Modeling of human pathways in animals: possibilities and limitations

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DET FRIE FORSKNINGSRÅD
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The big picture: AniGen project

- Enable researchers to answer the following question:

  Which animal models would be most useful to generate reliable hypotheses about human with respect to a given phenotype?

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- **Part I: State of the art**

  What kind of and how much data is available for animal models?

- **Part II: Pathways in animal models**

  How can we combine the available data to study pathways in animal models?

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- Literature knowledge (PubMed)
- Tissue expression data (TISSUES)
- Protein interactions (STRING)
- Pathways (KEGG)

Text mining: PubMed abstracts

- $\sim$30 mio abstracts on life sciences and biomedical topics
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mentions	mouse	rat	pig
organism	1 217 133	1 309 469	132 358
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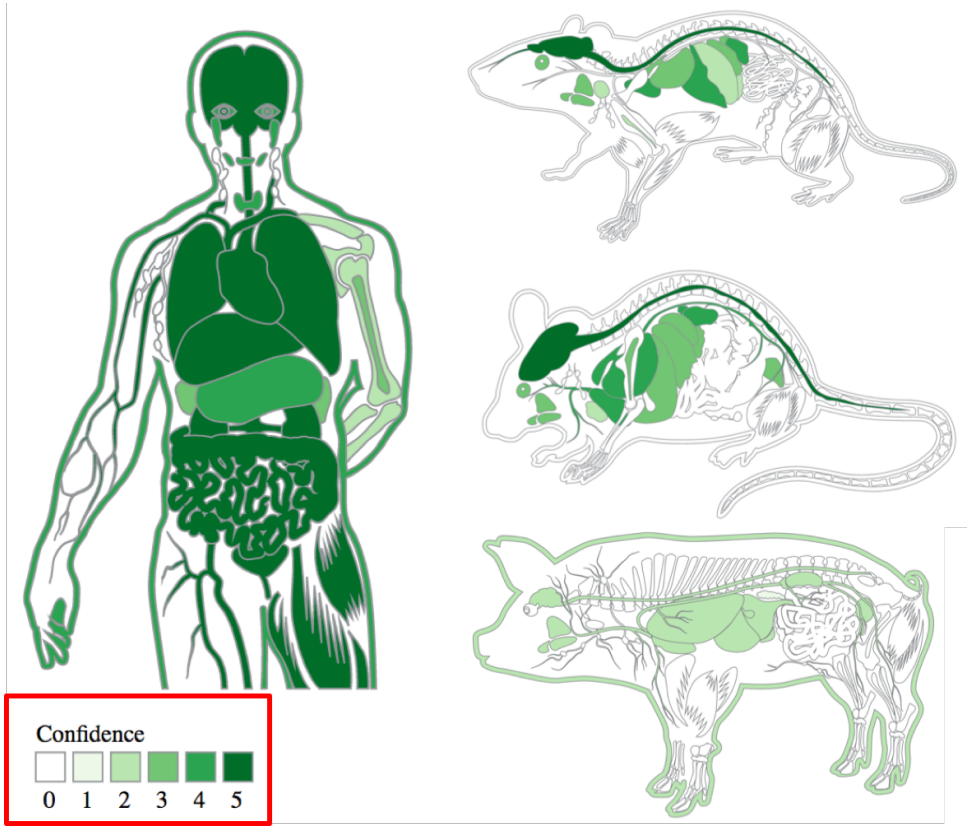
$\Rightarrow$ Challenge: pig is not studied as much as mouse and rat

Expression data: TISSUES database



- Covers human, mouse, rat, pig
- 14 transcriptomic datasets
- Text mining and manual curation
- Confidence scores comparable across datasets and organisms

`https://tissues.jensenlab.org`

Palasca *et al.* (2018), *Database*

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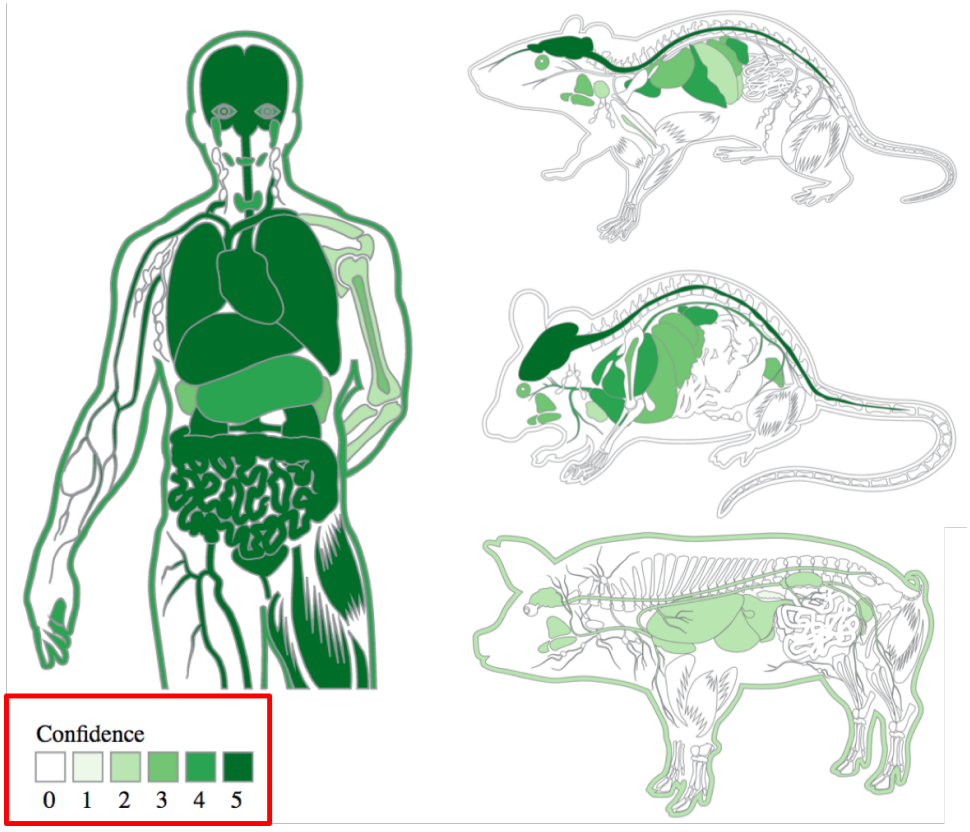

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⇒ However, comparable does not mean equal

⇒ Only few tissues covered by at least one/two datasets

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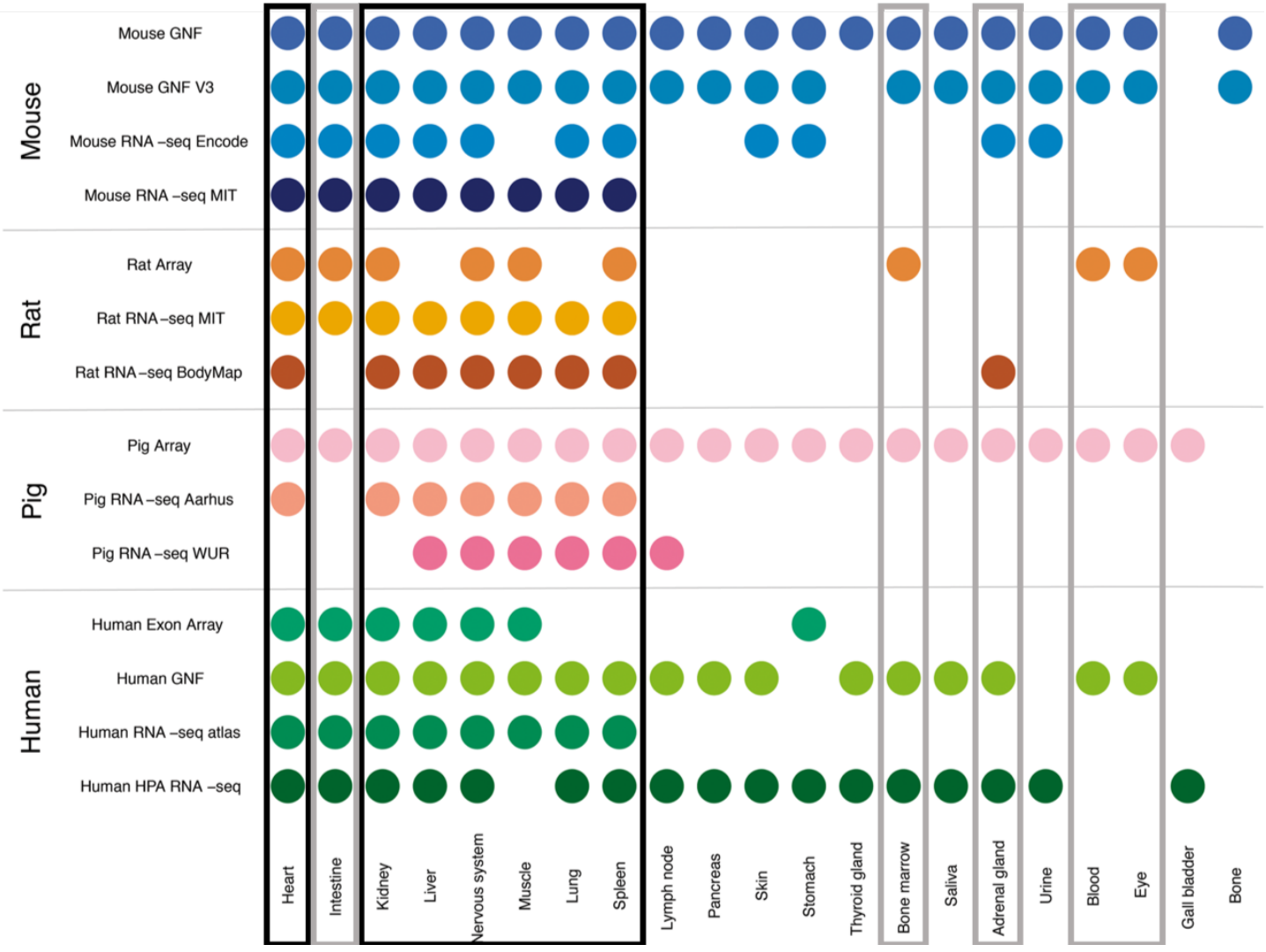
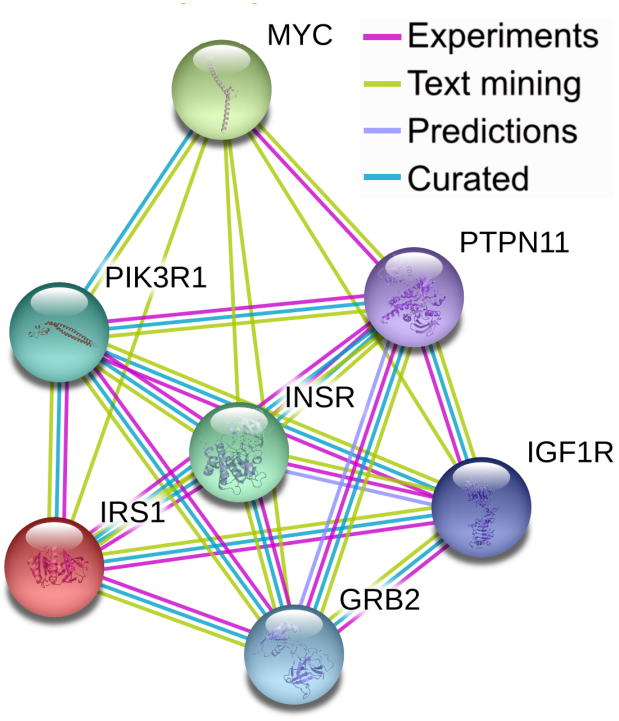


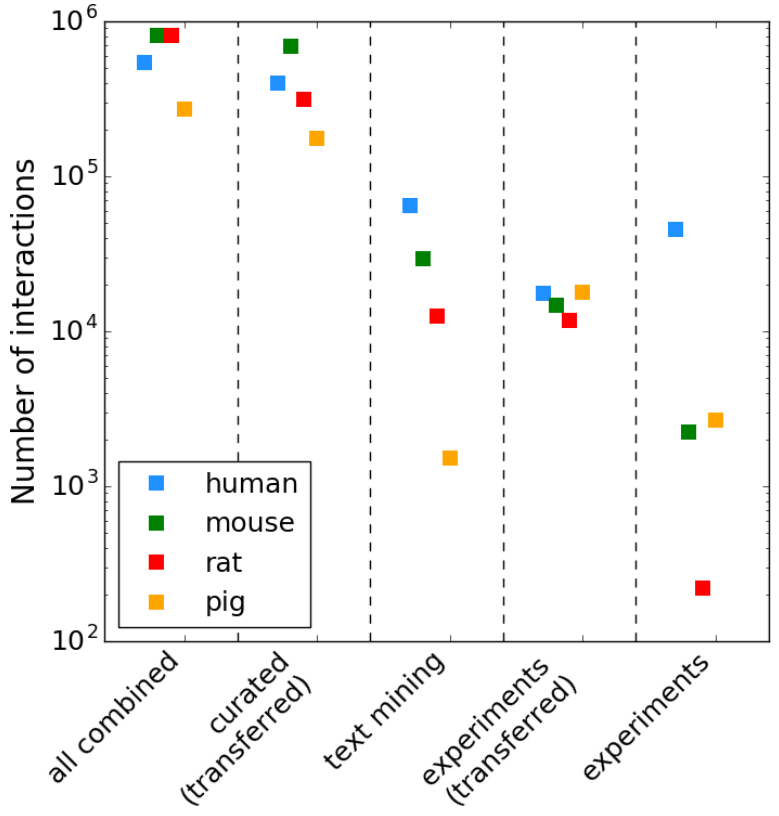
Datasets (rows) and tissues covered (columns) in each organism; tissues supported by at least one (grey) or two (black) datasets are highlighted

Interaction databases: STRING

1380 mio interactions between 9.6 mio proteins in 2031 organisms



High-confidence interactions (score ≥ 0.8) for each evidence type



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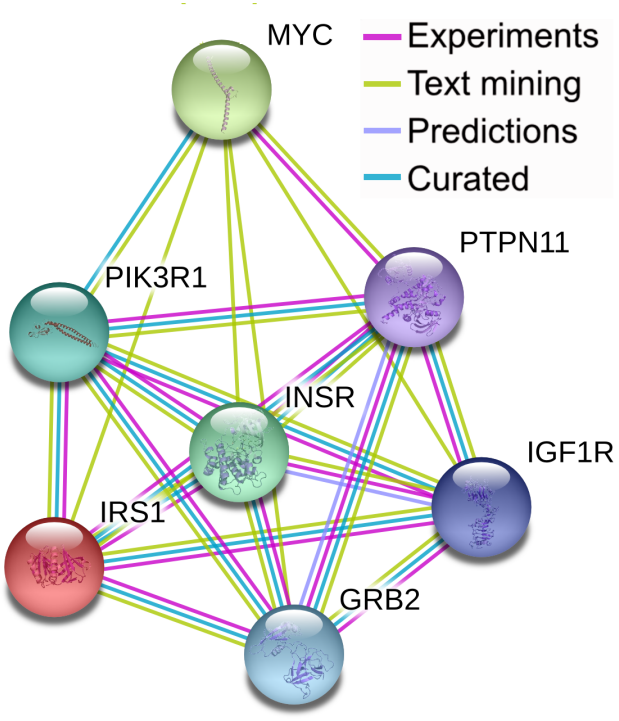

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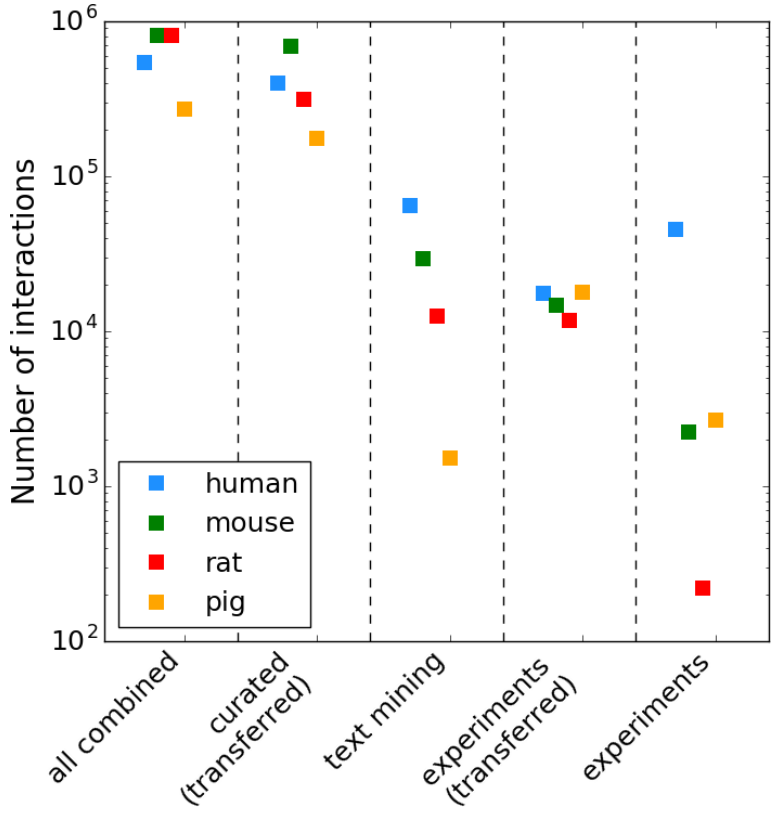

⇒ Very few experimentally determined interactions for animals

⇒ We need orthology transfer from human & data integration

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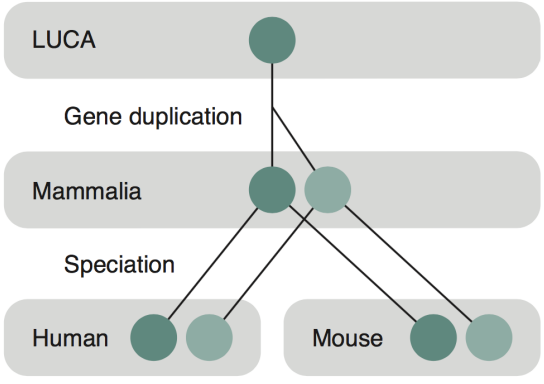
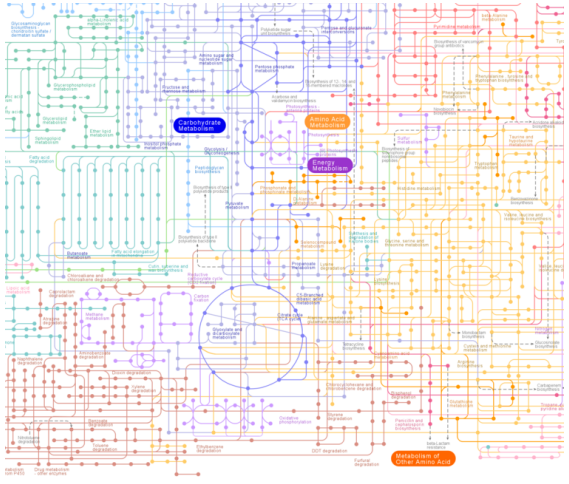
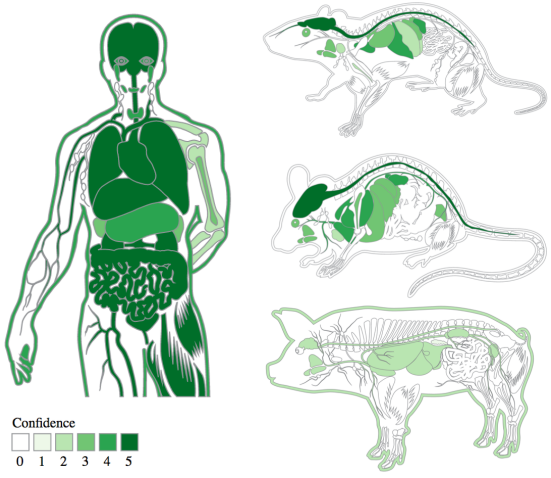


eggNOG: orthology relationships between mammals

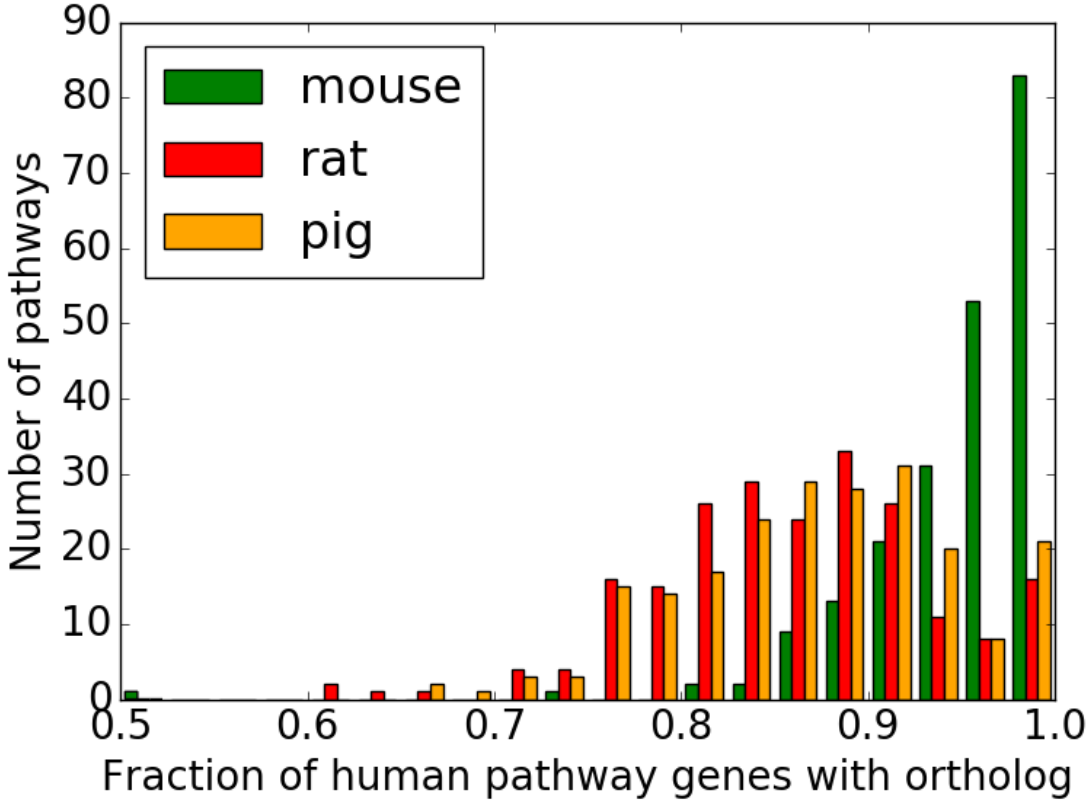


KEGG: curated & high-quality human pathways



TISSUES: healthy tissue expression data in mammals

Orthology-based transfer of 216 human pathways



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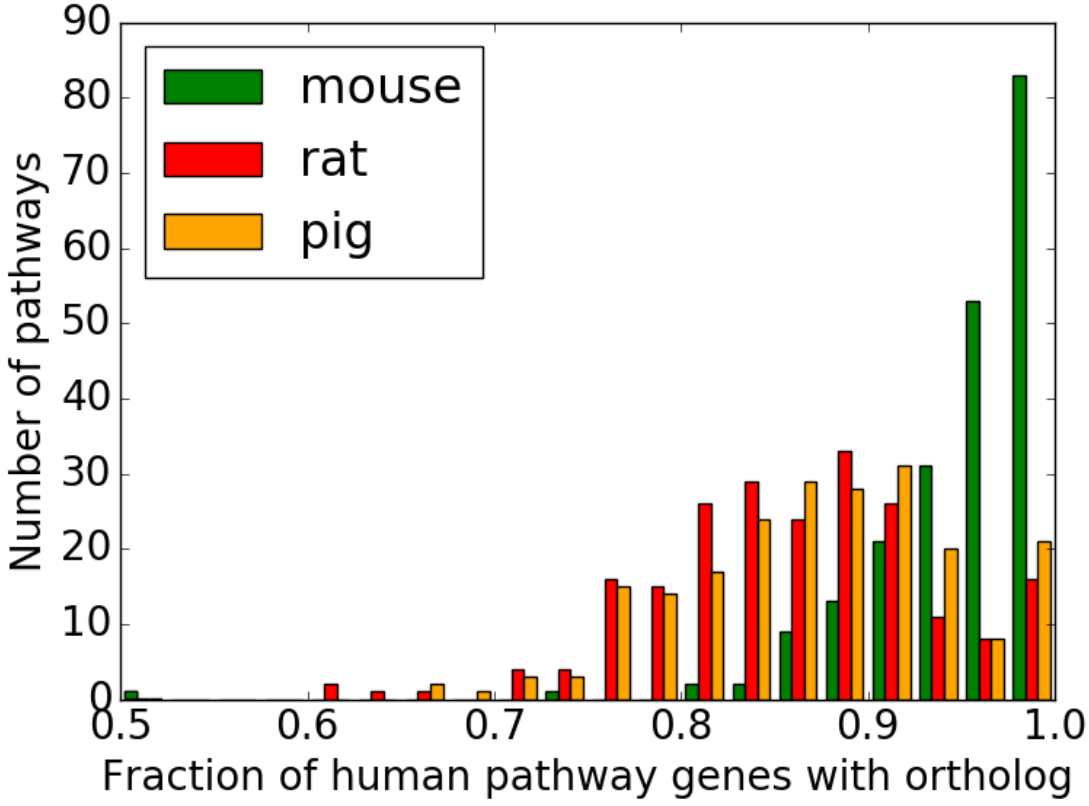

- 35 % of the KEGG pathways overlap completely between human & mouse, while only 10 % between human & pig or human & rat

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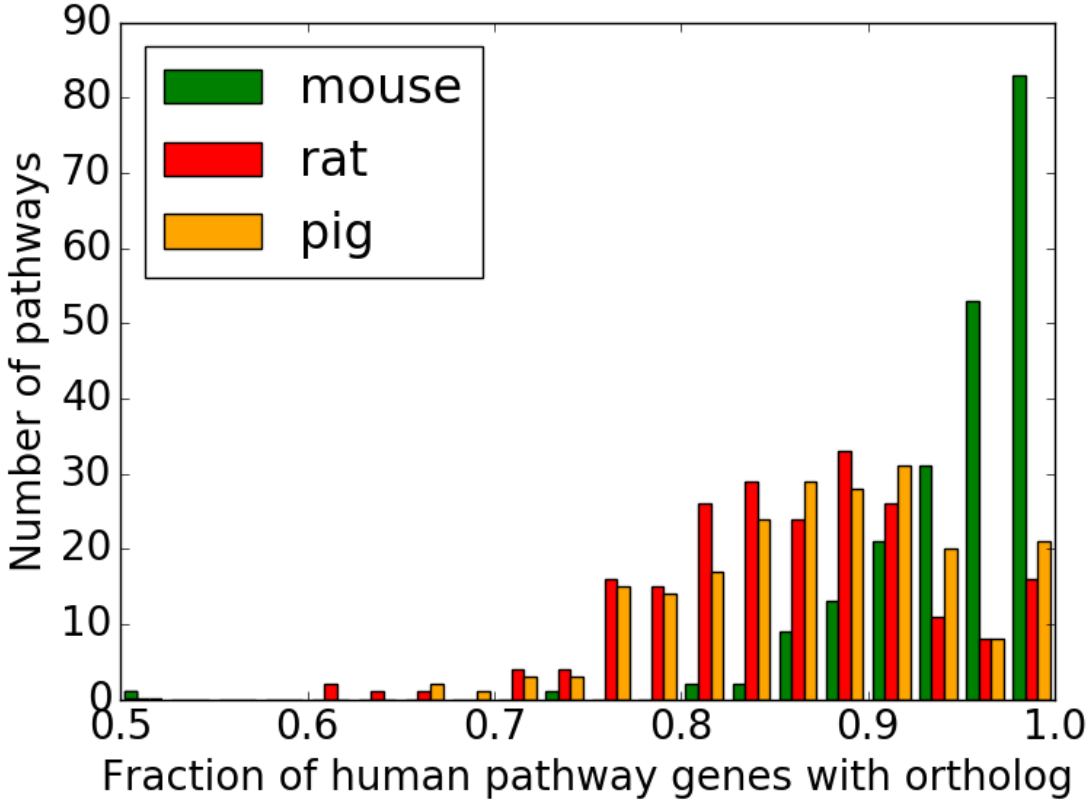

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⇒ We assess the **pathway gene/interaction overlap** between human and other organisms to highlight their similarities

Are there pathway differences?

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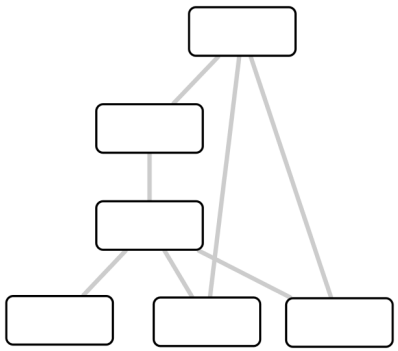

human pathway

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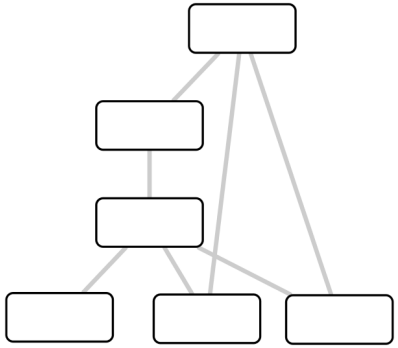
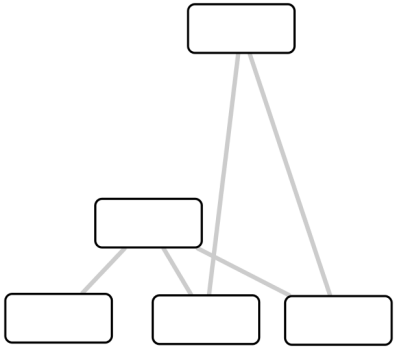


human pathway



transferred to mouse

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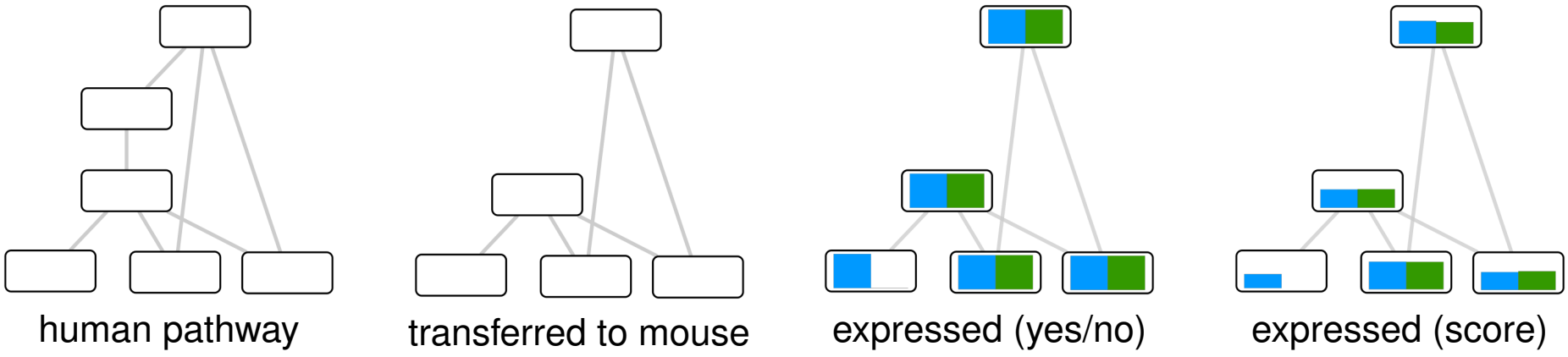

⇒ Overlay the orthology-transferred KEGG pathways with tissue expression data from the TISSUES database

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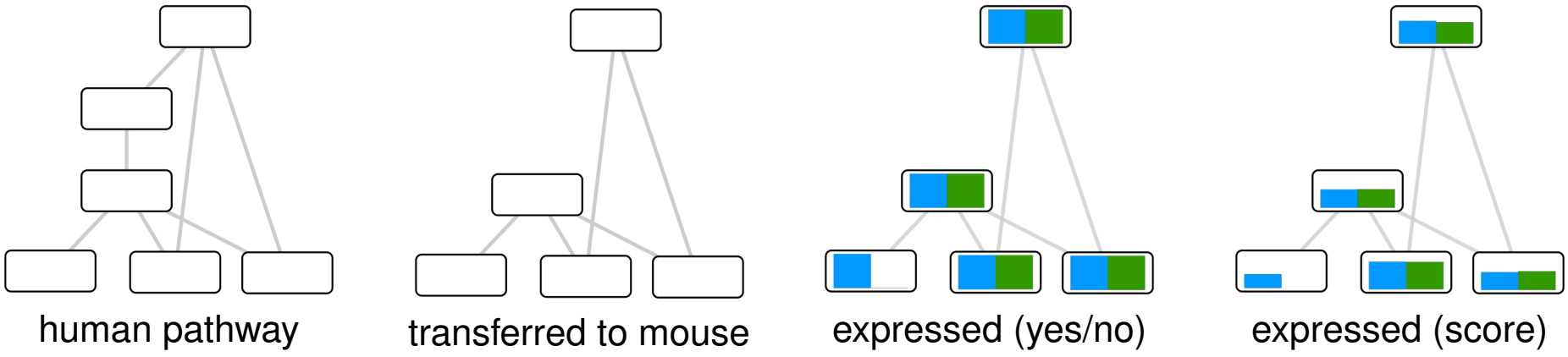

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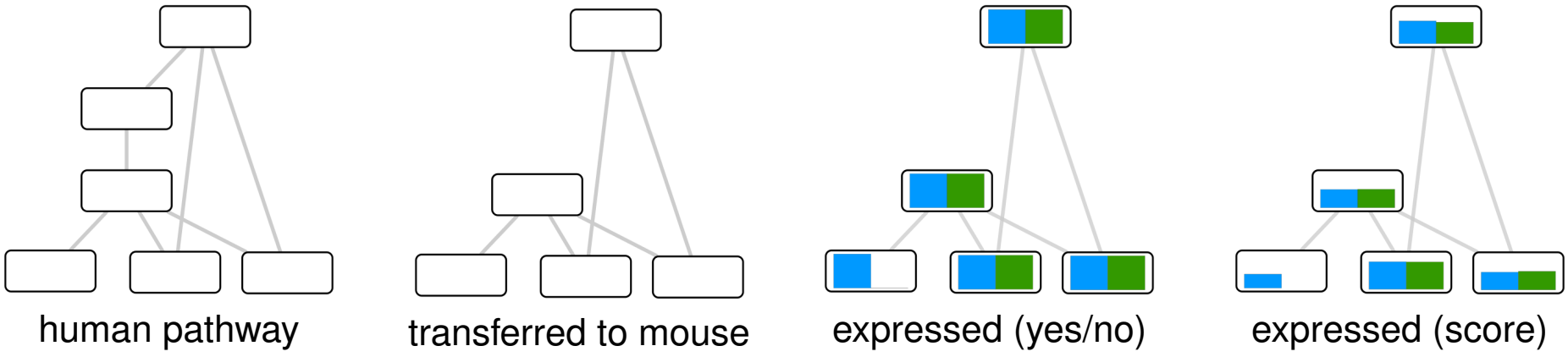

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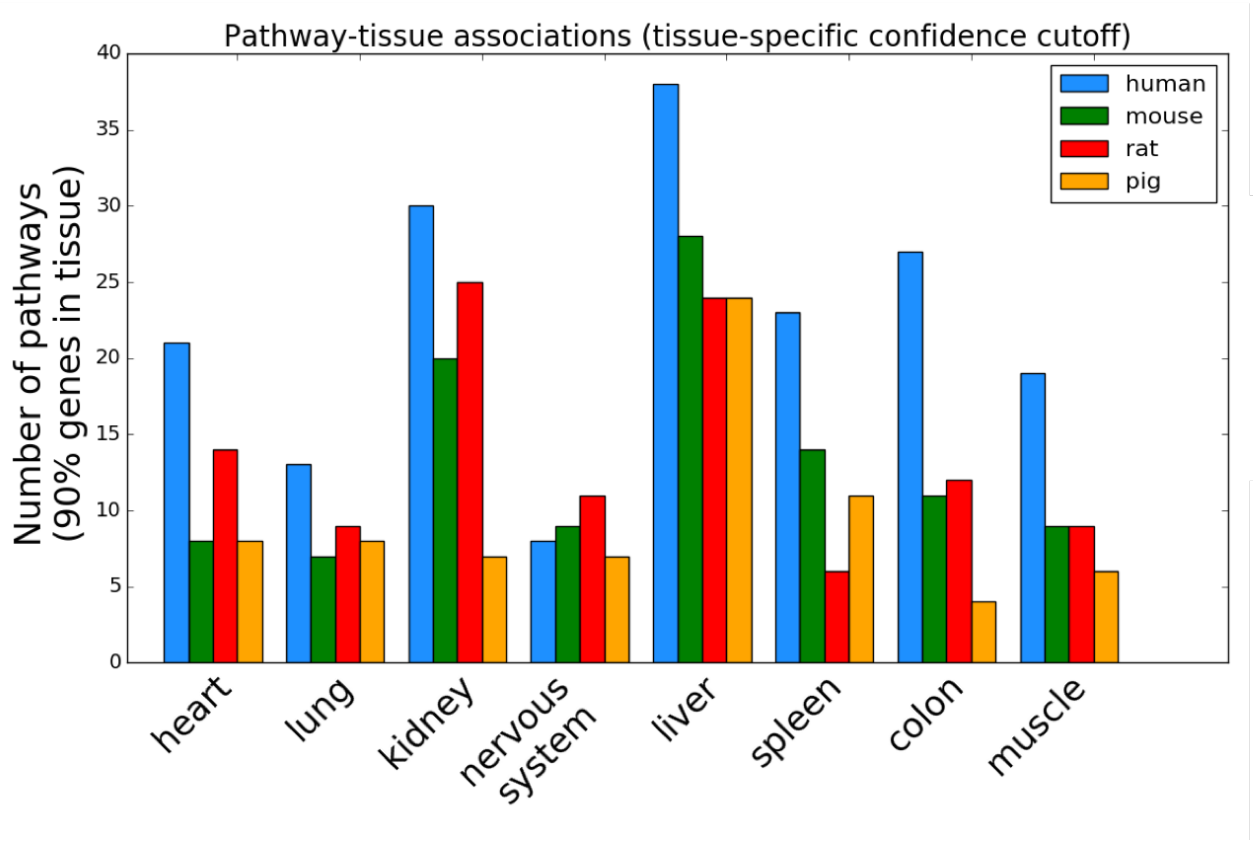
- For each pathway, organism & tissue, the respective gene is expressed if it has a score above a given confidence cutoff
- A pathway is considered expressed in a tissue, if 90 % of the pathway genes are expressed above a given confidence cutoff

Tissue distribution of the 216 transferred pathways



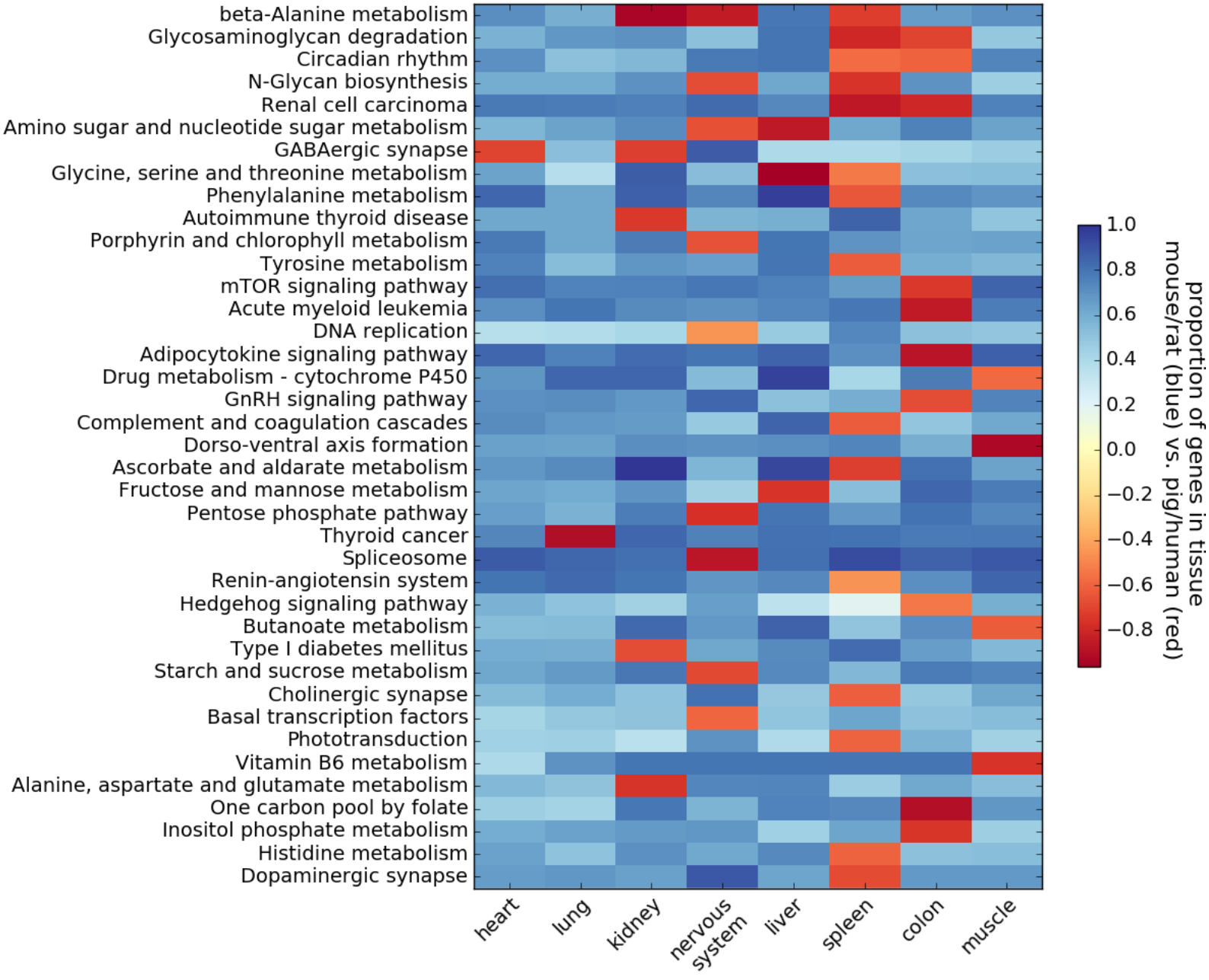
Range of tissue-specific confidence cutoffs:
Human: [0.87, 2.95]
Mouse: [0.59, 1.88]
Rat: [0.83, 1.25]
Pig: [0.42, 1.28]

- Given tissue & organism of interest, which are the expressed pathways?
- Are these pathways tissue-specific or broadly expressed?
- Are there organism- and/or tissue-specific pathways?

Organism- & tissue-specific pathways

Are there pathways or tissues, for which pig is better represented than mouse?

Organism- & tissue-specific pathways



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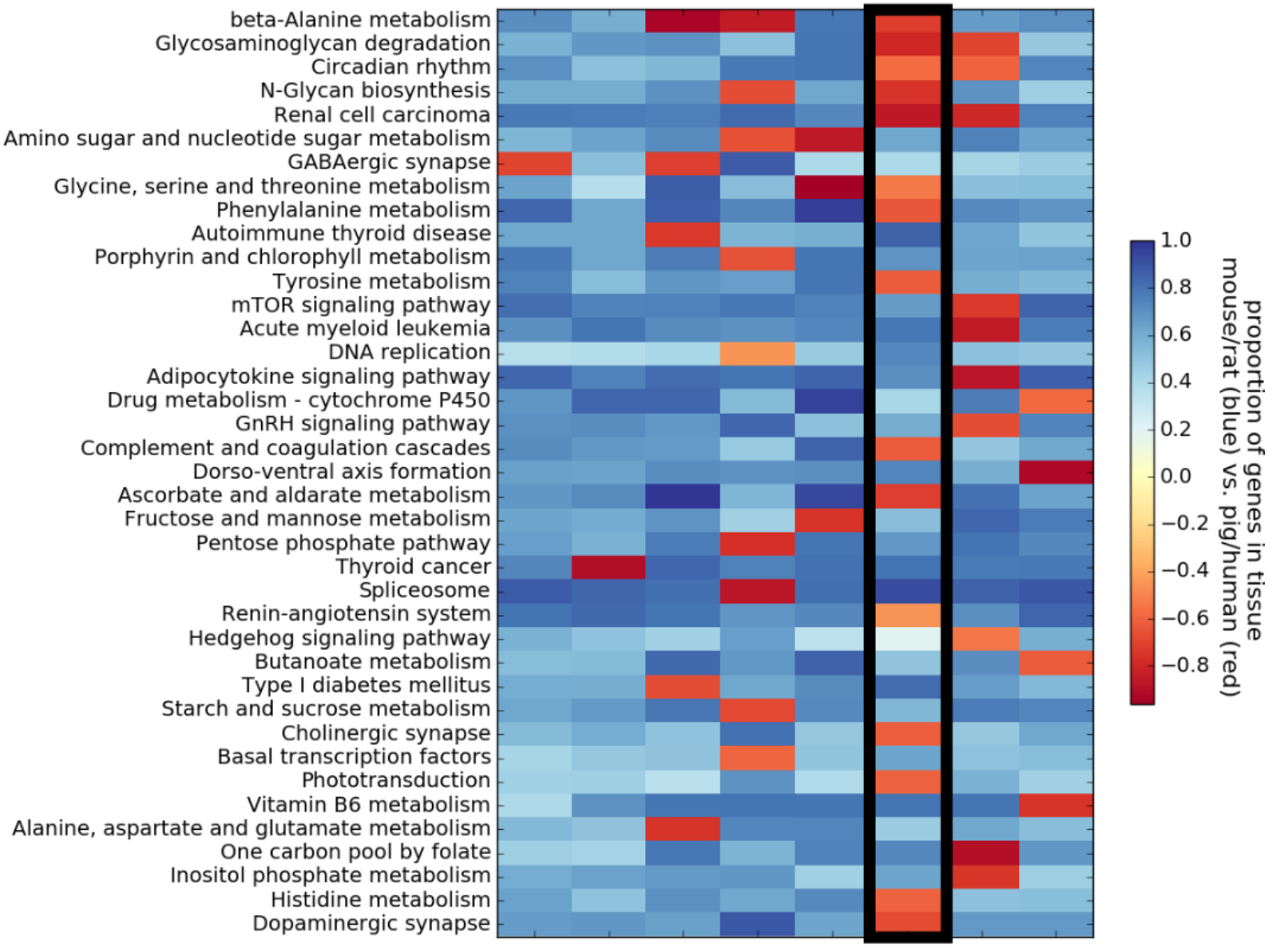

Is pig a good model for diseases related to spleen?

Conclusions and future work

- Transferred a set of mammalian pathways from human pathways
- Integrated them with tissue expression data
- Identified a set of tissue-and organism-specific pathways

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- Include non-coding RNAs in the pathways (RAIN)
- Take into account the pathway / network structure
- Include expression data from our mouse and pig disease models
- Perform the same analysis using gene-disease associations

Acknowledgements

- Oana Palasca
- Jan Gorodkin
- Lars Juhl Jensen
- Reza Yarani
- Flemming Pociot
- Thomas Litman
- RTH group
- Jensen group

RTH
CENTER FOR NON-CODING RNA IN TECHNOLOGY AND HEALTH

The Novo Nordisk Foundation
Center for Protein Research

REGION H Herlev Hospital

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LEO

THANK YOU!