Presentation : Development of an age-specific genome-scale model of skeletal muscle metabolism

PANINI
Physical Activity and Nutrition INfluences In ageing

TU/e Technische Universiteit Eindhoven University of Technology

“Development of an age-specific genome-scale model of skeletal muscle metabolism"

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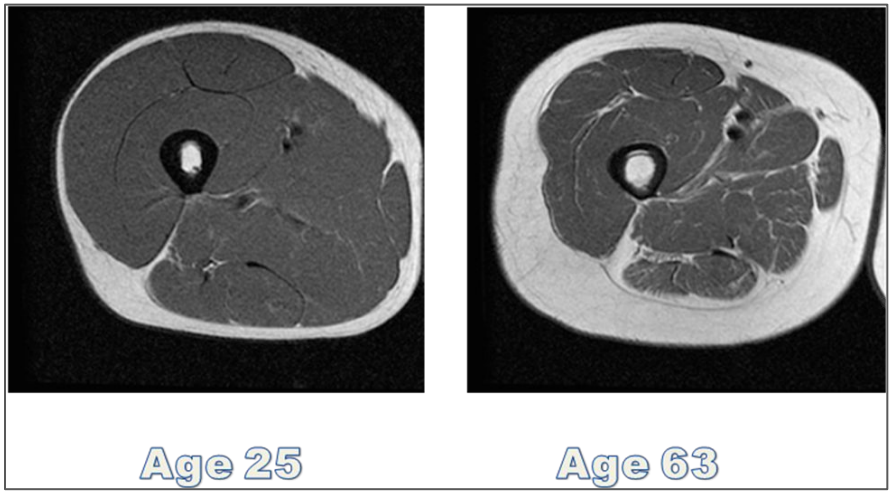
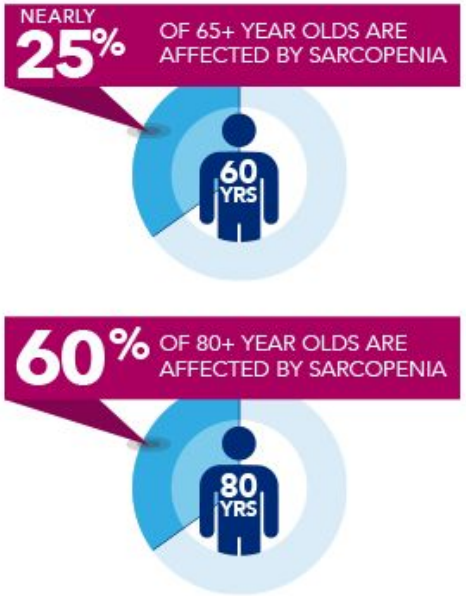
Where innovation starts

EC grant: 675003

Why model skeletal muscle metabolism in older adults?

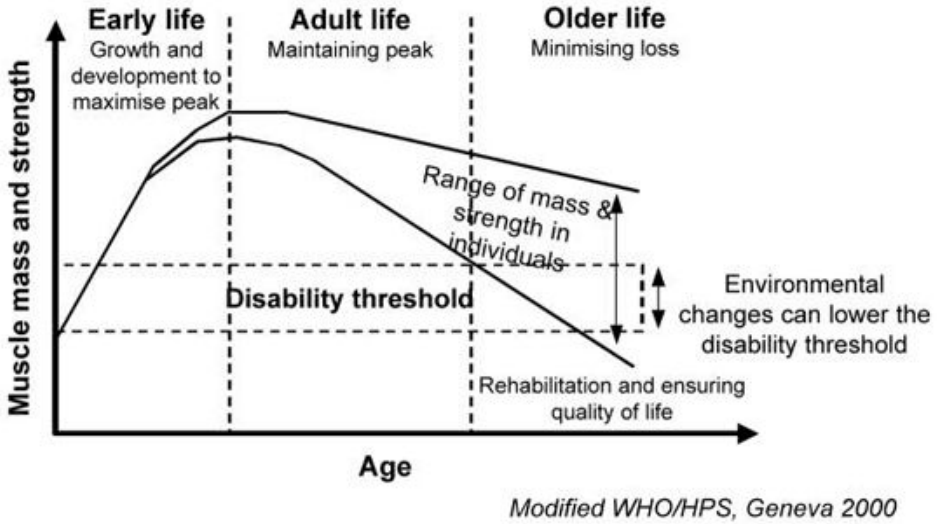
Sarcopenia, or the **loss of skeletal muscle volume and strength with age**, is one of the most prevalent causes of functional decline and loss of independence in older adults.



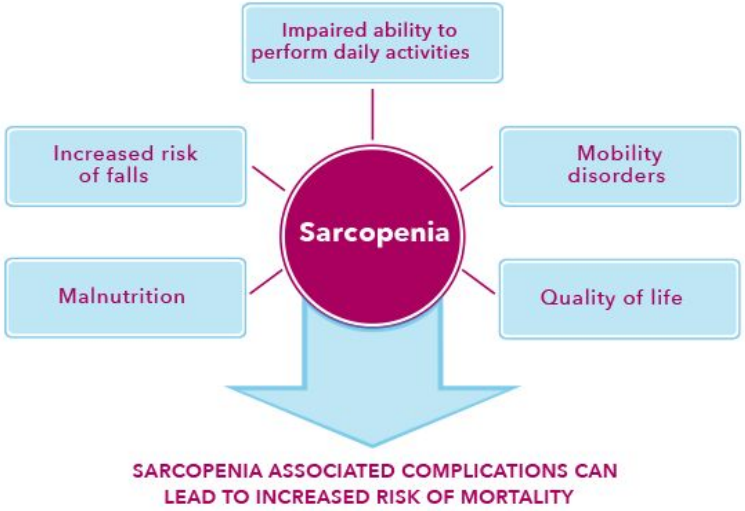


Janssen I, Heymsfield SB, Ross R., *J Am Geriatr* Soc.2002;

Annual loss of muscle mass is 1% to 2% from the age of 50 *(Buford et al. 2010; Marcell 2003)*



Modified WHO/HPS, Geneva 2000



What is the impact of nutrition and active lifestyle on sarcopenia prevention?

Physical Activity and Nutrition INfluences In ageing (PANINI)

EU Horizon2020 Marie Curie Innovative Training Network (ITN)

Beneficiaries

- VU University Amsterdam (VU)
- University of Birmingham (UoB)
- Jyväskylä University (UJ)
- Personal Genomics s.r.l. (PG)
- Università di Bologna (UNIBO)
- Universidade do Minho (UMINHO)
- Eindhoven University of Technology (TU/e)
- (TNO)

Partner Organisations

- Age UK London
- Move it or Lose it Limited (MIOLI)
- Danone Nederland B.V.
- Hur Labs
- University Hospital Birmingham (UHB)
- Maastricht University (MU)
- Università di Verona (UV)

Network of academic and non-academic partners aiming to implement multidisciplinary ageing research and training from basic biomedical science to applied clinical practice

Examining the influence of physical activity and nutrition on age-related changes from gene to societal level

www.birmingham.ac.uk/panini

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Physical Activity and Nutrition INfluences In ageing (PANINI)

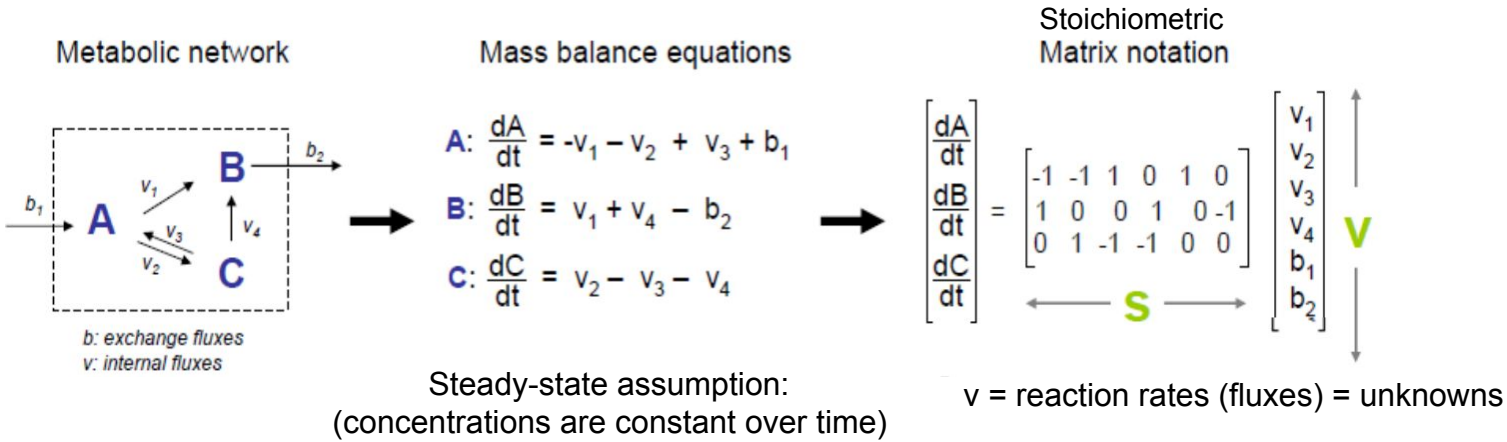
- Understanding the factors that contribute to healthy ageing
- Validating interventions to slow and reverse frailty conditions
- Influencing policies to promote healthy ageing in Europe

AGEING & LIFESTYLE IMPACT ON SKELETAL MUSCLE FUNCTION

- **Build an Age-specific model of skeletal muscle metabolism**
- **Connect metabolic dysfunction with muscle decline during ageing**
- **Develop a metabolic strategy / lifestyle intervention to offset muscle loss in elderly subjects**

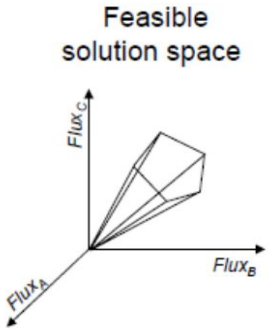
Constraint-based metabolic modeling:

Genome-scale metabolic models (GSMs) are mathematical representations of the whole metabolic network of an organism:



Under-determined system of equations: **not** a single possible solution

Flux Balance Analysis



Constraints:

(1) Mass balance $S \cdot v = 0$

(2) Thermodynamic

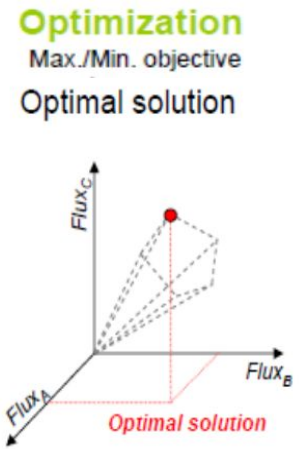
(3) Enzymatic capacity $\alpha \leq v_i \leq \beta$

(4) Nutrients availability

Introduce a mathematical objective function:
(i.e. the "aim" of the cell):

e.g:

- Maximize total ATP production
- Maximize Biomass production
- …..



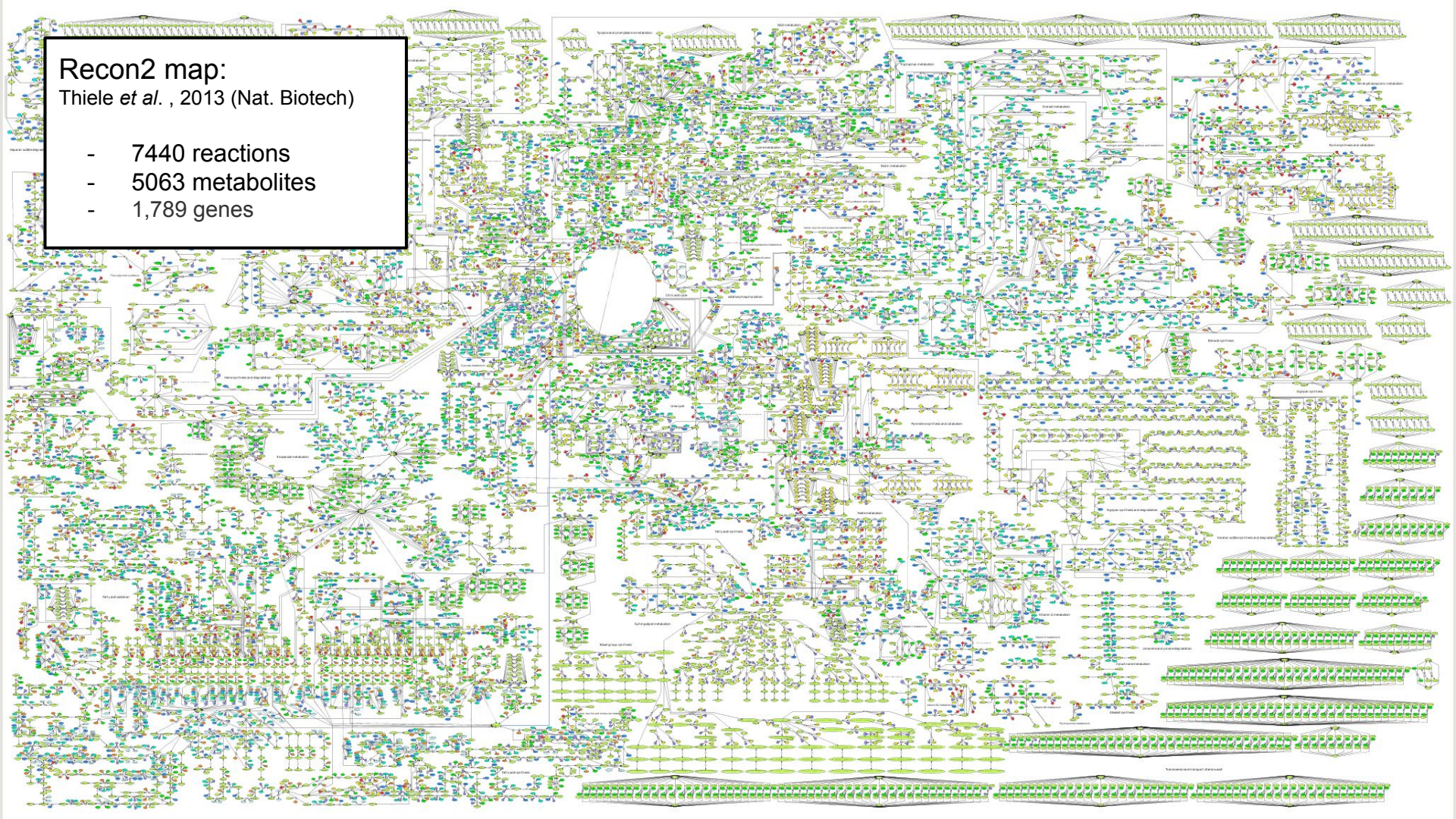
Linear programming is used to optimize (solve) the system, and find the solution that maximizes the objective function

Mass balance and experimental data can constrain the allowable flux values (v), shrinking the feasible solution space

COnstraint **B**ased **R**econstruction and **A**nalysis (**COBRA**) toolbox available for Matlab and Python

https://opencobra.github.io

openCOBRA


Recon2 map:
Thiele *et al*. , 2013 (Nat. Biotech)
- 7440 reactions
- 5063 metabolites
- 1,789 genes

Genome Scale Metabolic Models:

Advantages:

- Enable analysis of whole metabolic network at a system level
- Allow integration of multivariate "-omics" data:
  - Tissue and cell-specific reconstructions
  - Healthy vs pathological state (e.g. cancer metabolism, ….)

Limitations:

- Qualitative rather than quantitative analysis
- Relies on several biologically unlikely assumptions (metabolic optimality, steady state)
- Problems with polymeric metabolites with large heterogeneity (lipids, polysaccharides…)

Model building:

- **Tissue-specific:** created from a generic human metabolic reconstruction (RECON 2.2,Swainston et al. 2016), and skeletal muscle gene expression data.

- **Age-specific:** data gathered from muscle tissue biopsies of **older adults** (Avg. 78 years old)

- **36** subjects (**15 young**, avg. 25yo , **21 old** avg. 78yo), 19 female, 17 male
  Downloaded from GEO, accession number: GSE25941

Published in :

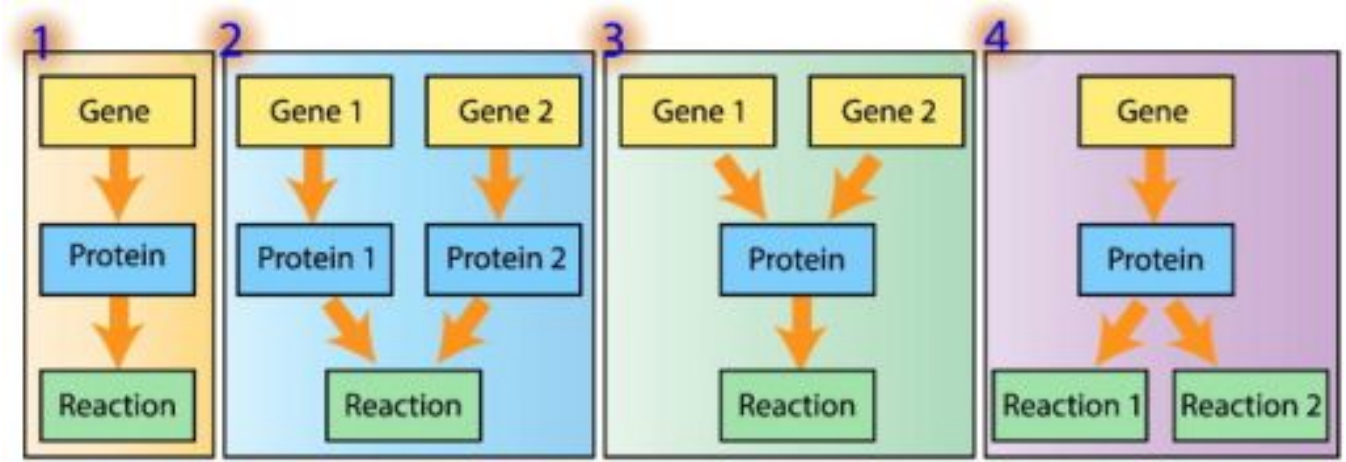
Raue U, et al.

"Transcriptome signature of resistance exercise adaptations:

mixed muscle and fiber type specific profiles in young and old adults."

J Appl Physiol 2012 May;112(10):1625-36. PMID: 22302958

Gene-Protein-Reaction rules



"AND"
(i.e.protein complex)

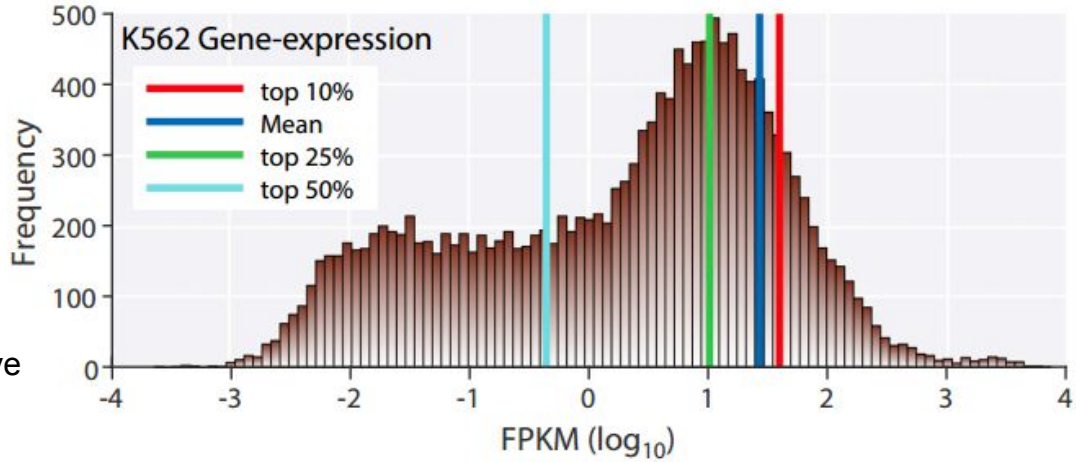
"OR"
(i.e. isozymes)

Boolean logic is used to describe gene-protein-reaction (GPR) association rules of varying complexity.

Reactions are considered active if and only if the correct combination of genes is expressed.

Model building:

Several algorithms exist to extract cell-line- or tissue-specific- models from a GSM:
Most of them require users to define a **threshold** to decide which genes are "expressed"



Too high:
Decreased predictive power,
Inclusion of false positives.

Too Strict:
Less model functionality, "patchy" network.

New methods to define gene- or reaction-specific thresholds are needed

"A Systematic Evaluation of Methods for Tailoring Genome-Scale Metabolic Models", *Opdam S. et al. ,* ***Cell Systems (2017)***

(Manual) Model Curation:

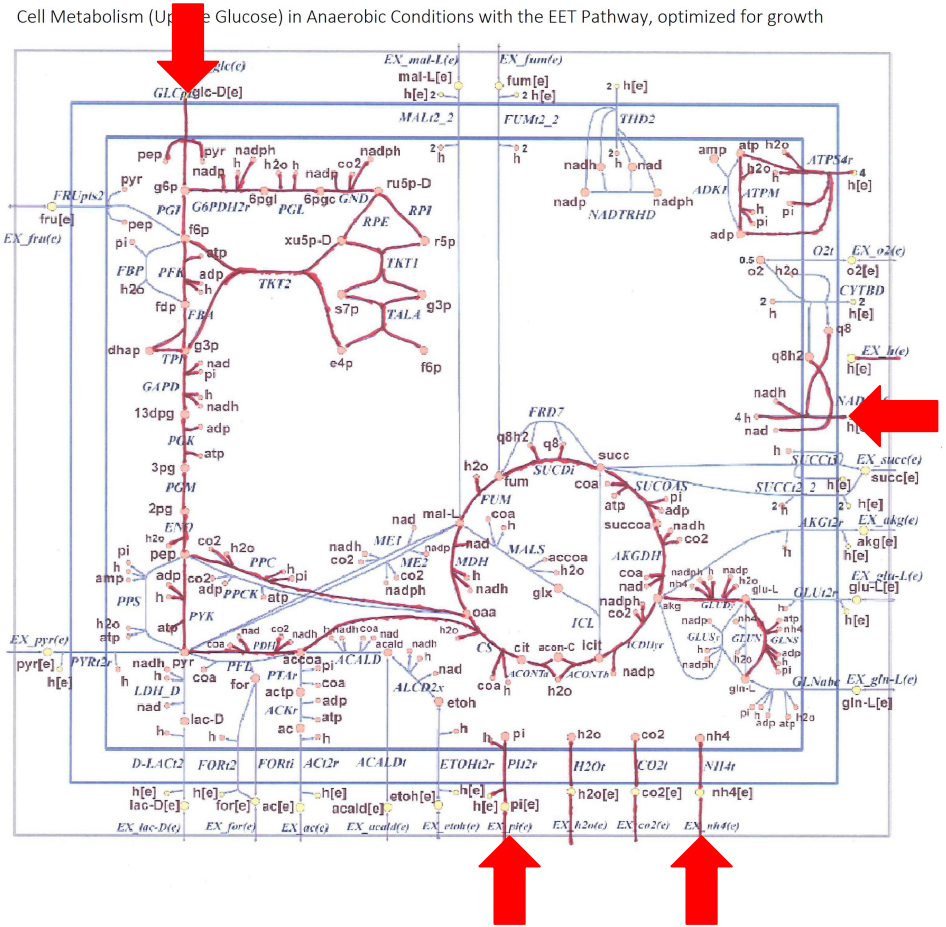
Tissue-specific model extraction algorithms are used to draft the model, but it still needs manual curation:

- Fix model inconsistencies:
  - Check charge and mass balance
  - Gap-fill (FastGapfill (Thiele 2014), or manually add missing reactions)

- Compare model predictions with physiological properties of the tissue:
  - Consumption of Glucose, Fatty Acids, TAG as "fuel"
  - Production of ATP, Glycogen storage…
  - Secretion profile: Alanine (Cori cycle), lactate (in anaerobiosis) …

- Extend the model capabilities:
  - Added skeletal muscle proteins metabolism:
    - synthesis of actin, myosin, troponin, tropomyosin
    - muscle fibers (type I , Type IIa, II b) synthesis/degradation pathways

Cell Metabolism (Up[illegible]e Glucose) in Anaerobic Conditions with the EET Pathway, optimized for growth



What is the effect of different nutritional intervention on muscle fibers synthesis/degradation ratio?

Simulation: putting constraints on the amount of nutrients allowed to enter the system

Replicating the effects of e.g:

- **Protein supplement**
- **Western high fat/high sugar diet**
- **Malnutrition**

Input fluxes values for 11 different diets available at:

Virtual Metabolic Human
https://vmh.uni.lu/#nutrition

Validation:

Experimental validation

- Intracellular and/or exchange 13C-flux data (isotope tracer)

Validation by comparison with other models:

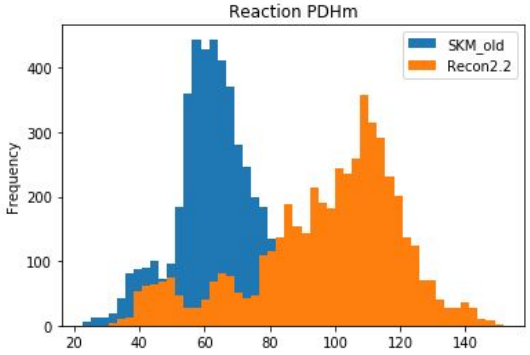
- State-of-the-art muscle-specific metabolic models (**Nogiec 2015, Väremo 2015**)
- Generic human models (RECON2.2, iHSA)
- "Young muscle" model, which is being developed in parallel with the "elderly muscle" model, created with the same method from gene expression data of young subjects' (avg 25 years) muscle tissue.

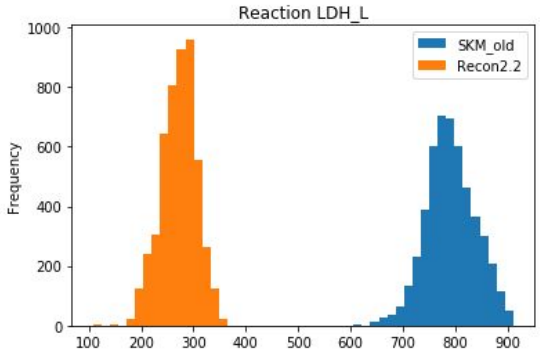
How?

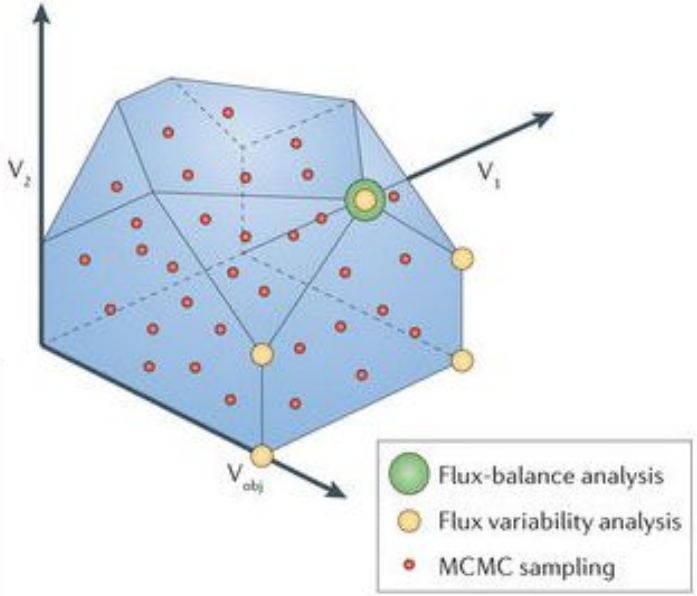
- Number of shared and unique reactions and metabolites,
- Testing achievable metabolic tasks: (i.e. glycogen storage or protein synthesis)
- Secretion profile analysis (what does the model produce?)
- Markov Chain Monte Carlo sampling of the system's solution space.

MonteCarlo Sampling:

- Objective function assumption doesn't hold well in higher organisms: *"What is the "aim" of a myocyte?"*
- FBA outcome is just one of many solutions
- Uniform sampling of the solution space gives a more complete overview of model capabilities







What's next?:

- **Refining the model-building process:** decrease the need of manual curation, optimize use of the information contained in gene expression datasets, integration of (age-specific) proteomic data during the building process.

- **Use more gene expression datasets:** iterate quickly the model-building phase and generate different models from experimental data (e.g: elderly muscle gene expression before, during and after 12 weeks of resistance training), one model for each different "context".

- **Generate patient-specific models,** and investigate the effect of the same diet and exercise regime on different subjects.

Thank you for your attention!