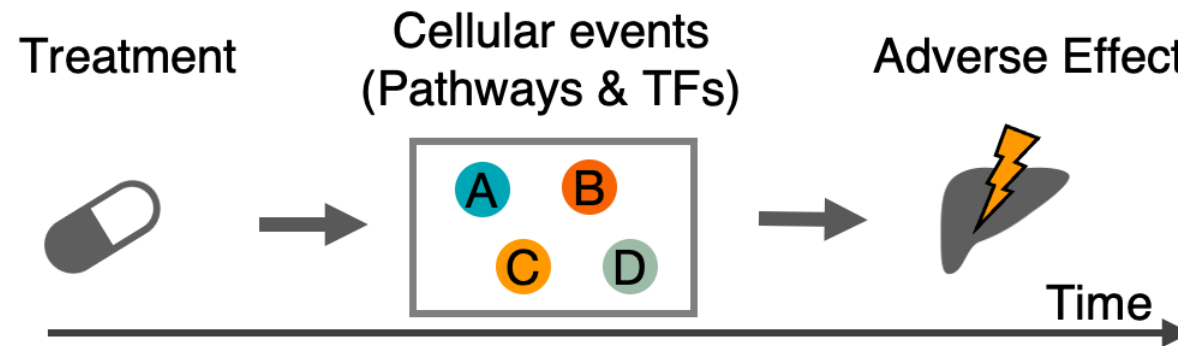


Deriving Time-Concordant Event Cascades from Gene Expression Data: A Case Study for Drug-Induced Liver Injury (DILI)

Anika Liu^{1,2,3}, Namshik Han^{1,4}, Jordi Munoz-Muriedas², Andreas Bender³

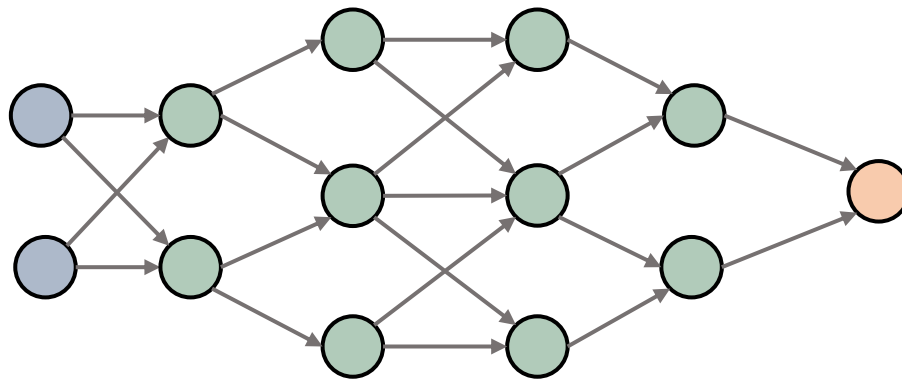
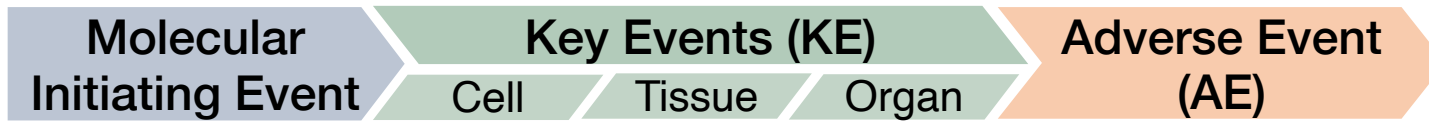
PLOS Comput. Biol. **2022**, 18 (6), e1010148. <https://doi.org/10.1371/journal.pcbi.1010148>.



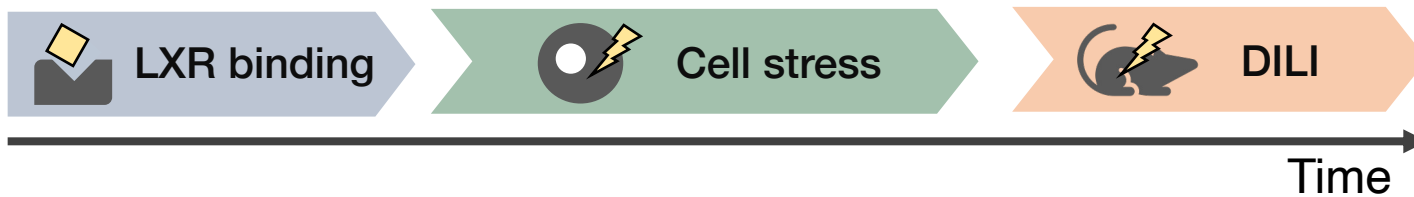
¹ Milner Therapeutics Institute, University of Cambridge, UK | ² Computational Sciences, GSK, UK | ³ Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, UK | ⁴ Cambridge Centre for AI in Medicine, Department of Applied Mathematics and Theoretical Physics, University of Cambridge, UK

Adverse Outcome Pathways (AOPs)

Formalizing mechanistic knowledge on adverse events



Example



Objectives

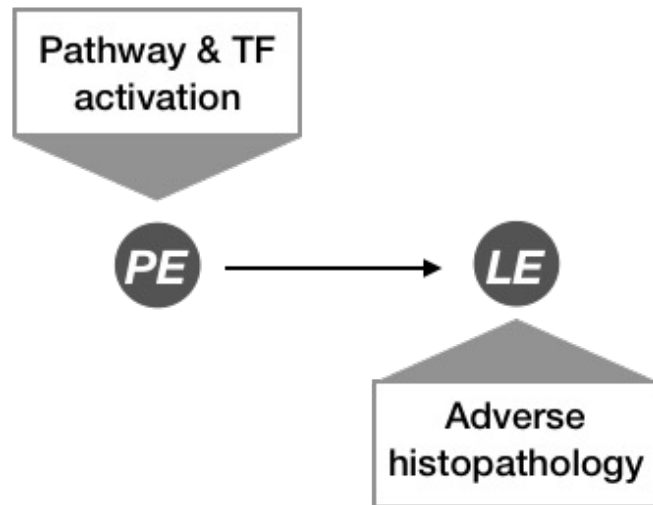
1. Quantify time concordance of KE-AE relationships



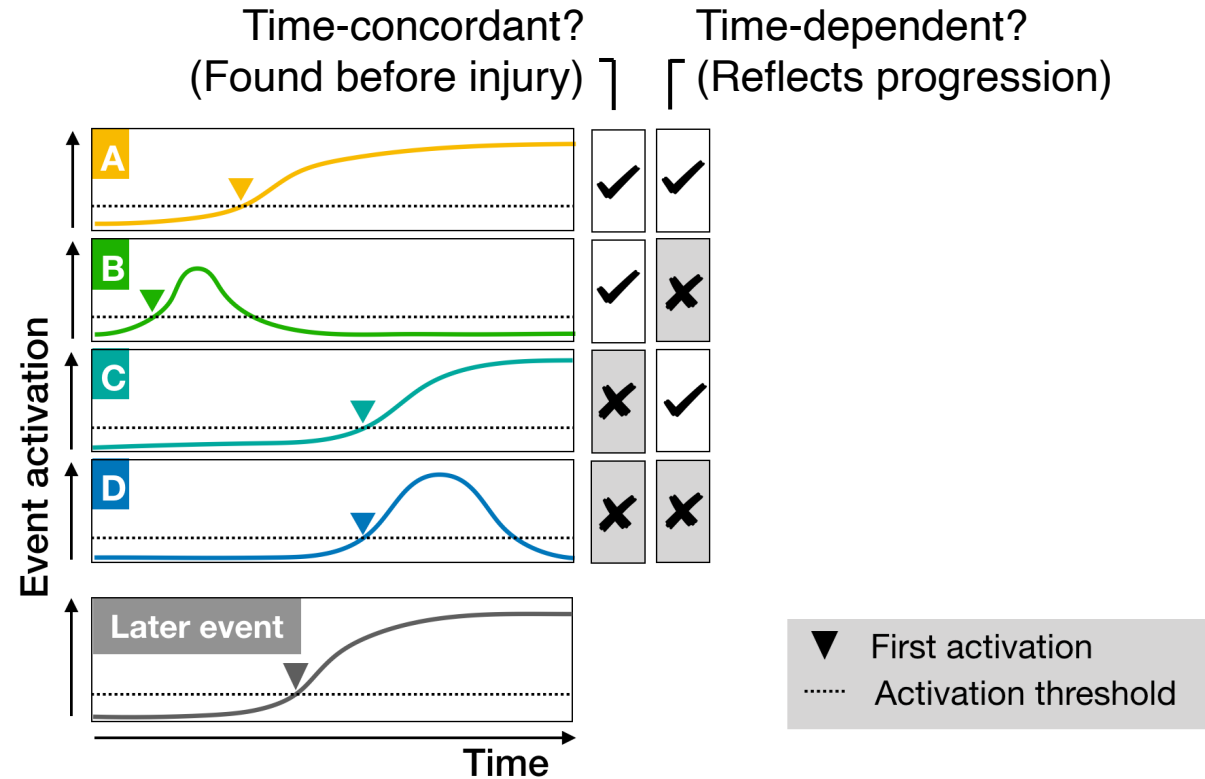
2. Identify new early key events in DILI



Distinction between time concordance and time dependence

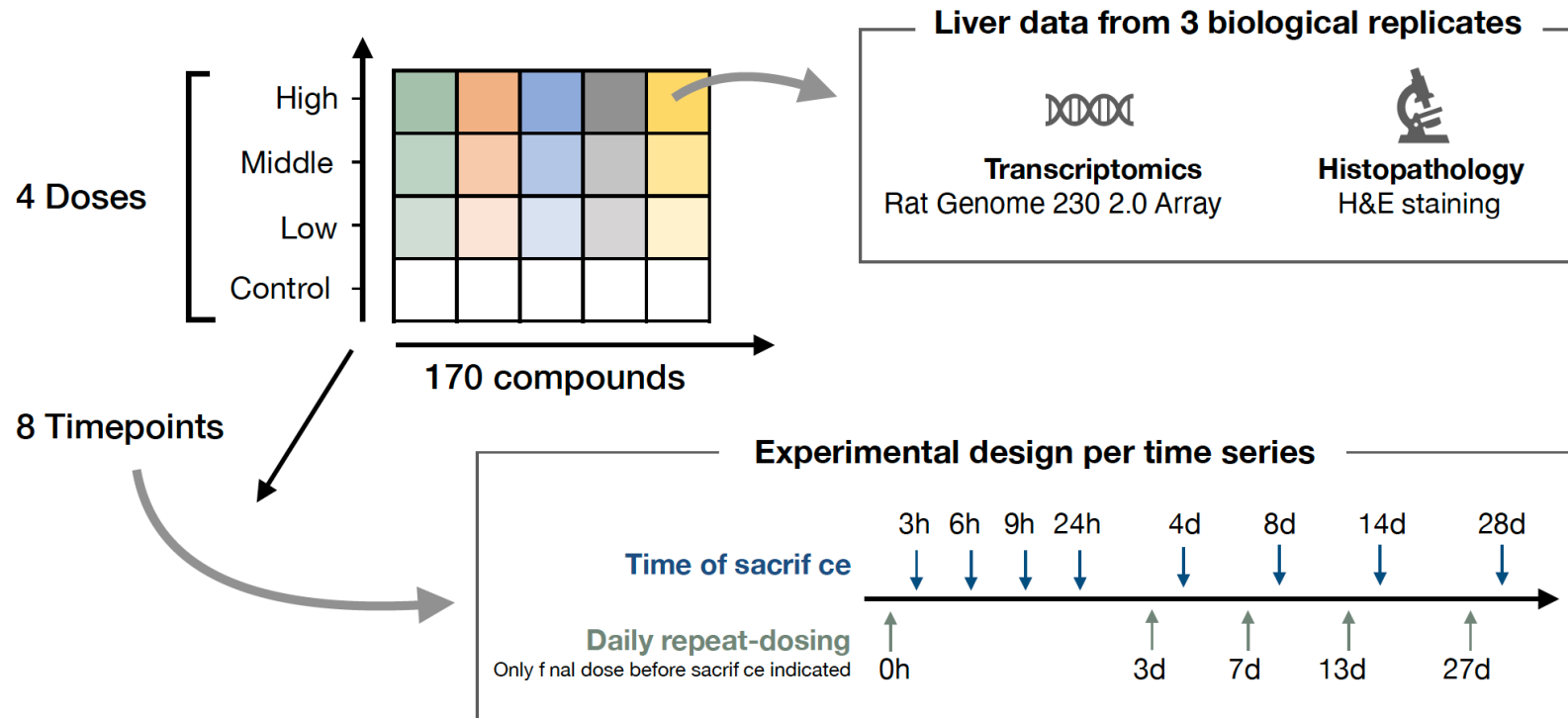


PE: Potential preceding event
LE: Potential later event or outcome

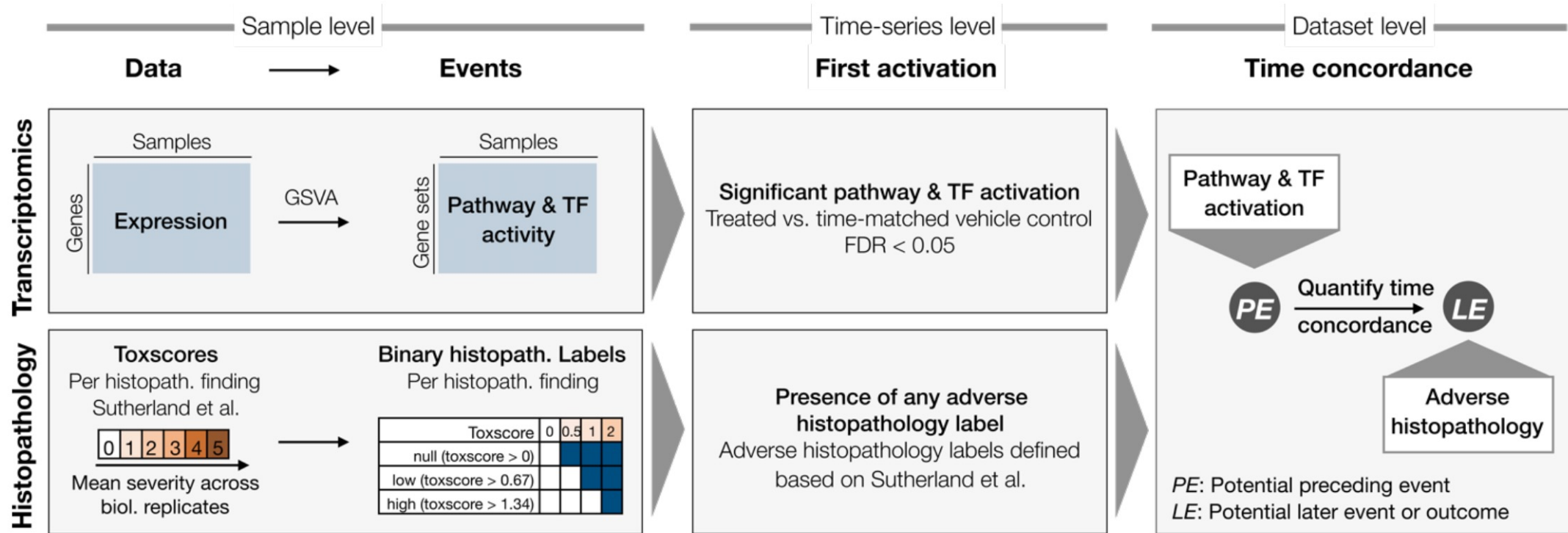


Open TG-GATEs

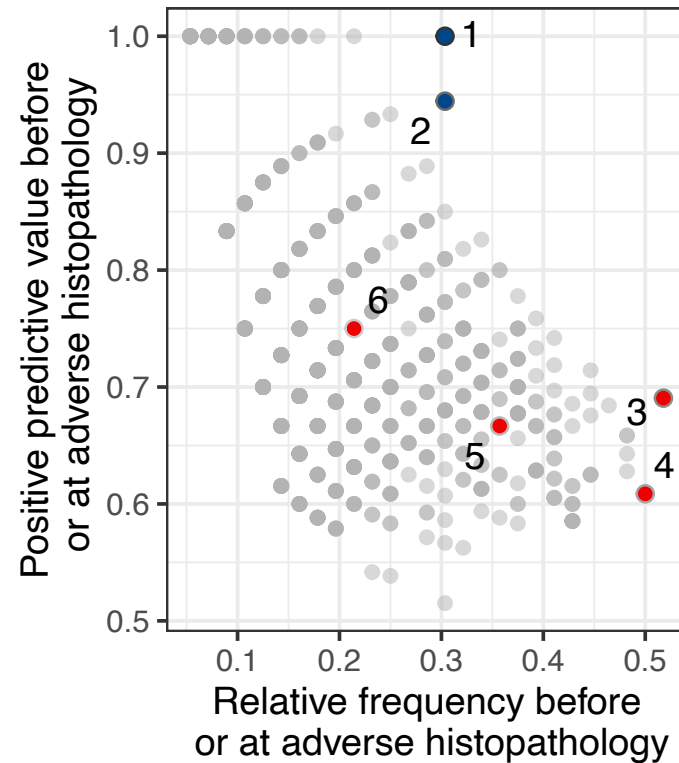
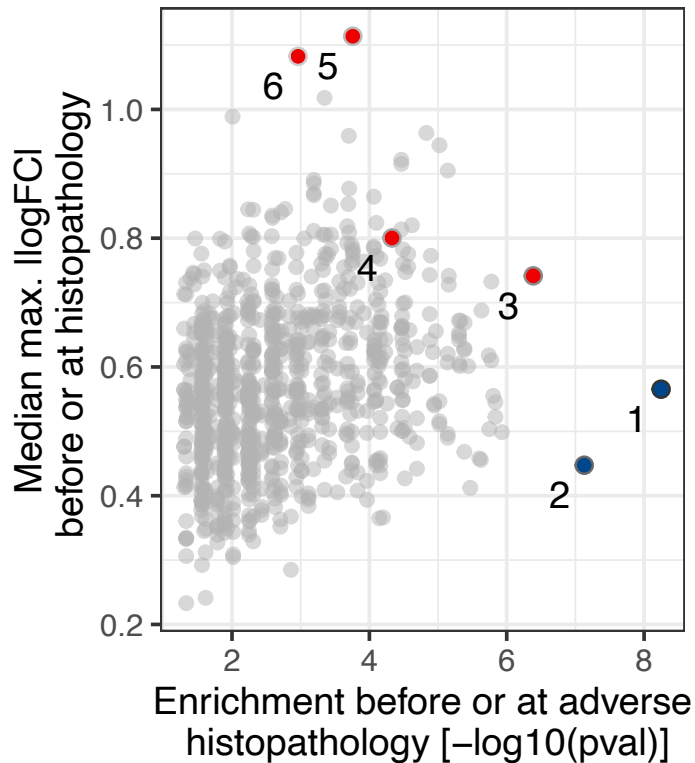
Toxicogenomics Project-Genomics Assisted Toxicity Evaluation System



Workflow to quantify time concordance between cellular events and adverse histopathology



Time concordance prioritizes known and plausible cellular events preceding adverse liver histopathology



- 1) Recycling of bile acids and salts
 - 2) Diseases associated with glycosaminoglycan metabolism
 - 3) Cytosolic tRNA aminoacylation
 - 4) Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S
 - 5) mitochondrial fatty acid beta-oxidation of unsaturated fatty acids
 - 6) Beta oxidation of decanoyl-CoA to octanoyl-CoA-CoA
- Down-regulated
● Up-regulated

DILI Cascades

Event class

TF
 Pathway
 Histopathology

Adverse histopathology ?

Biliary Hyperplasia (high), Biliary Hyperpla ▾

Use default from paper

Background histopathology ?

Nothing selected ▾

Use default from paper (None)

Include same time as time concordant ?

P-value cut-off:

0.0001 1

Summary Table

Copy CSV Excel Search:

event	direction	active	bg	ratio_active	ratio_bg	jaccard
Tfap4 (Down)	Down	13	2	0.224	0.0206	0.217
Hoxb13 (Down)	Down	11	1	0.19	0.0103	0.186
E2f2 (Up)	Up	19	8	0.328	0.0825	0.288
Sox13 (Down)	Down	13	3	0.224	0.0309	0.213
Tead1 (Down)	Down	11	2	0.19	0.0206	0.183
Foxl2 (Up)	Up	9	1	0.155	0.0103	0.153
Hnf4a (Down)	Down	9	1	0.155	0.0103	0.153
Mafb (Down)	Down	9	1	0.155	0.0103	0.153
Ebf1 (Down)	Down	14	5	0.241	0.0515	0.222
Etv4 (Down)	Down	15	6	0.259	0.0619	0.234

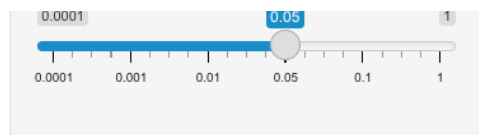
Showing 1 to 10 of 321 entries Previous **1** 2 3 4 5 ... 33 Next

1

Explore events preceding specific types of histopathology

https://anikaliu.shinyapps.io/dili_cascades

DILI Cascades



EDT1 (Down)	Down	14	5	0.241	0.0515	0.222
Etv4 (Down)	Down	15	6	0.259	0.0619	0.234

Showing 1 to 10 of 89 entries Previous 1 2 3 4 5 ... 9 Next

Plots

Multiple metrics overview

Two metrics in detail

x-axis

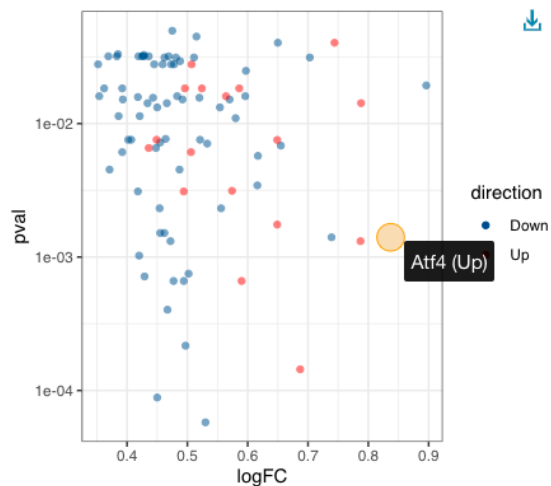
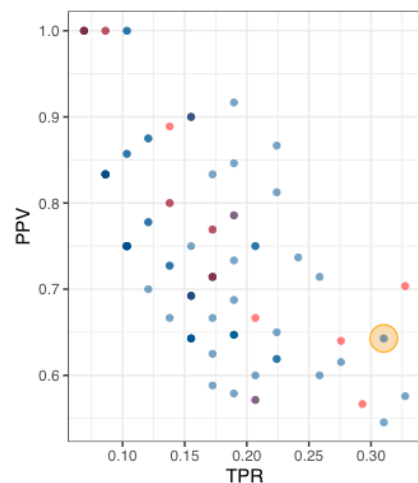
logFC

y-axis

pval

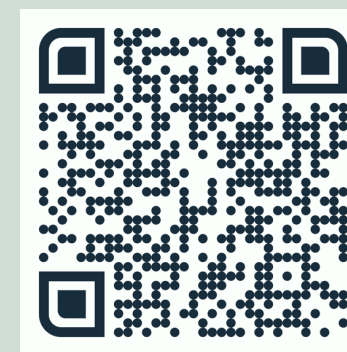
Logarithmic x-axis

Logarithmic y-axis



1

Explore events preceding specific types of histopathology



https://anikaliu.shinyapps.io/dili_cascades

DILI Cascades

DILI Cascades Overview **Before adverse histopathology** Two events of interest

Preceding event ?

Event class

TF Pathway Histopathology

Event

Atf4 (Up)

Later event ?

Event class

TF Pathway Histopathology

Event

Biliary Hyperplasia (high), Biliary Hyperplasia (low),

Use adverse conditions from paper

Definitions

Definition of preceding event (Source)

Occurrences of any of the following TF events: Atf4 (Up)

Definition of later event (Target)

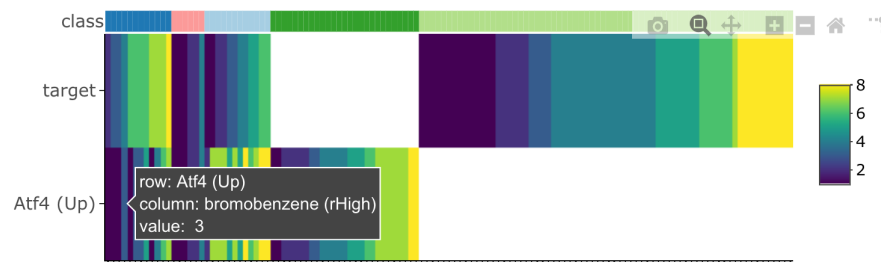
Occurrences of any of the following Histopathology events: Biliary Hyperplasia (high), Biliary Hyperplasia (low), Biliary Hyperplasia (null), Fibrosis (low), Fibrosis (null), Hepatocellular Necrosis (high), Hepatocellular Necrosis (low), Hepatocellular Single Cell Necrosis (high), Hepatocellular Single Cell Necrosis (low), Hepatocellular Single Cell Necrosis (null), Increased Hepatocellular Mitosis (high), Inflammation (low)

Results

Overview

Individual time series

Heatmap



Color legend

3 hr 6 hr 9 hr 24 hr 4 day 8 day 15 day 29 day

1 2 3 4 5 6 7 8

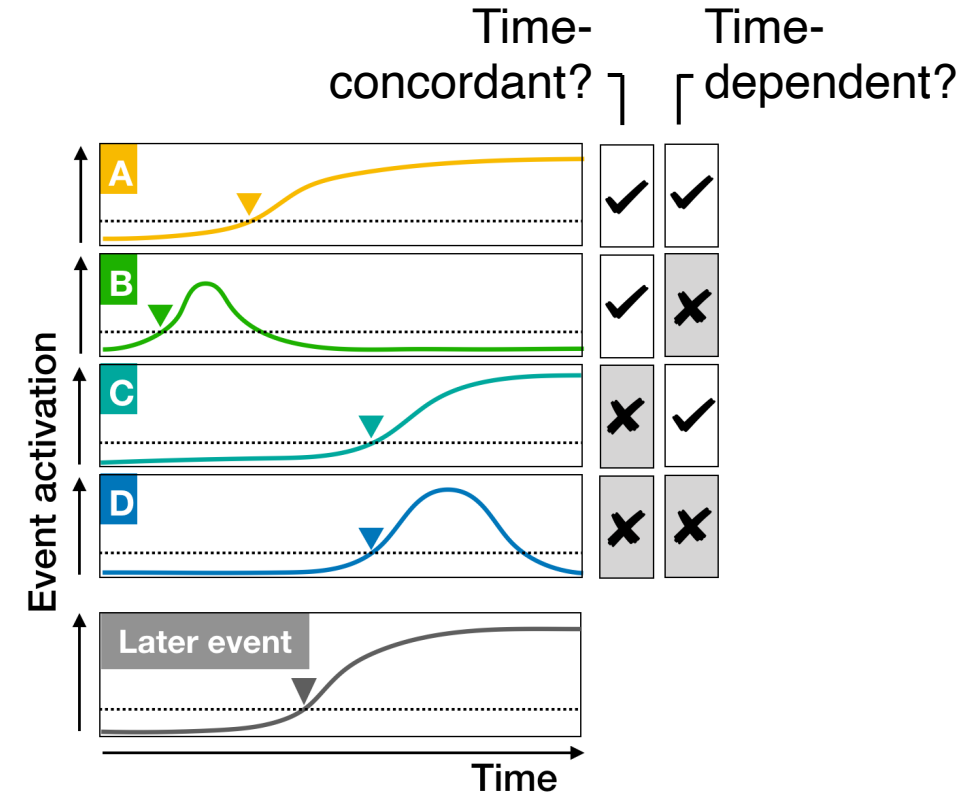
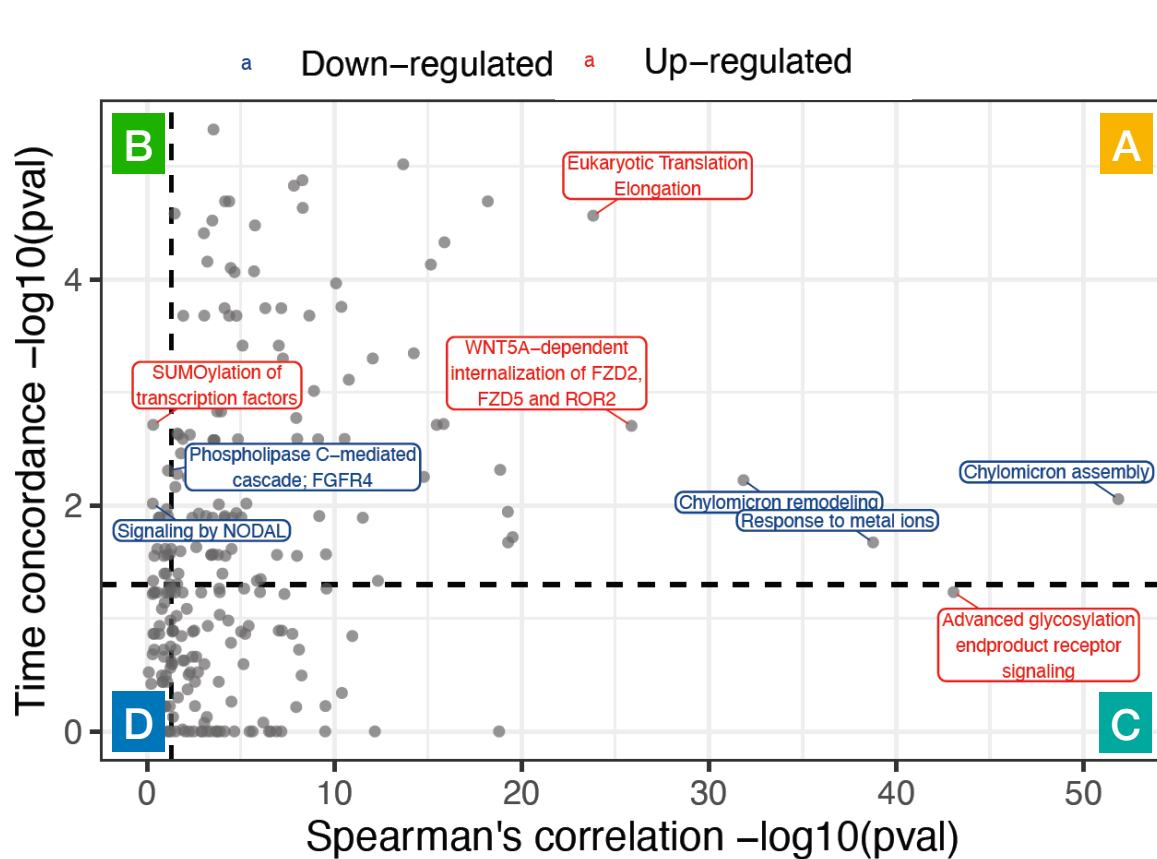
2

Explore the relation between two events in more detail



https://anikaliu.shinyapps.io/dili_cascades

Time concordance vs. time-dependence

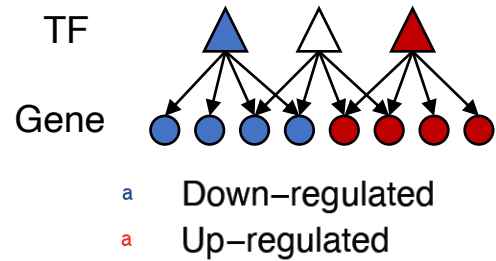


▼ First activation
 Activation threshold

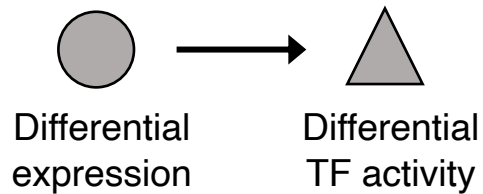
- 86.1% and 70.4% of the time concordant pathways and TFs are time-dependent
- 59.9% and 48.7% of the time-dependent pathways and TFs are time-concordant

TF case study: Time concordance of TF expression and activity sheds light on mode of activation

1) Inference of TF activity^[1]

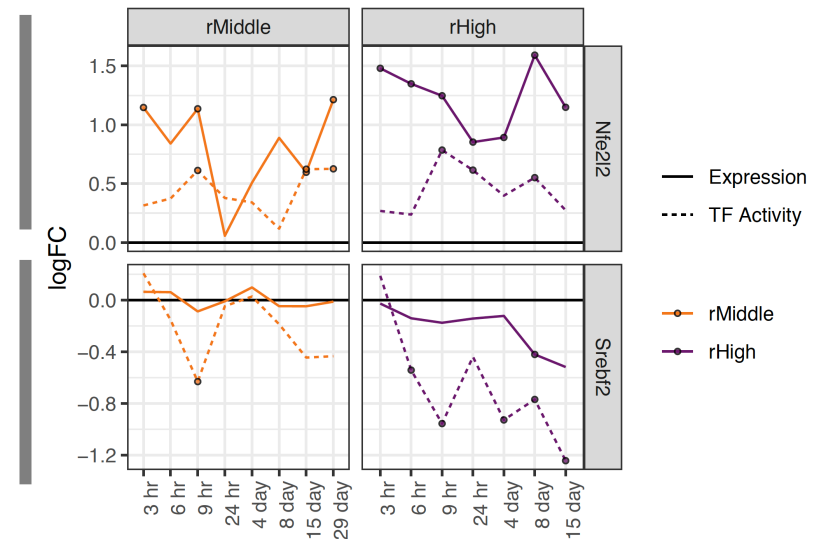


2) Evidence of transcriptional induction?

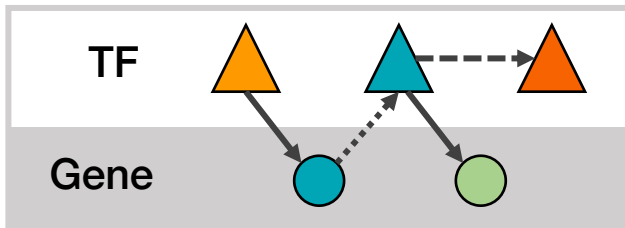


Induced TF
Differential expression
before TF activity

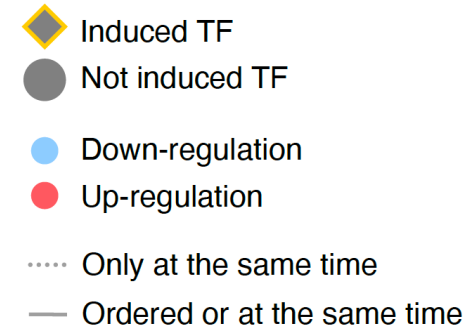
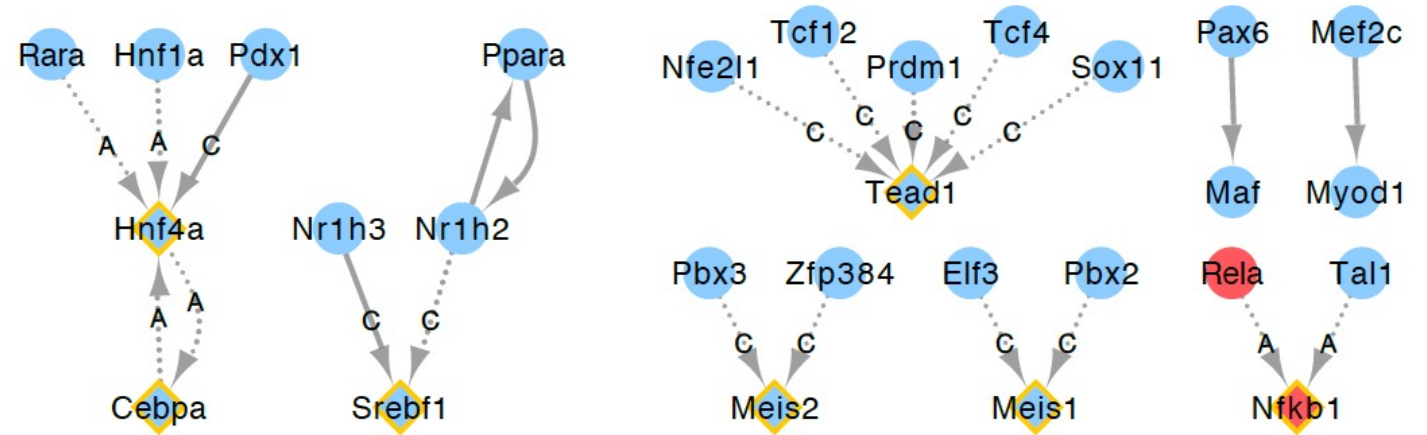
Directly activated TF
No differential expression
before TF activity



TF case study: Time concordance combined with a prior knowledge network sheds light on TF interactions



- Central dogma of molecular biology
- TF-target gene interaction^[1]
- Protein-protein interaction^[2]



Summary

- Time concordance, derived from time-resolved transcriptomics and histopathology data, is able to prioritize mechanistically relevant events in DILI.
- Combining time concordance and prior knowledge, we can generate detailed hypotheses on the mode of regulation and upstream regulators of time-concordant TFs.
- We provide an app, allowing users to study time concordance in more detail for specific events

Deriving time-concordant event cascades from gene expression data: A case study for Drug-Induced Liver Injury (DILI)

Anika Liu, Namshik Han, Jordi Munoz-Muriedas, Andreas Bender

PLoS Comput. Biol. **2022**, 18 (6), e1010148.
<https://doi.org/10.1371/journal.pcbi.1010148>.

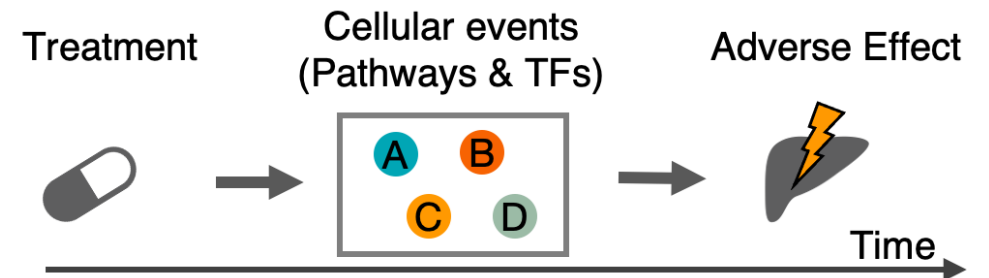
Acknowledgements



- Andreas Bender
- Namshik Han
- Bender Group
- Han Group



- Jordi Munoz Muriedas



App