From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research

Jaap van Milgen

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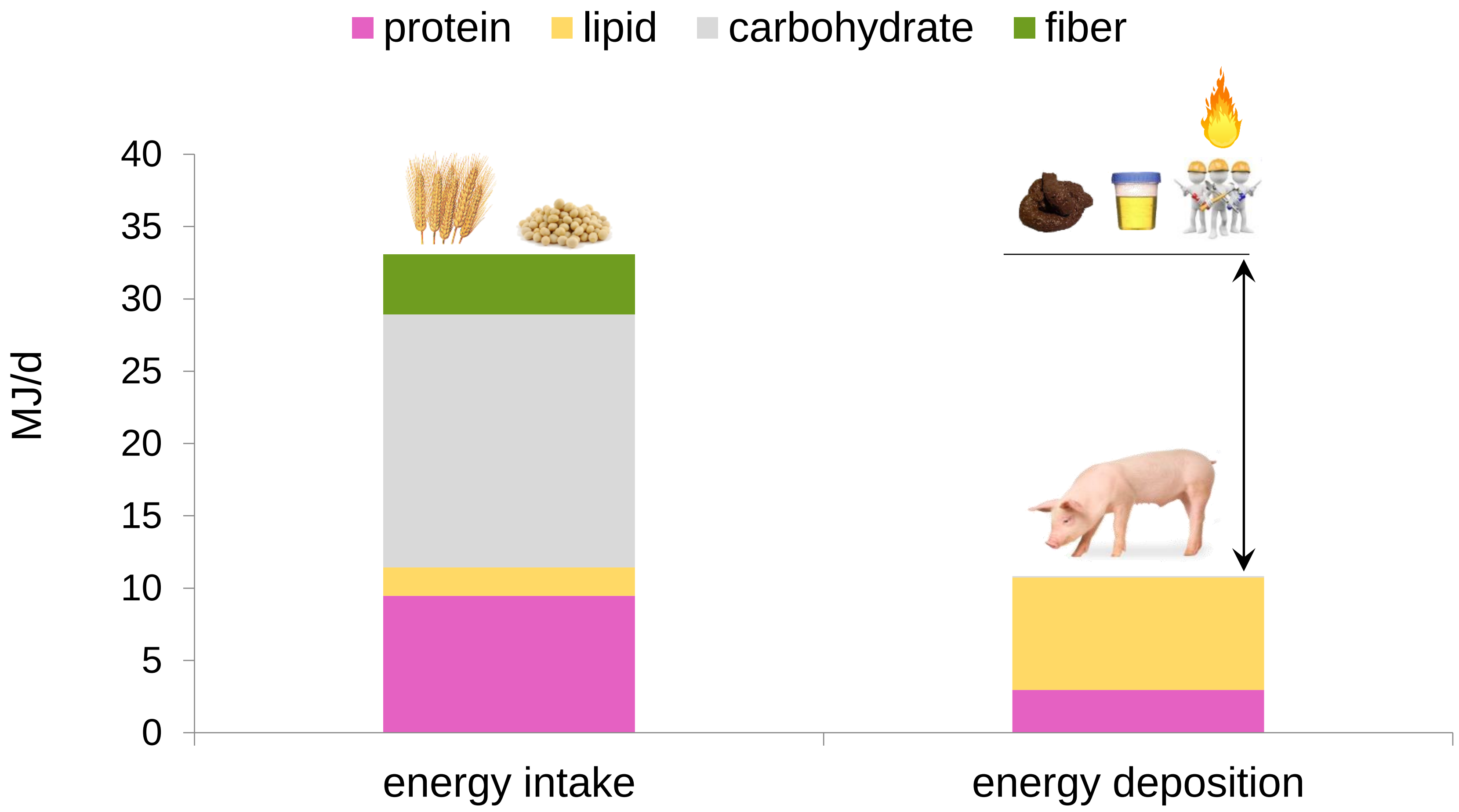
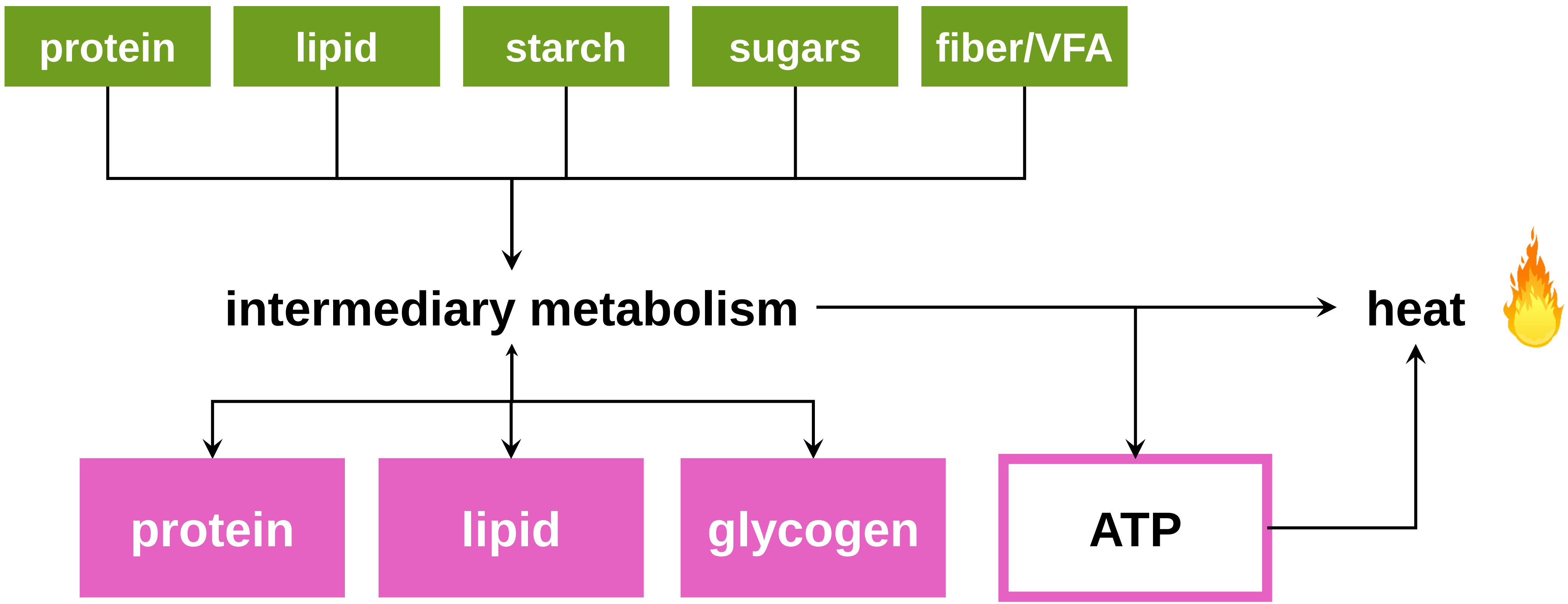
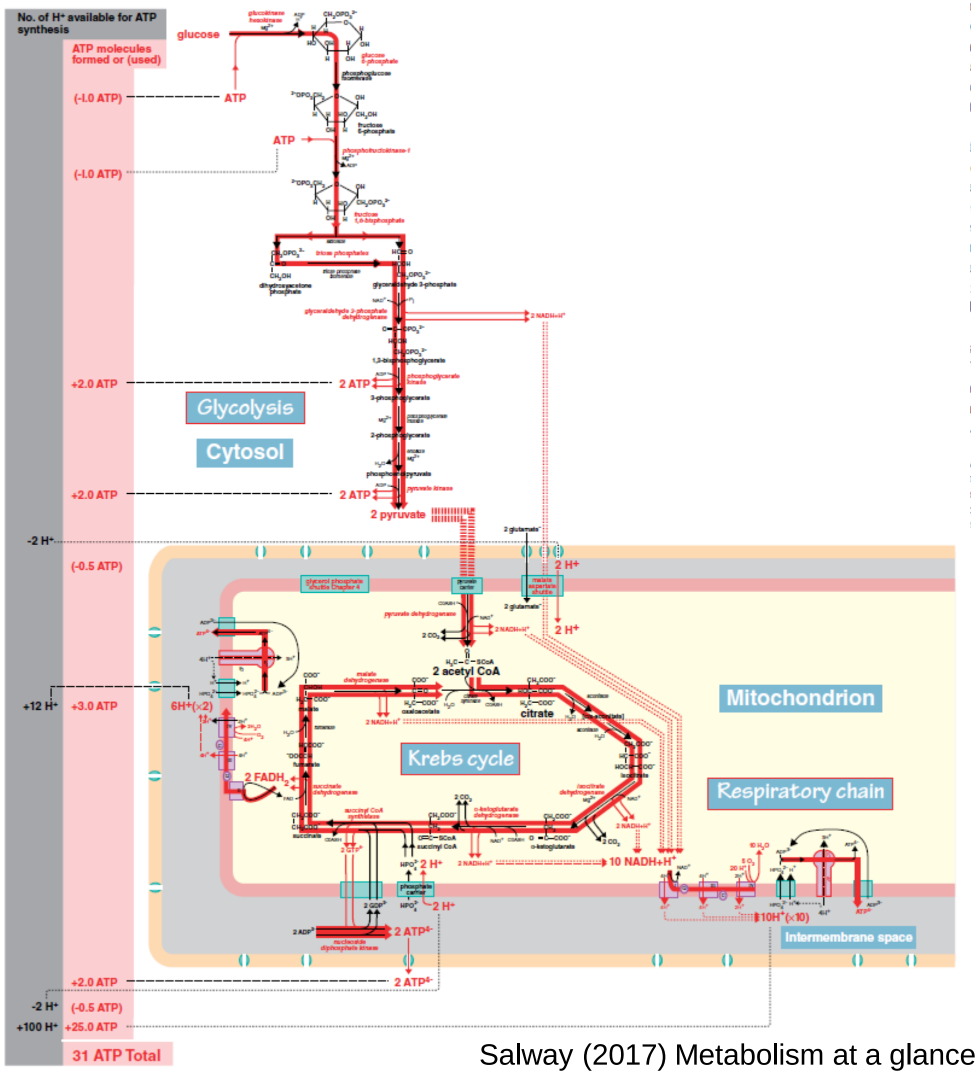
The energy efficiency of a growing pig



From nutrient intake to nutrient utilization



Finding your path in metabolism



Salway (2017) Metabolism at a glance

- 20 "carbon" metabolites involved:

  glucose, glucose 6-phosphate, fructose 6-phosphate, fructose 1,6-bisphosphate, dihydroxyacetone phosphate, glyceraldehyde 3-phosphate, 1,3-bisphosphoglycerate, 3-phosphoglycerate, 2-phosphoglycerate, phosphoenolpyruvate, pyruvate, acetyl-CoA, citrate, isocitrate, α-ketoglutarate, succinyl CoA, succinate, fumarate, malate, oxaloacetate

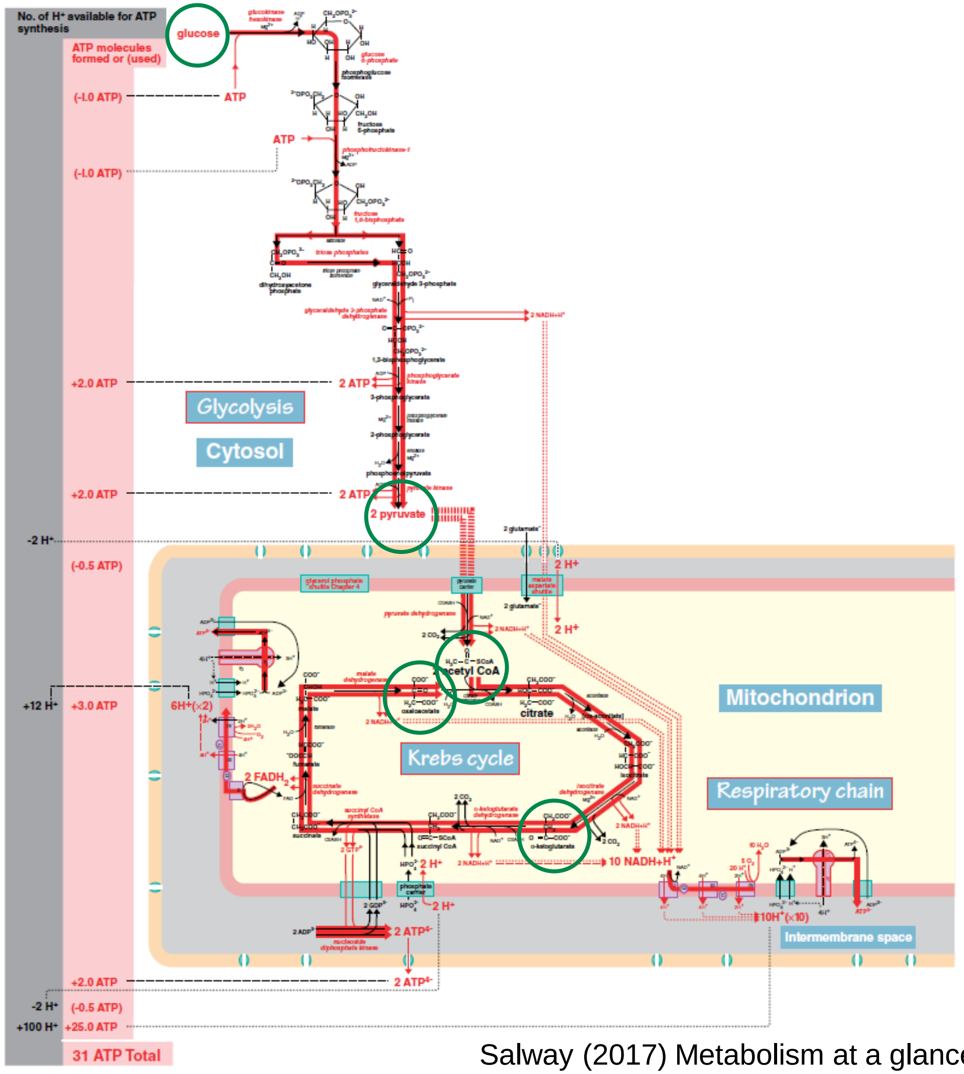
- And also:

  ATP, GTP, NADH, $FADH_2$, H^+ (proton motive force), O_2, CO_2
  Other cofactors

- And regulations:

  enzymes, hormones, metabolite concentrations, genes

Finding your path in metabolism



Salway (2017) Metabolism at a glance

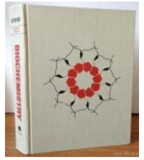
Nutritional Models

Modeling Biochemical Aspects of Energy Metabolism in Mammals[1]

Jaap van Milgen[2]

INRA, Unité Mixte de Recherches sur le Veau et le Porc, 35590 Saint-Gilles, France

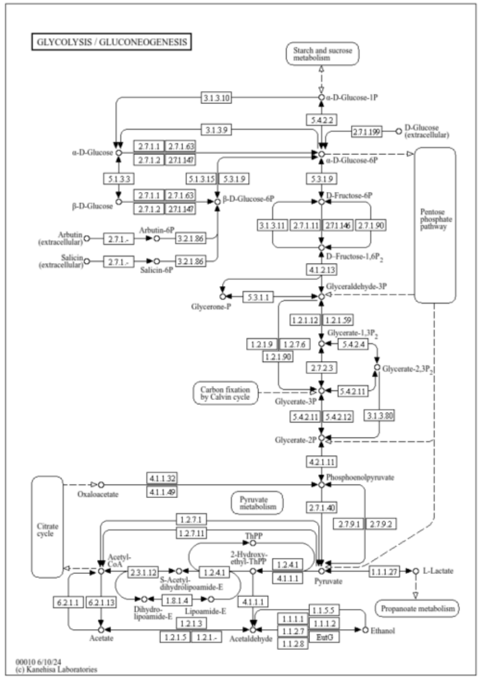
J. Nutr. (2002) 132: 3195-3202

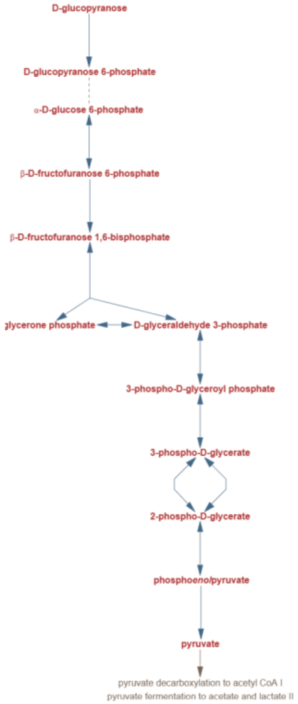


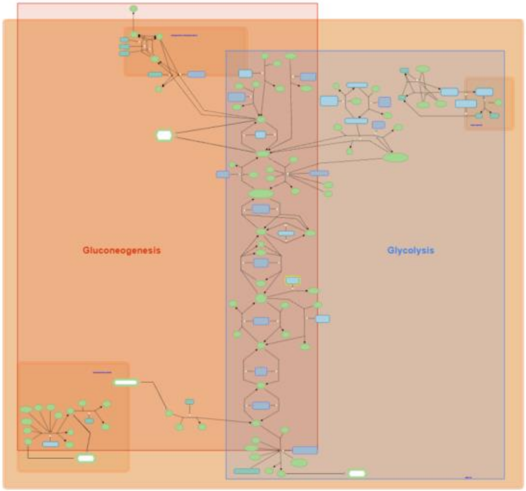
- “Metabolic calculator” (stoichiometric matrix):
  - 14 metabolic nodes:
    - 6 carbon-containing metabolites (e.g., pyruvate, acetyl-CoA, CO_2)
    - 8 co-factors (e.g., ATP, NADH, NH_3, O_2)
  - 54 “meta-reactions”:
    - substrate → nodes
      (e.g., leucine + 2 ATP → 3 acetyl-CoA + 2 NADH + $FADH_2$ + NH_3)
    - nodes → nodes
      (e.g., acetyl-CoA + oxaloacetate → α-ketoglutarate + CO_2 + NADH)
    - nodes → product (e.g., NADH + 0.5 O_2 → 3 ATP)
- Allows the user to construct complete pathways from intermediate meta-reactions
- It quantifies <u>how</u> it happens, but not <u>if</u> it happens

What a lockdown can do to people …

COVID-19
Coronavirus








Results (76 reactions)

Reaction identifier	Equation
RHEA:71535	D-glucose 6-phosphate(in) + phosphate(out) = D-glucose 6-phosphate(out) + phosphate(in)
RHEA:20421	α-maltose 6'-phosphate + H_2O = D-glucose 6-phosphate + D-glucose
RHEA:11816	α-D-glucose 6-phosphate = β-D-fructose 6-phosphate
RHEA:16249	α-D-glucose 6-phosphate = β-D-glucose 6-phosphate
RHEA:37547	D-glucose 6-phosphate + NAD^+ = 3-dehydro-D-glucose 6-phosphate + NADH + H^+
RHEA:27294	oxidized coenzyme F_{420}-(γ-L-Glu)$_{(n)}$ + D-glucose 6-phosphate + H^+ = 6-phospho-D-glucono-1,5-lactone + reduced coenzyme F_{420}-(γ-L-Glu)$_{(n)}$
RHEA:15841	D-glucose 6-phosphate + $NADP^+$ = 6-phospho-D-glucono-1,5-lactone + NADPH + H^+
RHEA:20864	α,α-trehalose 6-phosphate + phosphate = β-D-glucose 1-phosphate + D-glucose 6-phosphate

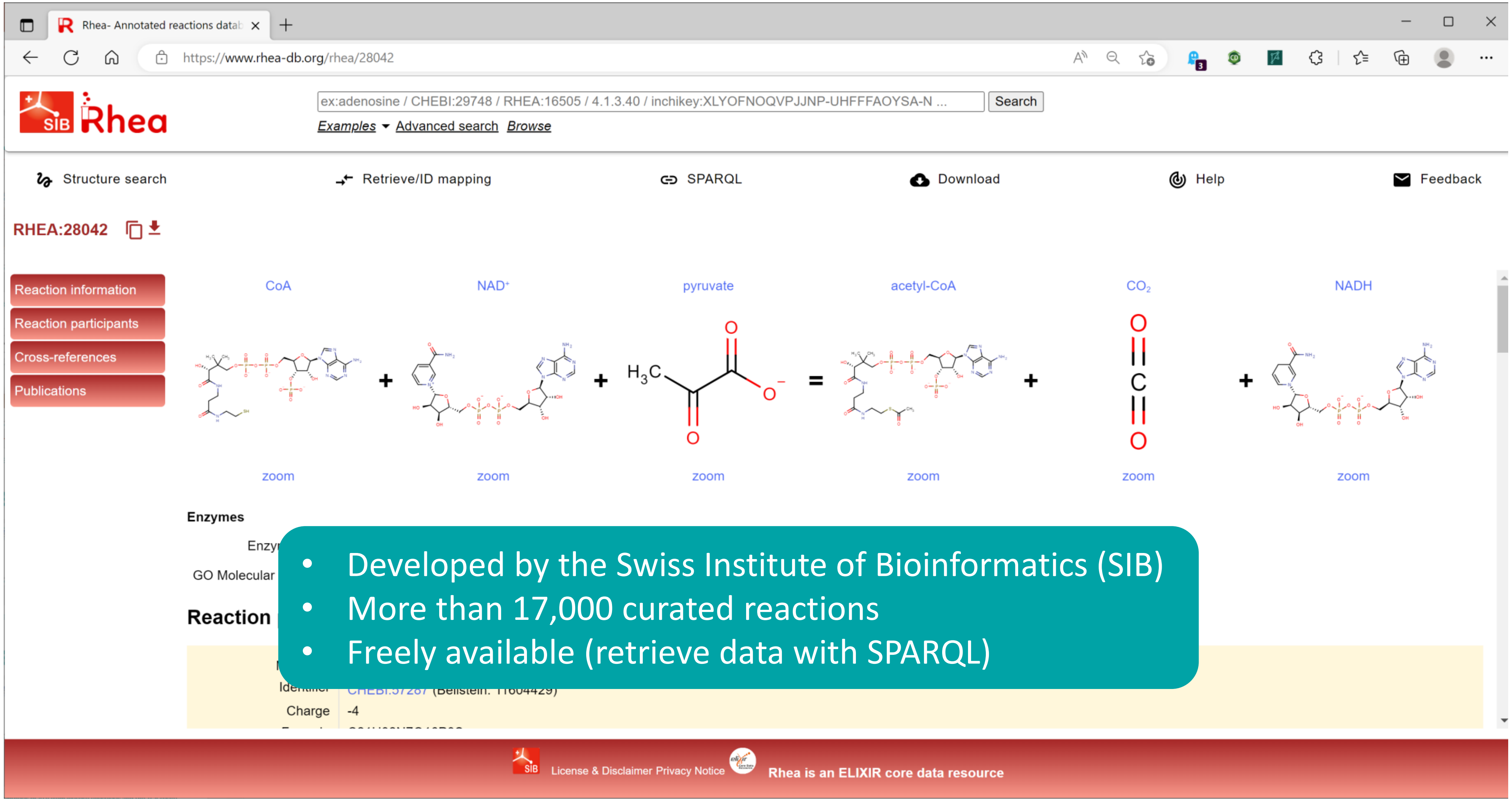
Kyoto Encyclopedia of Genes and Genomes KEGG

METACYC

reactome

Rhea

Rhea, a database with chemical and transport reactions



- Developed by the Swiss Institute of Bioinformatics (SIB)
- More than 17,000 curated reactions
- Freely available (retrieve data with SPARQL)

SPARQL scripts to extract elements from the Rhea database

SIB Rhea

SPARQL Download Help Feedback

Your SPARQL query

Add common prefixes

```
##############################################################
#Sparql script to obtain the Rhea (Uniprot) names with the ChebiID

PREFIX rh: <http://rdf.rhea-db.org/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX up: <http://purl.uniprot.org/core/>
PREFIX ch: <http://purl.obolibrary.org/obo/>

SELECT DISTINCT ?ChebiID ?name
WHERE {
  ?rhea rdfs:subClassOf rh:Reaction ;
        rh:id ?RheaReactionID ;
        rh:side/rh:contains/rh:compound ?Compound .

  ?Compound (rh:chebi|(rh:reactivePart/rh:chebi)|(rh:underlyingChebi)) ?chebi .
```

Submit Query

About

This SPARQL endpoint contains Rhea reactions data (see statistics), and a snapshot of ChEBI data matching the Rhea release. It is free to access and supports the SPARQL 1.1 Standard.

There are 5,383,683 triples in this release (2025_03). The query timeout is 45 minutes. All triples are available in the default graph. There are two named graphs: Rhea and ChEBI.

Documentation

1. Statistics and diagrams
2. Tutorial on using SPARQL with Rhea
3. Example queries
4. Release data

Examples

1. Select all Rhea reactions Use
2. Select all Rhea reactions annotated with a given Pubmed ID Use
3. Select the specific form of RHEA:11628, a reaction that deals with general chemical classes (i.e. select the equivalent reactions involving instances of the chemical classes in RHEA:11628 Use

SPARQL scripts to extract elements from the Rhea database

SIB Rhea

SPARQL Download Help Feedback

Results

Sparql XML | Sparql JSON | CSV | Show query | Share

ChebiID	name
"35924"xsd:string	"a hydroperoxide"xsd:string
"30879"xsd:string	"an alcohol"xsd:string
"15377"xsd:string	"H2O"xsd:string
"57783"xsd:string	"NADPH"xsd:string
"58321"xsd:string	"(S)-2-amino-6-oxohexanoate"xsd:string
"29985"xsd:string	"L-glutamate"xsd:string
"15378"xsd:string	"H(+)"xsd:string
"58349"xsd:string	"NADP(+)"xsd:string
"57951"xsd:string	"L-saccharopine"xsd:string
"15354"xsd:string	"choline"xsd:string
"30023"xsd:string	"(E)-sinapate"xsd:string
"16353"xsd:string	"O-sinapoylcholine"xsd:string
"28938"xsd:string	"NH4(+)"xsd:string
"31011"xsd:string	"pentanoate"xsd:string

SPARQL scripts to extract elements from the Rhea database

SIB Rhea

SPARQL Download Help Feedback

Results

Sparql XML | Sparql JSON | CSV | Show query | Share

ReactionID	ChebiID	Side	nbmol	PI	InOut
"10008"xsd:string	"35924"xsd:string	"L"xsd:string	"1"xsd:string		""xsd:string
"10008"xsd:string	"30879"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10008"xsd:string	"15377"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"57783"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"58321"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"29985"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"15378"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"15377"xsd:string	"L"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"58349"xsd:string	"L"xsd:string	"1"xsd:string		""xsd:string
"10020"xsd:string	"57951"xsd:string	"L"xsd:string	"1"xsd:string		""xsd:string
"10016"xsd:string	"15354"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10016"xsd:string	"15378"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10016"xsd:string	"30023"xsd:string	"R"xsd:string	"1"xsd:string		""xsd:string
"10016"xsd:string	"15377"xsd:string	"L"xsd:string	"1"xsd:string		""xsd:string

SPARQL scripts to extract elements from the Rhea database

Metabolite names

(RheaMetabolites.csv; 12,000 lines)

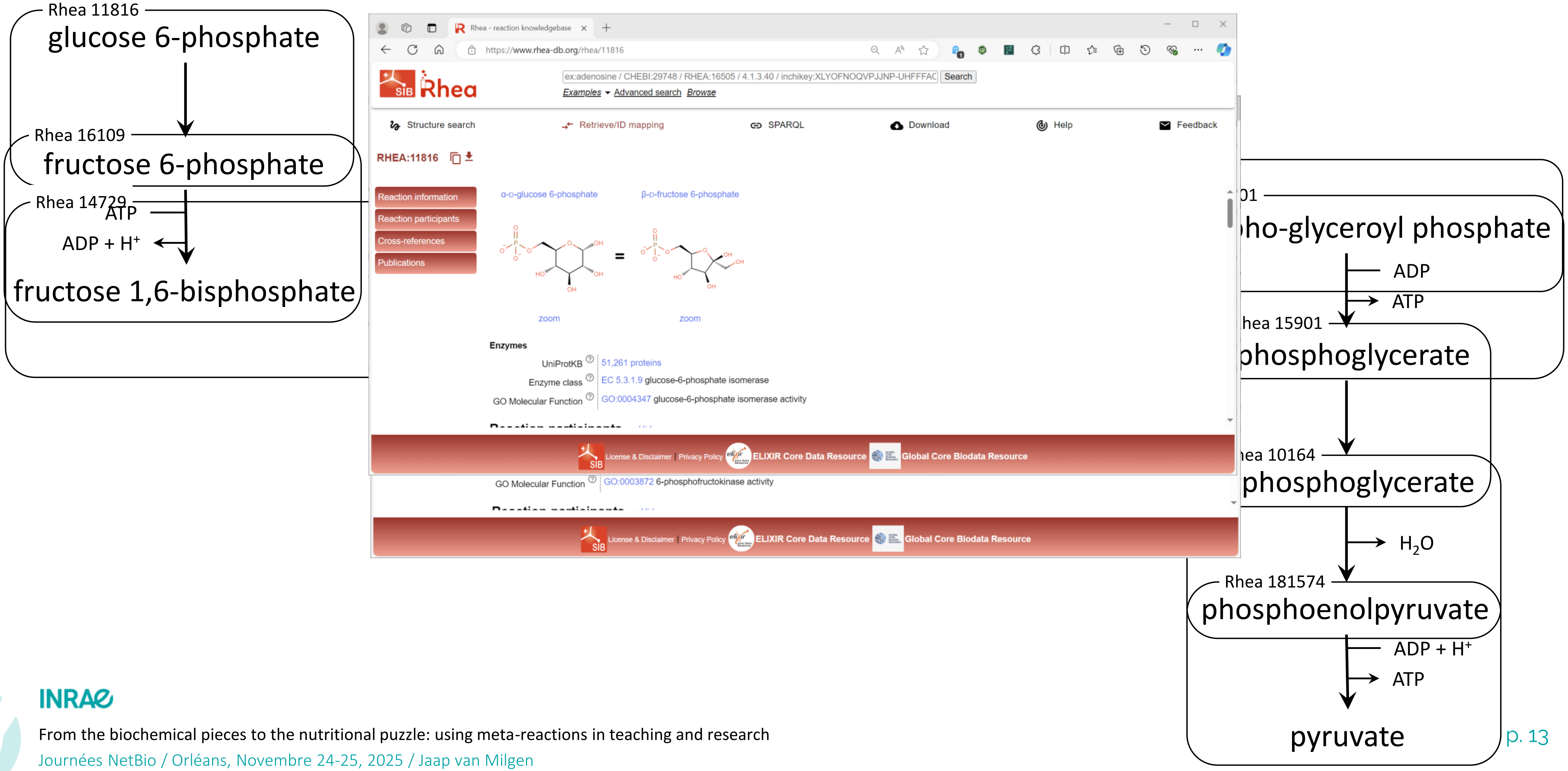
```
ChebiID, name
"15377","H2O"
"16459","pentanamide"
"28938","NH4(+)"
"31011","pentanoate"
"17484","benzyl isothiocyanate"
"16017","benzyl thiocyanate"
"35924","a hydroperoxide"
"30879","an alcohol"
"58413","(R)-6-hydroxynicotine"
"15379","O2"
"58225","alpha-D-glucose 6-phosphate"
"57634","beta-D-fructose 6-phosphate"
```

Reaction elements

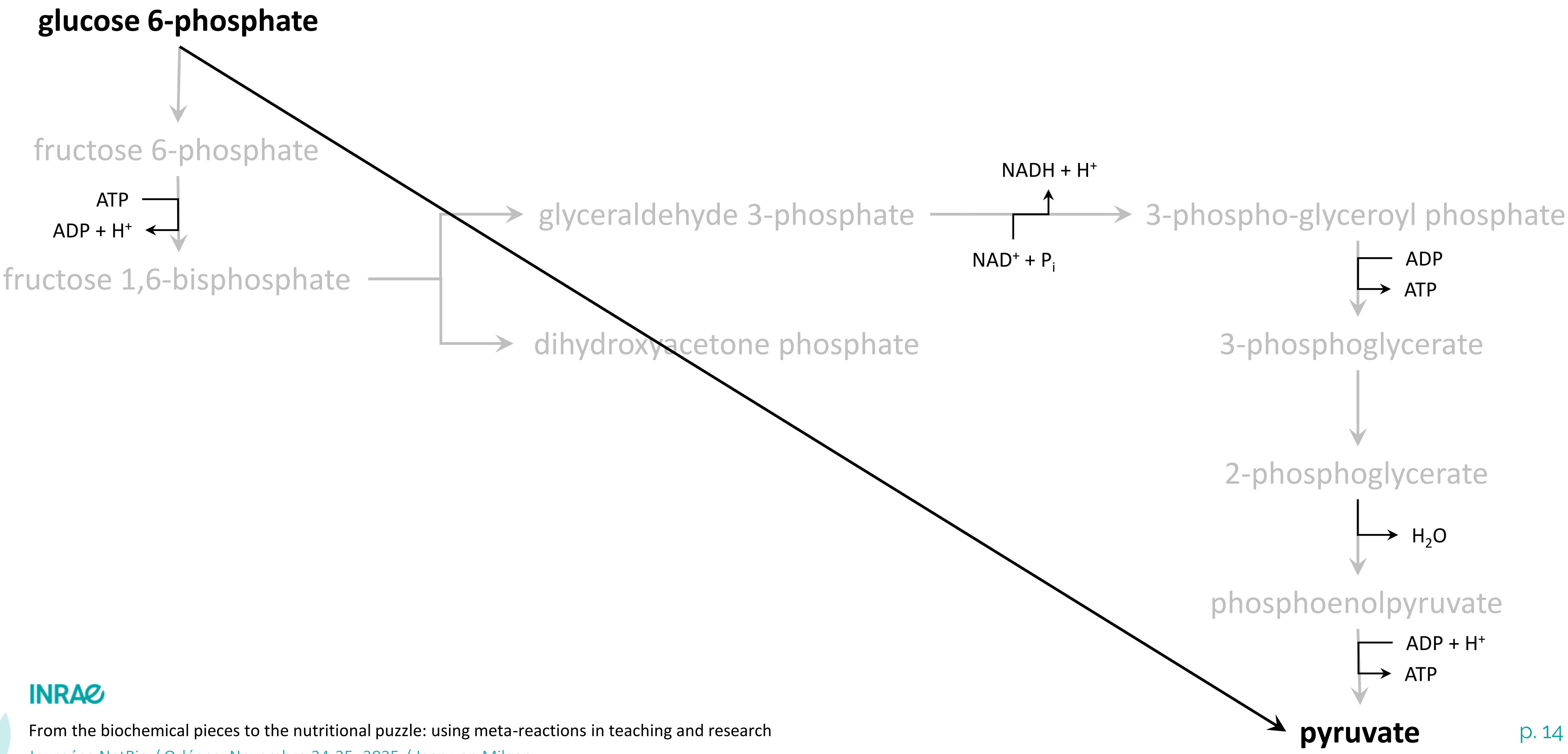
(RheaStoichiometry.csv; 80,000 lines)

```
ReactionID, ChebiID, Side, nbmol, PI, InOut
"10012","58413","L","1",,""
"10012","15377","L","1",,""
"10012","15379","L","1",,""
"10012","58682","R","1",,""
"10012","16240","R","1",,""
"11816","58225","L","1",,""
"11816","57634","R","1",,""
"16109","30616","L","1",,""
"16109","57634","L","1",,""
"16109","456216","R","1",,""
"16109","32966","R","1",,""
"16109","15378","R","1",,""
```

A meta-reaction is the outcome reaction of a series of coupled individual (Rhea) reactions



A meta-reaction is the outcome reaction of a series of coupled individual (Rhea) reactions



Construction of meta-reactions

Meta-reactions, manual construction

(Meta-reactions.csv)

```
Meta-reactionID;Dataset;ReactionID;Flux;Order
1;1;36495;1;1
2;1;11816;1;1
2;1;16109;1;2
2;1;14729;1;3
2;1;18585;-1;4
2;1;10300;2;5
2;1;14801;-2;6
2;1;15901;-2;7
2;1;10164;2;8
2;1;18157;-2;9
3;1;19189;1;1
3;1;17017;-1;2
3;1;15045;1;3
```

Reaction elements, from Rhea

(RheaStoichiometry.csv)

```
ReactionID, ChebiID, Side, nbmol, PI, InOut
"10012","58413","L","1",,""
"L","1",,""
"L","1",,""
"10012","58682","R","1",,""
"10012","16240","R","1",,""
"11816","58225","L","1",,""
"11816","57634","R","1",,""
"16109","30616","L","1",,""
"16109","57634","L","1",,""
"16109","456216","R","1",,""
"16109","32966","R","1",,""
"16109","15378","R","1",,""
```

Meta-reaction 2 (i.e., glucose 6-phosphate →pyruvate) is composed of nine Rhea reactions

Reactions 11816 and 16109 involve seven metabolites

Metabolite 57634 (i.e., fructose 6-phosphate) is first produced (R) and then used (L)

Processing CSV-files to create a user-interface

RheaStoichiometry.csv
RheaMetabolites.csv
Meta-reactions.csv
UserStoichiometry.csv (user-defined stoichiometry)
UserMetabolites.csv (information about specific metabolites)
UserMetareactions.csv (information about the meta-reactions)

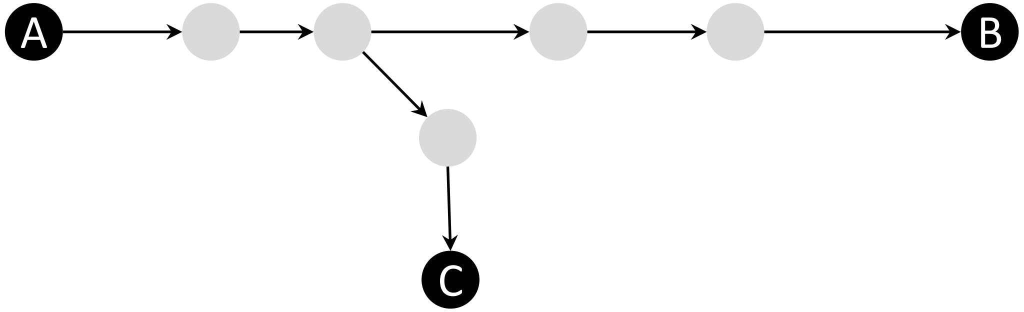
Excel's PowerQuery
(Extract, Transform, Load)

Meta-reactionID	Level	Meta-reaction
1	1	glucose + ATP → glucose 6-phosphate + ADP + H^+
2	1	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)
3	1	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2
4	1	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)
5	1	α-ketoglutarate + 0.75 ADP + 0.75 P_i + 2 NAD^+ + FAD + 1.25 H_2O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H^+ + $FADH_2$ + CO_2 (TCA cycle)
9	1	glutamate + 0.5 glucose 6-phosphate + 0.5 ADP + 2 NAD^+ + H_2O → serine + α-ketoglutarate + 0.5 ATP + 2 NADH + 2.5 H^+
10	1	serine + THF → glycine + N^5,N^{10}-methylene THF + H_2O (Ser hydroxymethyltransferase)
11	1	serine → pyruvate + NH_4^+ (Ser dehydratase)

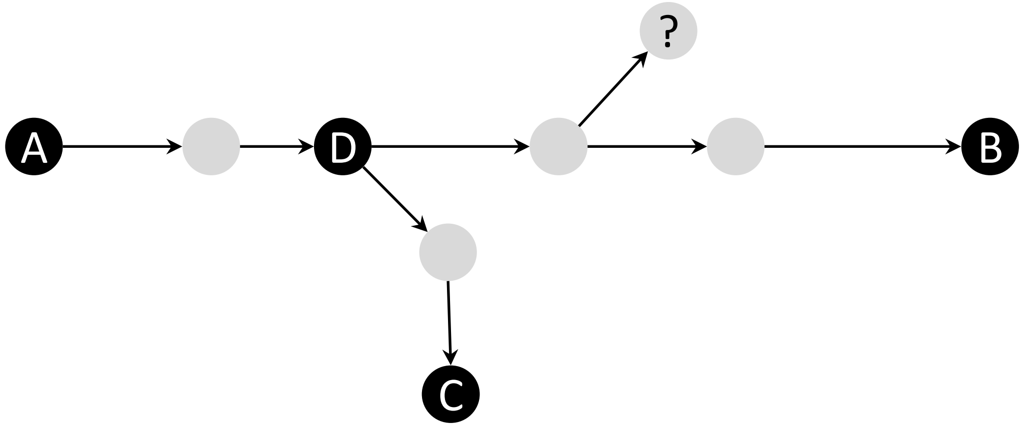
Organizing meta-reactions to create a user-interface

Type	Beginner	Intermediate	Advanced
carbohydrates	4	4	6
amino acids, peptides and polyamines	21	30	50
fatty acids and lipids	2	2	20
intermediate metabolites	6	8	13
volatile fatty acids and ketones	2	4	6
1-carbon metabolism	5	5	8
electron transport and ATP metabolism	5	5	8
other	1	1	2
nitrogen metabolism		3	5
other organic metabolites		2	4
nucleotides			17
hormones and neurotransmitters			17
vitamins and co-factors			6

Organizing meta-reactions to create a user-interface

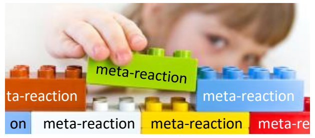


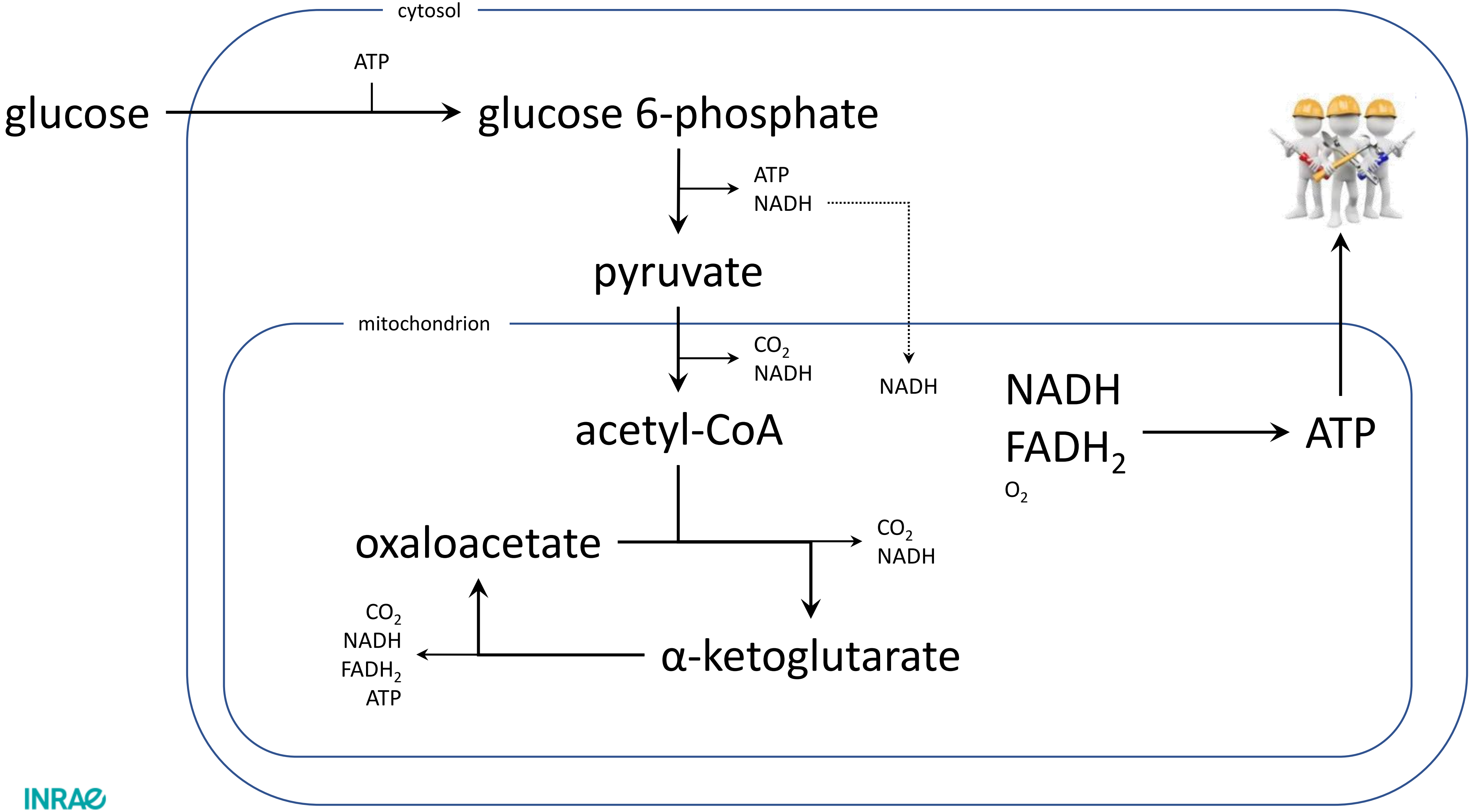
- simple for the user
- A → B in 1 step



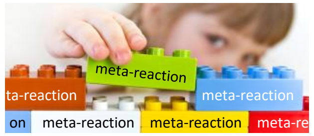
- biologically more realistic
- A → B in 2 steps (i.e., A → D and D → B)?

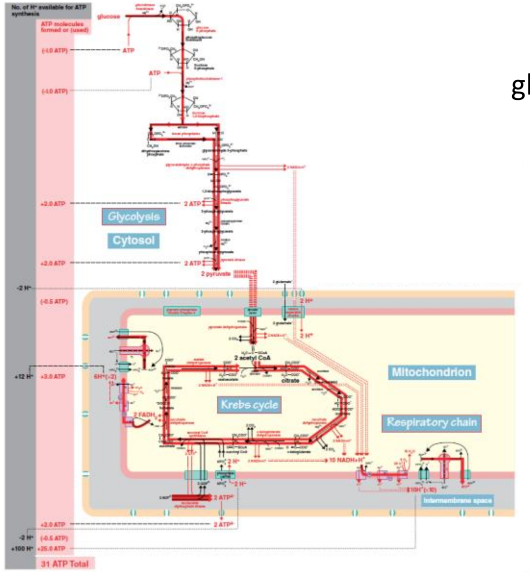
A pathway is the outcome reaction of a series of coupled meta-reactions

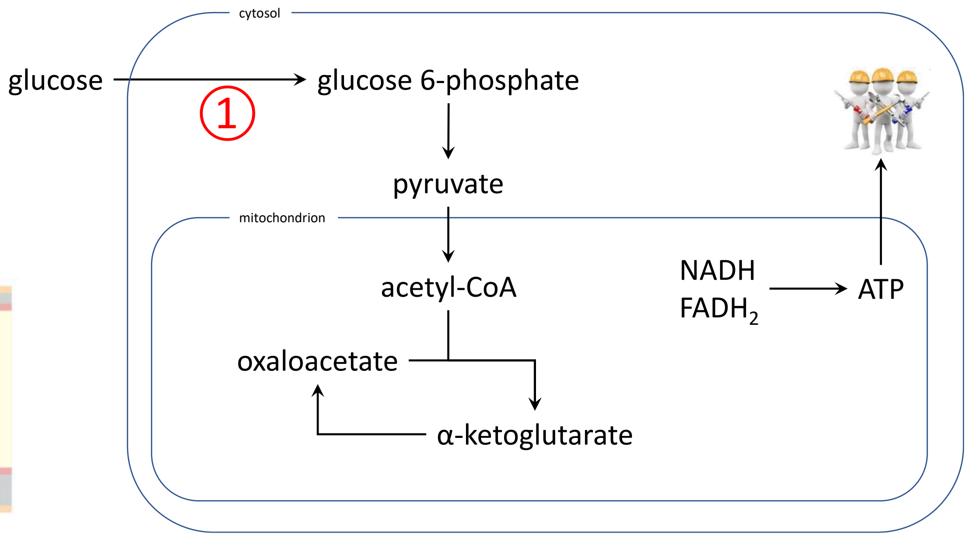




Constructing pathways using the Excel tool





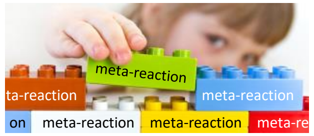


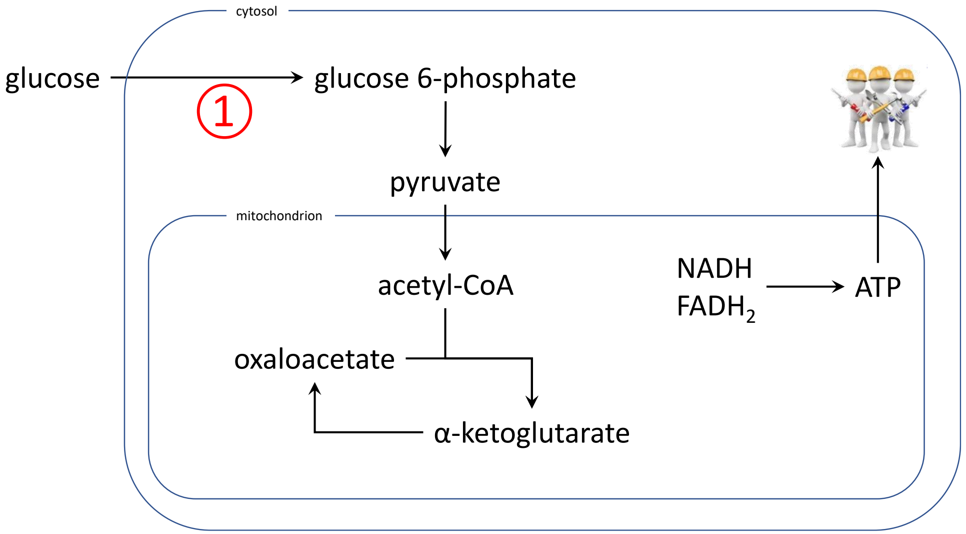
No meta-reactions selected yet

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux

- carbohydrates
- amino acids, peptides, and polyamines
- fatty acids and lipids
- volatile fatty acids and ketones
- other organic metabolites
- intermediate metabolites
- electron transport and ATP metabolism
- 1-carbon metabolism

Constructing pathways using the Excel tool



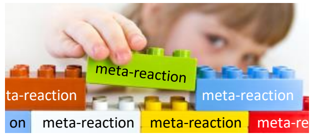


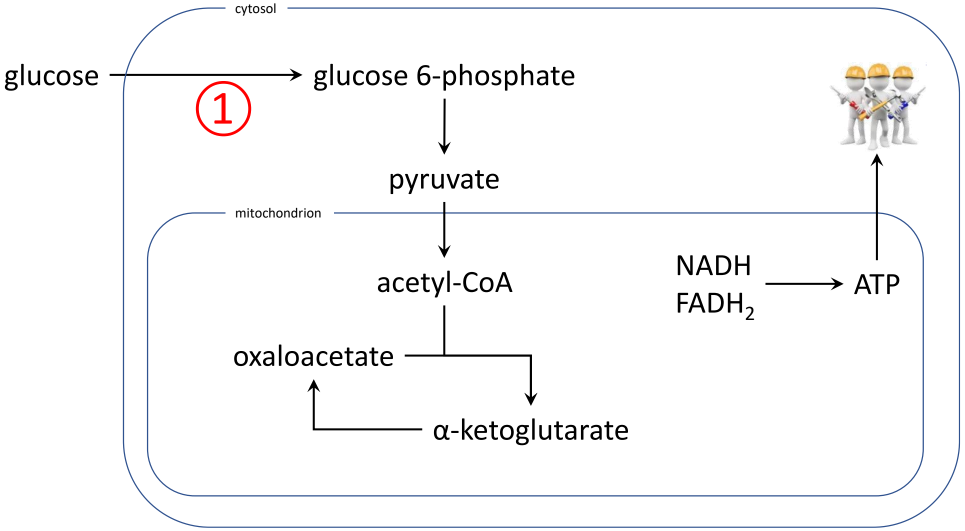
No meta-reactions selected yet

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates					

fructose
galactose
glucose
glycogen
lactose
sucrose

Constructing pathways using the Excel tool



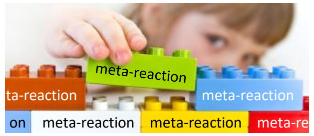


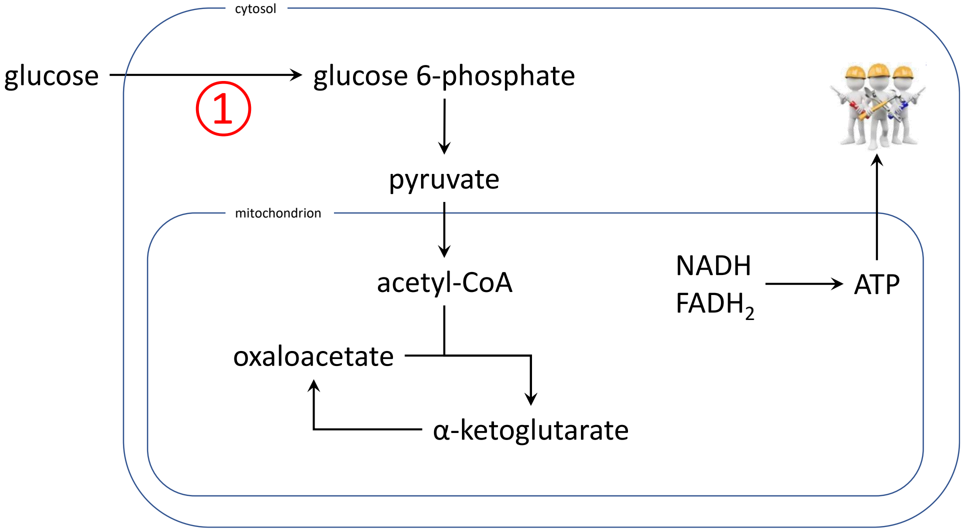
No meta-reactions selected yet

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose				

substrate
product

Constructing pathways using the Excel tool



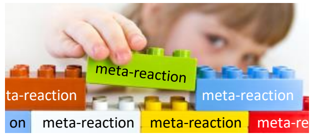


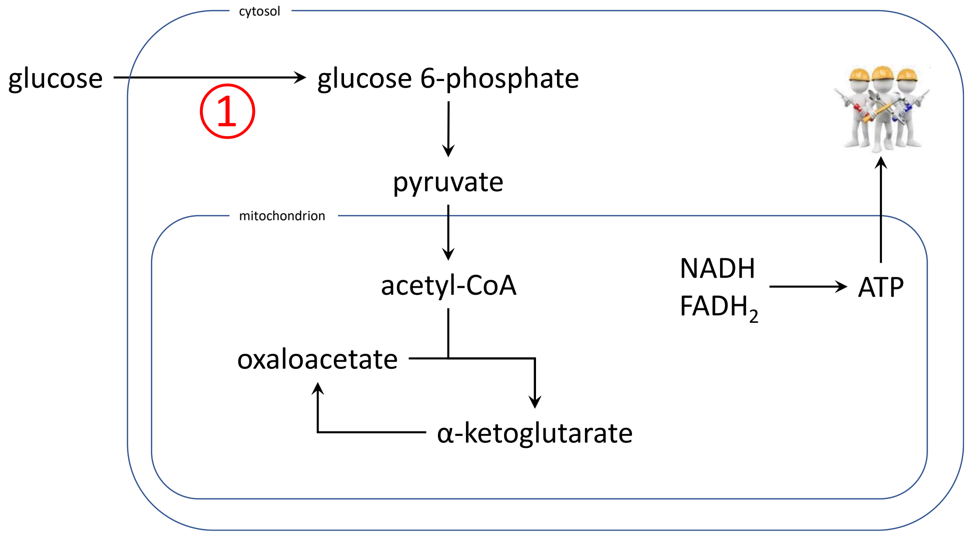
No meta-reactions selected yet

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate			

glucose 6-phosphate
with glucose 6-phosphate → lactose

Constructing pathways using the Excel tool

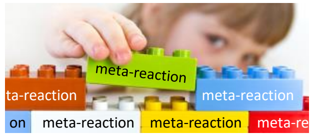


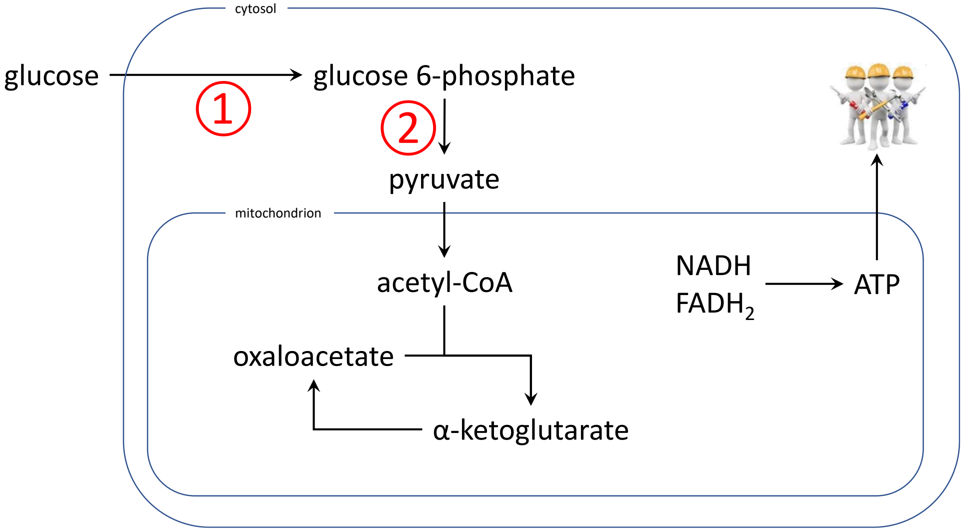


No "Flux" indicated yet

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	

Constructing pathways using the Excel tool

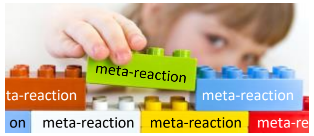


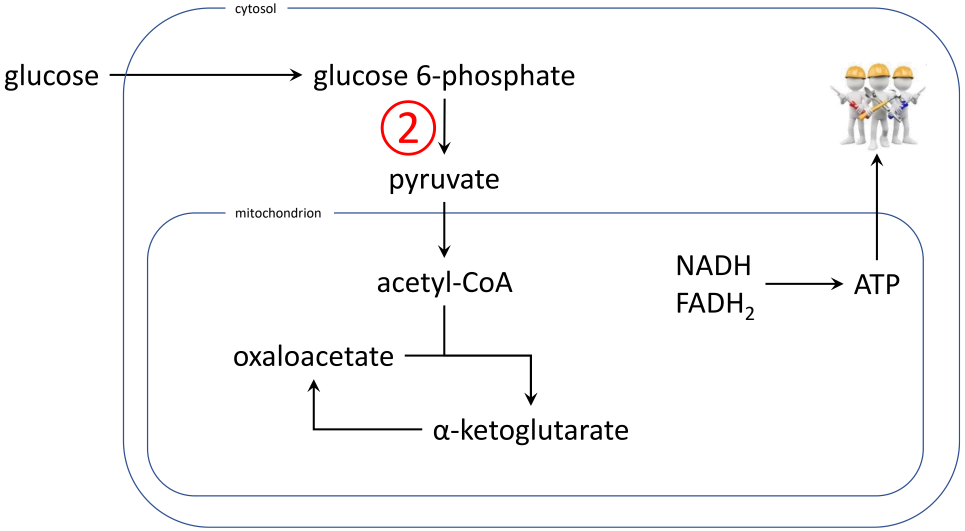


glucose + ATP → glucose 6-phosphate + ADP + H^+ (Q = 30 kJ)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1

Constructing pathways using the Excel tool

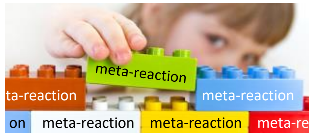


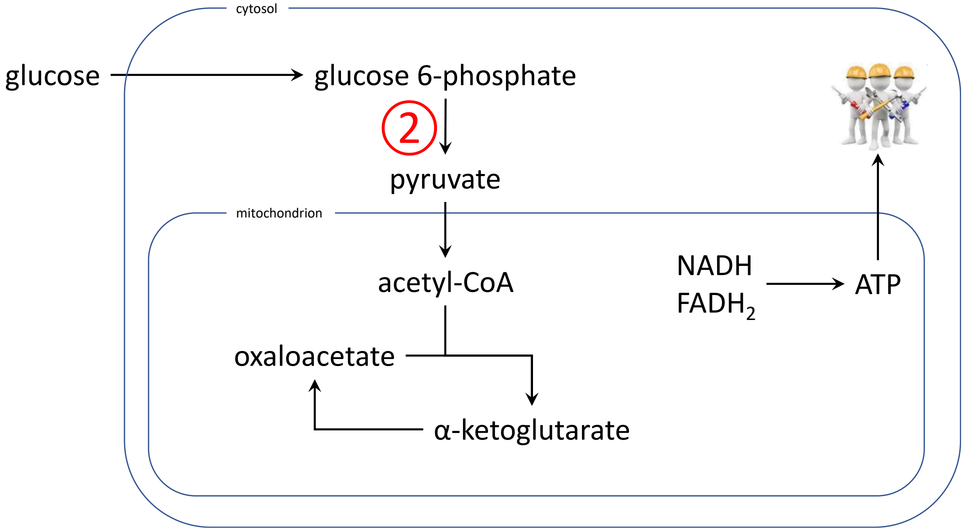


glucose + ATP → glucose 6-phosphate + ADP + H^+ (Q = 30 kJ)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	

Constructing pathways using the Excel tool

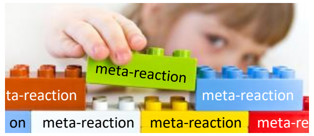


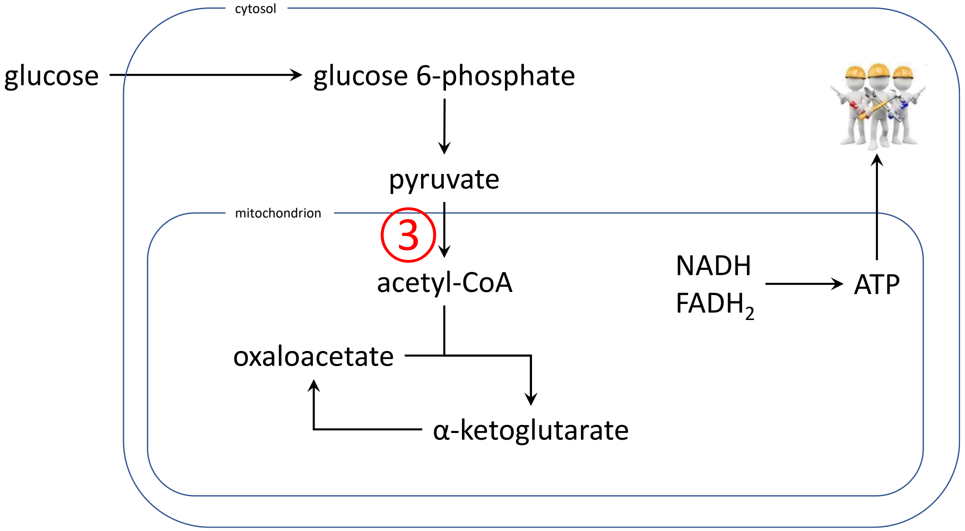


glucose + 2 ADP + 2 P_i + 2 NAD^+ → $\boxed{\text{2 pyruvate}}$ + 2 ATP + 2 NADH + 2 H^+ + 2 H_2O (Q = -63 kJ)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1

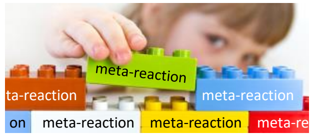
Constructing pathways using the Excel tool

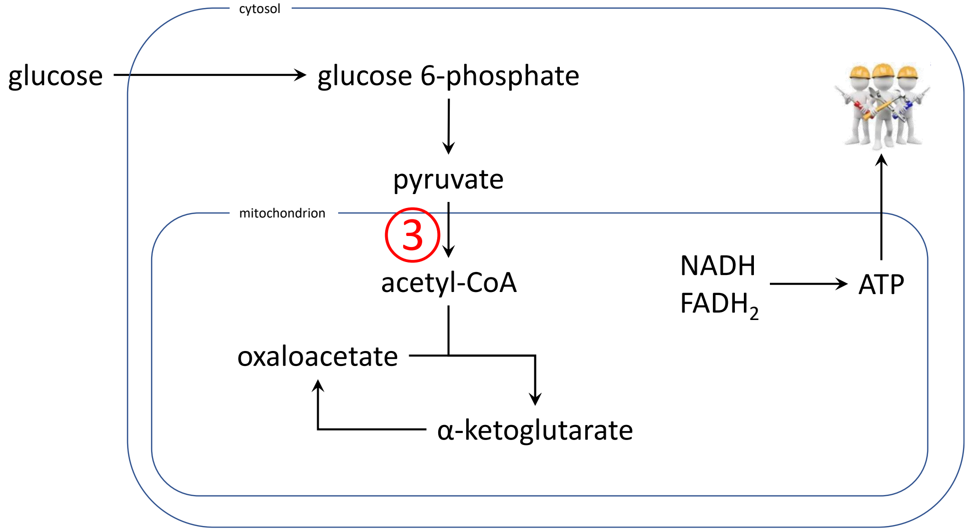




glucose + 2 ADP + 2 P_i + 2 NAD^+ → $\boxed{\text{2 pyruvate}}$ + 2 ATP + 2 NADH + 2 H^+ + 2 H_2O (Q = -63 kJ)					
Type	**Metabolite**	**As a ...**	**To/From ...**	**Meta-reaction**	**Flux**
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	

Constructing pathways using the Excel tool

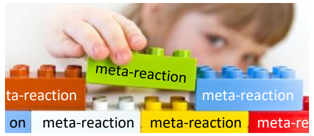


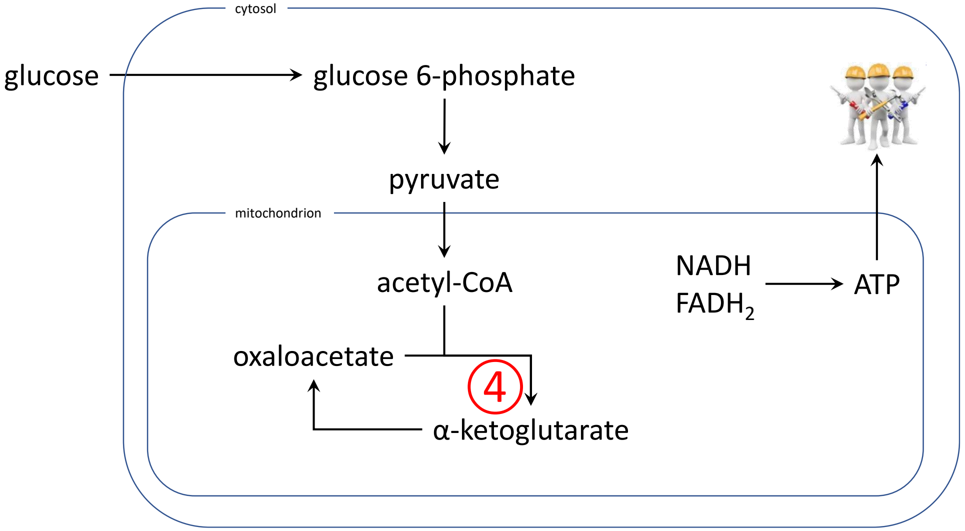


glucose + 2 ADP + 2 P_i + 2 CoA + 4 NAD^+ → 2 acetyl-CoA + 2 ATP + 4 NADH + 2 H^+ + 2 H_2O + 2 CO_2 (Q not available)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2

Constructing pathways using the Excel tool

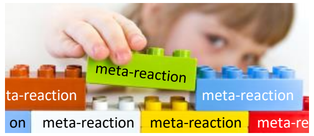


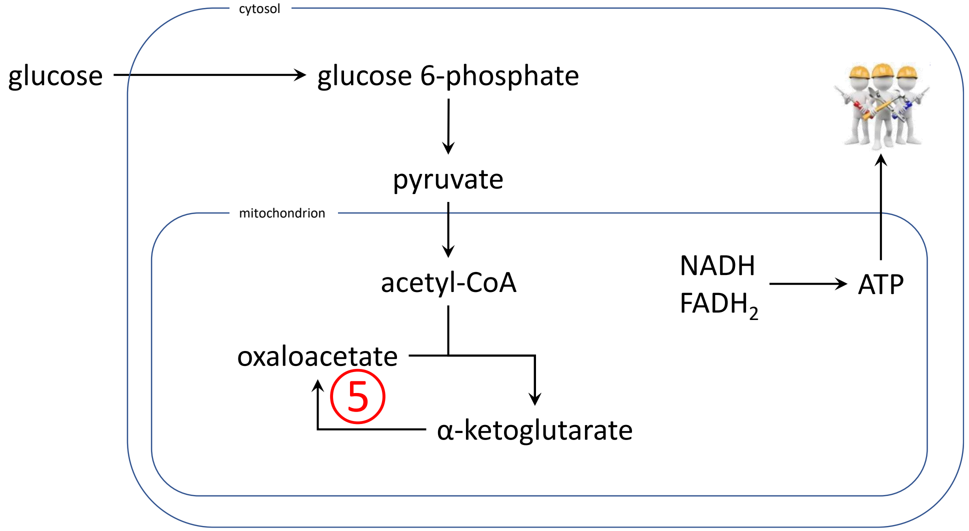


glucose + 2 oxaloacetate + 2 ADP + 2 P_i + 6 NAD^+ → $\boxed{\text{2 α-ketoglutarate}}$ + 2 ATP + 6 NADH + 4 H^+ + 4 CO_2 (Q = 42 kJ)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2
intermediate metabolites	acetyl-CoA	substrate	with oxaloacetate → α-ketoglutarate (TCA cycle)	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)	2

Constructing pathways using the Excel tool

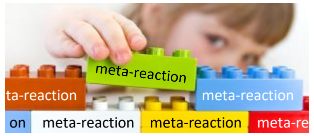


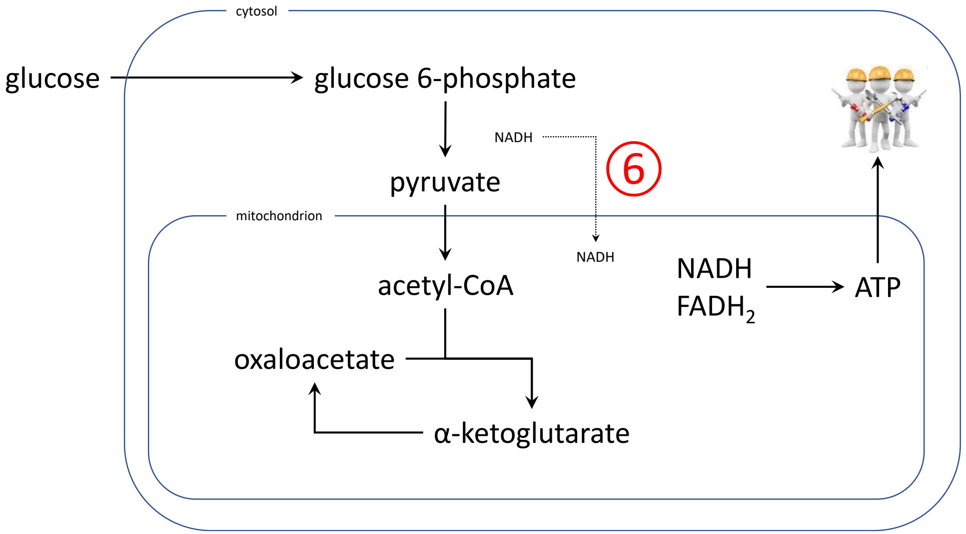


$\boxed{\text{glucose}} + 3.5\ ADP + 2.5\ H_2O + 3.5\ P_i + 2\ FAD + 10\ NAD^+ \rightarrow 3.5\ ATP + \boxed{2\ FADH_2 + 10\ NADH} + 4.5\ H^+ + \boxed{6\ CO_2}$ (Q not available)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2
intermediate metabolites	acetyl-CoA	substrate	with oxaloacetate → α-ketoglutarate (TCA cycle)	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)	2
intermediate metabolites	α-ketoglutarate	substrate	oxaloacetate (TCA cycle)	α-ketoglutarate + 0.75 ADP + 0.75 P_i + 2 NAD^+ + FAD + 1.25 H_2O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H^+ + $FADH_2$ + CO_2 (TCA cycle)	2

Constructing pathways using the Excel tool

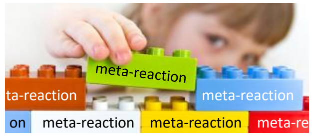


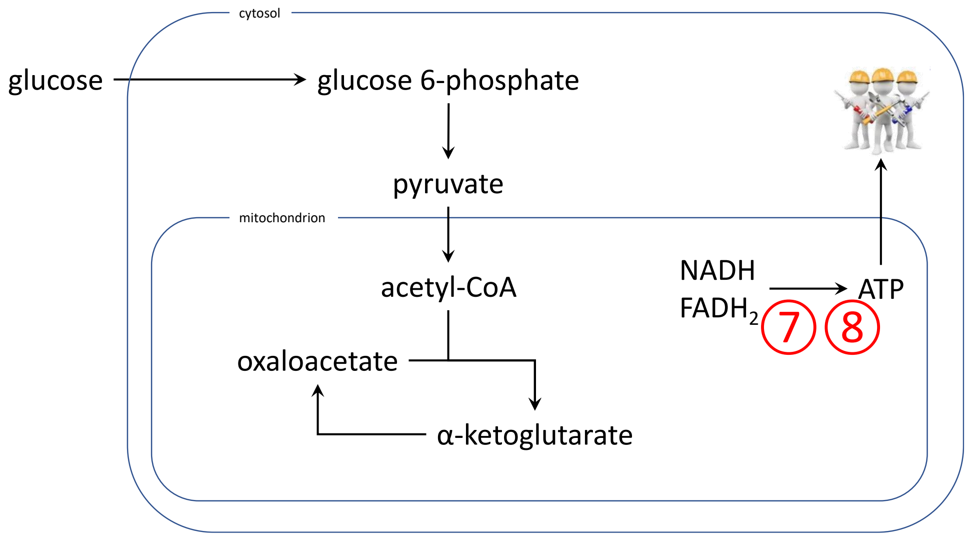


glucose + 3 ADP + 3 H_2O + 3 P_i + 2 FAD + 10 NAD^+ → 3 ATP + 2 $FADH_2$ + 10 NADH + 5 H^+ + 6 CO_2 (Q not available)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2
intermediate metabolites	acetyl-CoA	substrate	with oxaloacetate → α-ketoglutarate (TCA cycle)	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)	2
intermediate metabolites	α-ketoglutarate	substrate	oxaloacetate (TCA cycle)	α-ketoglutarate + 0.75 ADP + 0.75 P_i + 2 NAD^+ + FAD + 1.25 H_2O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H^+ + $FADH_2$ + CO_2 (TCA cycle)	2
electron transport and ATP metabolism	NADH	substrate	NADH cytosol → NADH mitochondrion	0.25 ATP + 0.25 H_2O → 0.25 ADP + 0.25 P_i + 0.25 H^+ (malate - aspartate shuttle)	2

Constructing pathways using the Excel tool

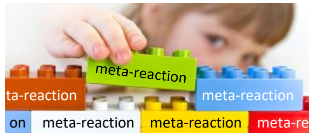


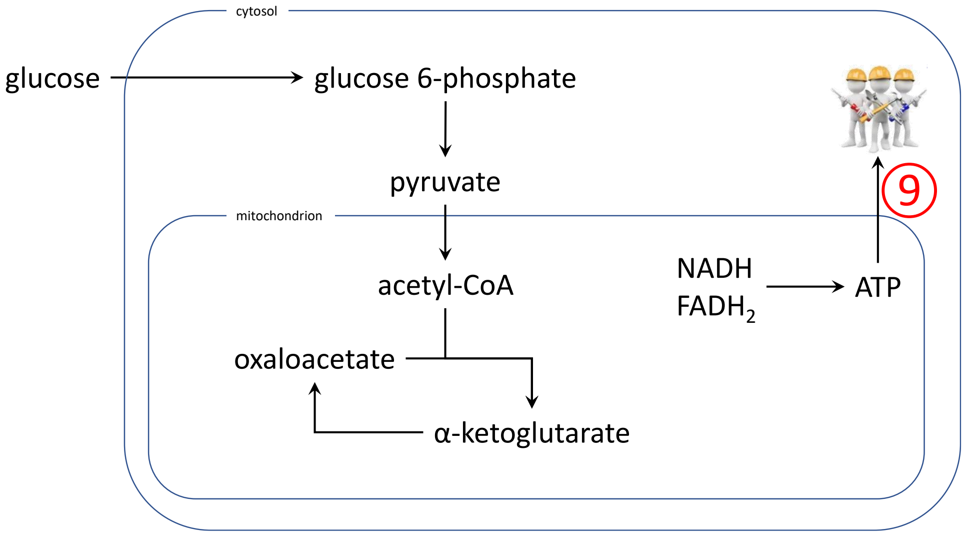


glucose + 31 ADP + 31 H^+ + 31 P_i + 6 O_2 → $\boxed{\text{31 ATP}}$ + 37 H_2O + 6 CO_2 $\boxed{Q = 1{,}927\ \text{kJ}}$

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2
intermediate metabolites	acetyl-CoA	substrate	with oxaloacetate → α-ketoglutarate (TCA cycle)	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)	2
intermediate metabolites	α-ketoglutarate	substrate	oxaloacetate (TCA cycle)	α-ketoglutarate + 0.75 ADP + 0.75 P_i + 2 NAD^+ + FAD + 1.25 H_2O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H^+ + $FADH_2$ + CO_2 (TCA cycle)	2
electron transport and ATP metabolism	NADH	substrate	NADH cytosol → NADH mitochondrion	0.25 ATP + 0.25 H_2O → 0.25 ADP + 0.25 P_i + 0.25 H^+ (malate - aspartate shuttle)	2
electron transport and ATP metabolism	NADH	substrate	ATP (oxidative phosphorylation)	2.5 ADP + 2.5 P_i + NADH + 3.5 H^+ + 0.5 O_2 → 2.5 ATP + NAD^+ + 3.5 H_2O (oxidative phosphorylation)	10
electron transport and ATP metabolism	$FADH_2$	substrate	ATP (oxidative phosphorylation)	1.5 ADP + 1.5 P_i + 0.5 H^+ + $FADH_2$ + 0.5 O_2 → 1.5 ATP + FAD + 2.5 H_2O (oxidative phosphorylation)	2

Constructing pathways using the Excel tool





glucose + 6 O_2 → 6 H_2O + 6 CO_2 (Q = 2,814 kJ)

Type	Metabolite	As a ...	To/From ...	Meta-reaction	Flux
carbohydrates	glucose	substrate	glucose 6-phosphate	glucose + ATP → glucose 6-phosphate + ADP + H^+	1
intermediate metabolites	glucose 6-phosphate	substrate	pyruvate (glycolysis)	glucose 6-phosphate + 3 ADP + 2 P_i + 2 NAD^+ → 2 pyruvate + 3 ATP + 2 NADH + H^+ + 2 H_2O (glycolysis)	1
intermediate metabolites	pyruvate	substrate	acetyl-CoA	pyruvate + NAD^+ + CoA → acetyl-CoA + NADH + CO_2	2
intermediate metabolites	acetyl-CoA	substrate	with oxaloacetate → α-ketoglutarate (TCA cycle)	acetyl-CoA + oxaloacetate + NAD^+ + H_2O → α-ketoglutarate + NADH + H^+ + CoA + CO_2 (TCA cycle)	2
intermediate metabolites	α-ketoglutarate	substrate	oxaloacetate (TCA cycle)	α-ketoglutarate + 0.75 ADP + 0.75 P_i + 2 NAD^+ + FAD + 1.25 H_2O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H^+ + $FADH_2$ + CO_2 (TCA cycle)	2
electron transport and ATP metabolism	NADH	substrate	NADH cytosol → NADH mitochondrion	0.25 ATP + 0.25 H_2O → 0.25 ADP + 0.25 P_i + 0.25 H^+ (malate - aspartate shuttle)	2
electron transport and ATP metabolism	NADH	substrate	ATP (oxidative phosphorylation)	2.5 ADP + 2.5 P_i + NADH + 3.5 H^+ + 0.5 O_2 → 2.5 ATP + NAD^+ + 3.5 H_2O (oxidative phosphorylation)	10
electron transport and ATP metabolism	$FADH_2$	substrate	ATP (oxidative phosphorylation)	1.5 ADP + 1.5 P_i + 0.5 H^+ + $FADH_2$ + 0.5 O_2 → 1.5 ATP + FAD + 2.5 H_2O (oxidative phosphorylation)	2
electron transport and ATP metabolism	ATP	substrate	e.g., maintenance, peptide synthesis	ATP + H_2O → ADP + P_i + H^+	31

Who is in control?

dehydrogenase
isomerase
hexokinase /glucokinase
mutase
phosphatase

glucose
glycerol 3-P
glycerol
glycogen
galactose

↔ glucose 6-phosphate

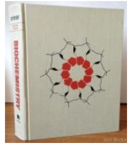
serine

pyruvate

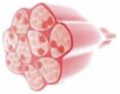
NADPH
(pentose phosphate pathway)

oxaloacetate

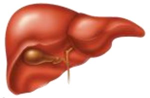
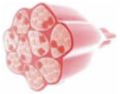
Who is in control?



glucose → 31 ATP

glucose → glycogen → ? ATP

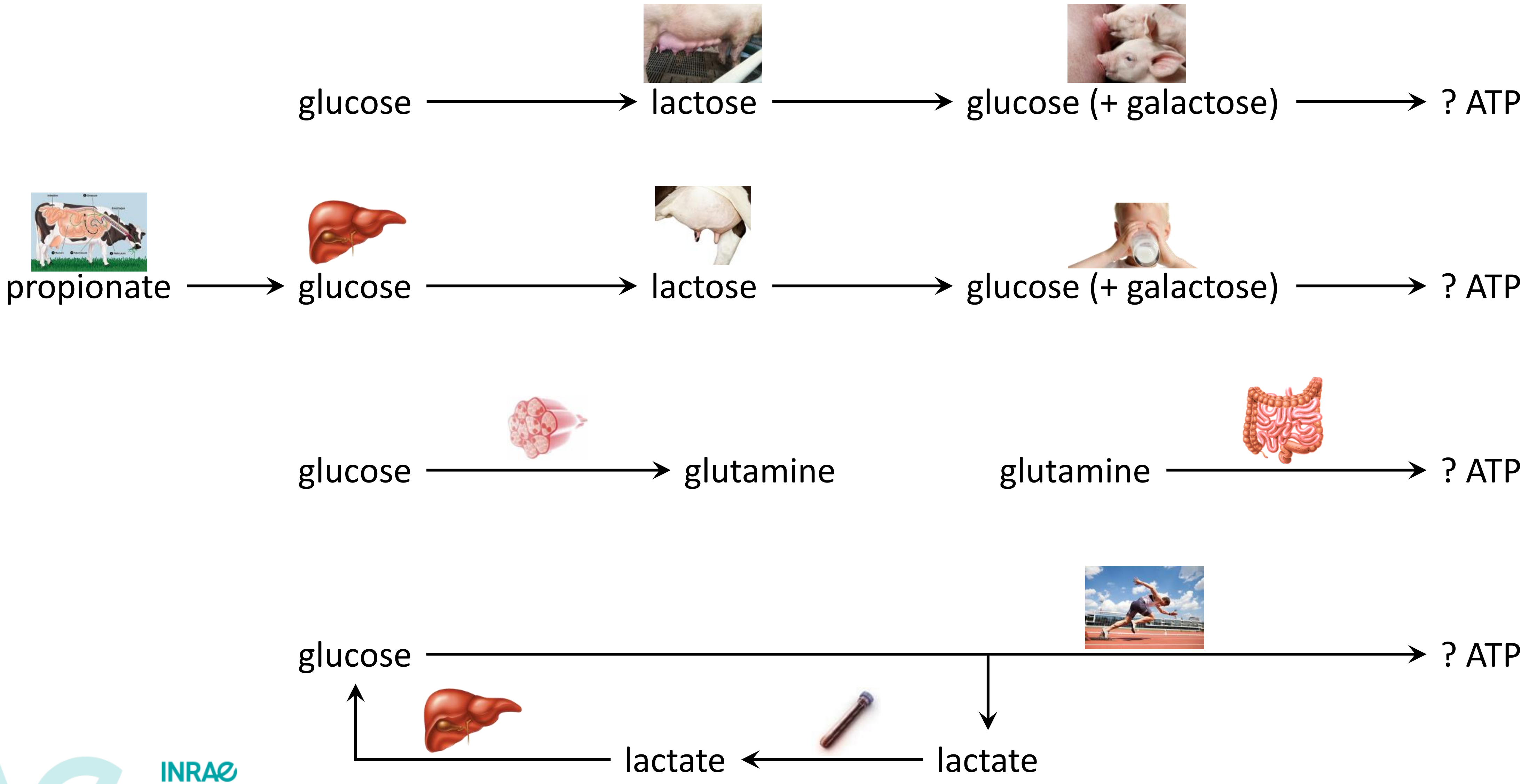
   

glucose → glycogen → glucose → ? ATP

glucose → lipid → ? ATP

Who is in control?

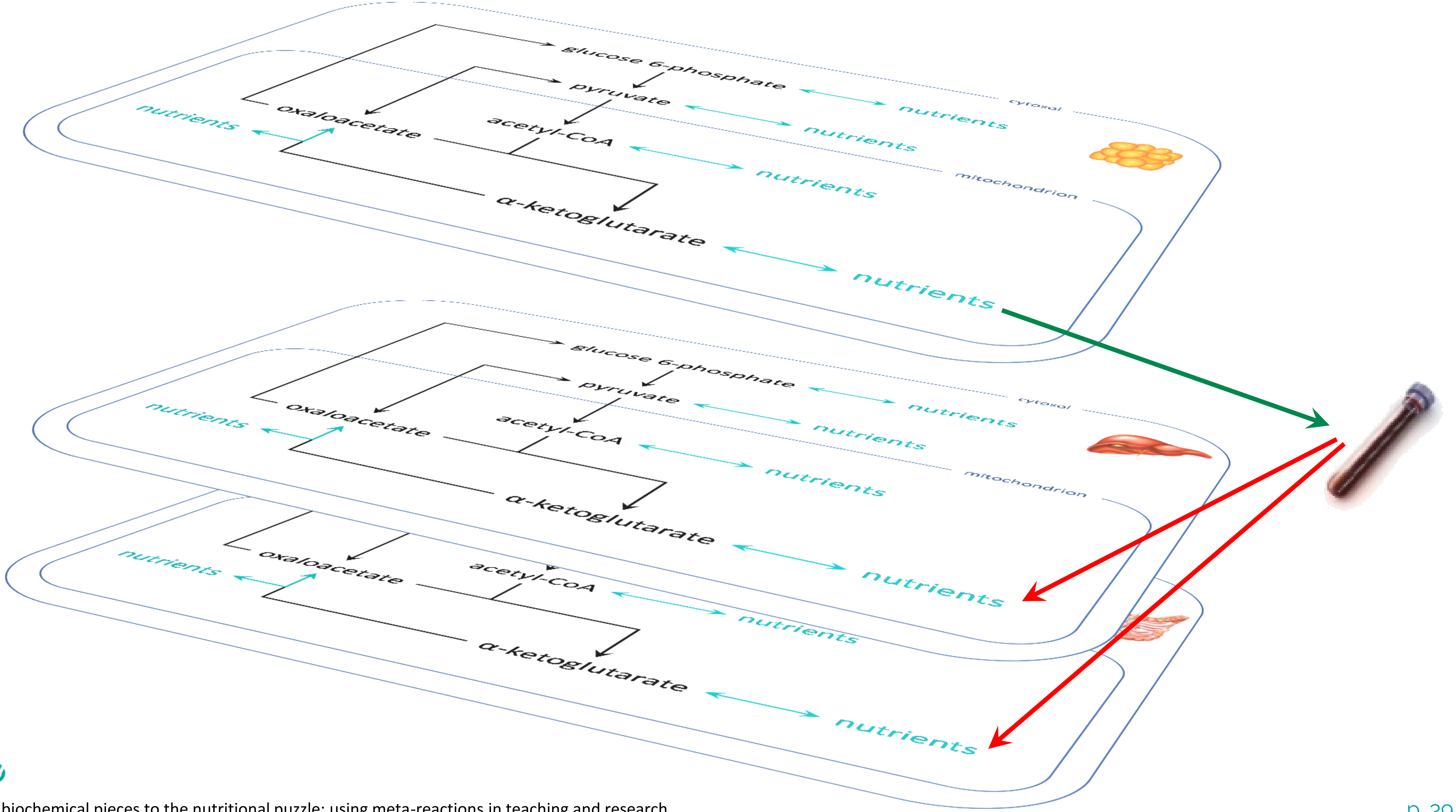


Who is in control?

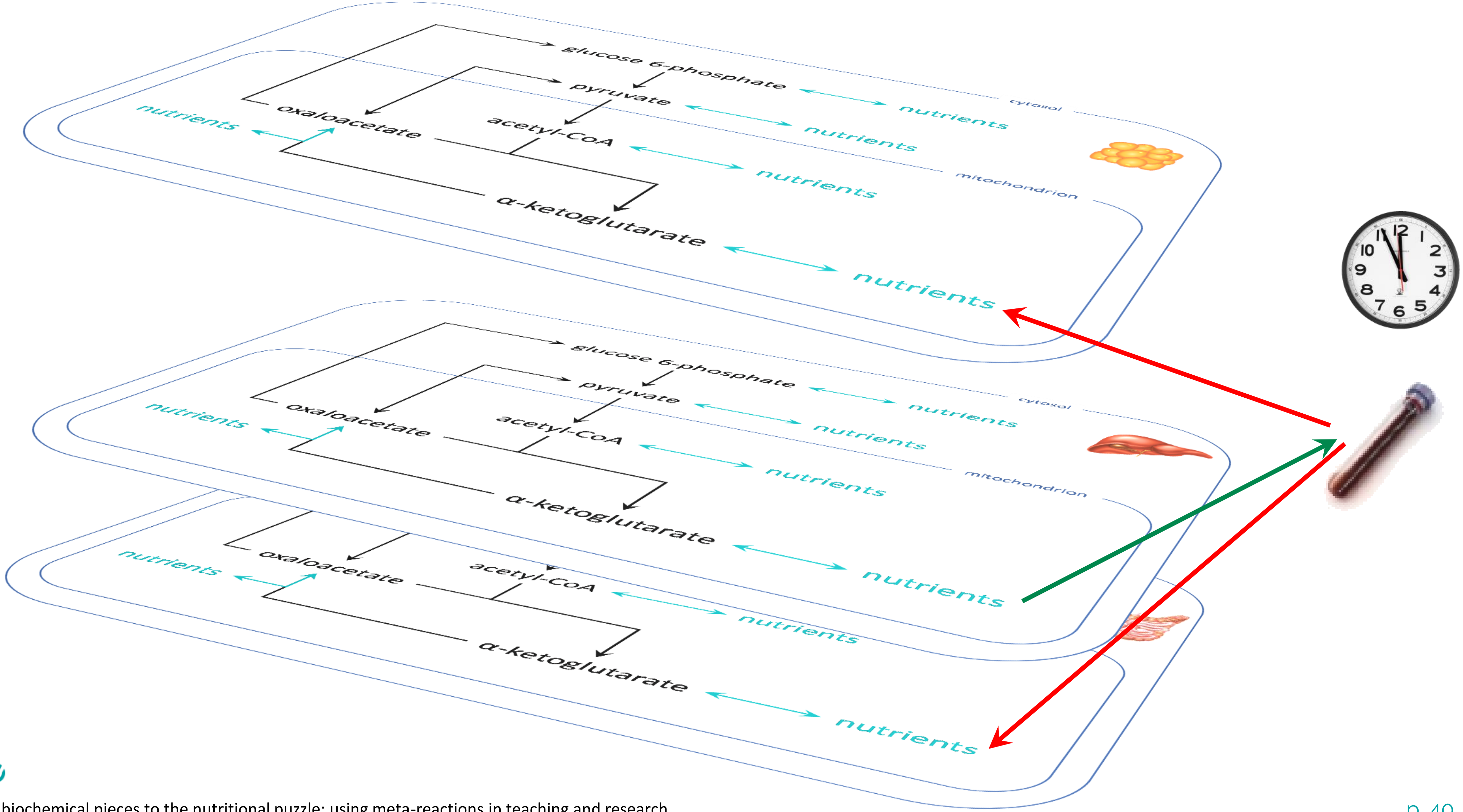
glucose → intermediate → ATP

Intermediate (in 2 steps)	ATP-1	ATP-2	ATP	Efficiency
Direct			31	100%
Tripalmitin (adipose tissue and muscle)	-0.02	23.59	23.57	76%
Glycogen (liver and muscle)	-2	31	29	94%
Glycogen (muscle and muscle)	-2	32	30	97%
Lactate (liver and muscle; Cori cycle)	2	25	27	87%
Lactate (muscle and muscle)	2	29	31	100%
Glutamate (intestine and muscle)	22	8	30	97%
Lactose (mother and newborn)	-1	31	30	97%

Compartmental and dynamic aspects of metabolism



Compartmental and dynamic aspects of metabolism



Control and robustness in nutrition and metabolism

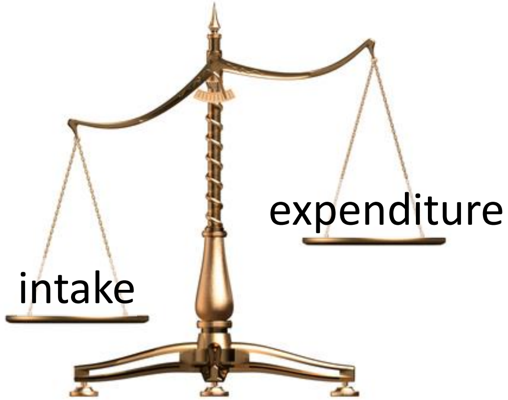
Both are well balanced.
What about their energy balance?

energy intake = energy expenditure

energy intake = 1.005 x energy expenditure

Control and robustness in nutrition and metabolism

Item	Energy
Maintenance energy requirement	2580 kcal/d
0.5% imbalance	13 kcal/d
Deposited as lipid	1.3 g/d
Per year	481 g/yr
Between 20 and 60 years of age	19 kg of lipid



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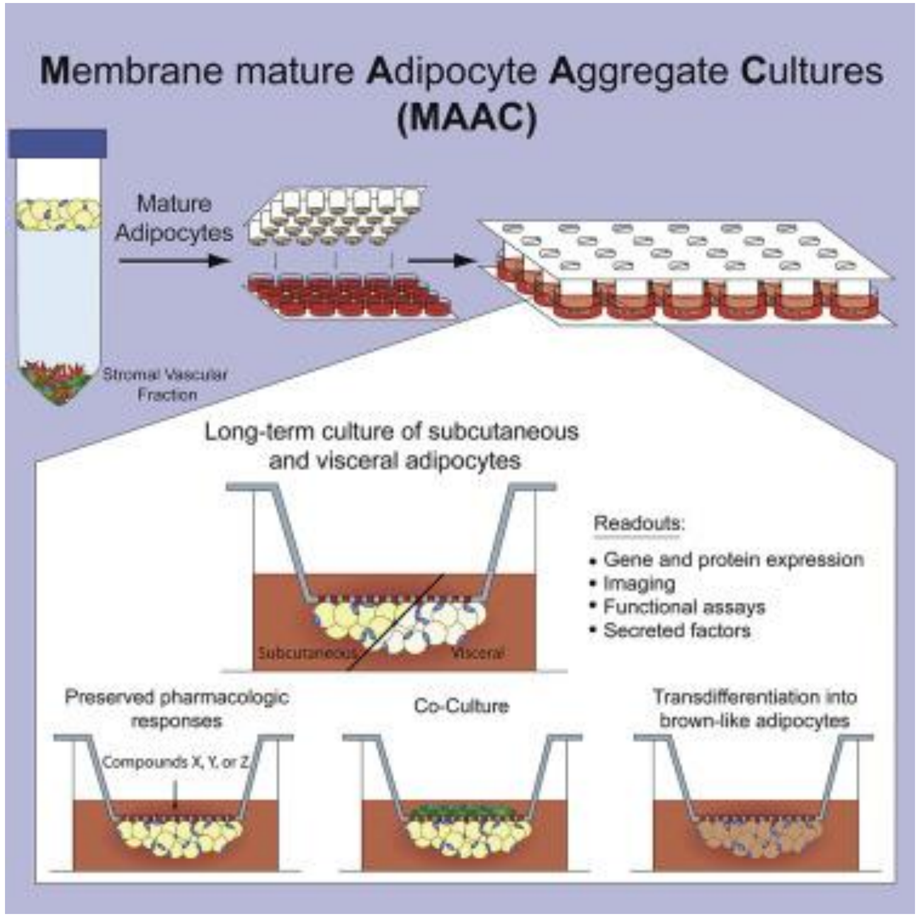
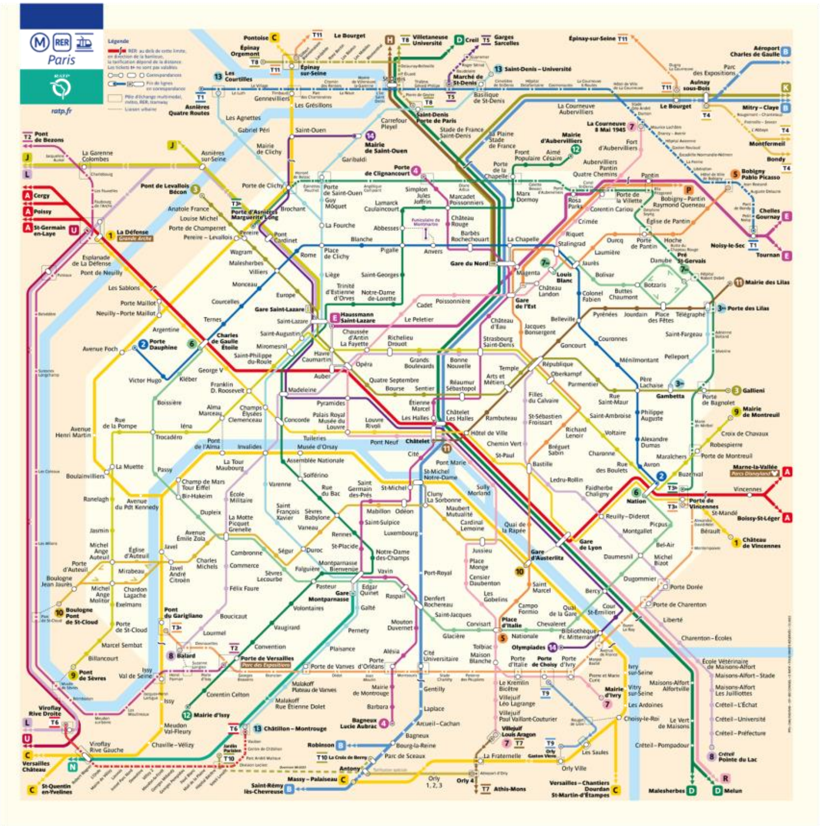
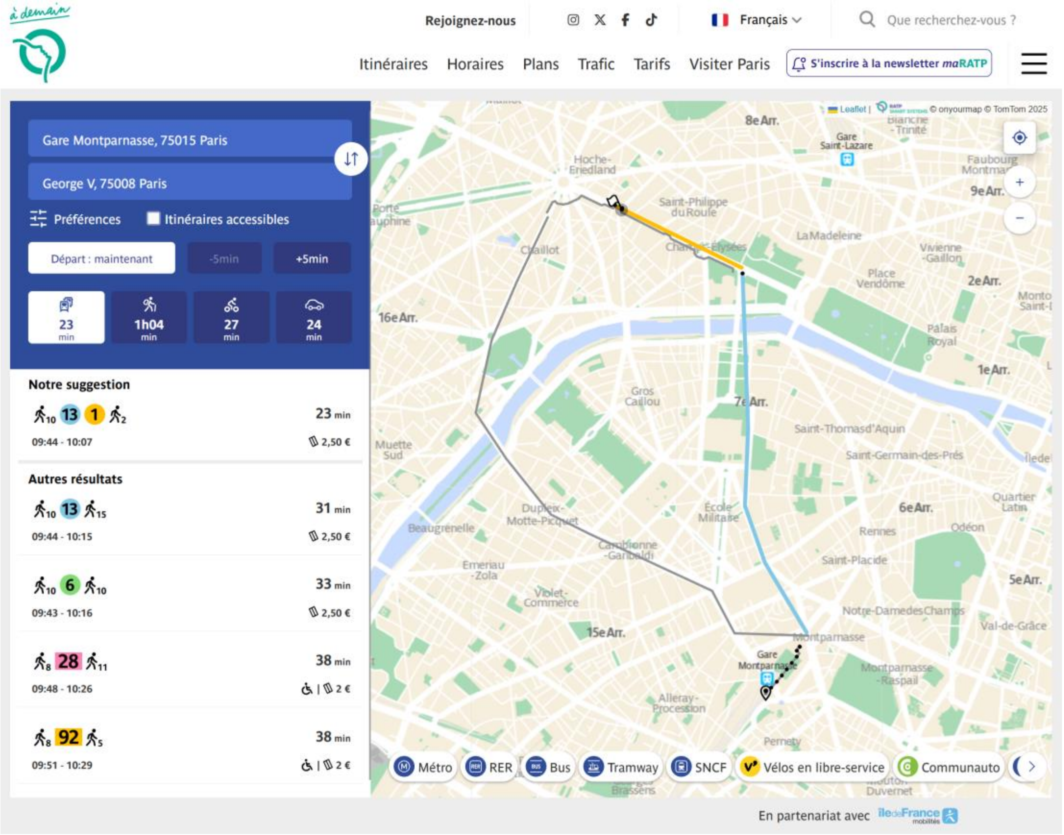
Who is in control? Adipocytes have a life of their own



Harms *et al*. (2019). Mature human white adipocytes cultured under membranes maintain identity, function, and can transdifferentiate into brown-like adipocytes. Cell Reports 27: 213-225

Finding your way in Paris

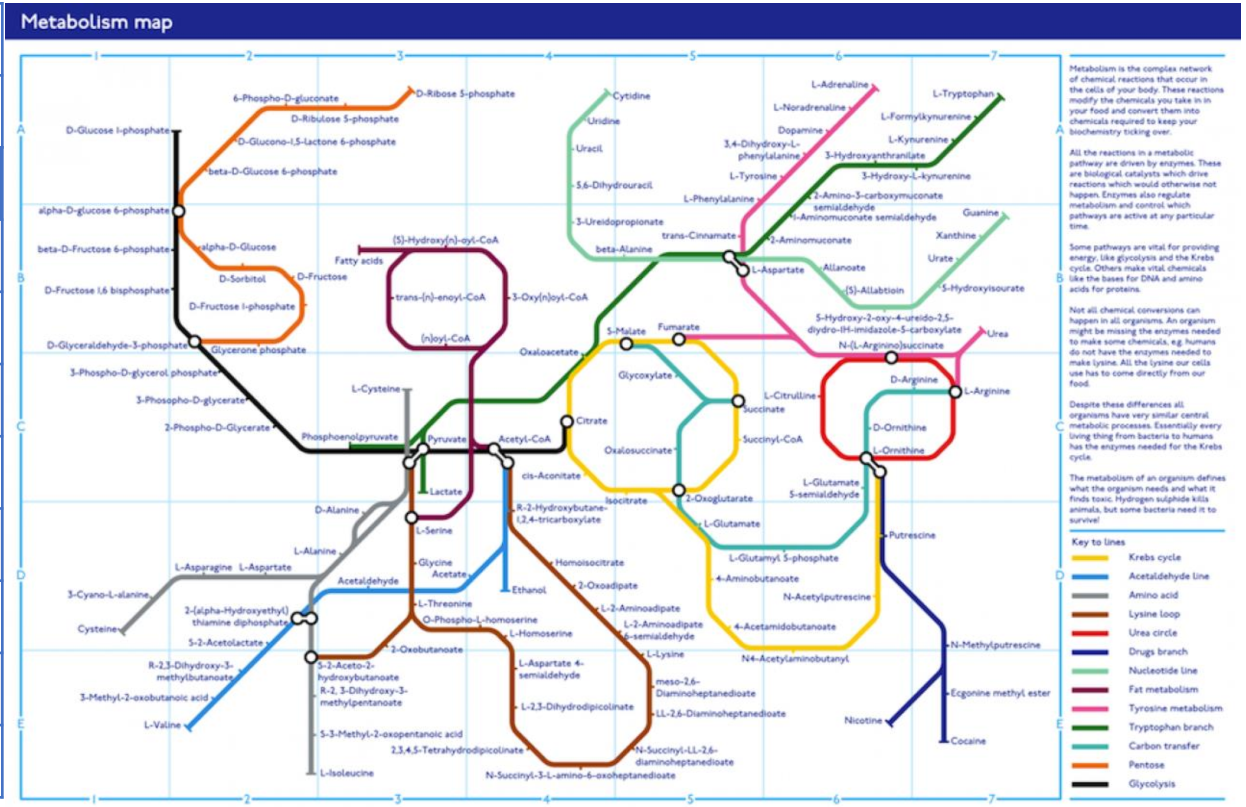




Finding your way in metabolism?

From	glucose
To	ATP

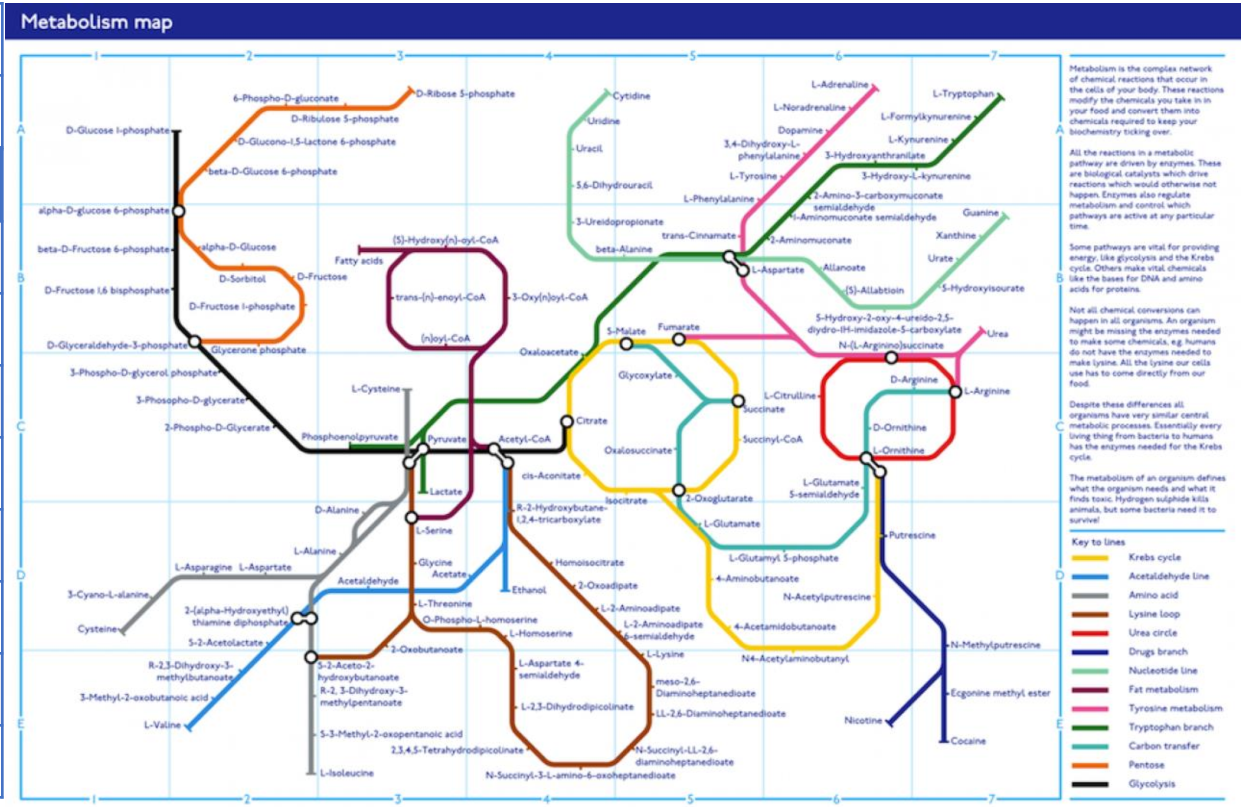
Route	**ATP**



Finding your way in metabolism?

From	glucose
To	ATP

Route	ATP
Direct	31
via tripalmitin	23.57
via glycogen (liver and muscle)	29
via glycogen (muscle and muscle)	30
via lactate (liver and muscle; Cori cycle)	27
via lactate (muscle and muscle)	31
via glutamate (intestine and muscle)	30
via lactose (mother and newborn)	30



Conclusion

- Meta-reactions are useful to teach nutritional biochemistry
- For research, meta-reactions can be used to analyze nutritional balances
- Compartmentalization of metabolism has an impact on “efficiency”
- Metabolism is very well controlled, which is dynamic and occurs at multiple levels
- Meta-reactions in other domains (e.g., plant science, microbiology) can be developed

Further reading

Animal 18 (2024) 101204

Contents lists available at ScienceDirect

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The international journal of animal biosciences

From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research

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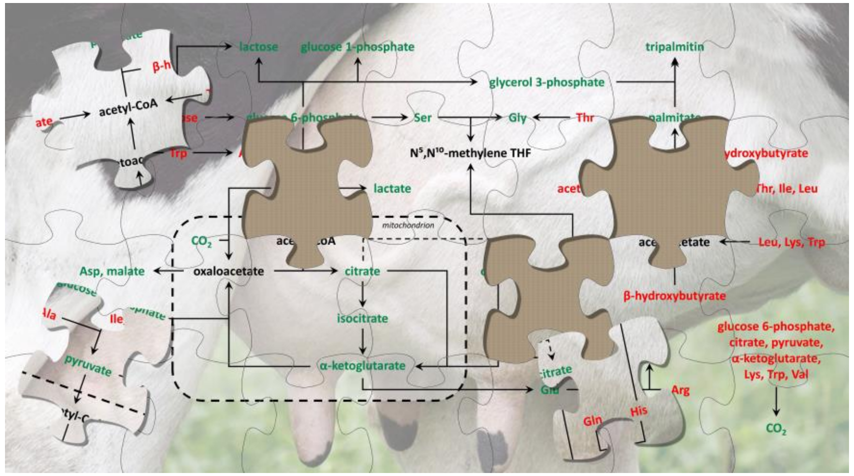
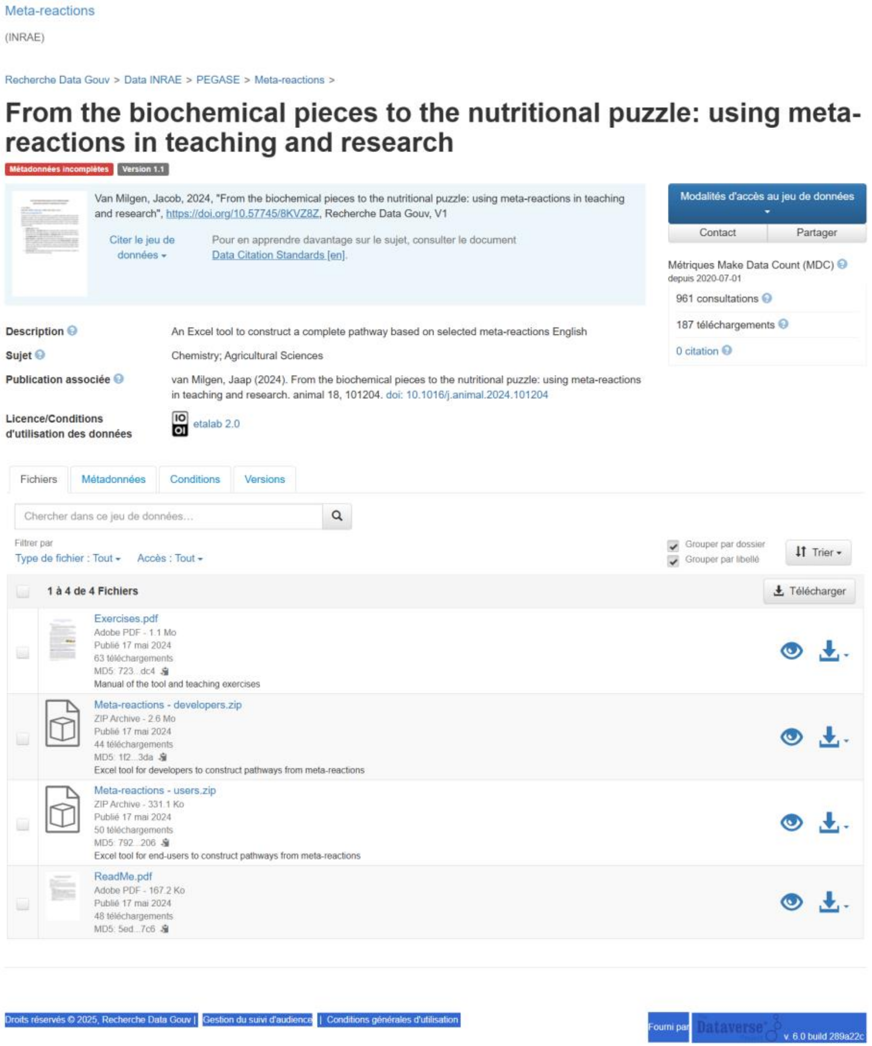
PEGASE, INRAE, Institut Agro, 35590 Saint Gilles, France

https://doi.org/10.1016/j.animal.2024.101204





Meta-reactions

(INRAE)

Recherche Data Gouv > Data INRAE > PEGASE > Meta-reactions >

From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research

Métadonnées incomplètes | Version 1.1

Van Milgen, Jacob, 2024, "From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research", https://doi.org/10.57745/8KVZ8Z, Recherche Data Gouv, V1

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Description An Excel tool to construct a complete pathway based on selected meta-reactions English

Sujet Chemistry; Agricultural Sciences

Publication associée van Milgen, Jaap (2024). From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research. animal 18, 101204. doi: 10.1016/j.animal.2024.101204

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  - Univ. Illinois (Urbana-Champaign, USA)
  - Sichuan Agricultural Univ. (Chengdu, China)
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  - Univ. California (Davis), Iowa State Univ., South Dakota State Univ., Univ. Minnesota, Univ. Missouri, Univ. Nebraska, Kansas State Univ.
- Sanjana Anan (Univ. Guelph, Canada)
-