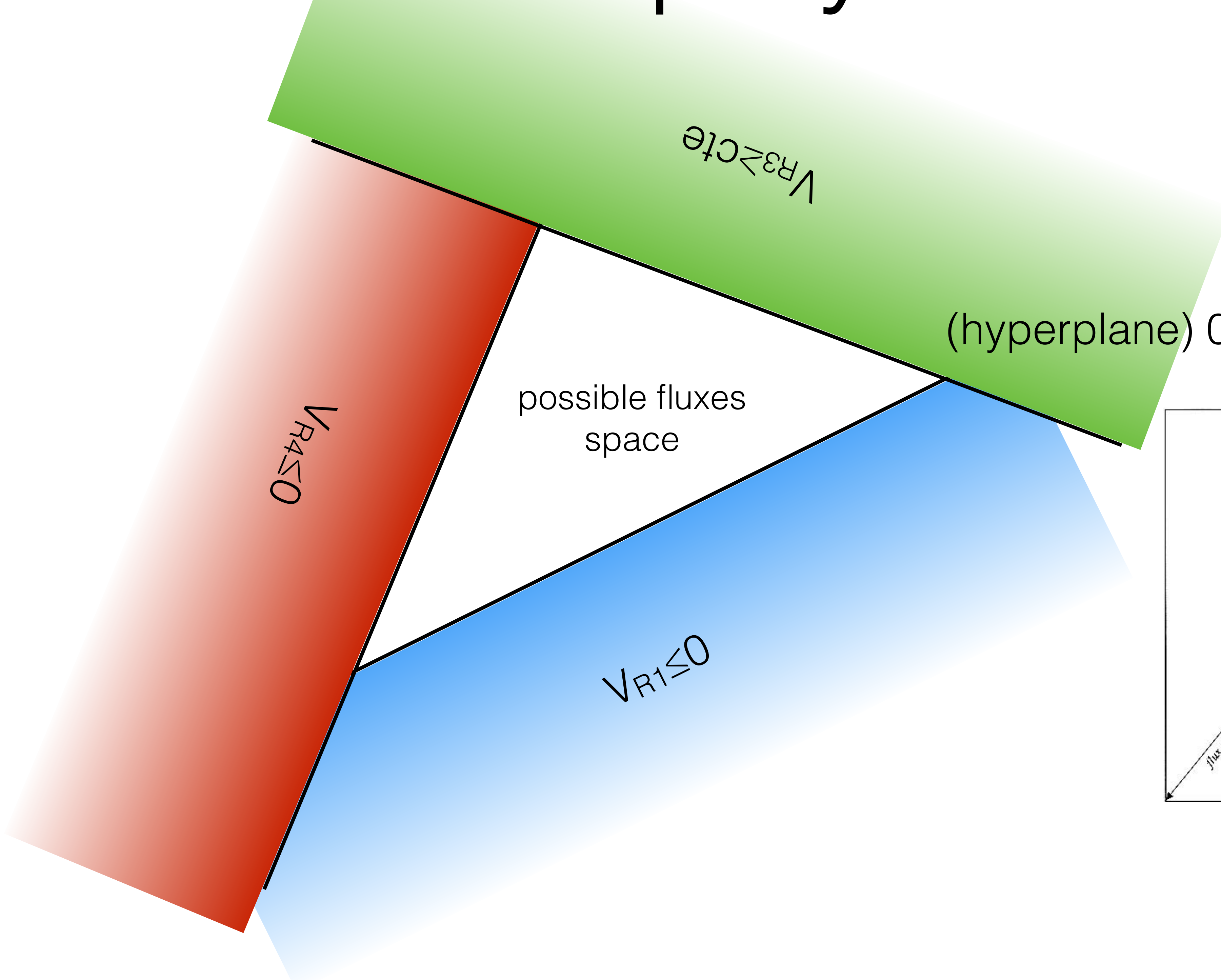

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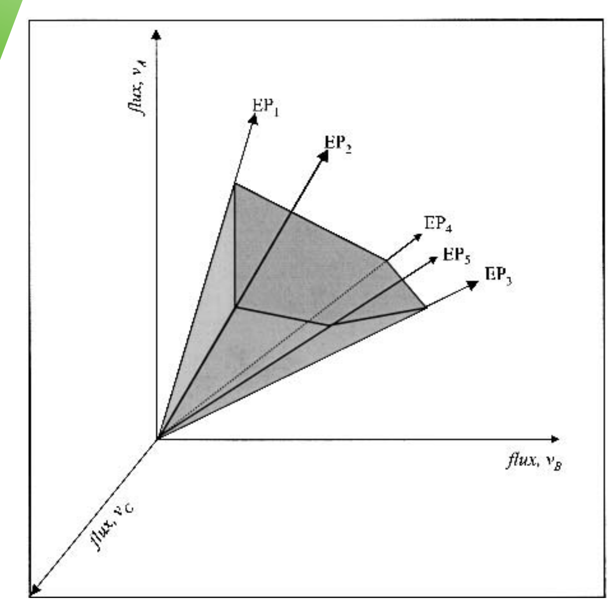

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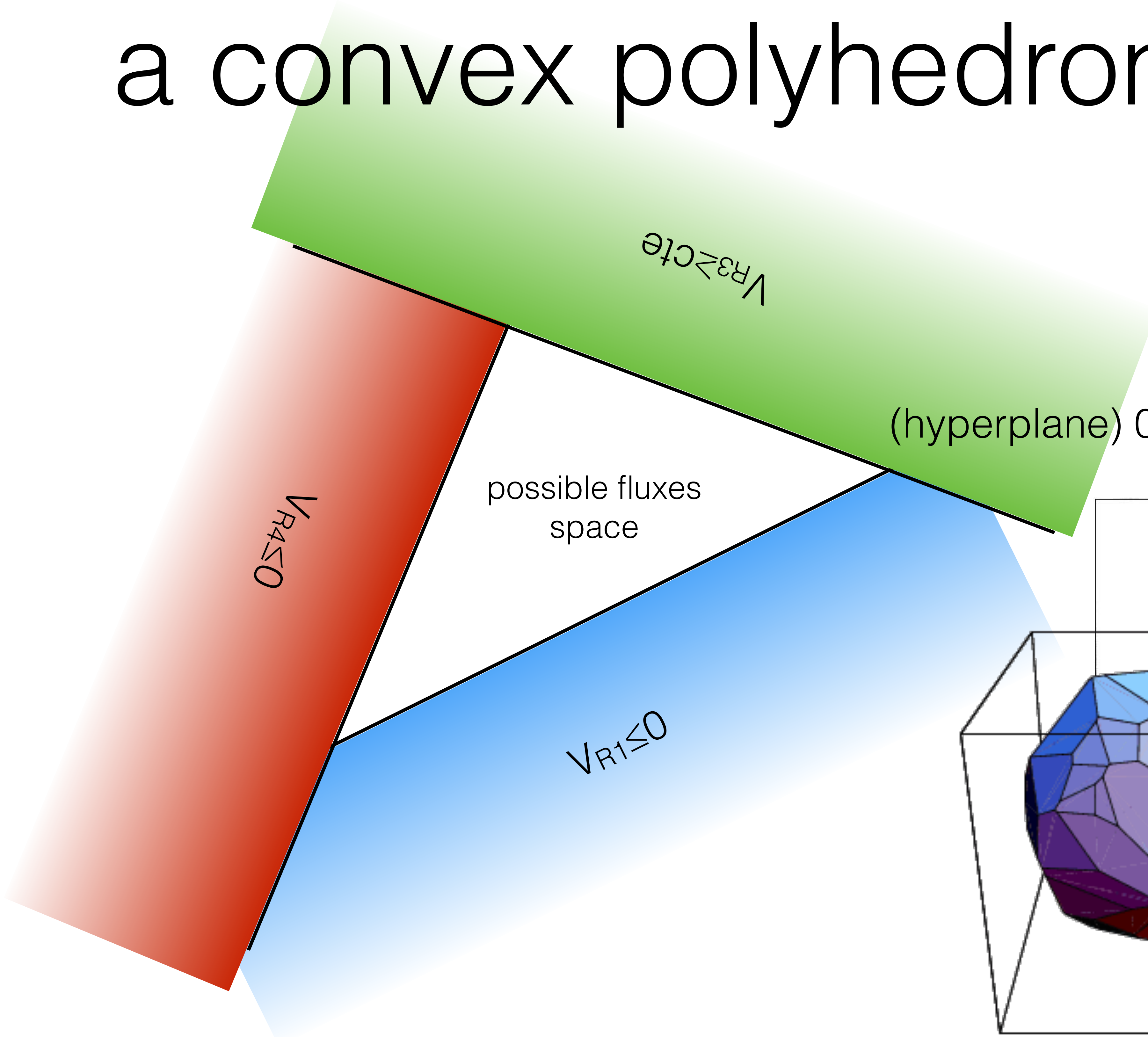

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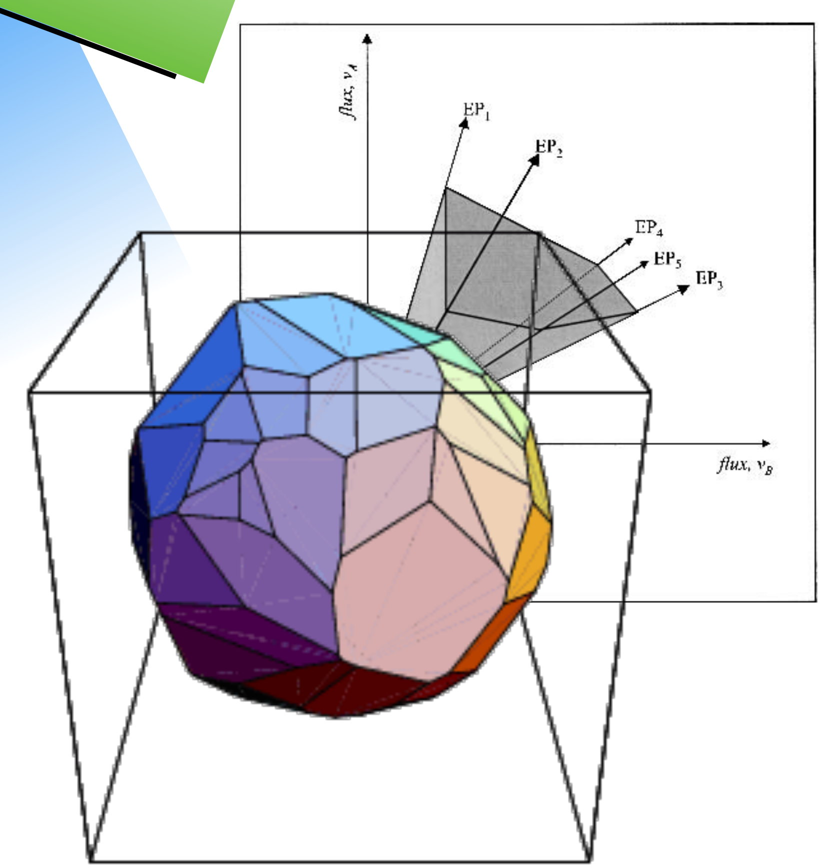

Why it is so important ?

From biology to computer science and back….

- There exists some very efficient algorithms that solves optimization problems when the solution is to be found in a convex polyhedron (=simplex).

- In computer science, it refers as Linear Programming (LP), Quadratic Programming (QP) or Mixed Integer Linear Programming (MILP) depending on the shape of the function that has to be optimized in the convex polyhedron.

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From biology to computer science and back….

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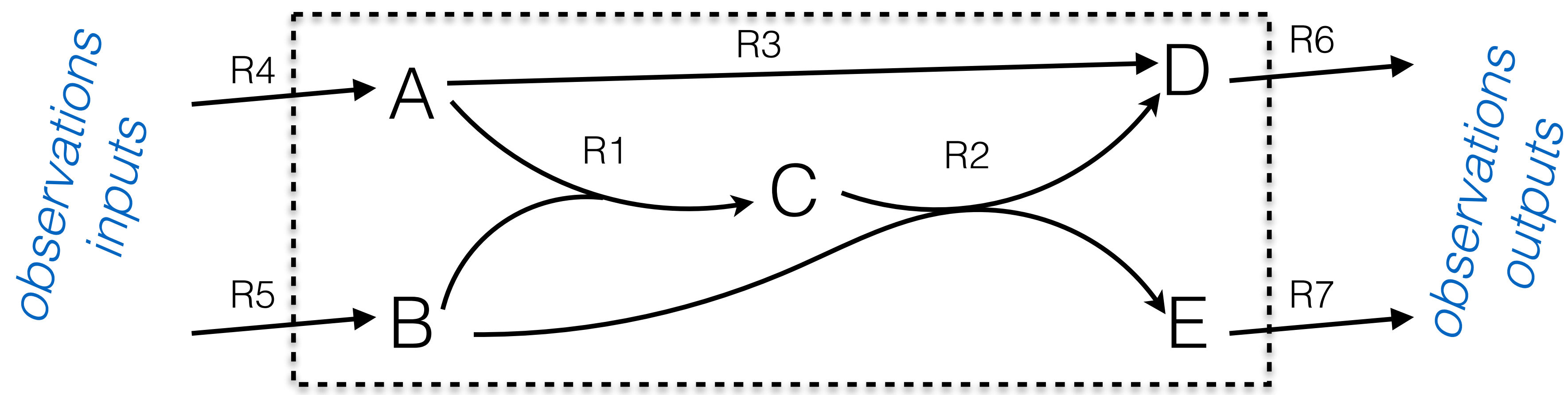
Program   ng (QP) or Mixed Integer Linear Programming (MILP) depending on the shape of the function that has to be optimized in the convex polyhedron.

The remaining task consists in modeling the biological problem in a way a solver from computer science can handle it and interpret the obtained results in a biological flavor

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
Question 4 : Suppose that we observe V4 = 1 and V7 = 2 and solve the system
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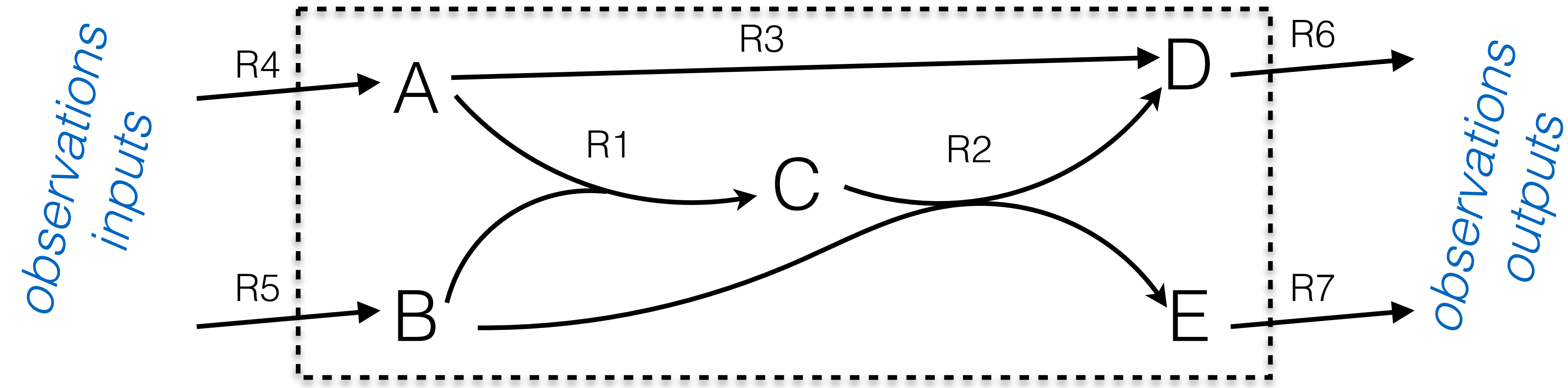

Question 1 : Write the stoichiometric matrix

	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
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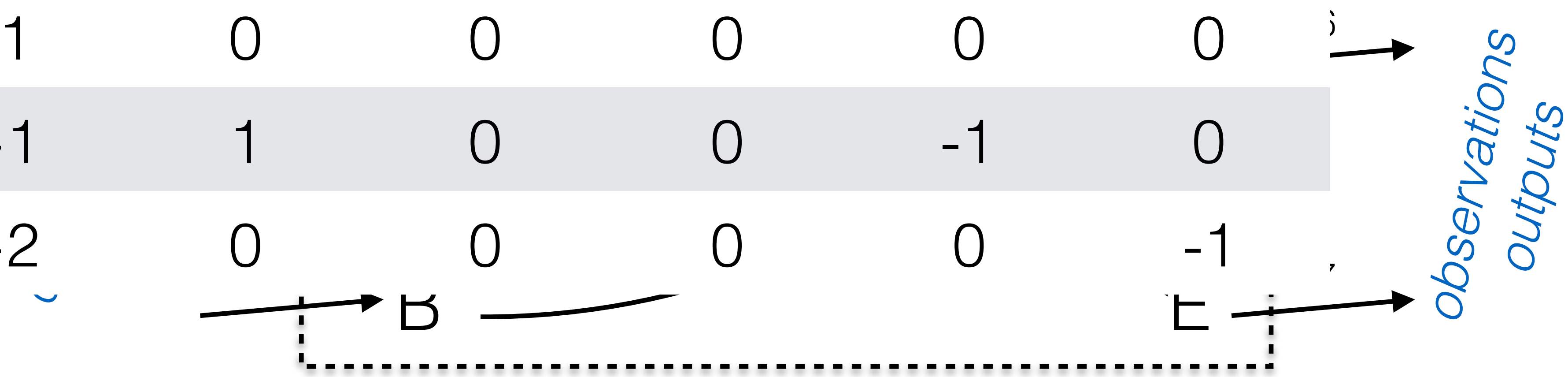

R6 : D —>
R7 : E —>

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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.

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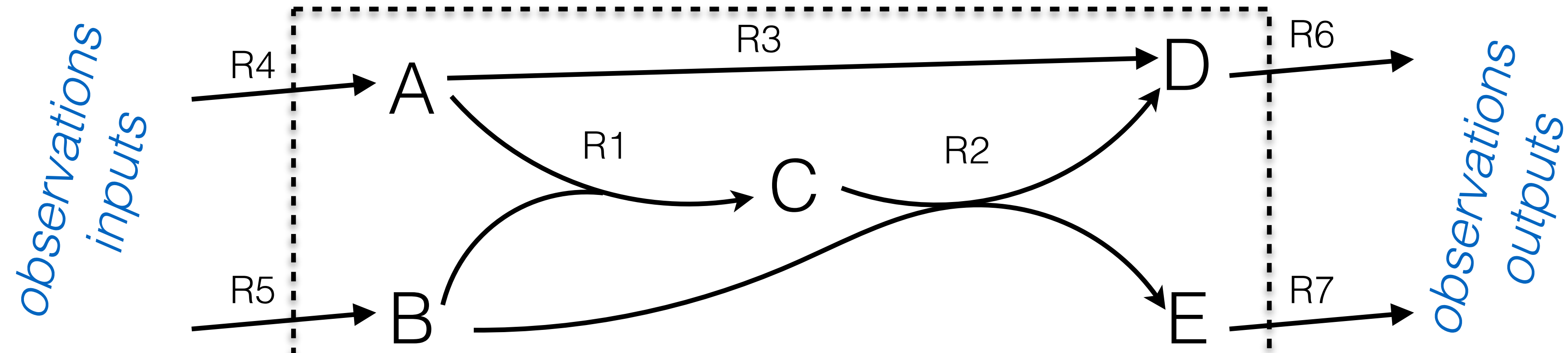

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V1 = V2 = 0.5, V3 = 0, V4 = 1, V5 = 1, V6 = 0.5, V7 = 1

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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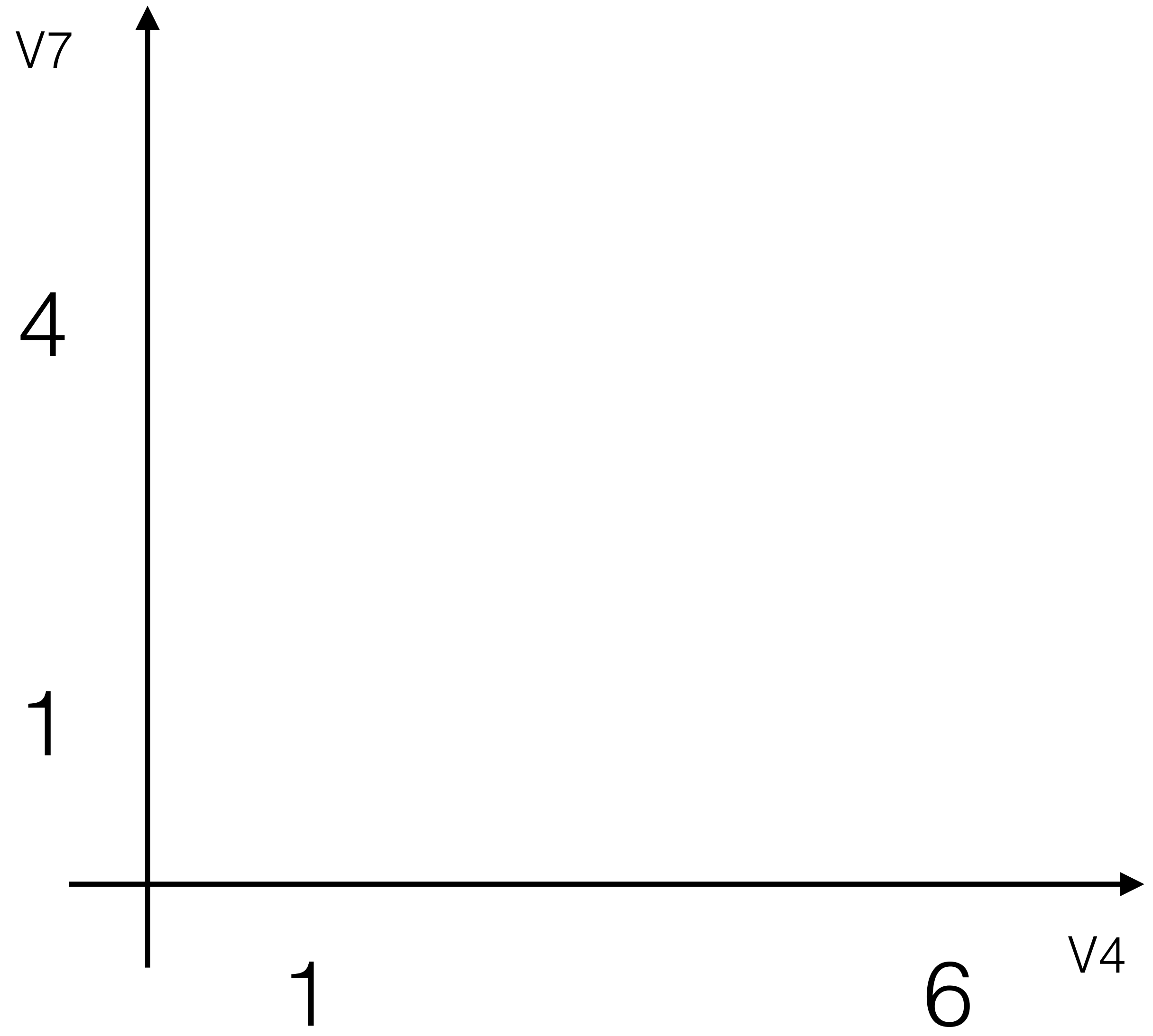

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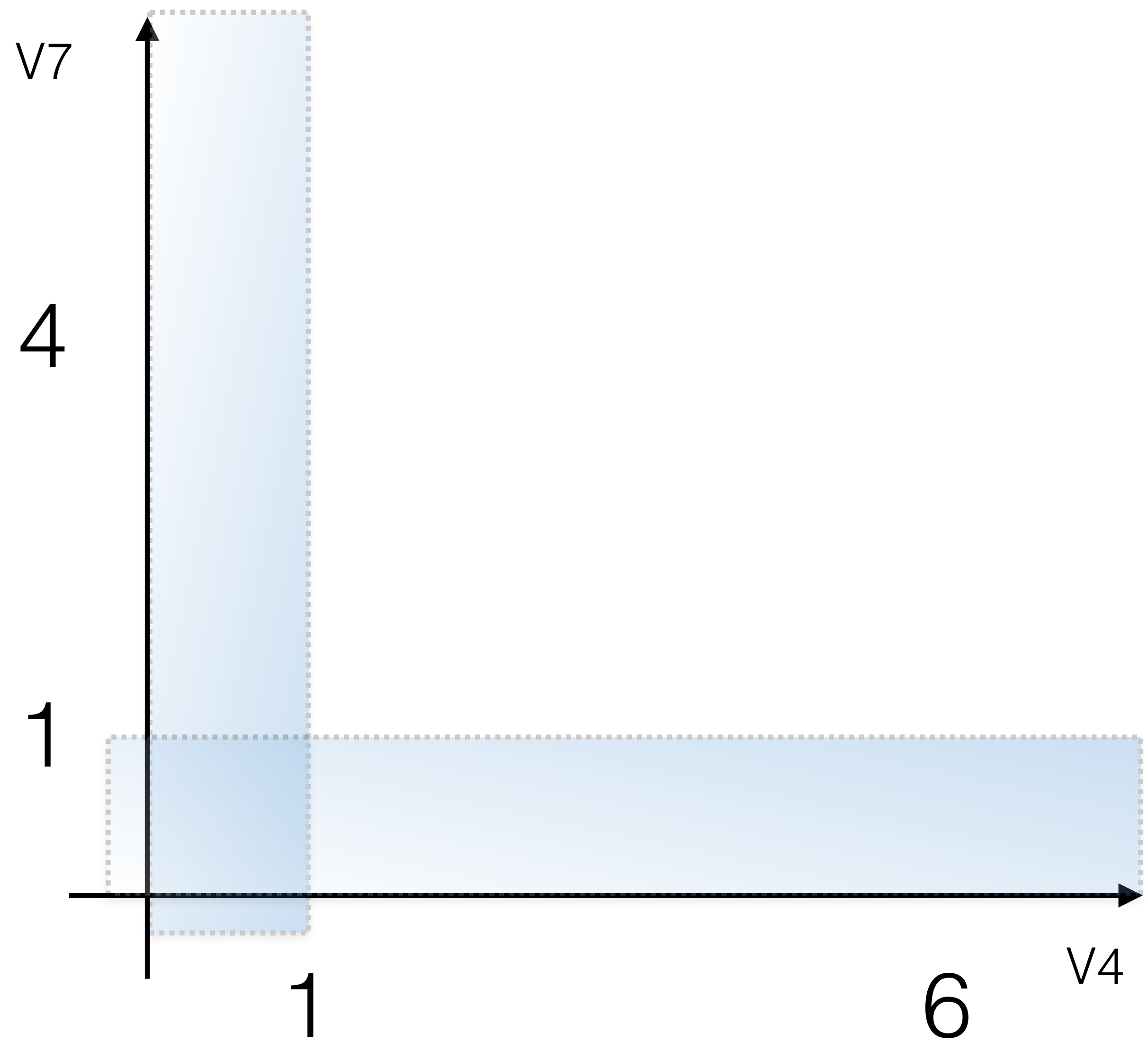

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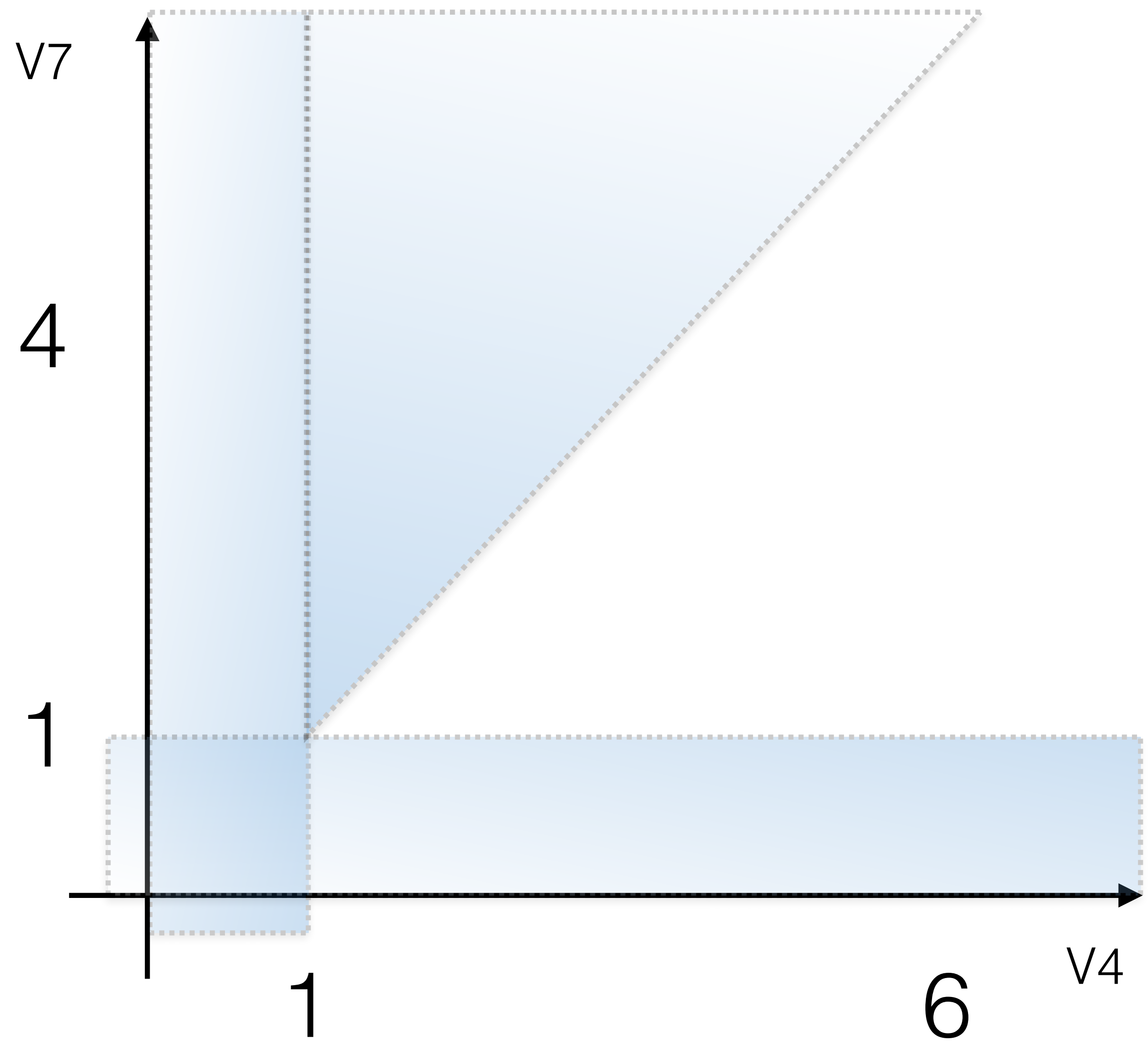

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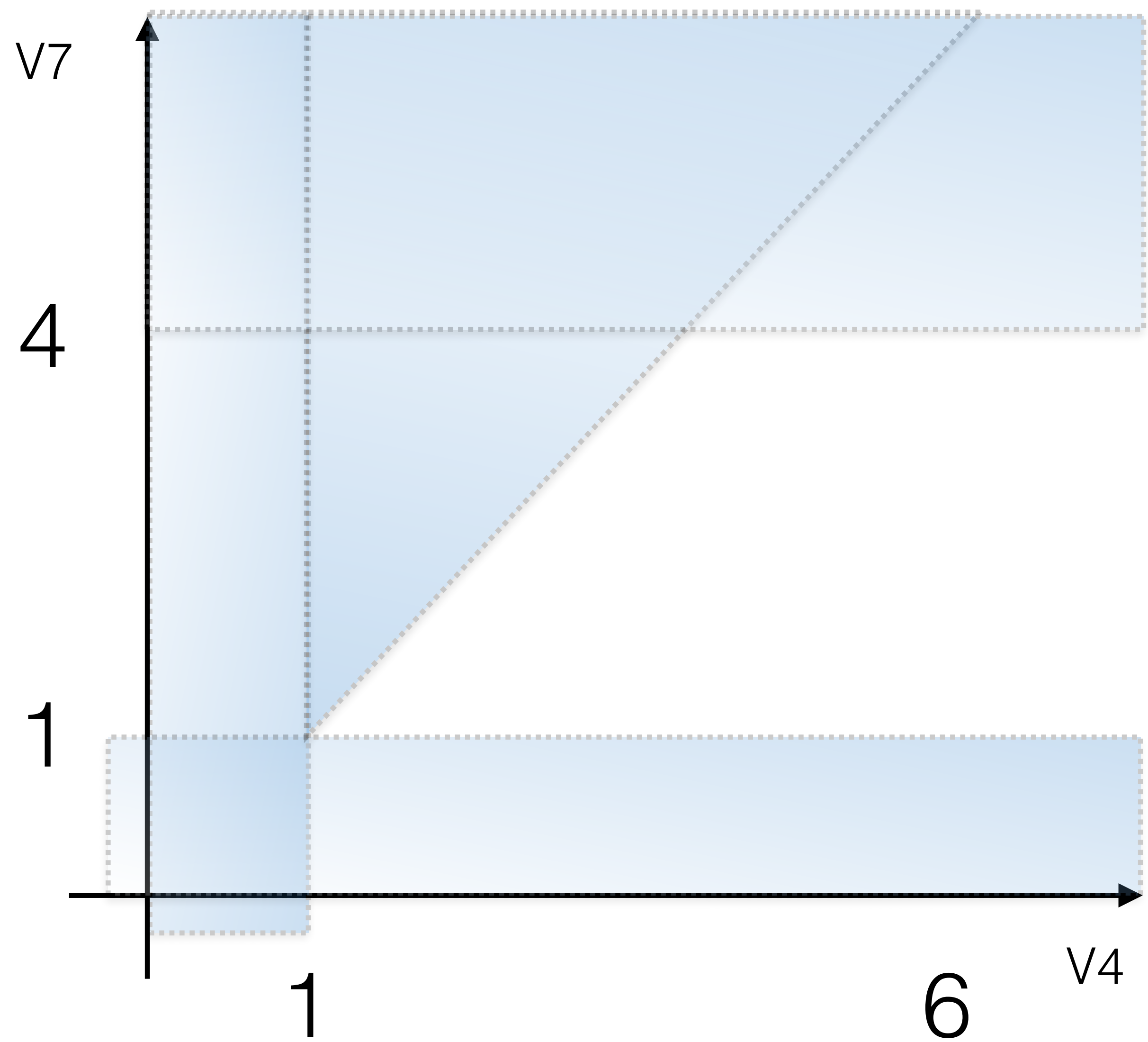

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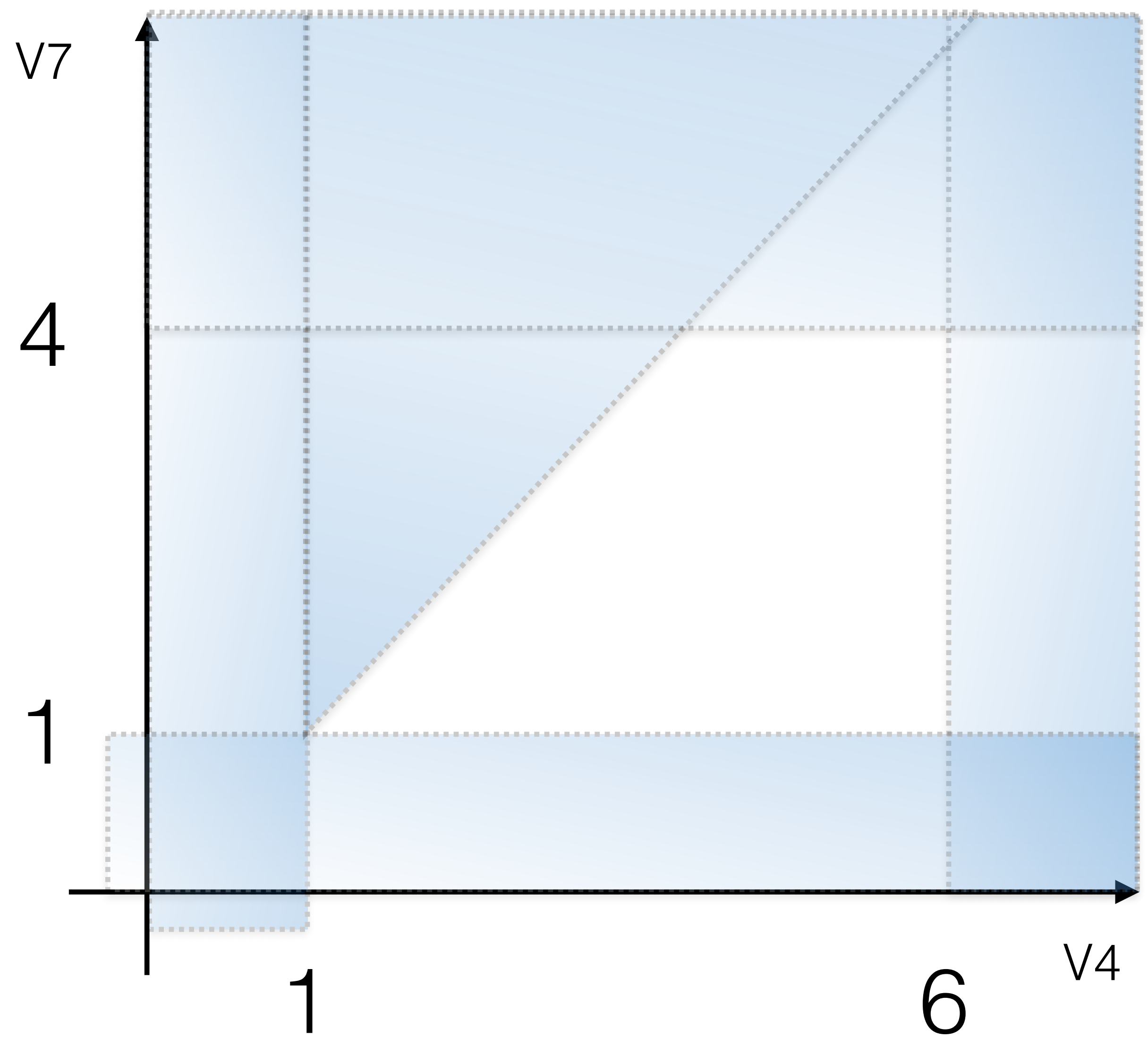

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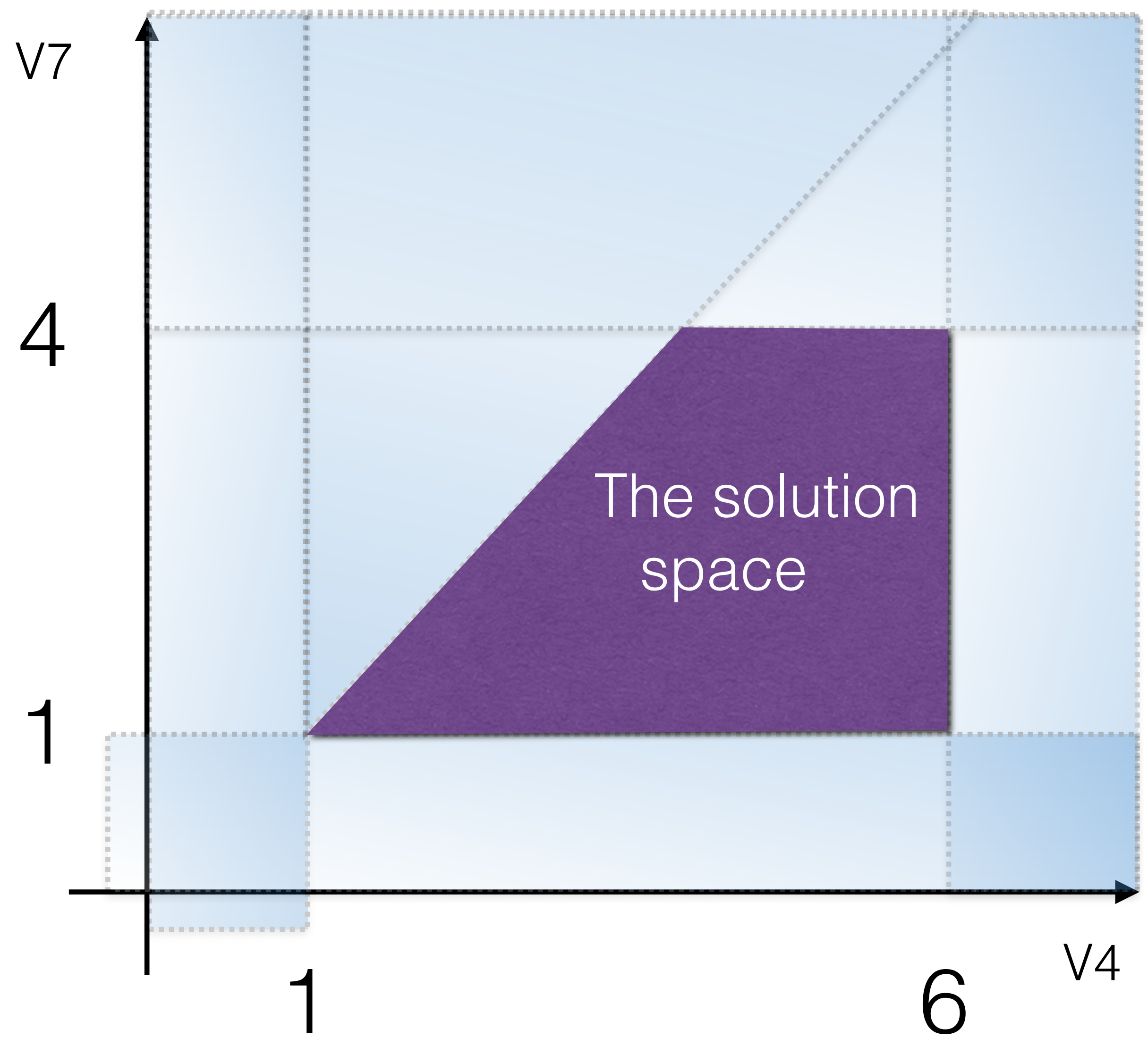

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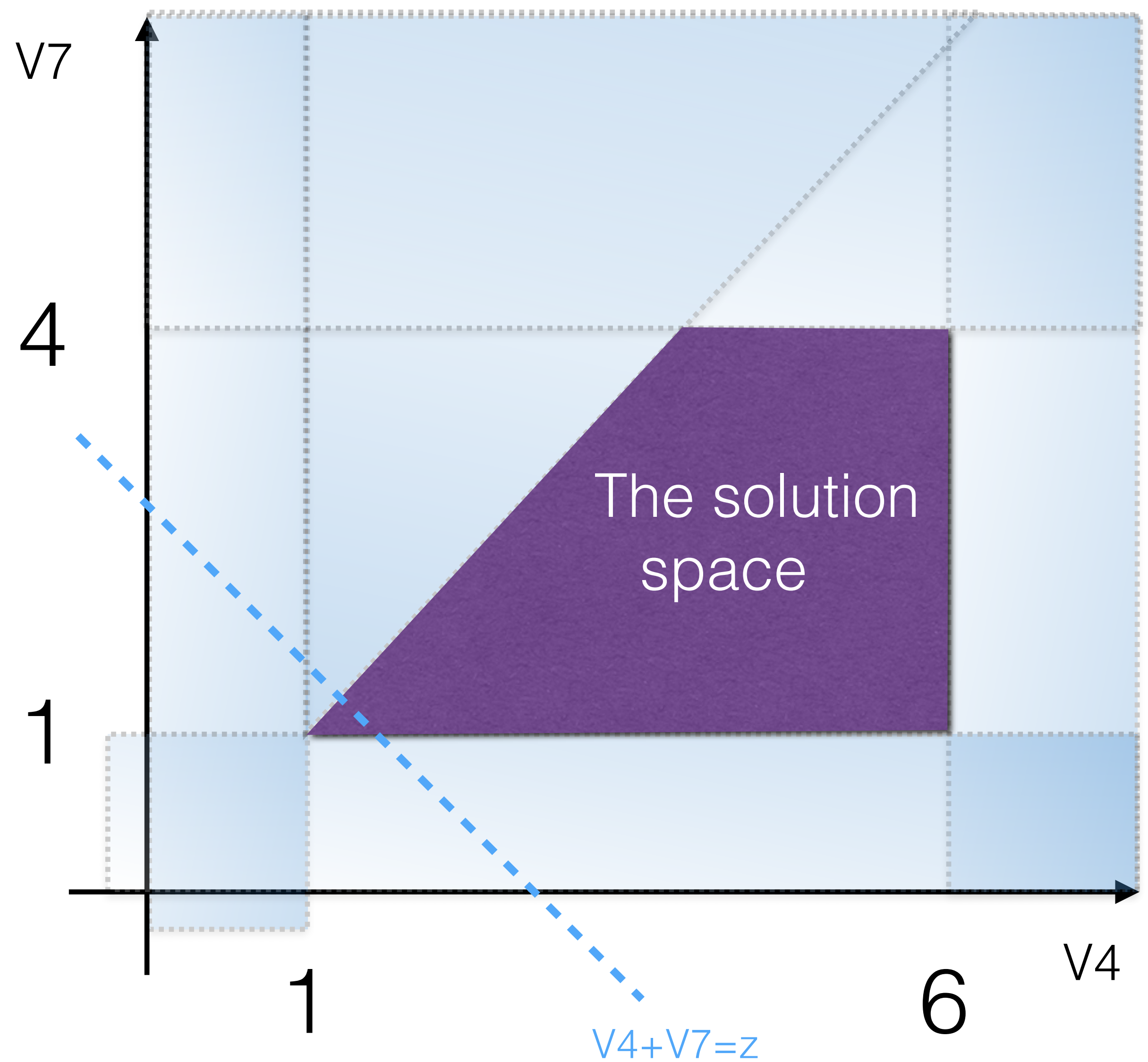

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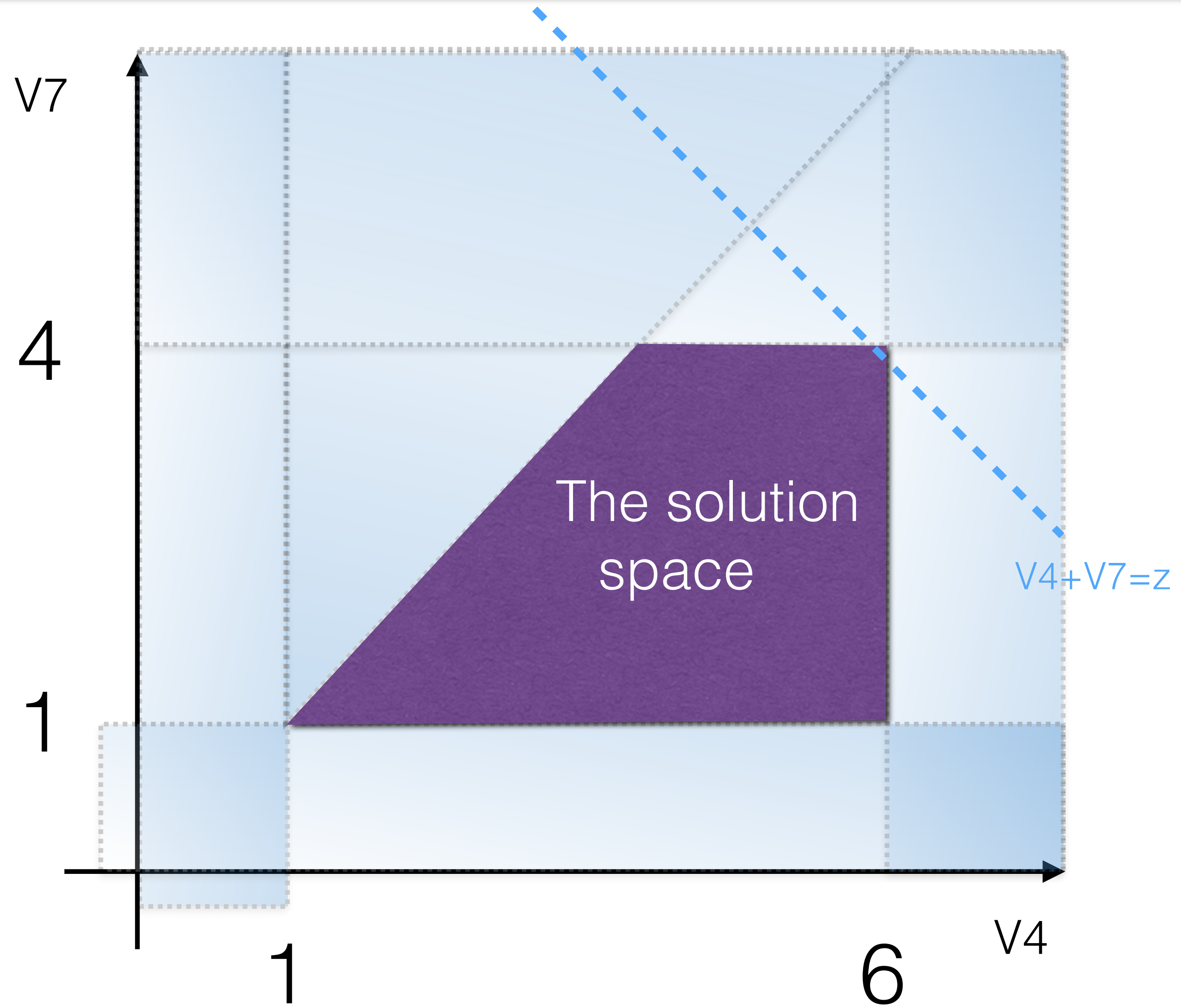

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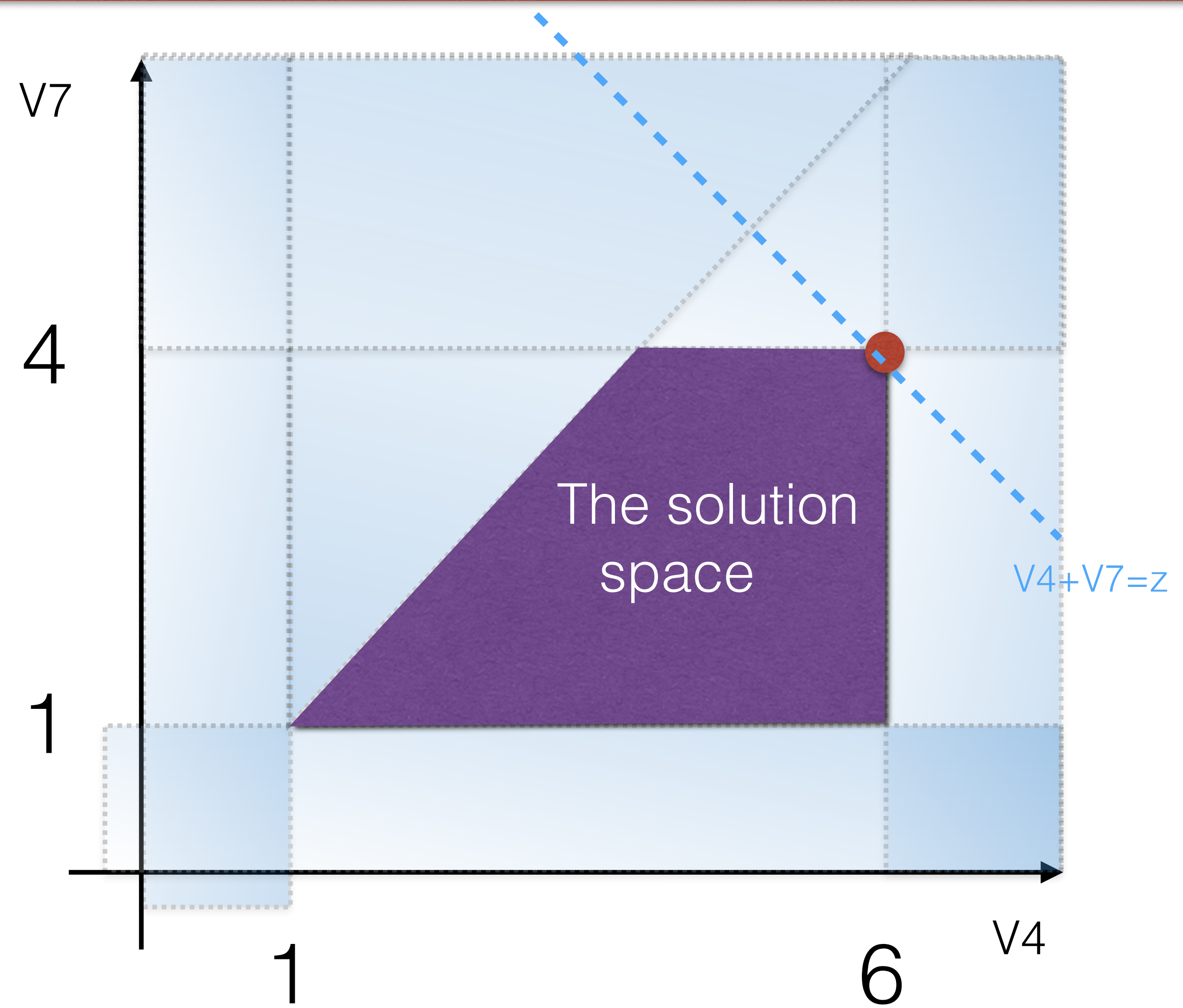
$\Downarrow$ expresses by means of V4 and V7

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

$1 < V4 < 6$, $1 < V7 < 4$ and $V1, \ldots, V6 > 0$



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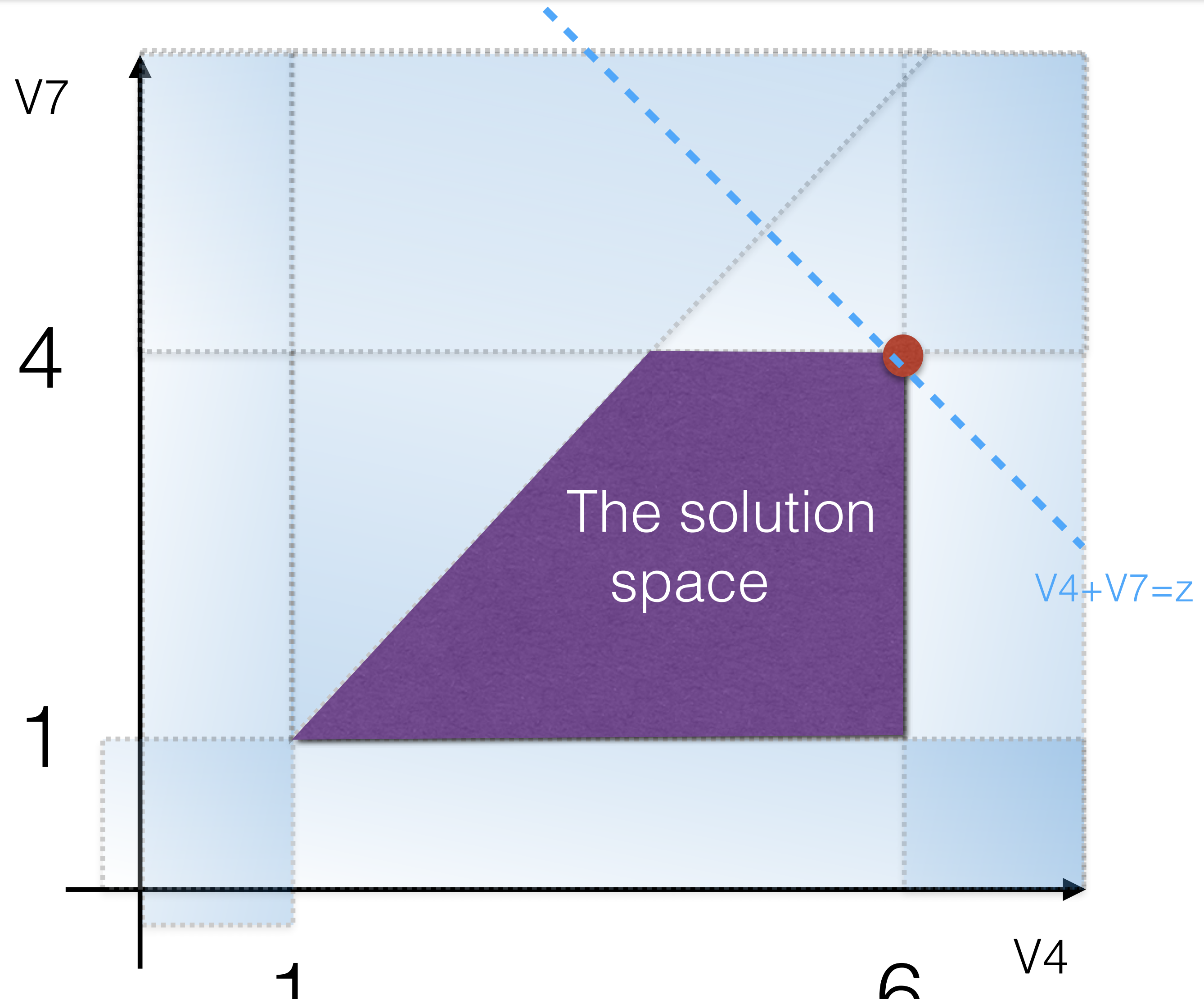

z is maximal when
V1=V2=2, V3=0.5, V4=4, V5=4, V6=2.5 and V7=6

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⇩ 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

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

V4

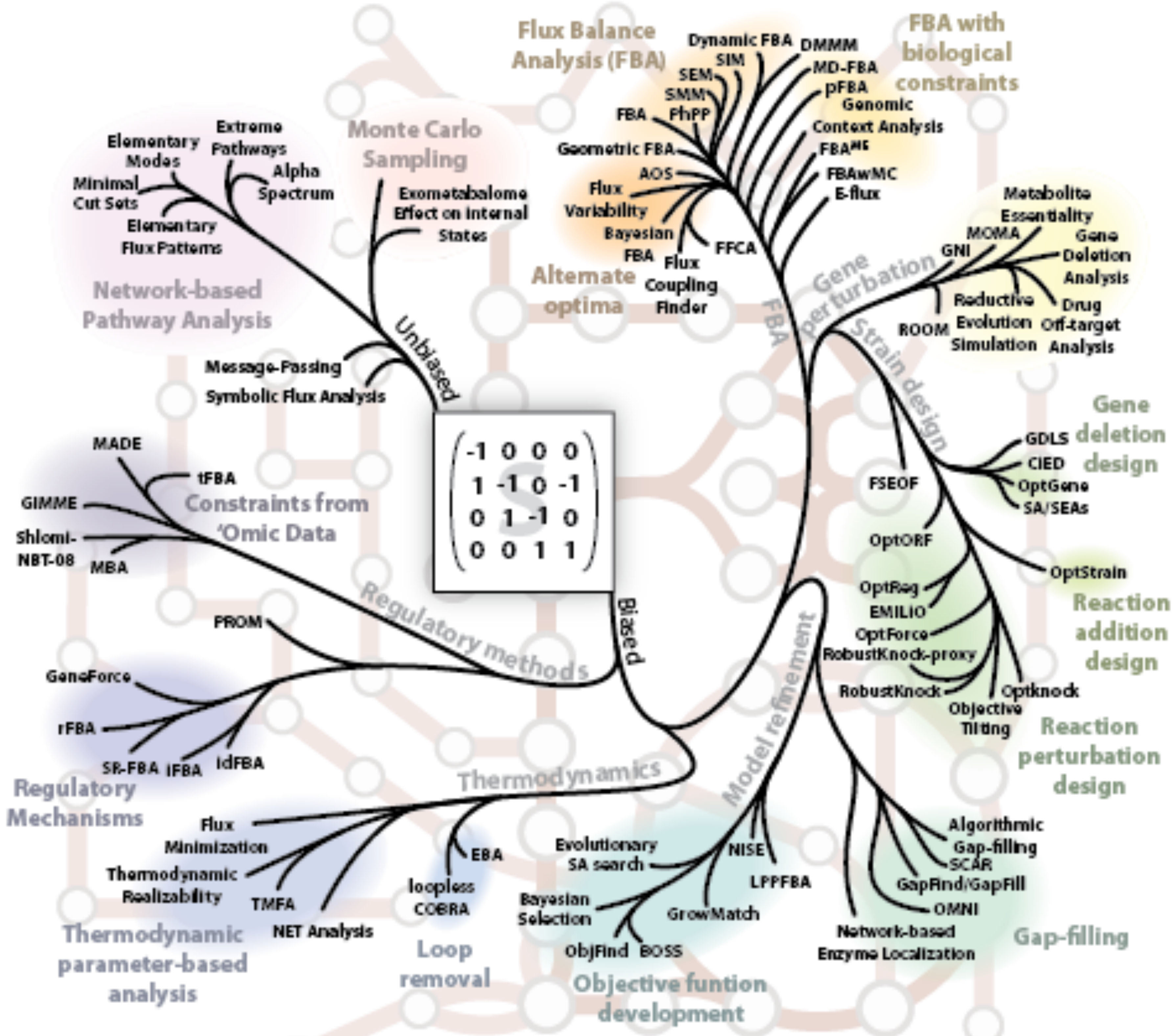
1

6

z is maximal when

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

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
FBA^{ME}
AOS
FBAwMC
Flux Variability
E-flux
Bayesian FBA
FFCA
Flux Coupling Finder
Alternate optima
Monte Carlo Sampling
Exometabalome Effect on internal States
Elementary Modes
Extreme Pathways
Alpha Spectrum
Minimal Cut Sets
Elementary Flux Patterns
Network-based Pathway Analysis
Unbiased
Message-Passing
Symbolic Flux Analysis
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
Regulatory methods
Biased
PROM
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

Focus 1 : Flux Balance Analysis

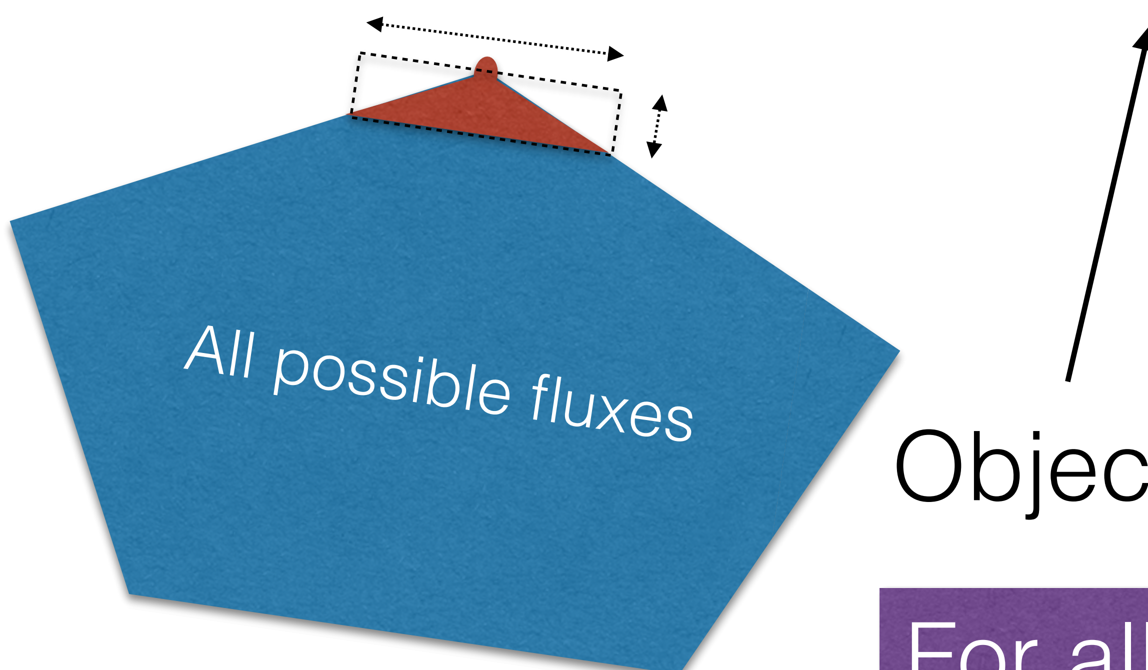
Objective : find an optimal flux vector (i.e., a flux vector for which a given objective function is maximal)

Objective function (or vector)

$$\text{Maximize}_v \ obj(v)$$
$$\text{s.t. } Sv = 0$$
$$lb < v < ub$$

Focus 2 : Flux Variability Analysis

Objective : Approximate the shape of the flux space around an optimal point



Objective function (or vector)

For all i, Min/Maximize$_v$ v_i

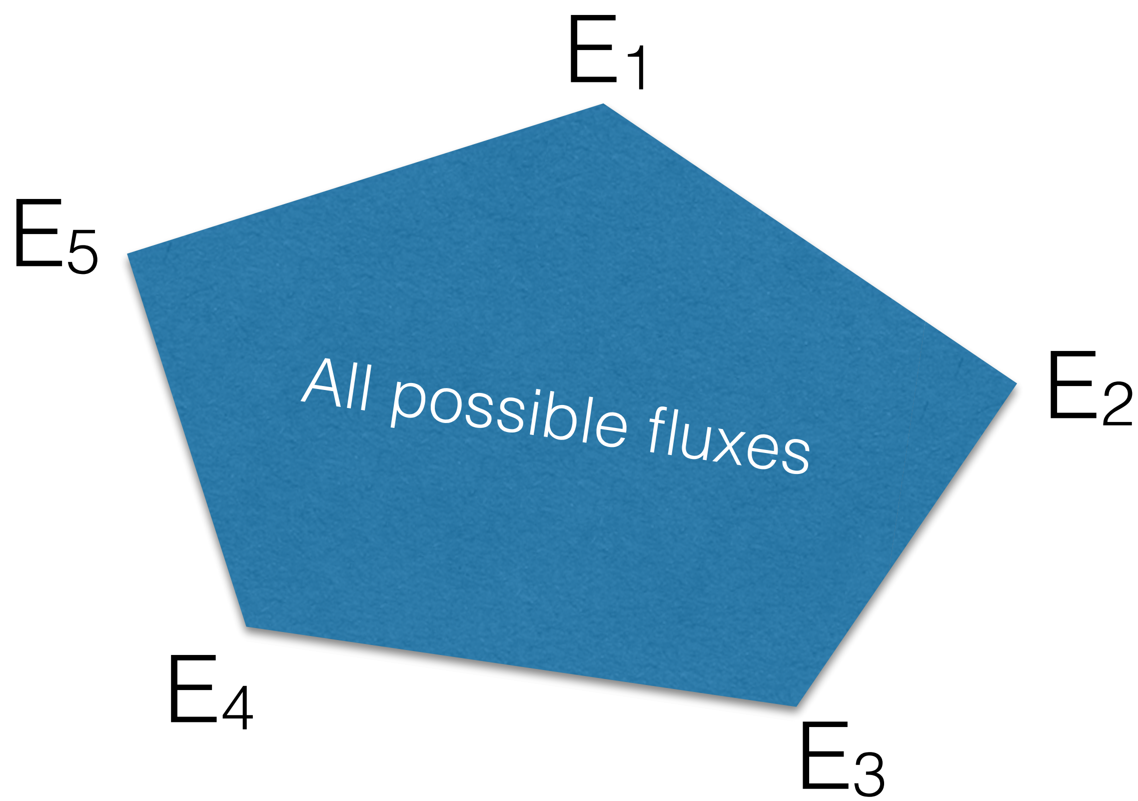
s.t. $Sv = 0$

$lb < v < ub$

$f(v) > \alpha f_{fba}$

Focus 3 : Flux space description

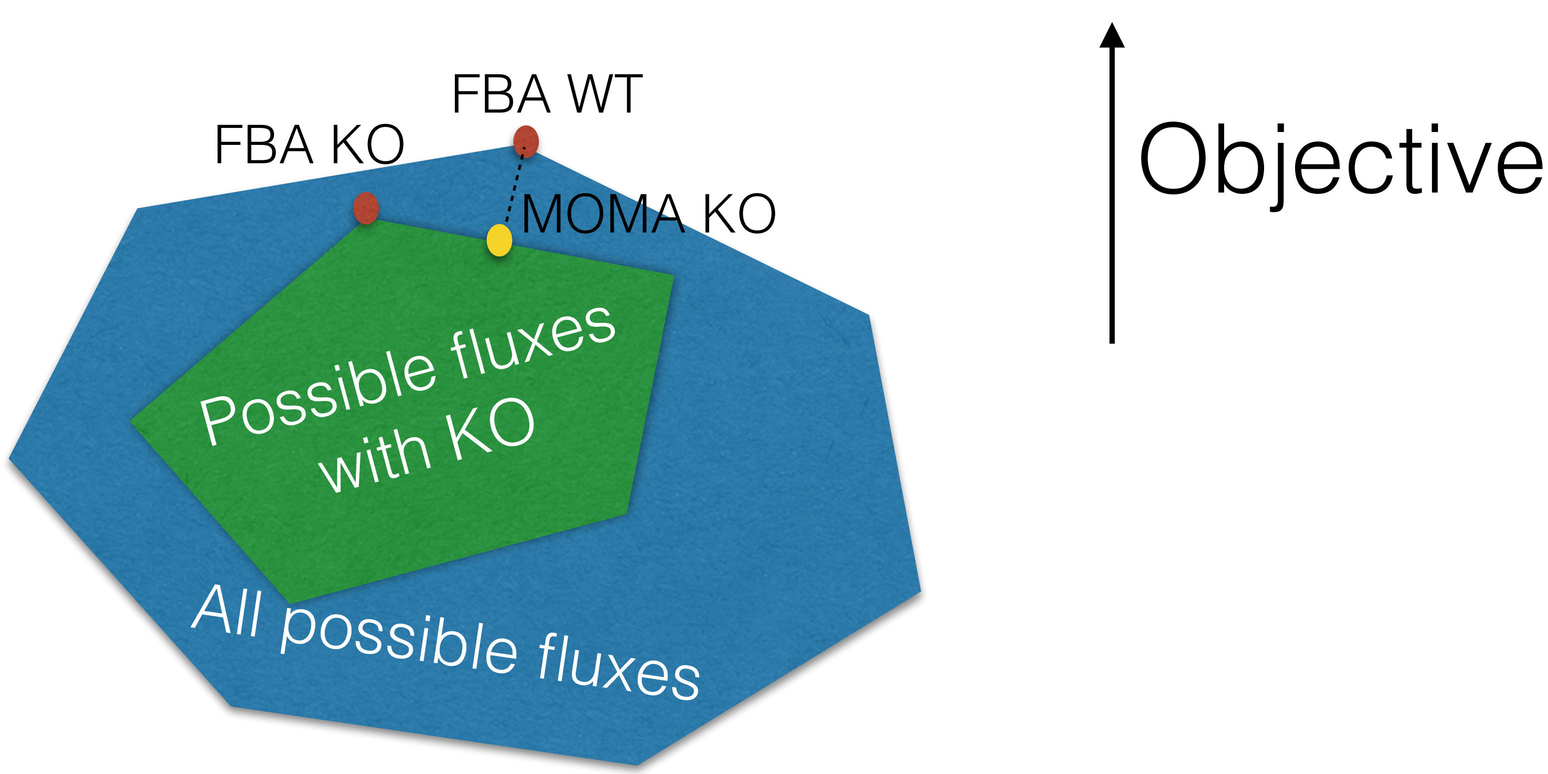
Objective : Describe (in an algebraic manner) the solution space in order to manipulate it. Several ways for defining an appropriate description (=basis)



Example problem :
Computes E_i such that
For all possible flux v
$$v = \sum_i \lambda_i E_i$$
With $\lambda_i \geq 0$ unique
$$\sum_i \lambda_i = 1$$

Focus 4 : Gene/reaction knockout

Objective : Study the effect of a gene/reaction knockout (with application to metabolic engineering)



MOMA = minimization of metabolic adjustment

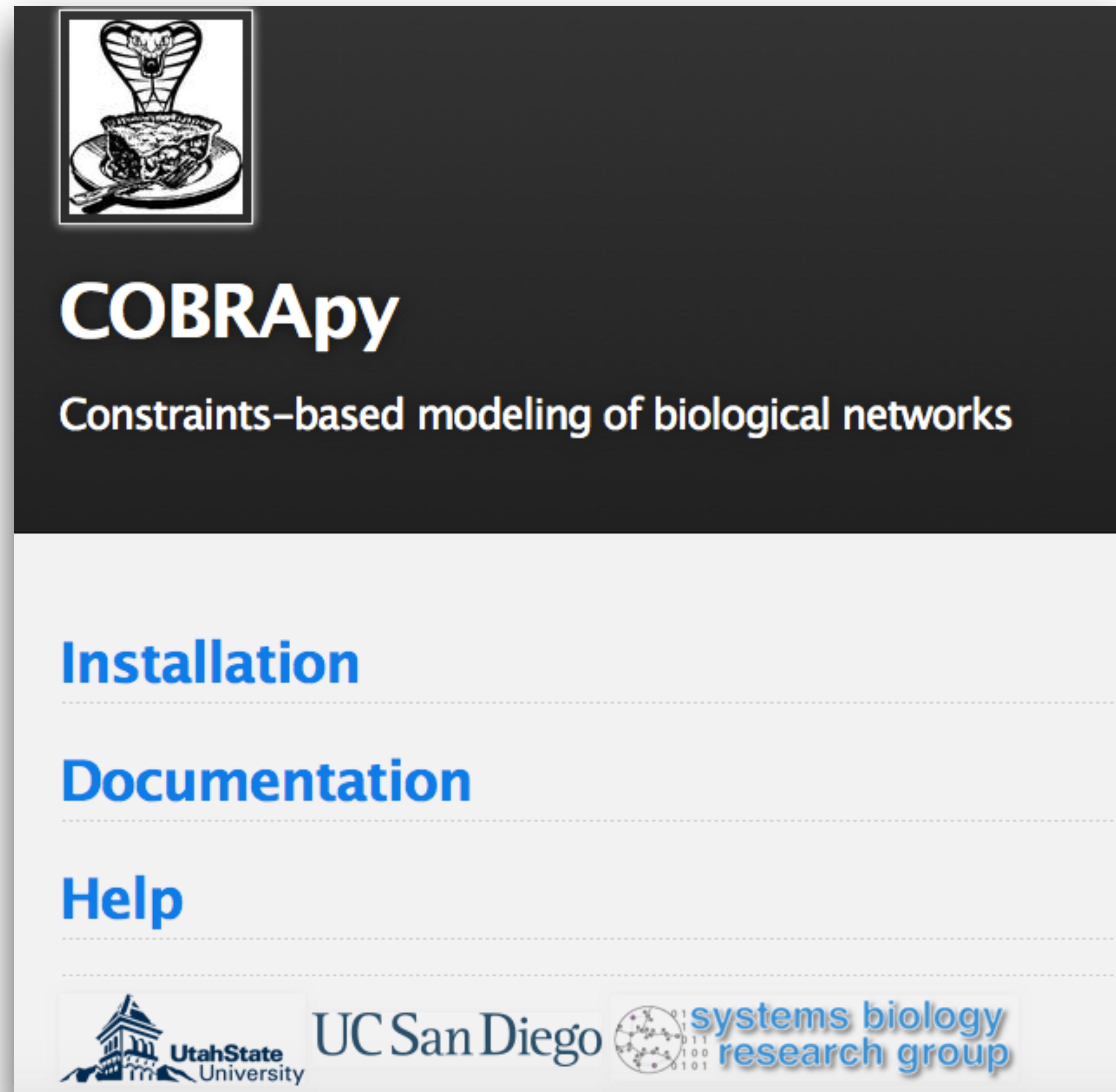
Why do we need a computer ?

- 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 tools

Many tools


COBRApy
Constraints-based modeling of biological networks
Installation
Documentation
Help
UtahState University
UC San Diego
systems biology research group