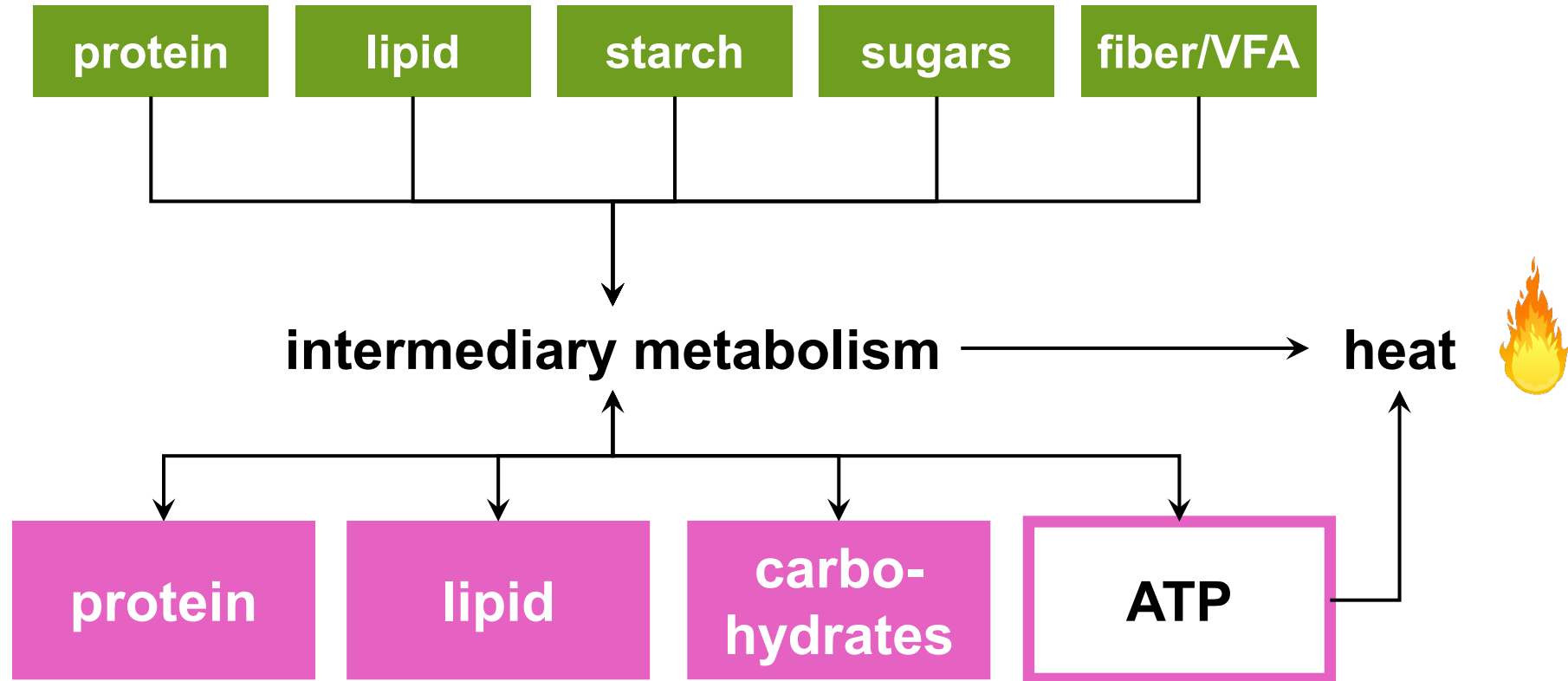




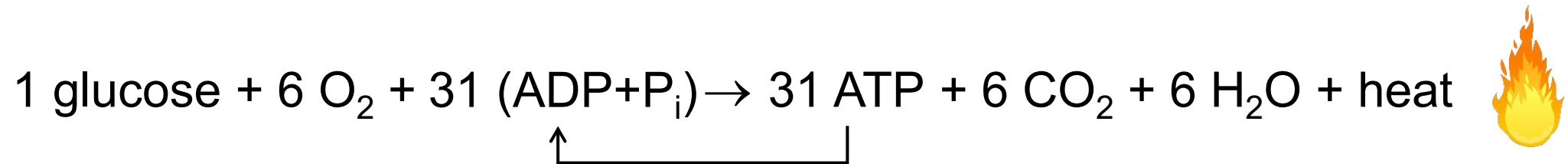
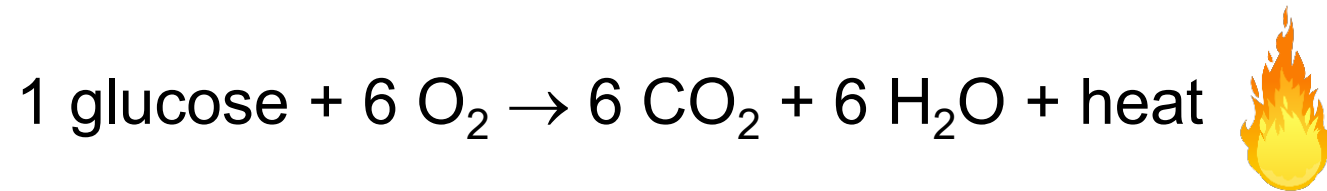
➤ From the biochemical pieces to the nutritional puzzle:  
using meta-reactions in teaching and research

Jaap van Milgen

## ➤ From nutrient intake to nutrient utilization



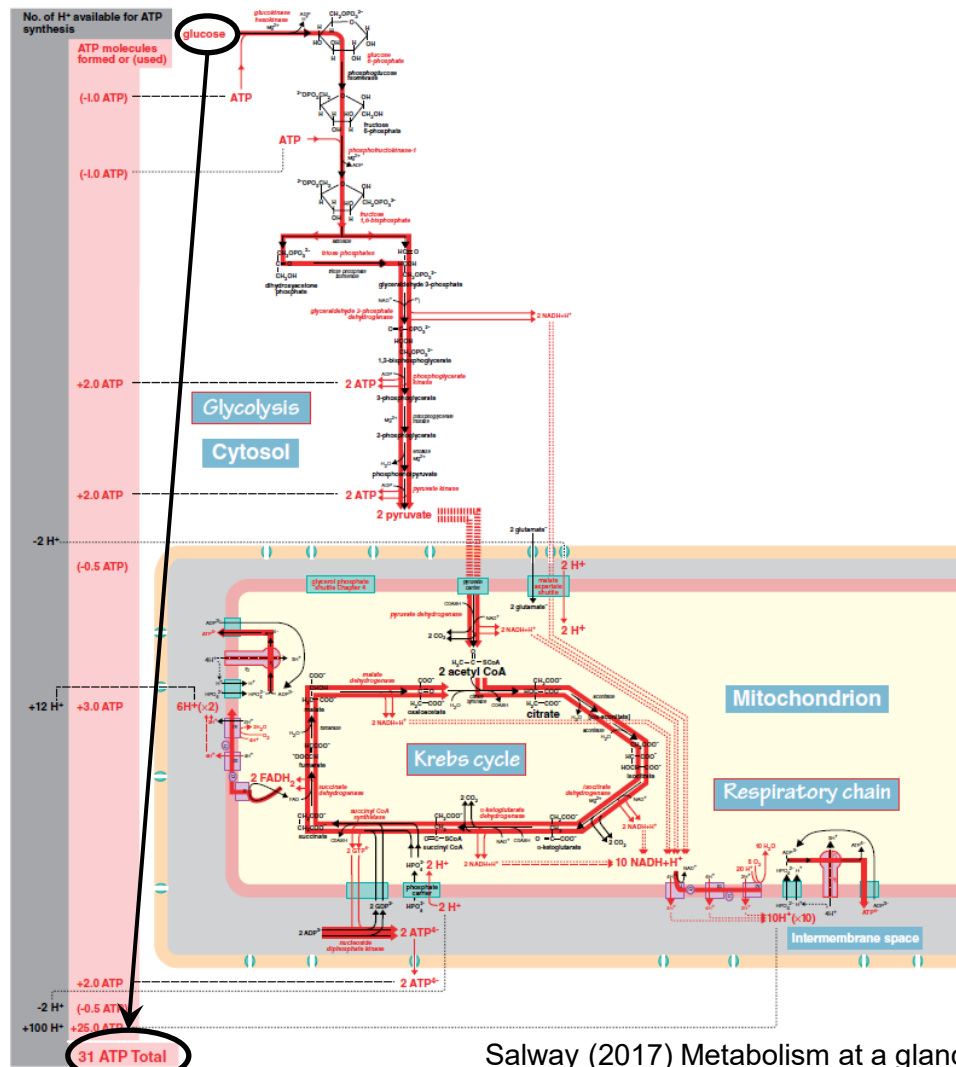
## ➤ The catabolism of glucose



“work” → heat



## ➤ Finding your way in metabolism



### ❖ 20 “carbon” metabolites involved:

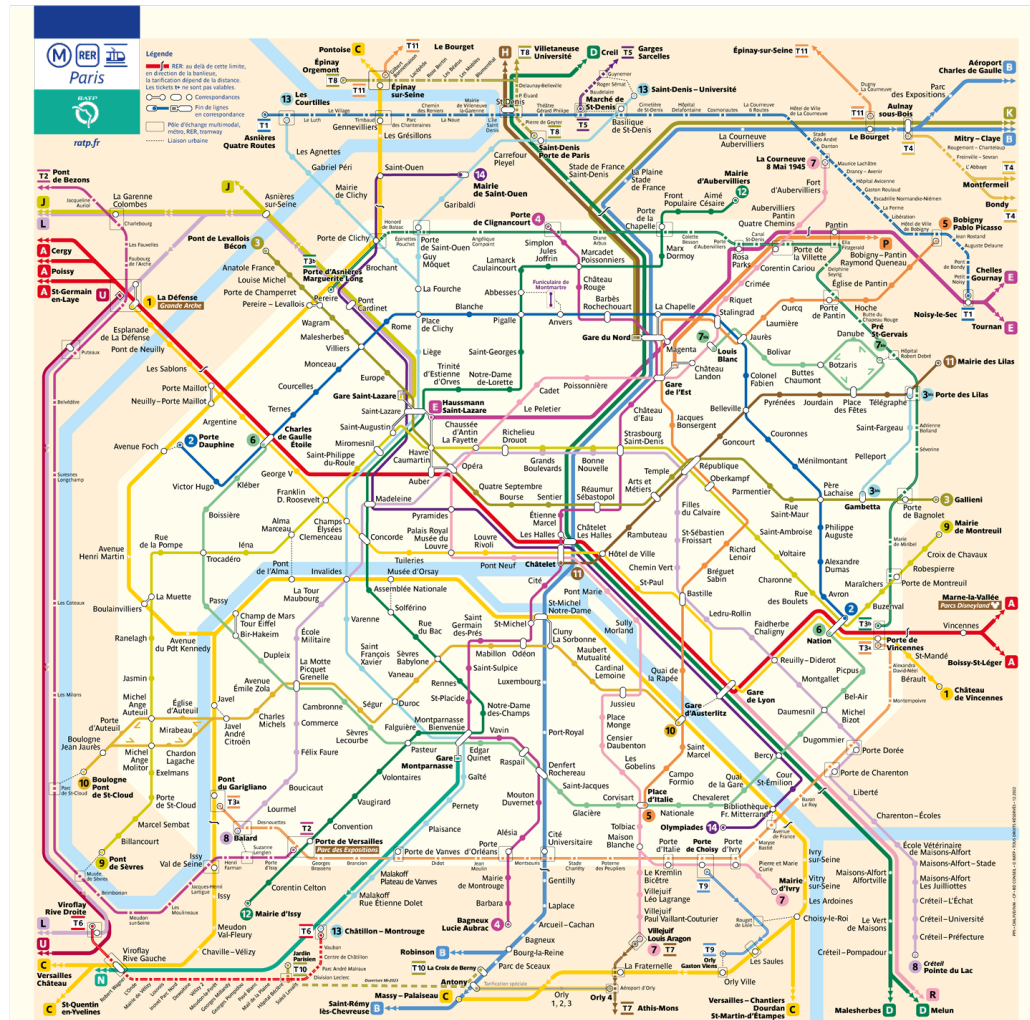
glucose, glucose 6-phosphate, fructose 6-phosphate, fructose 1,6-bisphosphate, dihydroxyacetone phosphate, glyceraldehyde 3-phosphate, 1,3-bisphosphoglycerate, 3-phosphoglycerate, 2-phosphoglycerate, phosphoenolpyruvate, pyruvate, acetyl-CoA, citrate, isocitrate,  $\alpha$ -ketoglutarate, succinyl CoA,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

### ❖ And also:

ATP, GTP, NADH,  $\text{FADH}_2$ ,  $\text{H}^+$  (proton motive force),  $\text{O}_2$ ,  $\text{CO}_2$   
Other cofactors  
Enzymes



# ➤ Finding your way in Paris



## Where to ?

From

To

☐
Itineraries accessible for persons with reduced mobility

Leave at
at

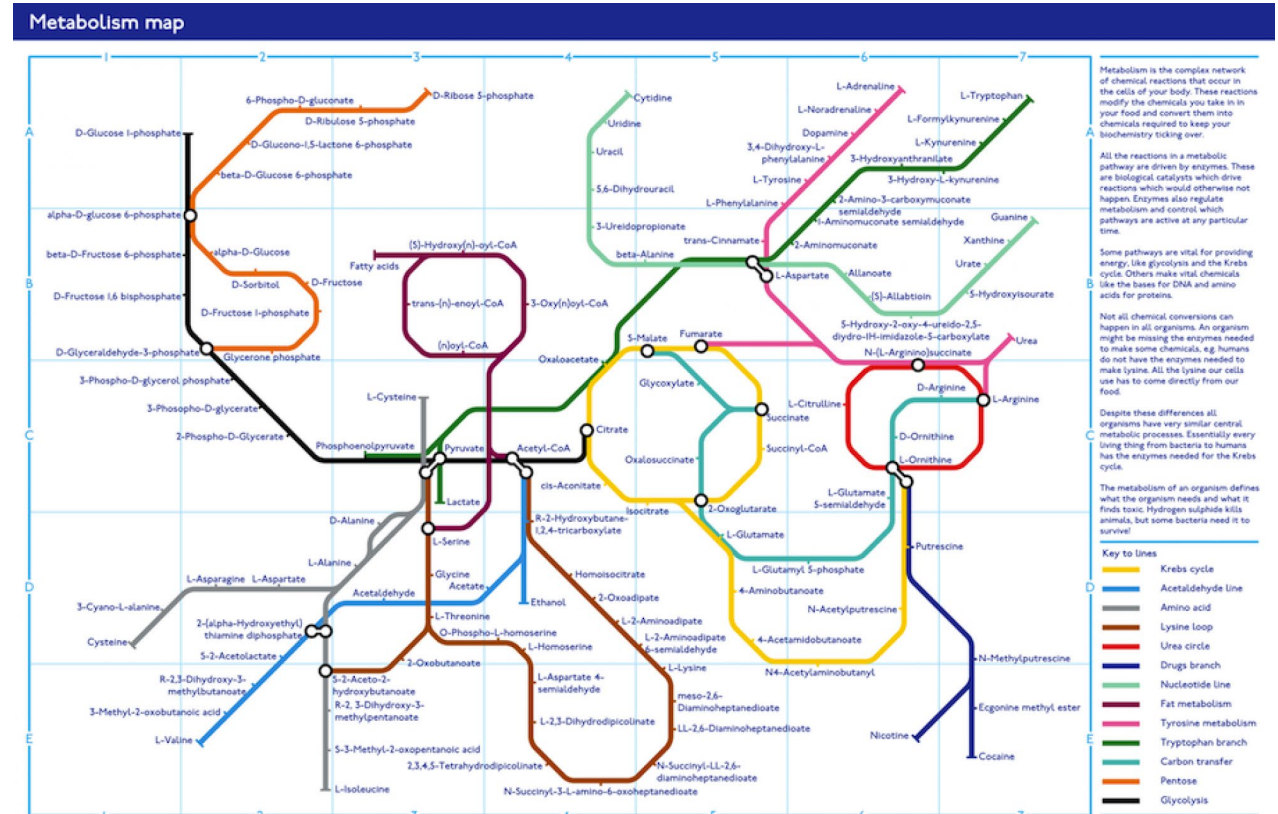
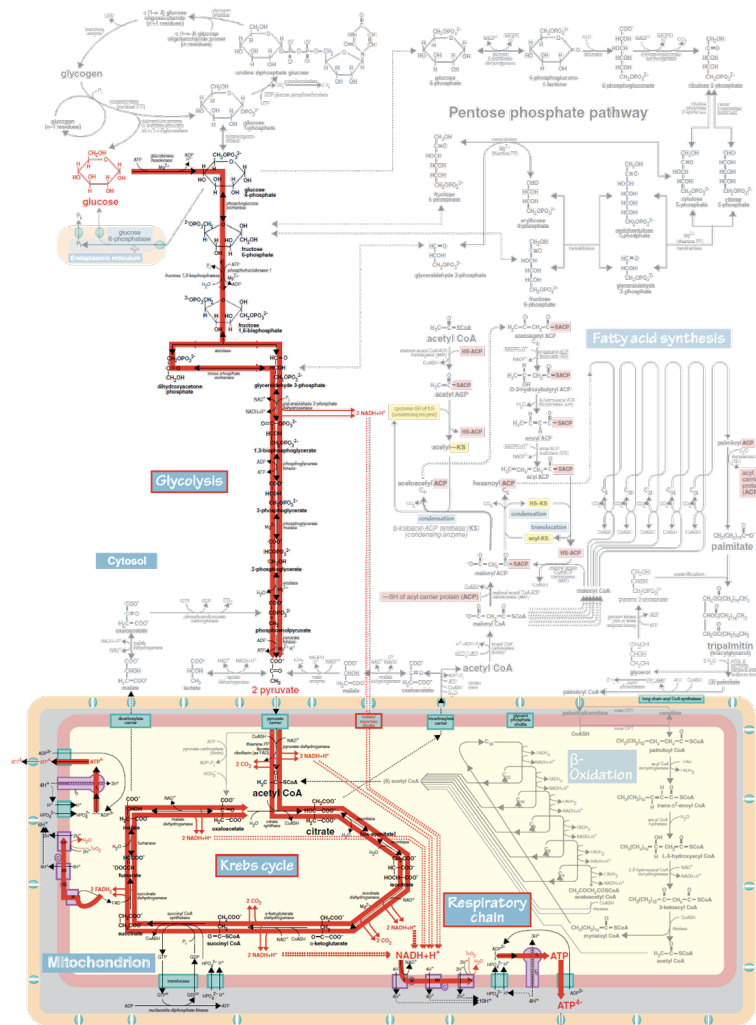
Let's go

Metro, bus, tramway  
See all maps

INRAE

From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research  
75<sup>th</sup> EAAP annual meeting / September 1-4, 2024 / Jaap van Milgen

# ➤ Finding your way in metabolism



Richard Wheeler

Salway (2017). Metabolism at a glance, 4<sup>th</sup> edition. Wiley Blackwell

INRAE

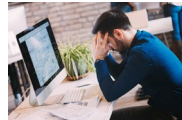
From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research

75<sup>th</sup> EAAP annual meeting / September 1-4, 2024 / Jaap van Milgen

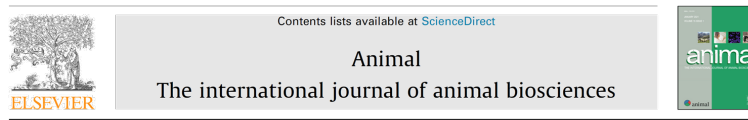
## ➤ Databases of metabolic pathways



What a lockdown can do to people ...



Animal 15 (2021) 100213



The role of energy, serine, glycine, and 1-carbon units in the cost of nitrogen excretion in mammals and birds

J. van Milgen

PEGASE, INRAE, Institut Agro, Le Clos, 35500 Saint Gilles, France



Animal 18 (2024) 101204



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

J. van Milgen

PEGASE, INRAE, Institut Agro, 35500 Saint Gilles, France



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

75<sup>th</sup> EAAP annual meeting / September 1-4, 2024 / Jaap van Milgen

# ➤ Rhea, an open database with curated chemical and transport reactions

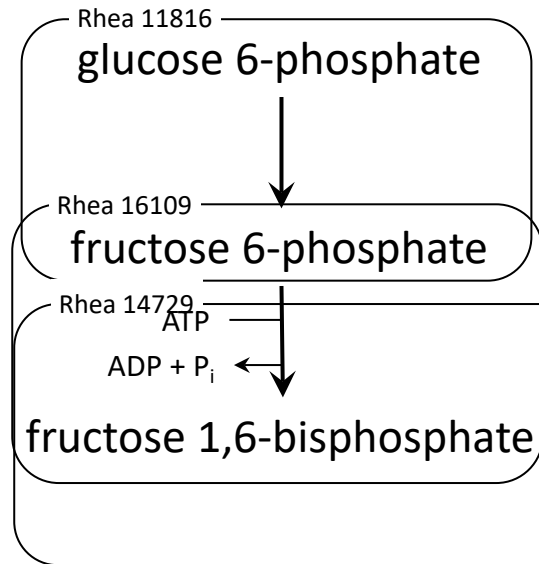
The screenshot displays the Rhea database interface in a web browser. The URL is <https://www.rhea-db.org/rhea/11816>. The page features a search bar with the text "ex:adenosine / CHEBI:29748 / RHEA:16505 / 4.1.3.40 / inchikey:~" and a "Search" button. Below the search bar are navigation links: "Examples", "Advanced search", and "Browse".

The main content area shows the reaction RHEA:11816. On the left, there are tabs for "Reaction information", "Reaction participants", "Cross-references", and "Publications". The reaction is depicted as a chemical equation:  $\alpha\text{-D-glucose 6-phosphate} = \beta\text{-D-fructose 6-phosphate}$ . Below the structures are "zoom" links. The "Enzymes" section lists: UniProtKB (51,261 proteins), Enzyme class (EC 5.3.1.9 glucose-6-phosphate isomerase), and GO Molecular Function (GO:0004347 glucose-6-phosphate isomerase activity).

The "Reaction participants" section is expanded, showing details for  $\alpha\text{-D-glucose 6-phosphate}$ : Name, Identifier (CHEBI:58225), Charge (-2), and Formula ( $C_6H_{11}O_6P_2$ ).

The footer contains logos for SIB, INRAE, ELIXIR Core Data Resource, and Global Core Biodata Resource, along with links for "License & Disclaimer" and "Privacy Policy".

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



Rhea - reaction knowledgebase

https://www.rhea-db.org/rhea/11816

ex:adenosine / CHEBI:29748 / RHEA:16505 / 4.1.3.40 / inchikey:XLYOFNOQVPJNP-UHFFFAC

Examples ▾ Advanced search Browse

Structure search Retrieve/ID mapping SPARQL Download Help Feedback

RHEA:11816

Reaction information

Reaction participants

Cross-references

Publications

α-D-glucose 6-phosphate β-D-fructose 6-phosphate

zoom zoom

Enzymes

UniProtKB 51,261 proteins

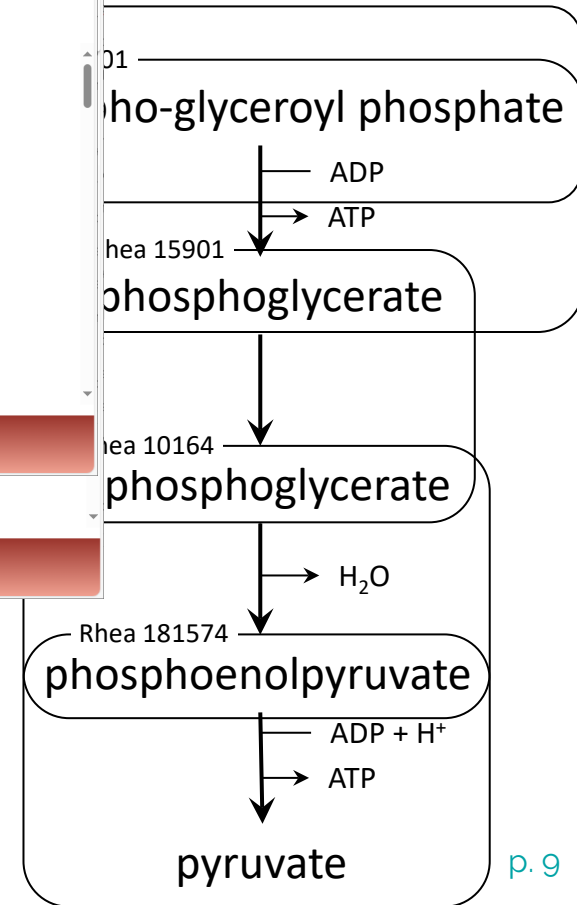
Enzyme class EC 5.3.1.9 glucose-6-phosphate isomerase

GO Molecular Function GO:0004347 glucose-6-phosphate isomerase activity

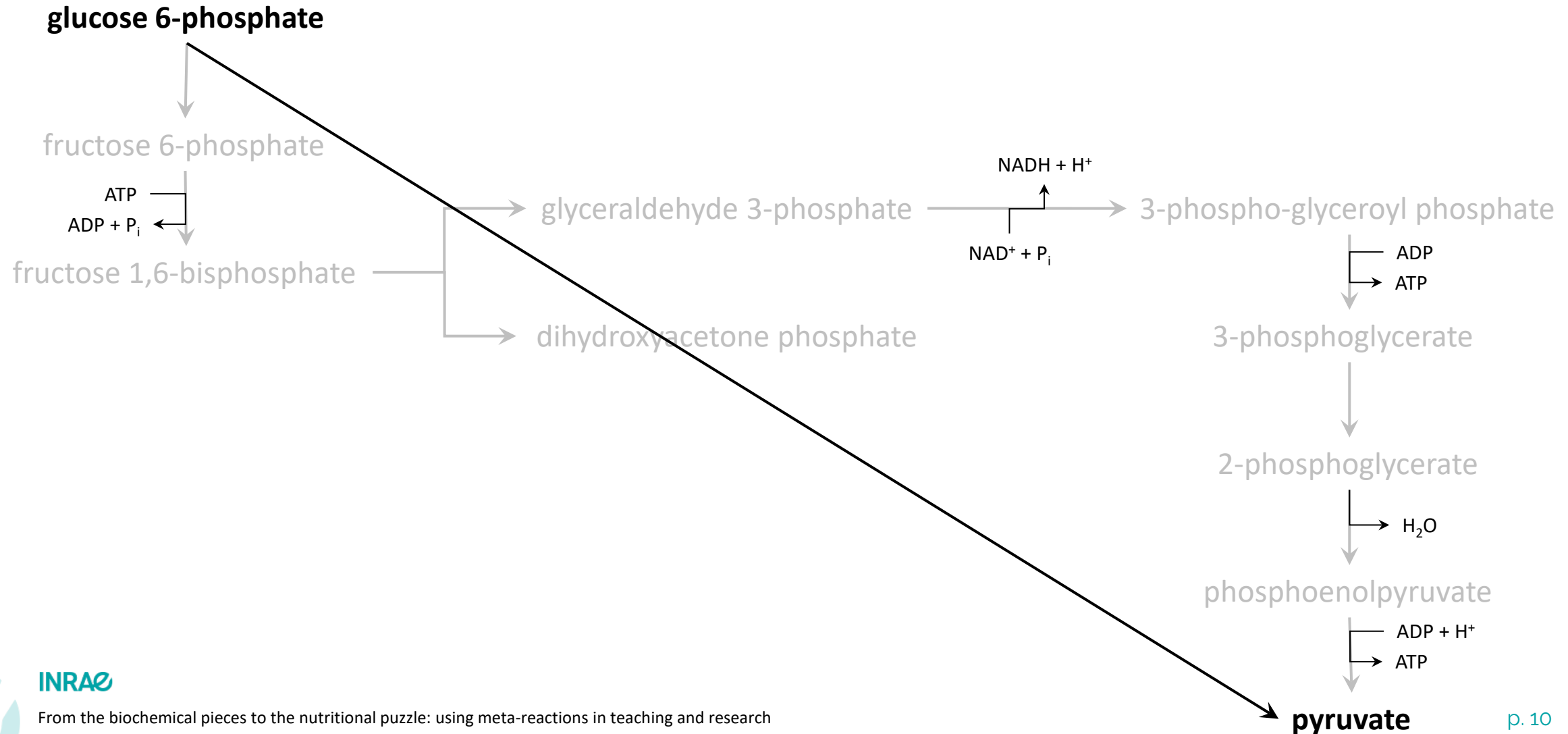
Reaction participants

GO Molecular Function GO:0003872 6-phosphofructokinase activity

License & Disclaimer Privacy Policy ELIXIR Core Data Resource Global Core Biodata Resource



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



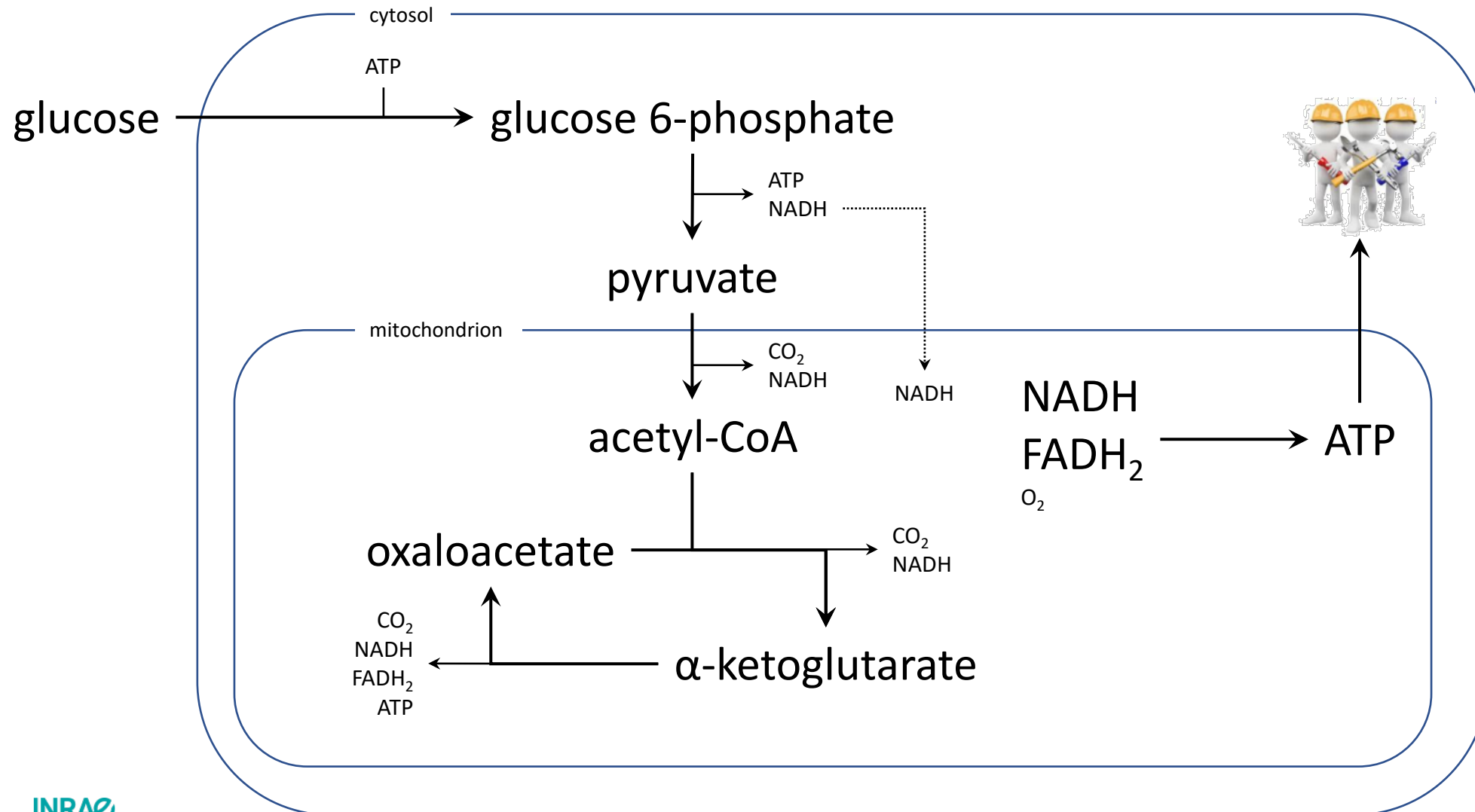


# ➤ A meta-reaction is the outcome reaction of a series of coupled individual (Rhea) reactions

| Meta-reaction | ReactionID | Flux | Reaction                                                                                                                      |
|---------------|------------|------|-------------------------------------------------------------------------------------------------------------------------------|
| 2             | 11816      | 1    | glucose 6-phosphate → beta-D-fructose 6-phosphate                                                                             |
| 2             | 16109      | 1    | ATP + beta-D-fructose 6-phosphate → ADP + H <sup>+</sup> + beta-D-fructose 1,6-bisphosphate                                   |
| 2             | 14729      | 1    | beta-D-fructose 1,6-bisphosphate → dihydroxyacetone phosphate + D-glyceraldehyde 3-phosphate                                  |
| 2             | 18585      | -1   | D-glyceraldehyde 3-phosphate ← dihydroxyacetone phosphate                                                                     |
| 2             | 10300      | 2    | P <sub>i</sub> + NAD <sup>+</sup> + D-glyceraldehyde 3-phosphate → NADH + H <sup>+</sup> + (2R)-3-phospho-glyceroyl phosphate |
| 2             | 14801      | -2   | ATP + (2R)-3-phosphoglycerate ← ADP + (2R)-3-phospho-glyceroyl phosphate                                                      |
| 2             | 15901      | -2   | (2R)-2-phosphoglycerate ← (2R)-3-phosphoglycerate                                                                             |
| 2             | 10164      | 2    | (2R)-2-phosphoglycerate → phosphoenolpyruvate + H <sub>2</sub> O                                                              |
| 2             | 18157      | -2   | pyruvate + ATP ← ADP + H <sup>+</sup> + phosphoenolpyruvate                                                                   |

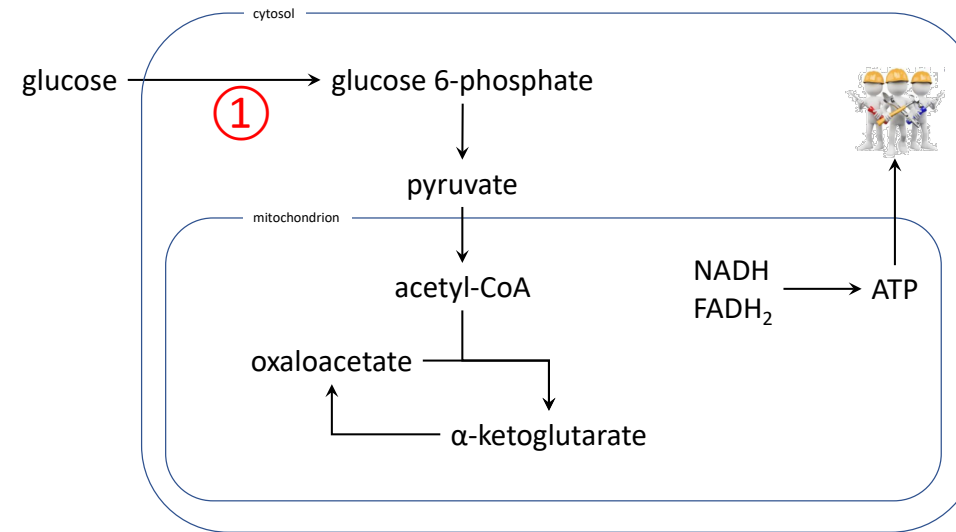


# ➤ A pathway is the outcome reaction of a series of coupled meta-reactions





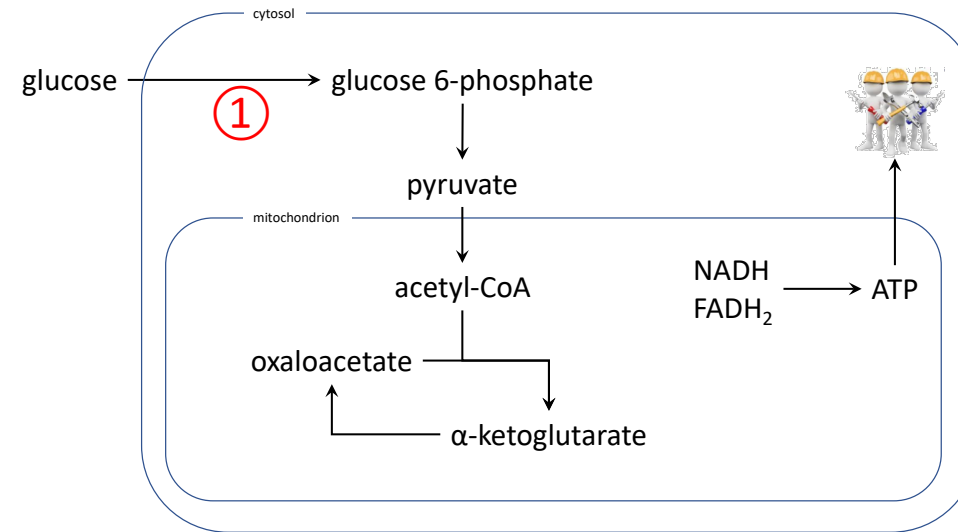
# ➤ Constructing pathways using the Excel tool



| 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                   |            |          |             |               |      |
|                                       |            |          |             |               |      |
|                                       |            |          |             |               |      |
|                                       |            |          |             |               |      |
|                                       |            |          |             |               |      |
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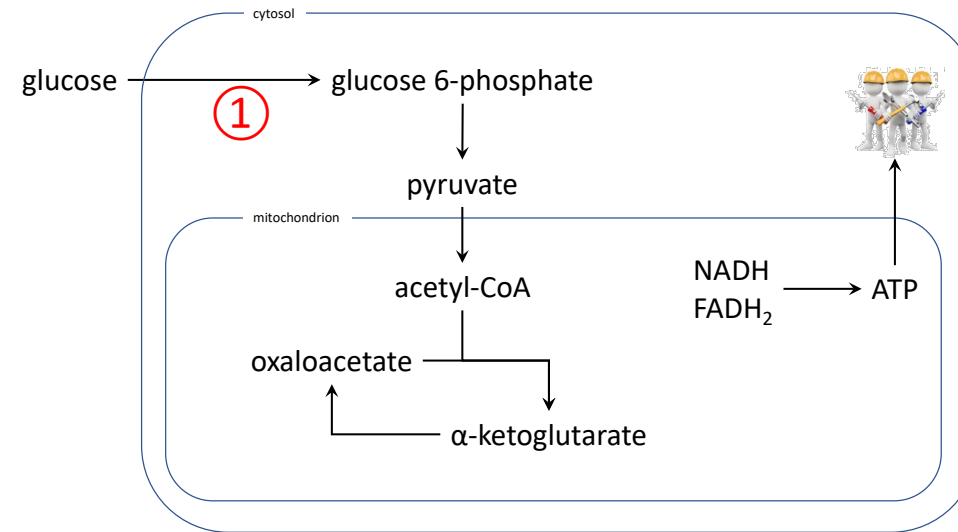
# > Constructing pathways using the Excel tool



| No meta-reactions selected yet |            |          |             |               |      |
|--------------------------------|------------|----------|-------------|---------------|------|
| Type                           | Metabolite | As a ... | To/From ... | Meta-reaction | Flux |
| carbohydrates                  | fructose   |          |             |               |      |
|                                | galactose  |          |             |               |      |
|                                | glucose    |          |             |               |      |
|                                | glycogen   |          |             |               |      |
|                                | lactose    |          |             |               |      |
|                                | sucrose    |          |             |               |      |
|                                |            |          |             |               |      |
|                                |            |          |             |               |      |
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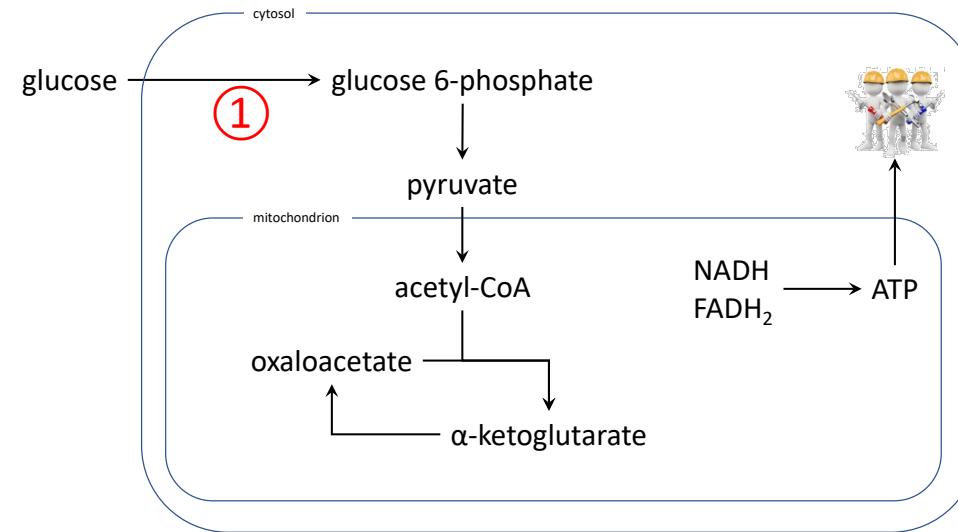
# ➤ Constructing pathways using the Excel tool



| No meta-reactions selected yet |            |           |             |               |      |
|--------------------------------|------------|-----------|-------------|---------------|------|
| Type                           | Metabolite | As a ...  | To/From ... | Meta-reaction | Flux |
| carbohydrates                  | glucose    | substrate |             |               |      |
|                                |            | product   |             |               |      |
|                                |            |           |             |               |      |
|                                |            |           |             |               |      |
|                                |            |           |             |               |      |
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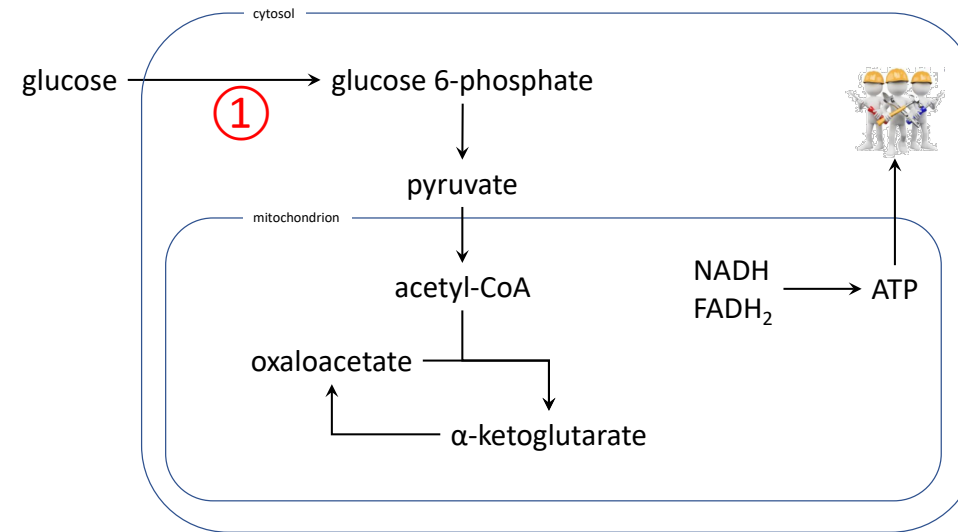
# ➤ Constructing pathways using the Excel tool



| 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 |               |      |  |
|                                |            |           |                                    |               |      |  |
|                                |            |           |                                    |               |      |  |
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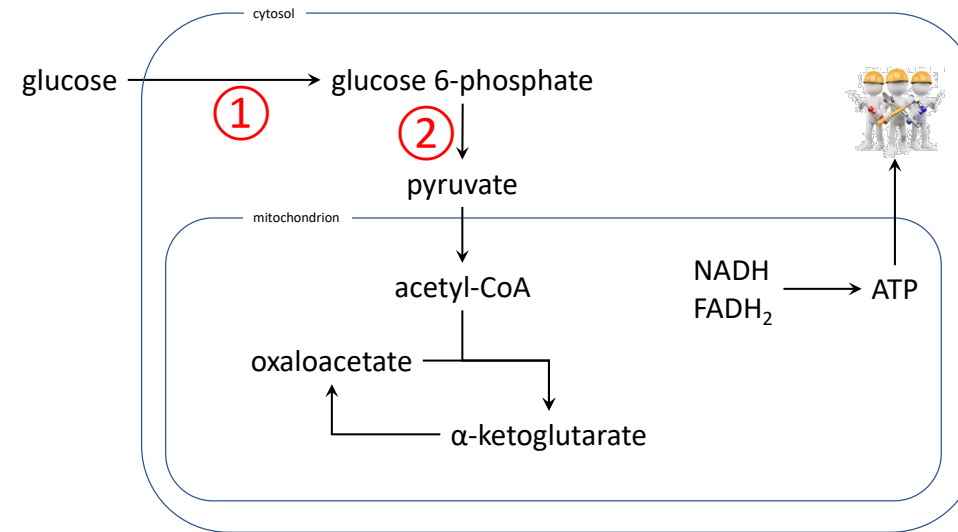
# ➤ Constructing pathways using the Excel tool



| 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 <sup>+</sup> |      |
|                         |            |           |                     |                                                            |      |
|                         |            |           |                     |                                                            |      |
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# > Constructing pathways using the Excel tool

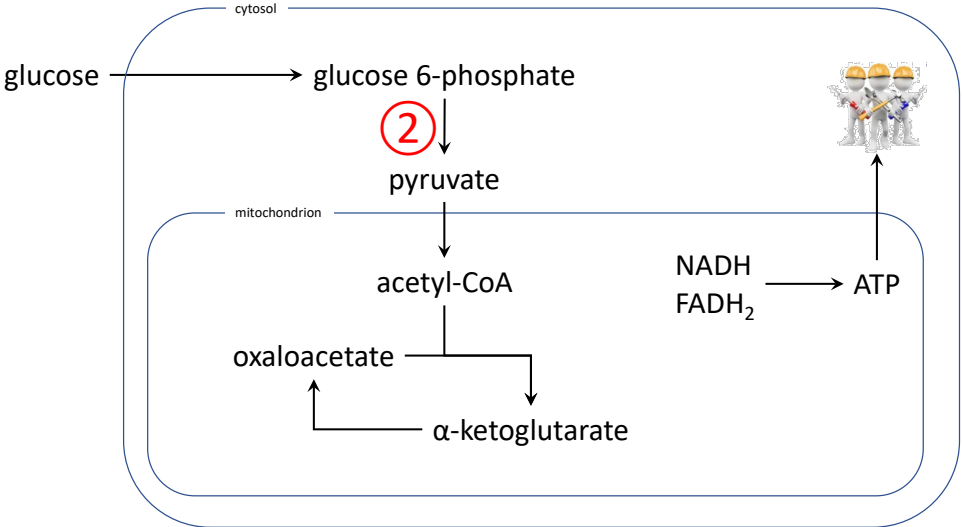


glucose + ATP → **glucose 6-phosphate** + ADP + H<sup>+</sup> (Q = 30 kJ)

| Type          | Metabolite | As a ...  | To/From ...         | Meta-reaction                                              | Flux |
|---------------|------------|-----------|---------------------|------------------------------------------------------------|------|
| carbohydrates | glucose    | substrate | glucose 6-phosphate | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup> | 1    |
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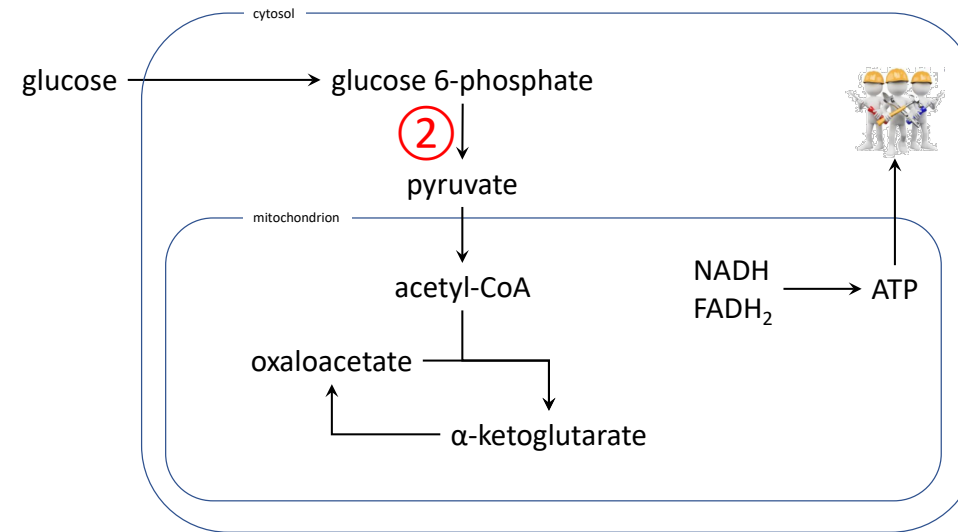
➤ Constructing pathways using the Excel tool



| glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup> (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 <sup>+</sup>                                                                                           | 1    |
| intermediate metabolites                                               | glucose 6-phosphate | substrate | pyruvate (glycolysis) | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis) |      |
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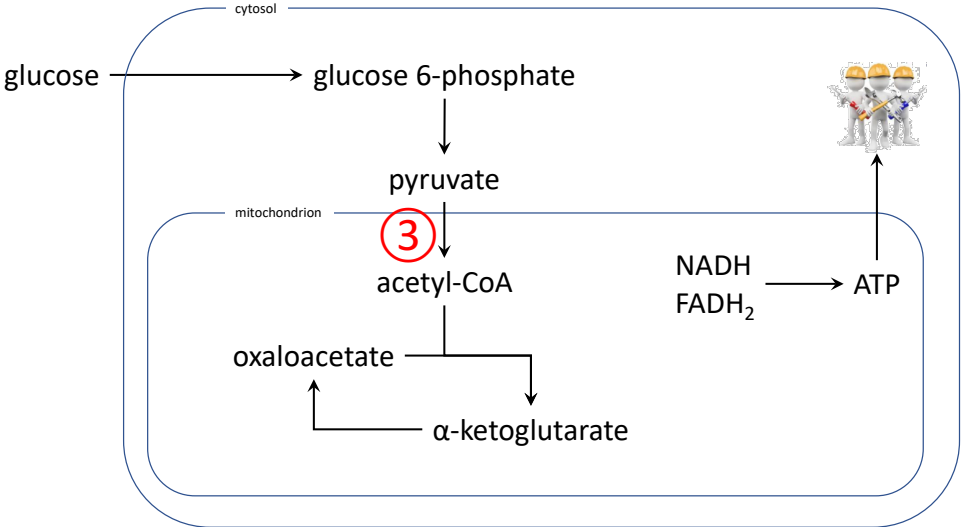
## ➤ Constructing pathways using the Excel tool



| Type                     | Metabolite          | As a ...  | To/From ...           | Meta-reaction                                                                                                                                        | Flux |
|--------------------------|---------------------|-----------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| carbohydrates            | glucose             | substrate | glucose 6-phosphate   | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                           | 1    |
| intermediate metabolites | glucose 6-phosphate | substrate | pyruvate (glycolysis) | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis) | 1    |
|                          |                     |           |                       |                                                                                                                                                      |      |
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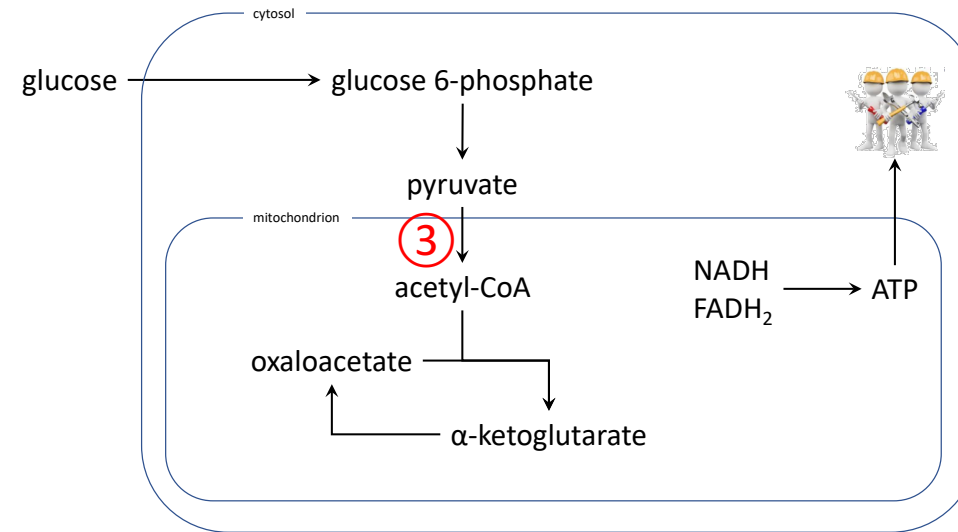
➤ Constructing pathways using the Excel tool



| glucose + 2 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 2 ATP + 2 NADH + 2 H <sup>+</sup> + 2 H <sub>2</sub> O (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 <sup>+</sup>                                                                                           | 1    |
| intermediate metabolites                                                                                                                   | glucose 6-phosphate | substrate | pyruvate (glycolysis) | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis) | 1    |
| intermediate metabolites                                                                                                                   | pyruvate            | substrate | acetyl-CoA            | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                              |      |
|                                                                                                                                            |                     |           |                       |                                                                                                                                                      |      |
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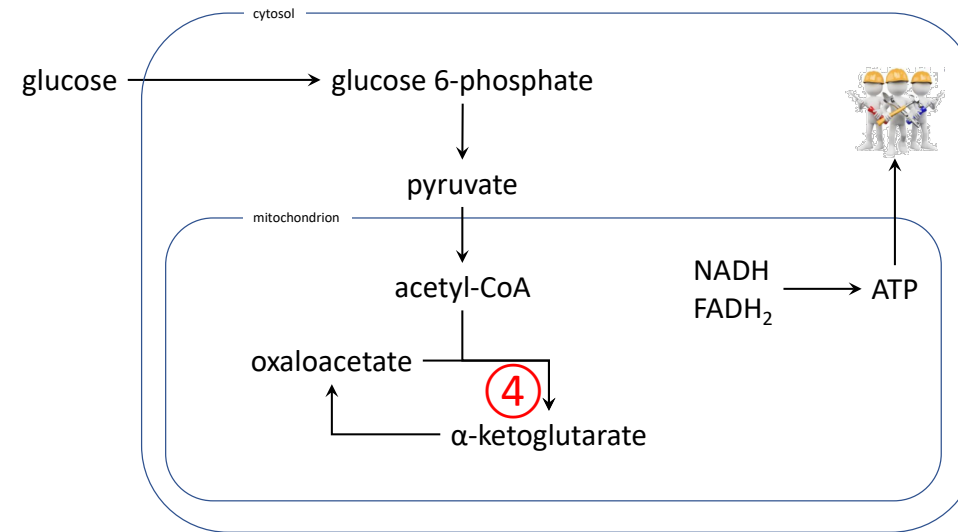


## ➤ Constructing pathways using the Excel tool



| glucose + 2 ADP + 2 P <sub>i</sub> + 2 CoA + 4 NAD <sup>+</sup> → 2 acetyl-CoA + 2 ATP + 4 NADH + 2 H <sup>+</sup> + 2 H <sub>2</sub> O + 2 CO <sub>2</sub> (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 <sup>+</sup>                                                                                           | 1    |
| intermediate metabolites                                                                                                                                                      | glucose 6-phosphate | substrate | pyruvate (glycolysis) | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis) | 1    |
| intermediate metabolites                                                                                                                                                      | pyruvate            | substrate | acetyl-CoA            | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                              | 2    |
|                                                                                                                                                                               |                     |           |                       |                                                                                                                                                      |      |
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## ➤ Constructing pathways using the Excel tool

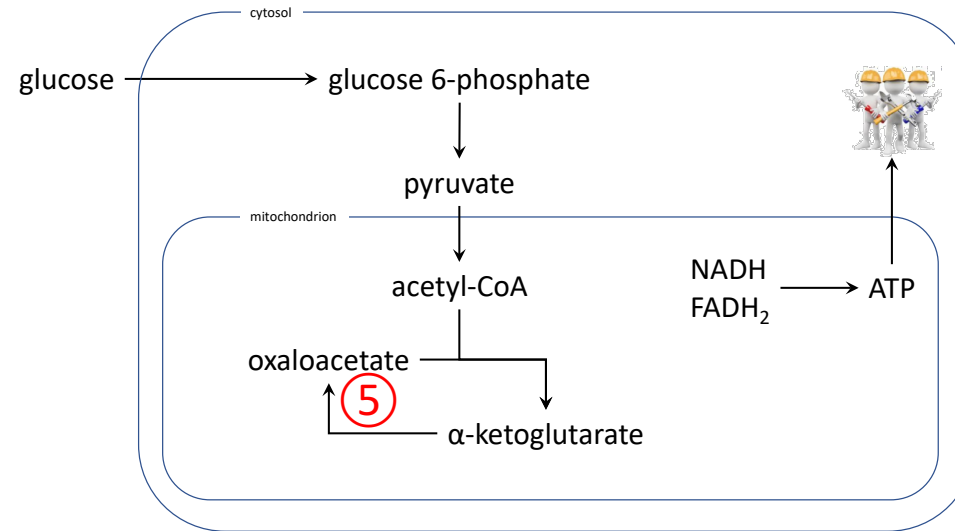


**glucose + 2 oxaloacetate + 2 ADP + 2 P<sub>i</sub> + 6 NAD<sup>+</sup> → 2 α-ketoglutarate + 2 ATP + 6 NADH + 4 H<sup>+</sup> + 4 CO<sub>2</sub> (Q = 42 kJ)**

| Type                     | Metabolite          | As a ...  | To/From ...                                     | Meta-reaction                                                                                                                                        | Flux |
|--------------------------|---------------------|-----------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| carbohydrates            | glucose             | substrate | glucose 6-phosphate                             | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                           | 1    |
| intermediate metabolites | glucose 6-phosphate | substrate | pyruvate (glycolysis)                           | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis) | 1    |
| intermediate metabolites | pyruvate            | substrate | acetyl-CoA                                      | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                              | 2    |
| intermediate metabolites | acetyl-CoA          | substrate | with oxaloacetate → α-ketoglutarate (TCA cycle) | acetyl-CoA + oxaloacetate + NAD <sup>+</sup> + H <sub>2</sub> O → α-ketoglutarate + NADH + H <sup>+</sup> + CoA + CO <sub>2</sub> (TCA cycle)        | 2    |
|                          |                     |           |                                                 |                                                                                                                                                      |      |
|                          |                     |           |                                                 |                                                                                                                                                      |      |
|                          |                     |           |                                                 |                                                                                                                                                      |      |
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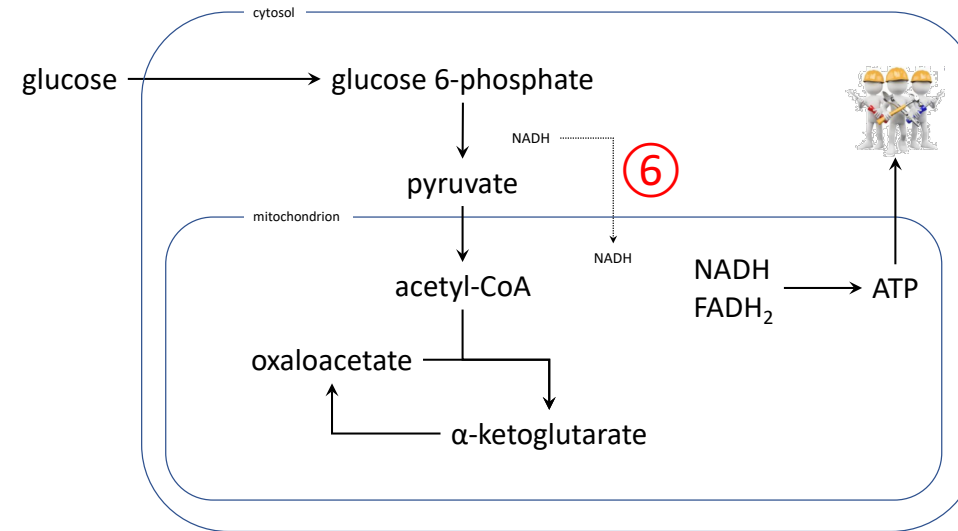
## ➤ Constructing pathways using the Excel tool



| Type                     | Metabolite          | As a ...  | To/From ...                                     | Meta-reaction                                                                                                                                                                                                  | Flux |
|--------------------------|---------------------|-----------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| carbohydrates            | glucose             | substrate | glucose 6-phosphate                             | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                                                                                     | 1    |
| intermediate metabolites | glucose 6-phosphate | substrate | pyruvate (glycolysis)                           | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis)                                                           | 1    |
| intermediate metabolites | pyruvate            | substrate | acetyl-CoA                                      | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                                                                                        | 2    |
| intermediate metabolites | acetyl-CoA          | substrate | with oxaloacetate → α-ketoglutarate (TCA cycle) | acetyl-CoA + oxaloacetate + NAD <sup>+</sup> + H <sub>2</sub> O → α-ketoglutarate + NADH + H <sup>+</sup> + CoA + CO <sub>2</sub> (TCA cycle)                                                                  | 2    |
| intermediate metabolites | α-ketoglutarate     | substrate | oxaloacetate (TCA cycle)                        | α-ketoglutarate + 0.75 ADP + 0.75 P <sub>i</sub> + 2 NAD <sup>+</sup> + FAD + 1.25 H <sub>2</sub> O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H <sup>+</sup> + FADH <sub>2</sub> + CO <sub>2</sub> (TCA cycle) | 2    |
|                          |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                          |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                          |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                          |                     |           |                                                 |                                                                                                                                                                                                                |      |
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|                          |                     |           |                                                 |                                                                                                                                                                                                                |      |



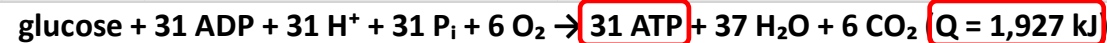
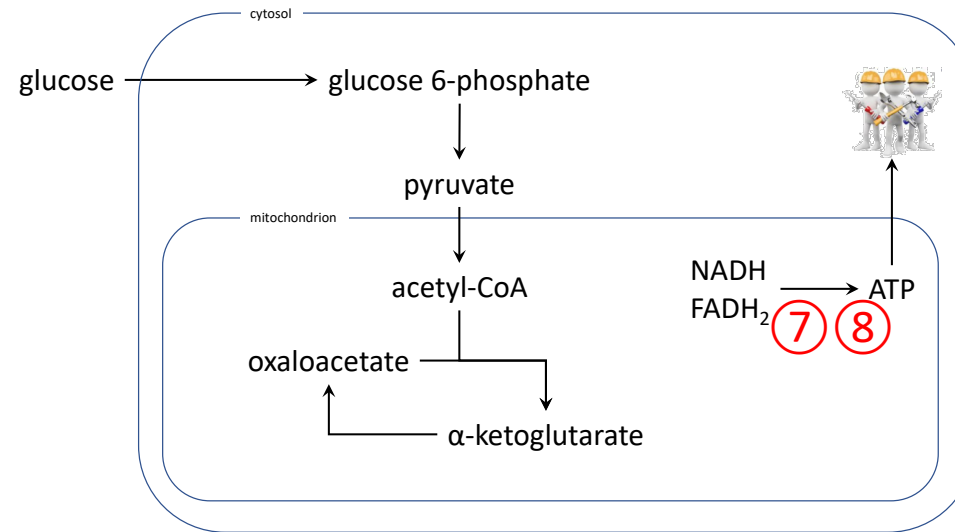
## ➤ Constructing pathways using the Excel tool



**glucose + 3 ADP + 3 H<sub>2</sub>O + 3 P<sub>i</sub> + 2 FAD + 10 NAD<sup>+</sup> → 3 ATP + 2 FADH<sub>2</sub> + 10 NADH + 5 H<sup>+</sup> + 6 CO<sub>2</sub> (Q not available)**

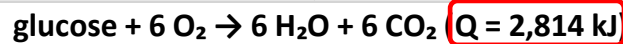
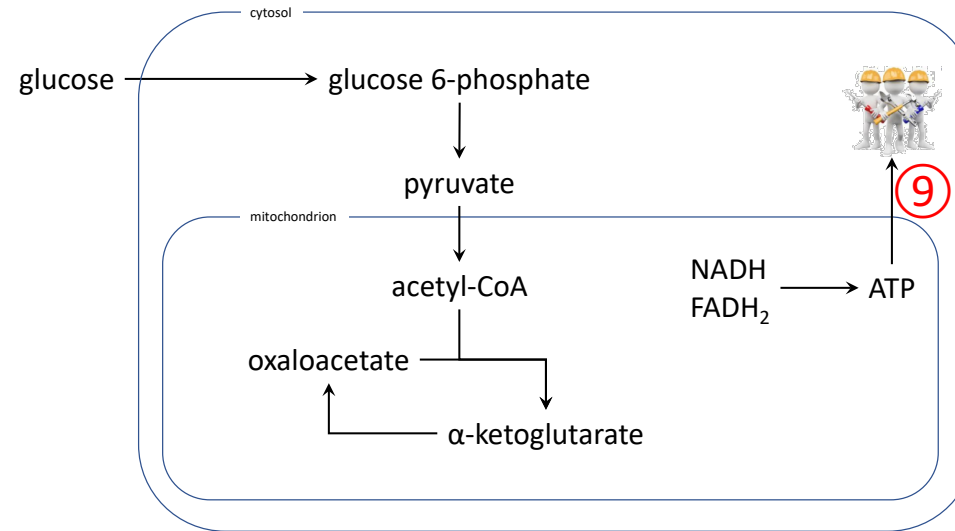
| Type                                  | Metabolite          | As a ...  | To/From ...                                     | Meta-reaction                                                                                                                                                                                                  | Flux |
|---------------------------------------|---------------------|-----------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| carbohydrates                         | glucose             | substrate | glucose 6-phosphate                             | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                                                                                     | 1    |
| intermediate metabolites              | glucose 6-phosphate | substrate | pyruvate (glycolysis)                           | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis)                                                           | 1    |
| intermediate metabolites              | pyruvate            | substrate | acetyl-CoA                                      | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                                                                                        | 2    |
| intermediate metabolites              | acetyl-CoA          | substrate | with oxaloacetate → α-ketoglutarate (TCA cycle) | acetyl-CoA + oxaloacetate + NAD <sup>+</sup> + H <sub>2</sub> O → α-ketoglutarate + NADH + H <sup>+</sup> + CoA + CO <sub>2</sub> (TCA cycle)                                                                  | 2    |
| intermediate metabolites              | α-ketoglutarate     | substrate | oxaloacetate (TCA cycle)                        | α-ketoglutarate + 0.75 ADP + 0.75 P <sub>i</sub> + 2 NAD <sup>+</sup> + FAD + 1.25 H <sub>2</sub> O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H <sup>+</sup> + FADH <sub>2</sub> + CO <sub>2</sub> (TCA cycle) | 2    |
| electron transport and ATP metabolism | NADH                | substrate | NADH cytosol → NADH mitochondrion               | 0.25 ATP + 0.25 H <sub>2</sub> O → 0.25 ADP + 0.25 P <sub>i</sub> + 0.25 H <sup>+</sup> (malate - aspartate shuttle)                                                                                           | 2    |
|                                       |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                                       |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                                       |                     |           |                                                 |                                                                                                                                                                                                                |      |
|                                       |                     |           |                                                 |                                                                                                                                                                                                                |      |

## ➤ Constructing pathways using the Excel tool



| Type                                  | Metabolite          | As a ...  | To/From ...                                     | Meta-reaction                                                                                                                                                                                                  | Flux |
|---------------------------------------|---------------------|-----------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| carbohydrates                         | glucose             | substrate | glucose 6-phosphate                             | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                                                                                     | 1    |
| intermediate metabolites              | glucose 6-phosphate | substrate | pyruvate (glycolysis)                           | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis)                                                           | 1    |
| intermediate metabolites              | pyruvate            | substrate | acetyl-CoA                                      | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                                                                                        | 2    |
| intermediate metabolites              | acetyl-CoA          | substrate | with oxaloacetate → α-ketoglutarate (TCA cycle) | acetyl-CoA + oxaloacetate + NAD <sup>+</sup> + H <sub>2</sub> O → α-ketoglutarate + NADH + H <sup>+</sup> + CoA + CO <sub>2</sub> (TCA cycle)                                                                  | 2    |
| intermediate metabolites              | α-ketoglutarate     | substrate | oxaloacetate (TCA cycle)                        | α-ketoglutarate + 0.75 ADP + 0.75 P <sub>i</sub> + 2 NAD <sup>+</sup> + FAD + 1.25 H <sub>2</sub> O → oxaloacetate + 0.75 ATP + 2 NADH + 0.25 H <sup>+</sup> + FADH <sub>2</sub> + CO <sub>2</sub> (TCA cycle) | 2    |
| electron transport and ATP metabolism | NADH                | substrate | NADH cytosol → NADH mitochondrion               | 0.25 ATP + 0.25 H <sub>2</sub> O → 0.25 ADP + 0.25 P <sub>i</sub> + 0.25 H <sup>+</sup> (malate - aspartate shuttle)                                                                                           | 2    |
| electron transport and ATP metabolism | NADH                | substrate | ATP (oxidative phosphorylation)                 | 2.5 ADP + 2.5 P <sub>i</sub> + NADH + 3.5 H <sup>+</sup> + 0.5 O <sub>2</sub> → 2.5 ATP + NAD <sup>+</sup> + 3.5 H <sub>2</sub> O (oxidative phosphorylation)                                                  | 10   |
| electron transport and ATP metabolism | FADH <sub>2</sub>   | substrate | ATP (oxidative phosphorylation)                 | 1.5 ADP + 1.5 P <sub>i</sub> + 0.5 H <sup>+</sup> + FADH <sub>2</sub> + 0.5 O <sub>2</sub> → 1.5 ATP + FAD + 2.5 H <sub>2</sub> O (oxidative phosphorylation)                                                  | 2    |
|                                       |                     |           |                                                 |                                                                                                                                                                                                                |      |

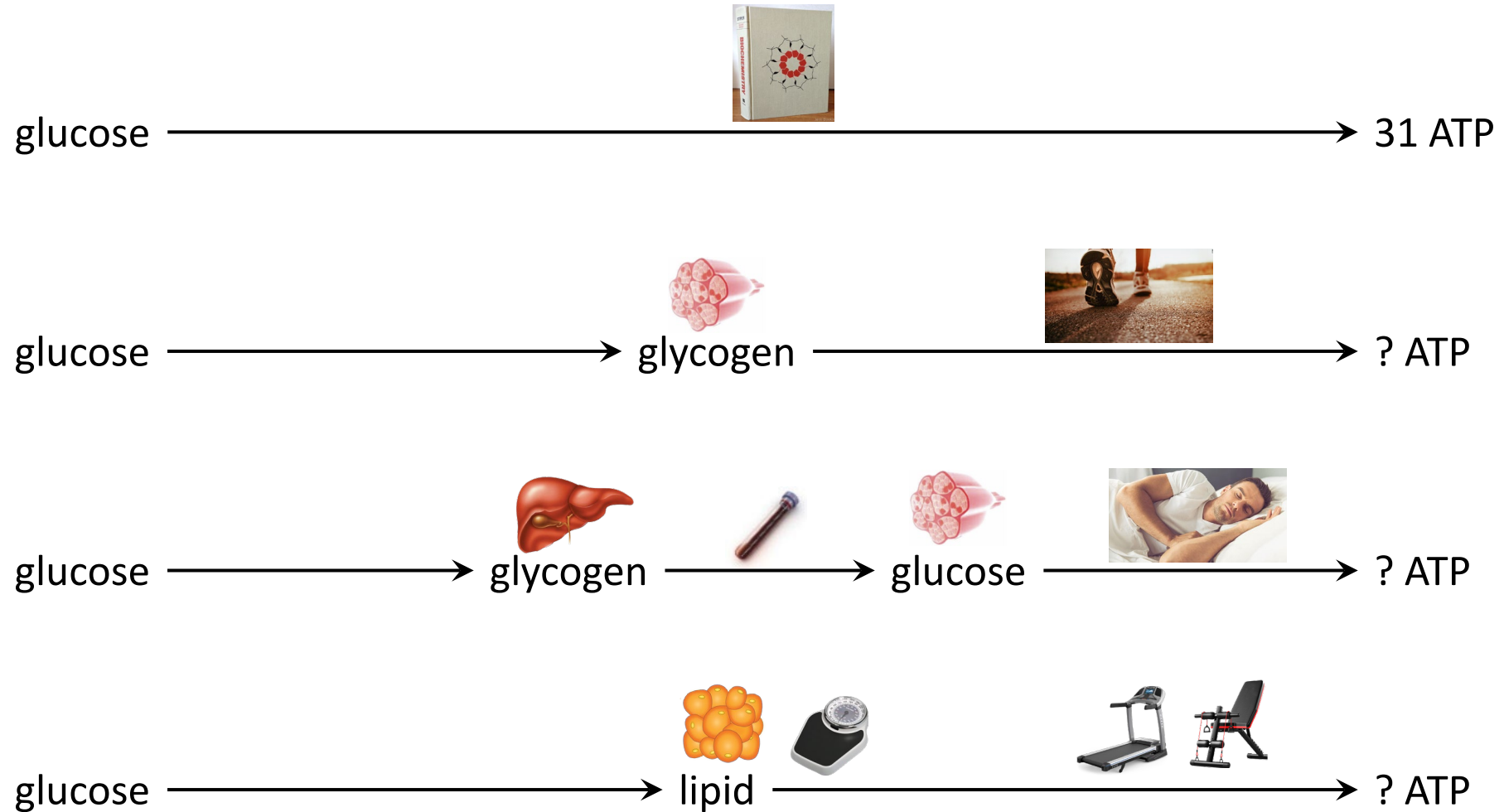
# ➤ Constructing pathways using the Excel tool



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

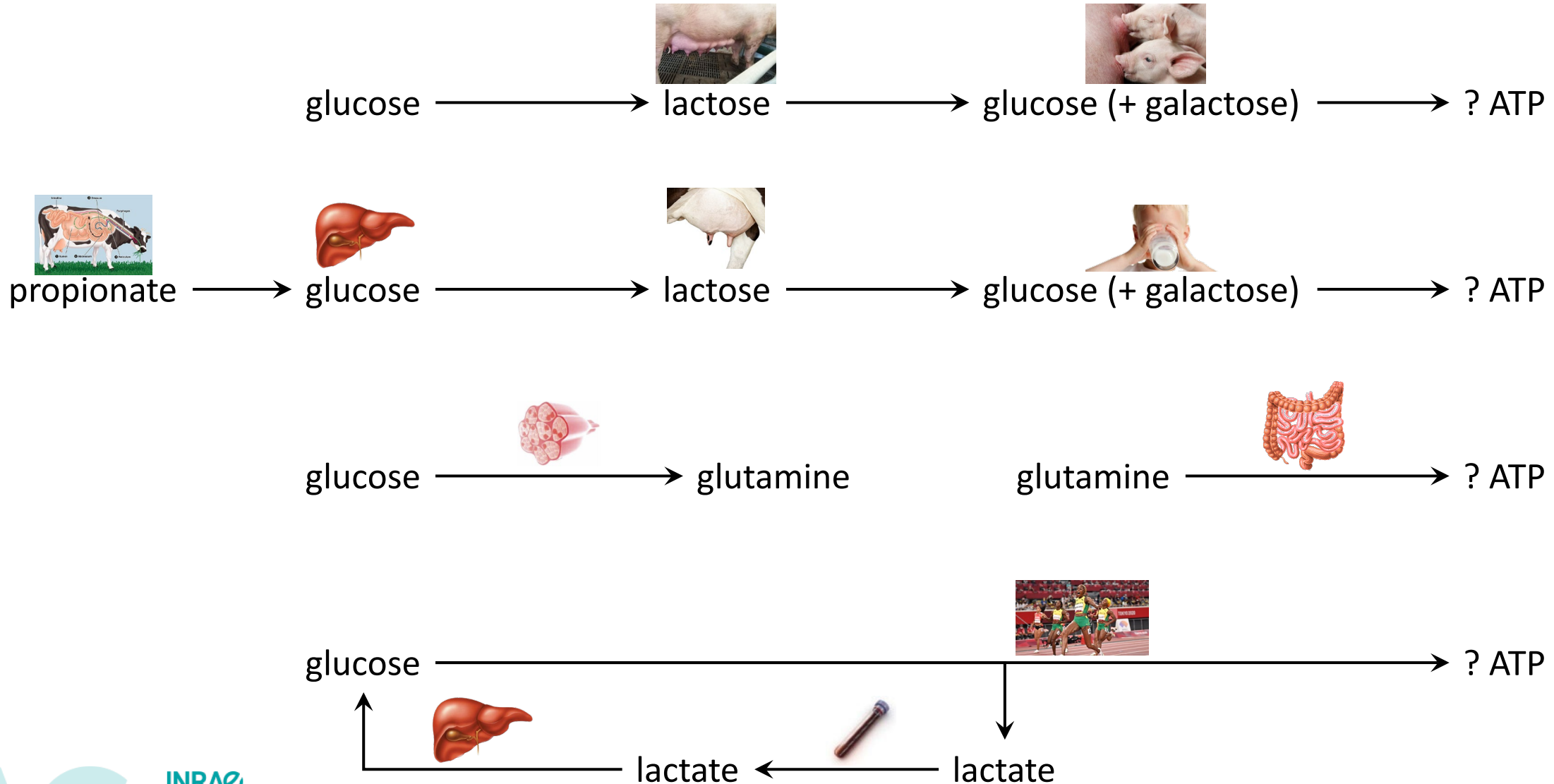


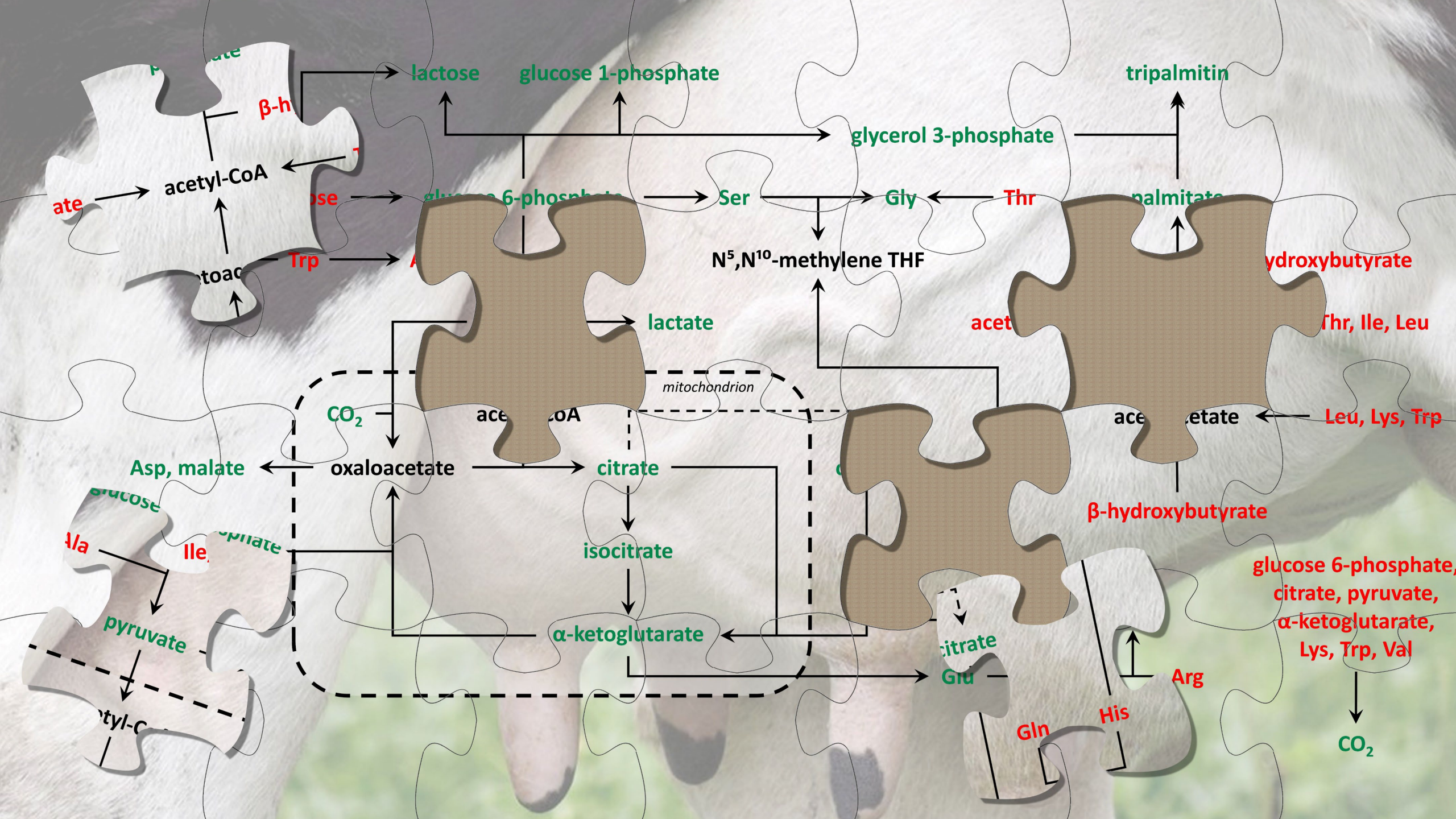
# ➤ Using meta-reactions to teach nutritional biochemistry





## ➤ Using meta-reactions to teach nutritional biochemistry







# ➤ Using meta-reactions to balance metabolites in the mammary gland

J. Dairy Sci. 92:6068–6082

doi:10.3168/jds.2009-2018

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## Whole-body glucose metabolism and mammary energetic nutrient metabolism in lactating dairy cows receiving digestive infusions of casein and propionic acid

S. Lemosquet,\*† G. Raggio,‡ G. E. Lobley,§ H. Rulquin,\*† J. Guinard-Flament,\*† and H. Lapierre#

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†Agrocampus Ouest, UMR1080 Dairy Production, F-35000 Rennes, France

‡Organic Dairy Research Centre, Guelph University, Alfred campus, 31 rue St-Paul, PO Box 580, Alfred, Ontario K0B 1A0, Canada

§Rowett Institute of Nutrition and Health, University of Aberdeen, Aberdeen AB21 9SB, United Kingdom

#Dairy and Swine Research and Development Centre, Agriculture and Agri-Food Canada, STN Lennoxville, Sherbrooke, Québec J1M 1Z3, Canada

J. Dairy Sci. 89:4340–4351

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## Effect of Casein and Propionate Supply on Mammary Protein Metabolism in Lactating Dairy Cows

G. Raggio,\* S. Lemosquet,† G. E. Lobley,‡ H. Rulquin,† and H. Lapierre§<sup>1</sup>

\*Department of Animal Science, Université Laval, Québec, Québec, Canada, G1K 7P4

†Institut National de la Recherche Agronomique, Unité Mixte de Recherches Production du Lait, 35590 Saint-Gilles, France

‡Rowett Research Institute, Aberdeen, UK, AB21 9SB

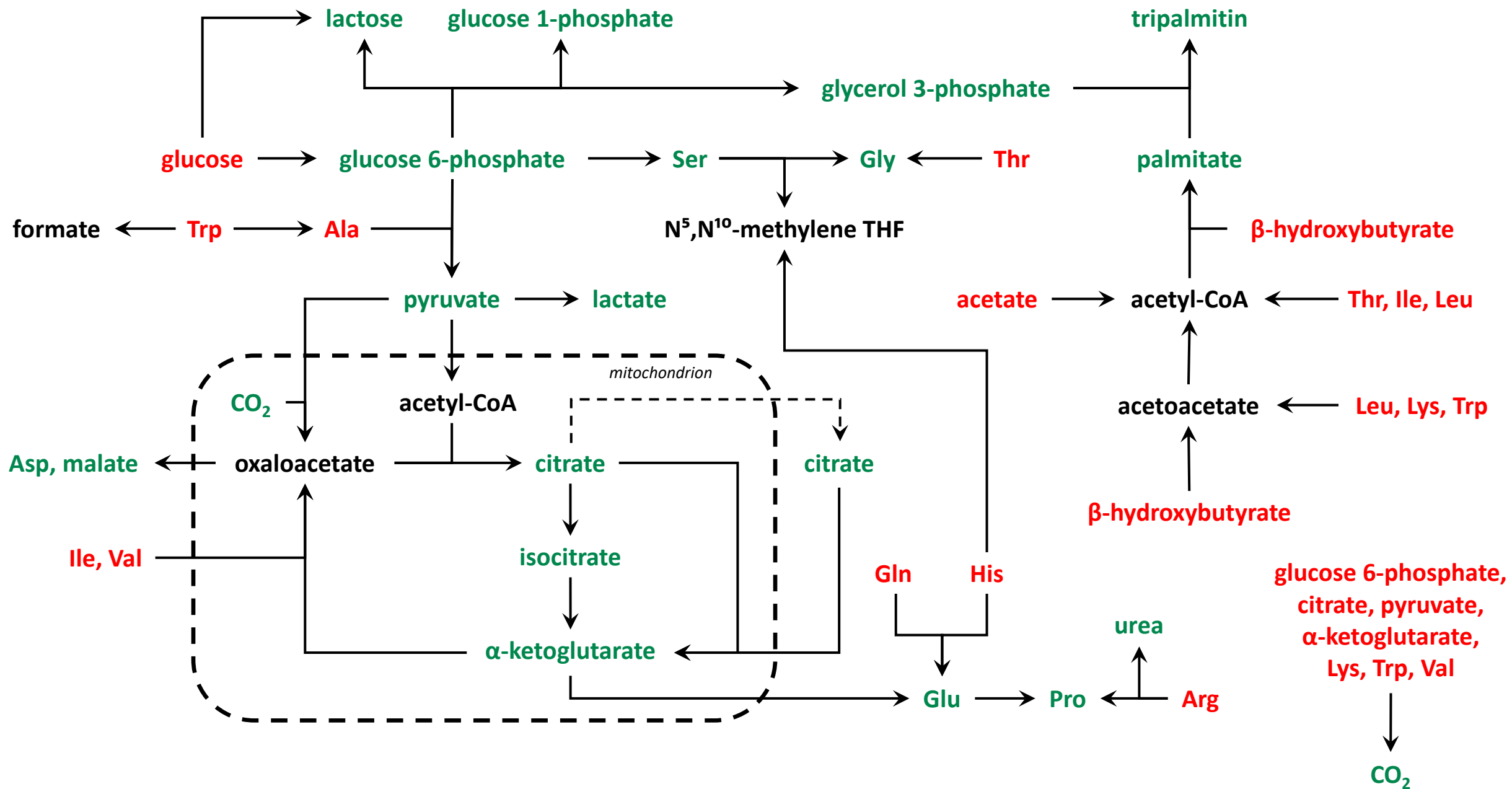
§Dairy and Swine Research & Development Centre, Agriculture and Agri-Food Canada, Sherbrooke, Quebec, Canada, J1M 1Z3

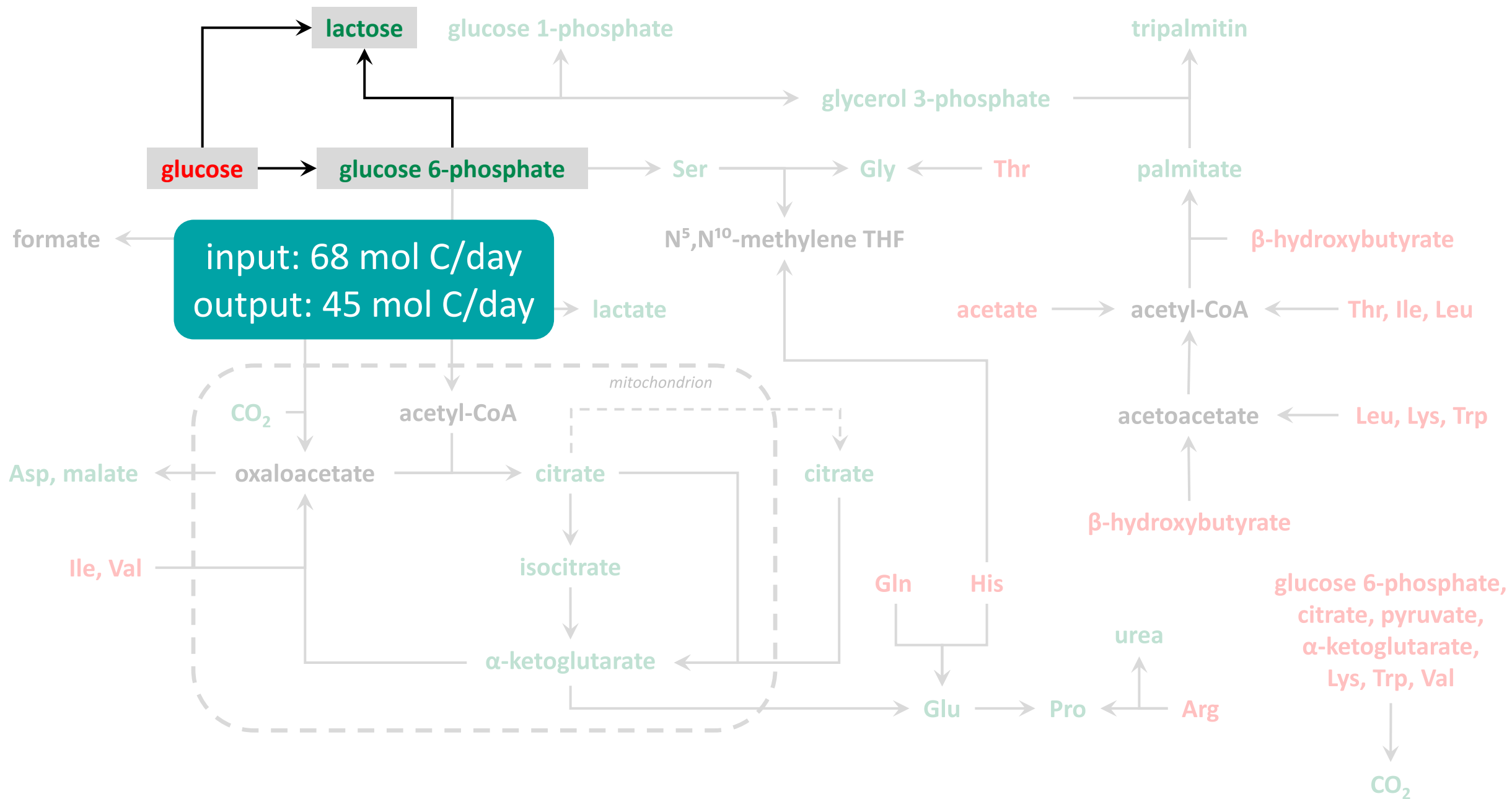
| Substrate (input) | mol/d | Product (output)            | mol/d |
|-------------------|-------|-----------------------------|-------|
| Glucose           | 11.36 | Lactose                     | 3.73  |
| Acetate           | 24.48 | Tripalmitin (C16:0)         | 0.73  |
| β-Hydroxybutyrate | 4.03  | Palmitate (C16:0)           | 0.12  |
| Alanine           | 0.02  | Aspartate                   | 0.16  |
| Arginine          | 0.21  | Cysteine                    | 0.01  |
| Glutamine         | 0.04  | Glutamate                   | 0.04  |
| Histidine         | 0.01  | Glycine                     | 0.22  |
| Isoleucine        | 0.10  | Proline                     | 0.54  |
| Leucine           | 0.10  | Serine                      | 0.38  |
| Lysine            | 0.12  | Lactate                     | 0.29  |
| Threonine         | 0.01  | Citrate                     | 0.27  |
| Tryptophan        | 0.001 | Isocitrate                  | 0.01  |
| Valine            | 0.12  | Glucose 1-phosphate         | 0.001 |
| O <sub>2</sub>    | 31.68 | Glucose 6-phosphate         | 0.001 |
|                   |       | Glycerol 3-phosphate        | 0.001 |
|                   |       | Malate                      | 0.01  |
|                   |       | Pyruvate                    | 0.001 |
|                   |       | α-Ketoglutarate             | 0.002 |
|                   |       | Urea (blood)                | 0.02  |
|                   |       | Non-protein nitrogen (milk) | 0.39  |
|                   |       | CO <sub>2</sub>             | 44.64 |

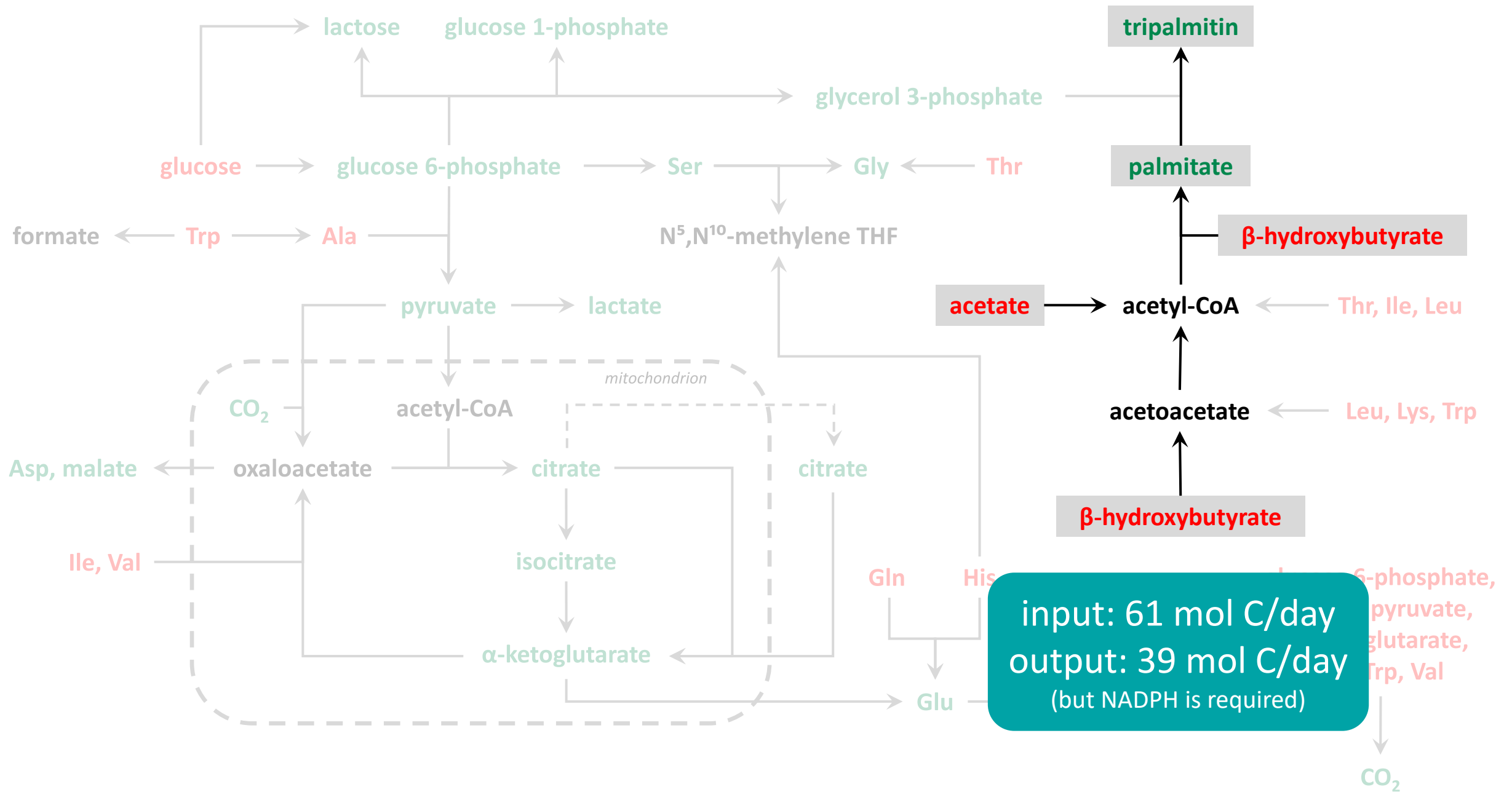
INRAE

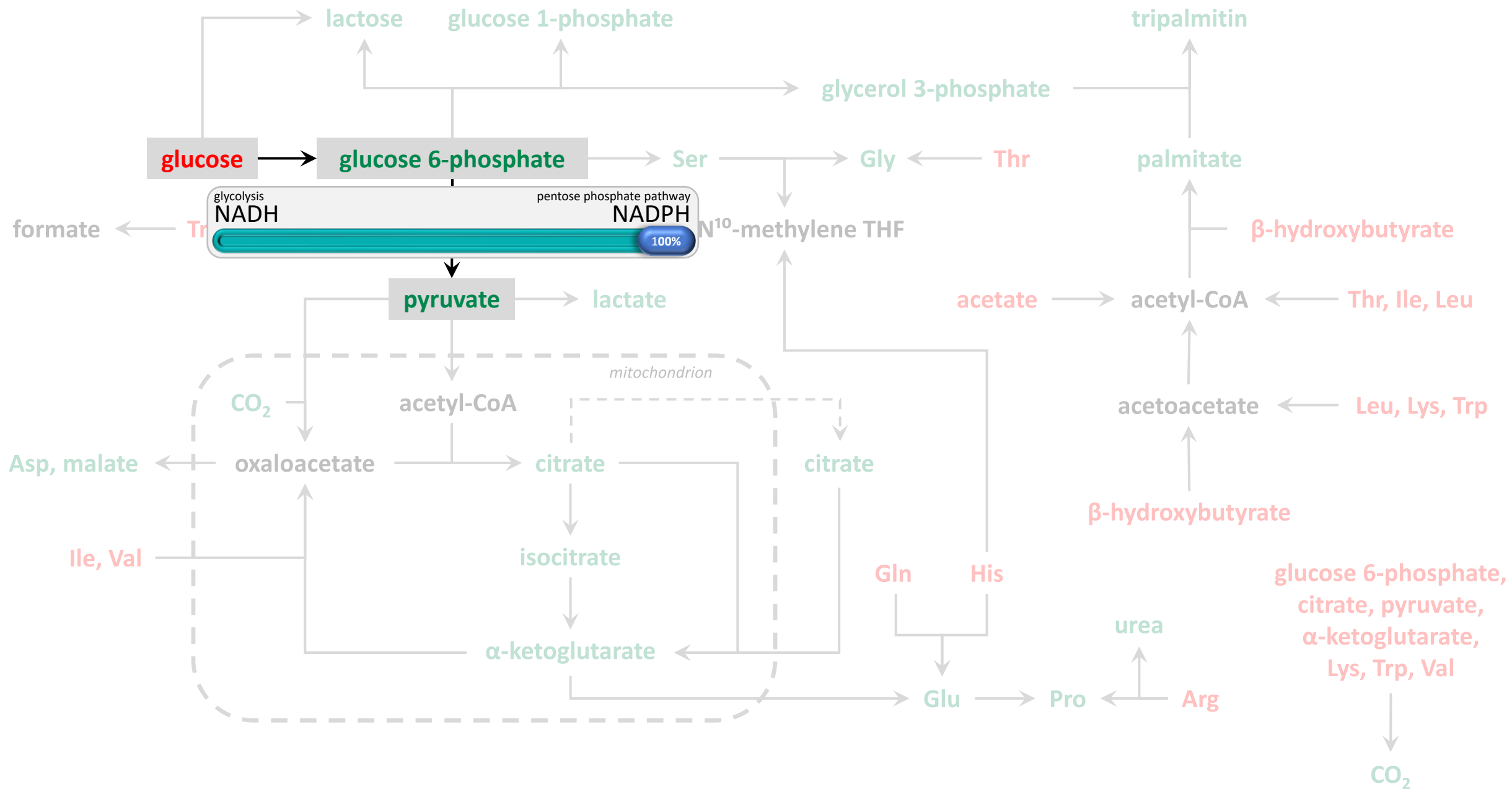
From the biochemical pieces to the nutritional puzzle: using meta-reactions in teaching and research

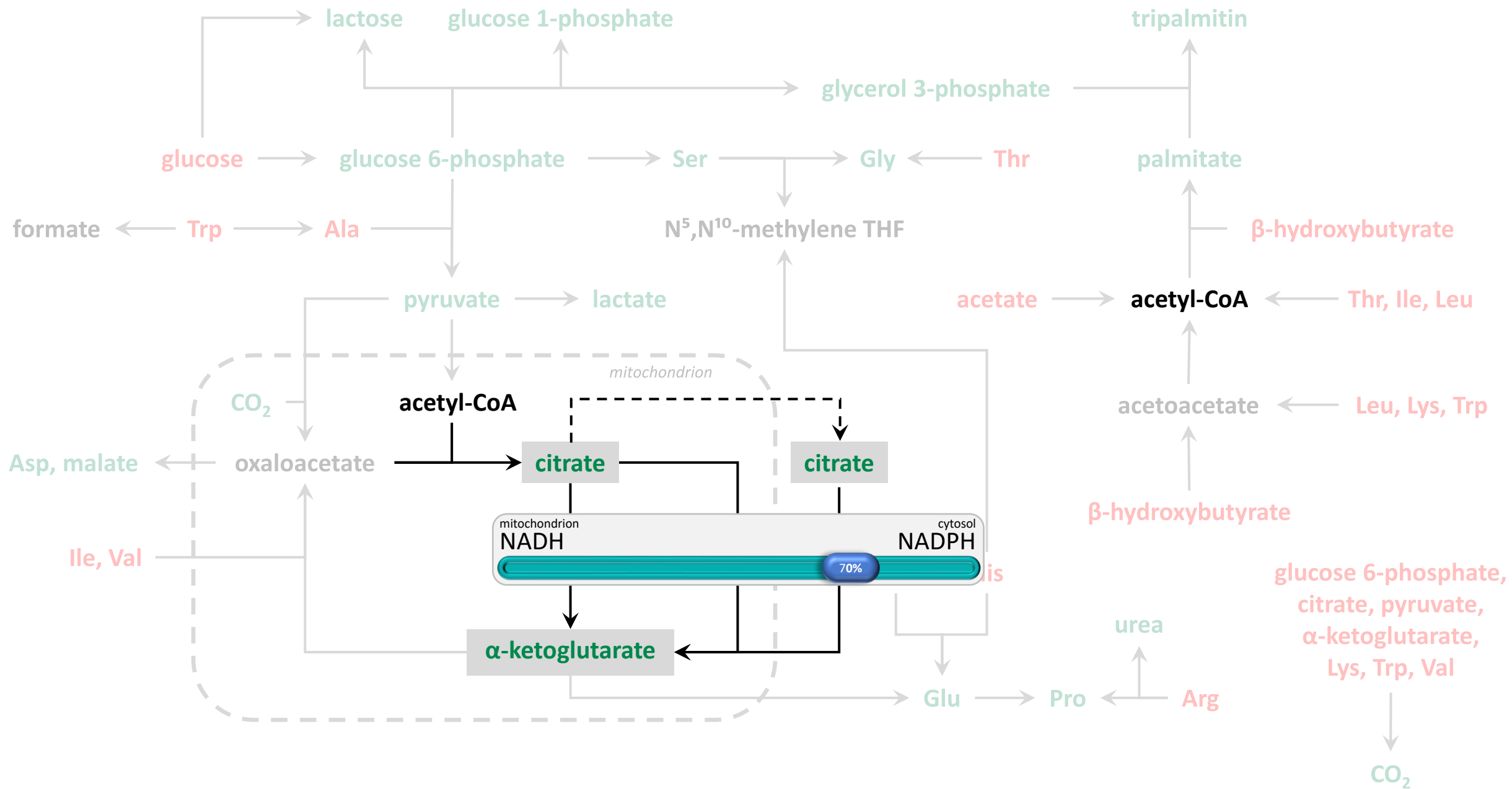
75<sup>th</sup> EAAP annual meeting / September 1-4, 2024 / Jaap van Milgen



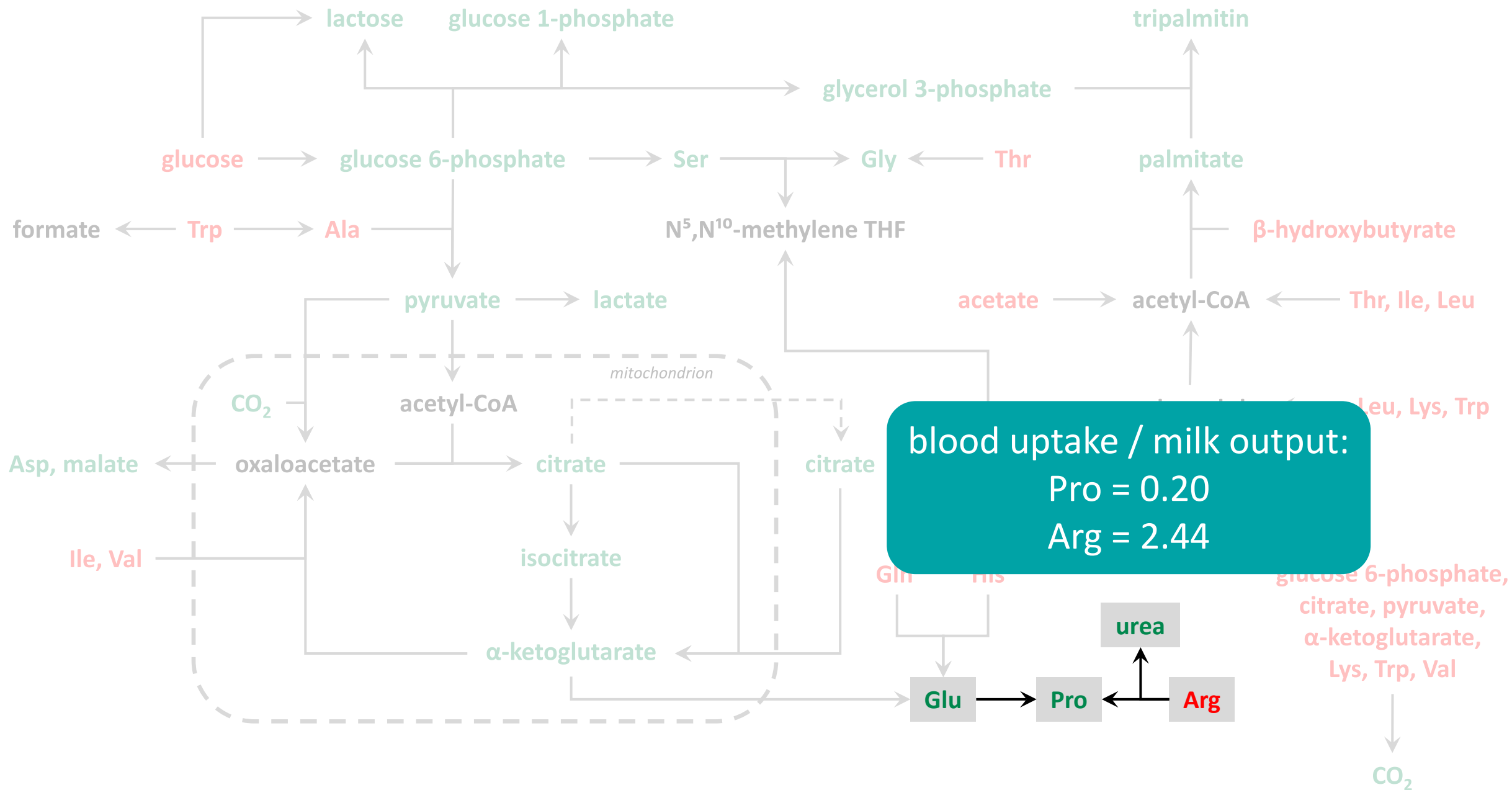












## ➤ Arginine metabolism in the mammary gland

### Metabolism of Arginine and Ornithine in the Cow and Rabbit Mammary Tissue<sup>1</sup>

J. H. CLARK, R. G. DERRIG, C. L. DAVIS,  
and H. R. SPIRES

Department of Dairy Science  
University of Illinois  
Urbana 61801

### The Importance of Ornithine as a Precursor for Proline in Mammalian Cells

ROBERT J. SMITH<sup>1</sup> AND JAMES M. PHANG<sup>2</sup>  
*Endocrinology Section, Metabolism Branch, National Cancer Institute,  
Bethesda, Maryland 20014*

Animal (2019), 13:4, pp 790–798 © The Animal Consortium 2018  
doi:10.1017/S1751731118002069



### Dietary L-arginine supplementation increased mammary gland vascularity of lactating sows

D. M. Holanda<sup>1</sup>, C. S. Marcolla<sup>1</sup>, S. E. F. Guimarães<sup>1</sup>, M. M. Neves<sup>2</sup>, G. J. Hausman<sup>3</sup>,  
M. S. Duarte<sup>1</sup>, M. L. T. Abreu<sup>4</sup> and A. Saraiva<sup>1†</sup>

<sup>1</sup>Department of Animal Sciences, Universidade Federal de Viçosa, Viçosa MG 36570-900, Brazil; <sup>2</sup>Department of Biology, Universidade Federal de Viçosa, Viçosa, MG 36570-900, Brazil; <sup>3</sup>United States Department of Agriculture, Agriculture Research Services, Athens, GA 30605, USA; <sup>4</sup>Department of Animal Sciences, Universidade Federal de Lavras, Lavras, MG 37200-000, Brazil

### Local Secretion of Nitric Oxide and the Control of Mammary Blood Flow<sup>1</sup>

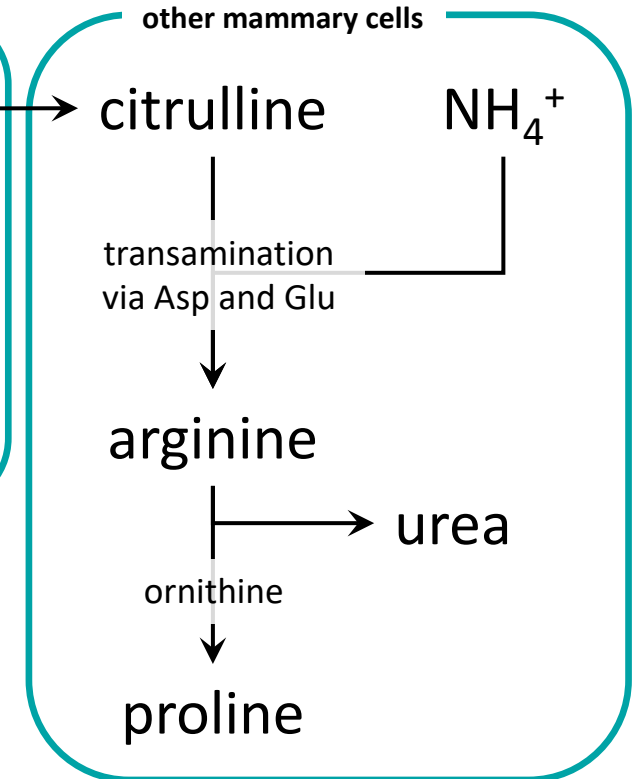
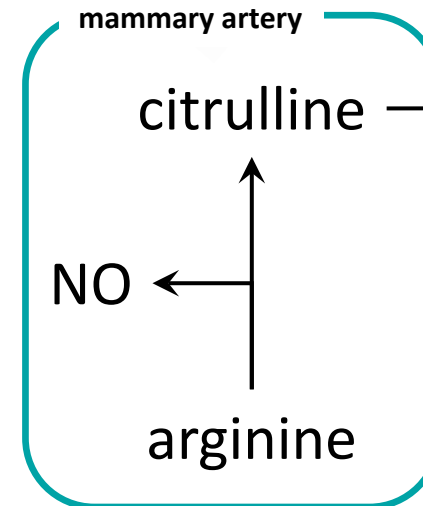
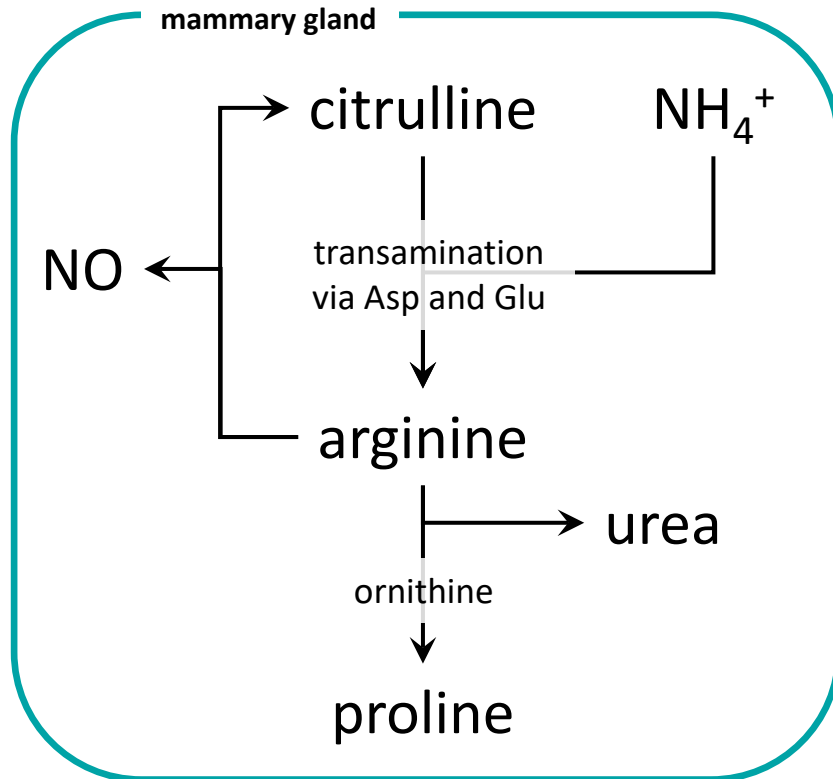
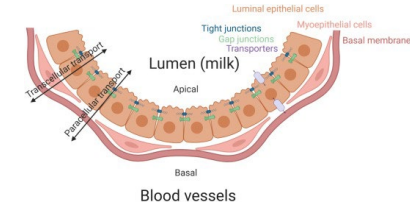
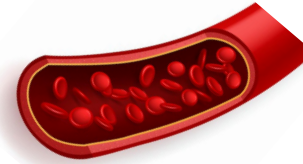
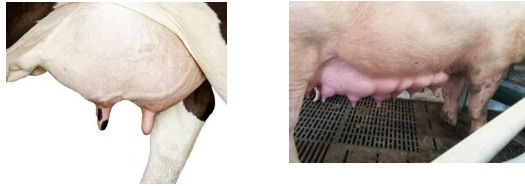
P. LACASSE,<sup>\*,2</sup> V. C. FARR,<sup>†</sup> S. R. DAVIS,<sup>†</sup> and C. G. PROSSER<sup>†,3</sup>

<sup>\*</sup>Agriculture and Agri-Food Canada, Dairy and Swine Research and Development Centre,  
PO Box 90, Lennoxville, QC, Canada J1M 1Z3

<sup>†</sup>Dairy Science Group, AgResearch, Ruakura Research Centre,  
Private Bag 3123, Hamilton, New Zealand

## ➤ Arginine metabolism in the mammary gland

compartmentalization of metabolism



## ➤ Conclusion

- Meta-reactions are useful to teach nutritional biochemistry
- Meta-reactions can be used to analyze nutritional balances
- Compartmentalization of metabolism has an impact on “efficiency”
- Meta-reactions can be developed for other domains



## ➤ Further information

Animal 18 (2024) 101204



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### Animal The international journal of animal biosciences



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

J. van Milgen

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



| Detail level                          | Energy unit         | As a...   | To/from...                                      | Meta-reaction                                                                                                                                                                                                             | Flux | Step | 10 max |
|---------------------------------------|---------------------|-----------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|--------|
| carbohydrates                         | glucose             | substrate | glucose 6-phosphate                             | glucose + ATP → glucose 6-phosphate + ADP + H <sup>+</sup>                                                                                                                                                                | 1    | 1    |        |
| intermediate metabolites              | glucose 6-phosphate | substrate | pyruvate (glycolysis)                           | glucose 6-phosphate + 3 ADP + 2 P <sub>i</sub> + 2 NAD <sup>+</sup> → 2 pyruvate + 3 ATP + 2 NADH + H <sup>+</sup> + 2 H <sub>2</sub> O (glycolysis)                                                                      | 1    | 2    |        |
| intermediate metabolites              | pyruvate            | substrate | acetyl-CoA                                      | pyruvate + NAD <sup>+</sup> + CoA → acetyl-CoA + NADH + CO <sub>2</sub>                                                                                                                                                   | 2    | 3    |        |
| intermediate metabolites              | acetyl-CoA          | substrate | with oxaloacetate → α-ketoglutarate (TCA cycle) | acetyl-CoA + oxaloacetate + NAD <sup>+</sup> + H <sub>2</sub> O → α-ketoglutarate + NADH + H <sup>+</sup> + CoA + CO <sub>2</sub> (TCA cycle)                                                                             | 2    | 4    |        |
| intermediate metabolites              | α-ketoglutarate     | substrate | oxaloacetate (TCA cycle)                        | α-ketoglutarate + 8.75 ADP + 8.75 P <sub>i</sub> + 2 H <sub>2</sub> O + H <sup>+</sup> + 1.25 H <sub>2</sub> O → oxaloacetate + 8.75 ATP + 2 NADH + 8.25 H <sup>+</sup> + NADH <sub>2</sub> + CO <sub>2</sub> (TCA cycle) | 2    | 5    |        |
| electron transport and ATP metabolism | NADH                | substrate | NADH cytosol → NADH mitochondrion               | 0.25 ATP + 0.25 H <sub>2</sub> O → 0.25 ADP + 0.25 P <sub>i</sub> + 0.25 H <sup>+</sup> (malate - aspartate shuttle)                                                                                                      | 2    | 152  |        |
| electron transport and ATP metabolism | NADH                | substrate | ATP (oxidative phosphorylation)                 | 2.5 ADP + 2.5 P <sub>i</sub> + NADH + 3.5 H <sup>+</sup> + 0.5 O <sub>2</sub> → 2.5 ATP + NAD <sup>+</sup> + 3.5 H <sub>2</sub> O (oxidative phosphorylation)                                                             | 10   | 190  |        |
| electron transport and ATP metabolism | FADH <sub>2</sub>   | substrate | ATP (oxidative phosphorylation)                 | 1.5 ADP + 1.5 P <sub>i</sub> + 0.5 H <sup>+</sup> + FADH <sub>2</sub> + 0.5 O <sub>2</sub> → 1.5 ATP + FAD + 2.5 H <sub>2</sub> O (oxidative phosphorylation)                                                             | 2    | 191  |        |

Two versions of the Excel tool:

- End-users: to teach nutritional biochemistry and for use in research
- Developers: to modify and add meta-reactions

## > Acknowledgements

- François Moreews and Sophie Lemosquet (UMR Pegase, INRAE)
- Student and staff:
  - Universidade Estadual Paulista “Júlio de Mesquita Filho” (UNESP), Jaboticabal (Brazil)
  - Guangdong Academy of Agricultural Science (GDAAS) in Guangzhou (China)
  - University of Illinois at Urbana-Champaign (USA)
-  **COVID-19**  
Coronavirus 

