Quantitative Modelling of Adverse Outcome Pathway for Risk Assessment

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I. Introduction

I.1. Toxicology in general

- Toxicology
  - Application domains: Cosmetics, Drug, etc.
- Objective: Risk assessment
- Approaches (Different types of routines)
  - *In vivo* test: Animal experiments
  - Alternative methods
    - *In vitro* test (Classic) - fast
    - *In vitro* test (advanced): High throughput screening - very fast
    - *In silico* test: computational modelling and simulation - we are working on this

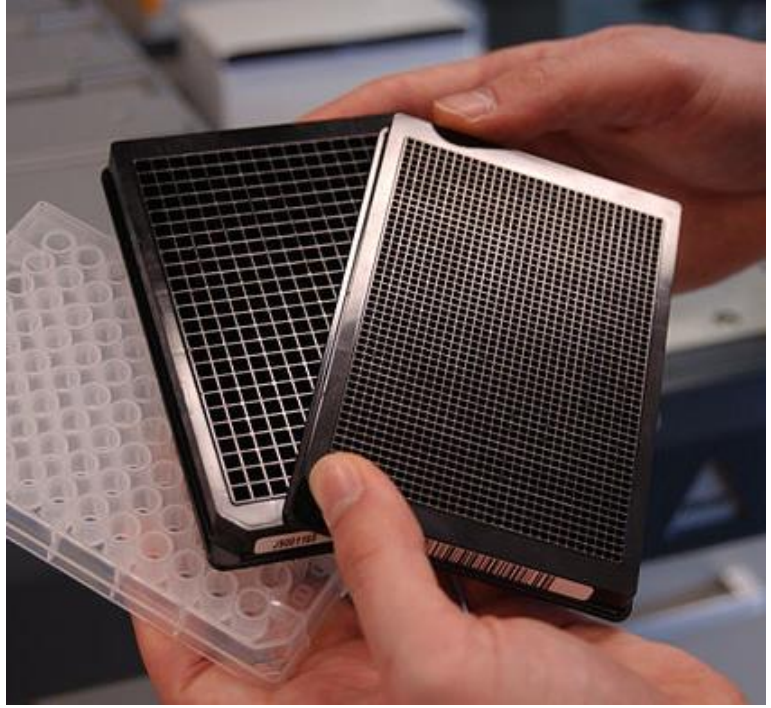
High-throughput screening

Robotic tools

384, 1536, 3456 wells

- Fast

- Low-cost



I.2. Project Eu-ToxRisk21

"An Integrated European 'Flagship' Programme Driving **Mechanism-based Toxicity Testing** and **Risk Assessment** for the 21st century."

Organisation :

- Long range 2016-2020 research program
- 41 international research teams (40 EU + 1 USA) from 13 countries
- 14 Work packages with sub-objectives
  - WP 10 : **Computational Modelling for Risk assessment**

Motivation :

- Partially replace animal experimentations
- Improve the predictive methods based on high-throughput toxicity tests

15 Case studies

Liver

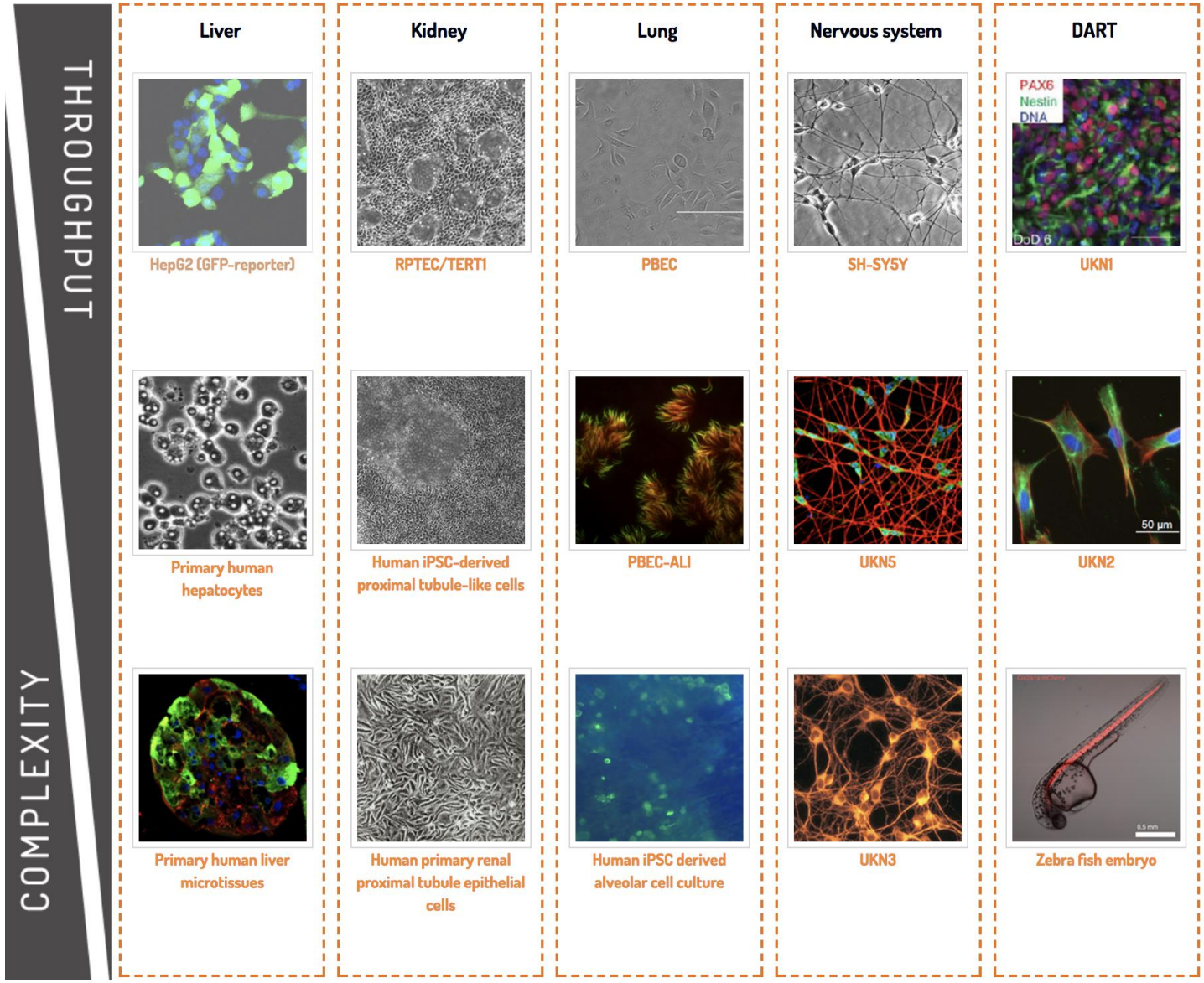
Kidney

Lung

Nervous system

Etc.

15 Cases are studied in the program Eu-ToxRisk21



I.3. AOP and qAOP

- **EU-ToxRisk21**
  - An Integrated European 'Flagship' Programme Driving **Mechanism-based** Toxicity Testing and **Risk Assessment** for the 21st century

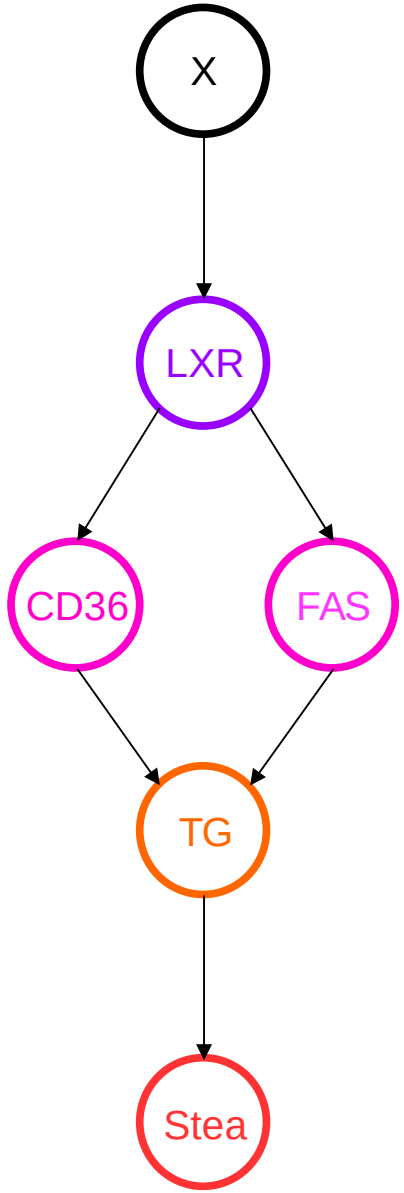
- **AOP :** Adverse outcome pathway – qualitative tool for **mechanism description**
- **qAOP :** quantitative AOP for **risk assessment**

Remark : Each case study corresponds to a set of AOPs.

AOP and qAOP

AOP : Adverse outcome pathway

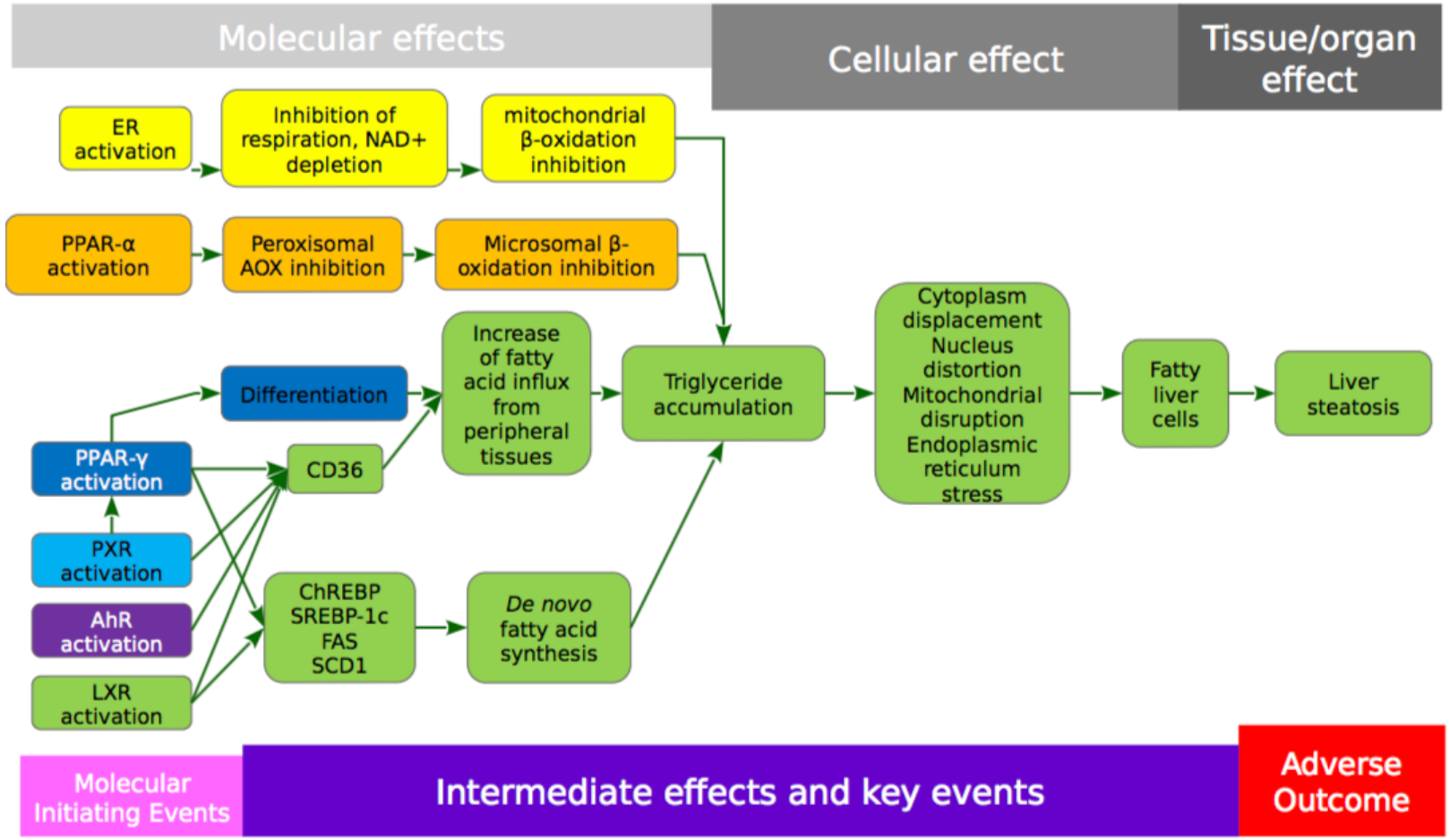
- Knowledge Exchange
- A qualitative tool for the structural representation of causal relationships (Dose-response)
  - Starting from a molecular perturbation (MIE)
  - Through key events (KE)
  - Arriving at an adverse outcome (AO)
- In this case : AO = Steatosis (fat liver)
- qAOP = quantitative AOP:
  - **Probabilistic model**
  - Predictive capacity : Decision Support Tool



A richer version of AOP : AOP Network

- Each node may have more than one parent.
- One node can be involved in different AOPs

9 AOPs are hidden here



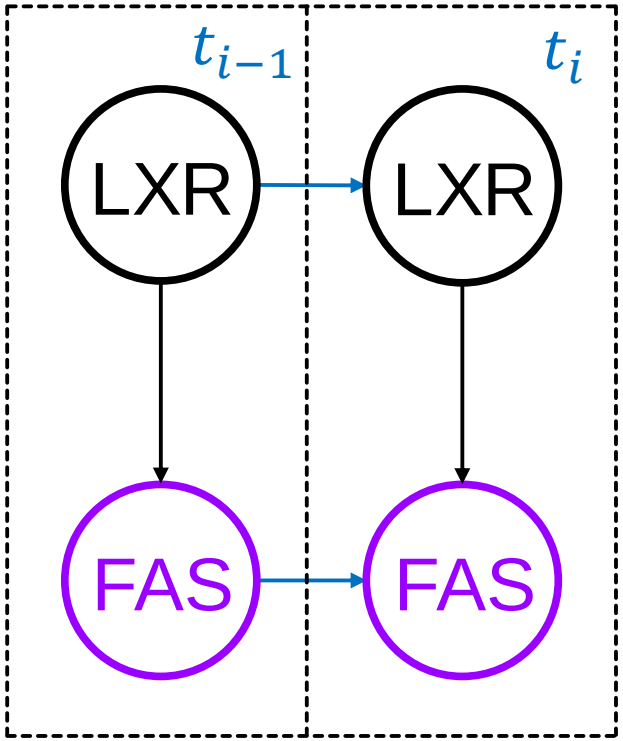
I.4. Objectives of my thesis

Objectives :

- Probabilistic modelling of AOP =: qAOP
- => Prediction of AO

Action plan :

- Fixed structure for mini AOP
  - Modelling of the strength cause-effect
  - Prediction
- Structural learning : more ambitious



II. Probabilistic Model

II.1. BN : Bayesian Networks

Def : BN : $(\mathcal{G}, P_{\mathcal{G}})$ with

- $\mathcal{G}$: BN Structure : DAG directed acyclic graph $\mathcal{G}(V, E)$
  - V : Set of vertices, nodes : variables $V = \{X_i | i \in 1{:}N\}$
  - E : Set of directed edges : causality relationships
- $P_{\mathcal{G}}$: multivariate distribution over V
  - specified as set of local conditional probability distribution (CPDs) associated with $\mathcal{G}$'s nodes.

$$P_{\mathcal{G}}(X) = \prod_{i=1:N} P_{\mathcal{G}}(X_i | \mathrm{Par}(X_i))$$

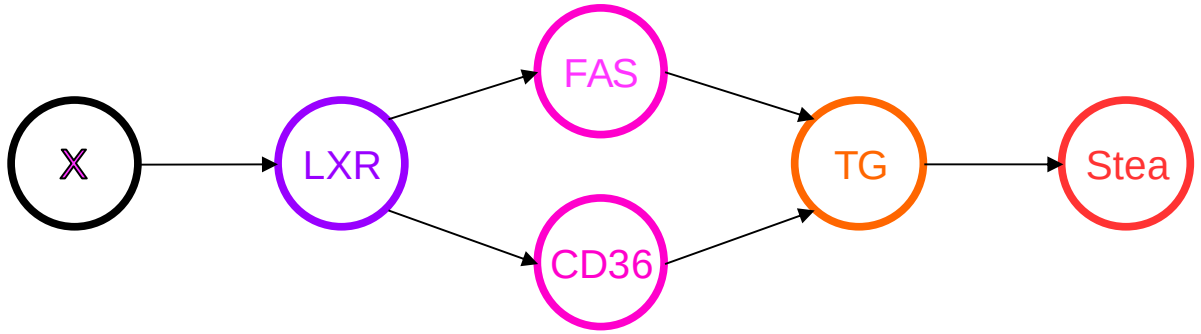
with $X = (X_1, \dots X_i, \dots X_N)$ system stat vector

BN : Bayesian Networks

$$P_{\mathcal{G}}(X) = \prod_{i=1:N} P_{\mathcal{G}}(X_i|\mathrm{Par}(X_i))$$

Local conditional distributions (CPD) and the DAG completely determine the joint distribution

Example : steatosis case



$$P(X, L, C, F, T, S) = P(X)P(L|X)P(C|L)P(F|L)P(T|C, F)P(S|T)$$

Problem in the context of qAOP : Child node = function (Parent node(s) , **time**)

II. 2. DBN : Dynamic Bayesian Networks

Extension of BNs to handle temporal models

Assumptions :

- the timeline discretised into a set of *time slices* :

$X^{(t_0)}, X^{(t_1)}, \ldots, X^{(t_m)}$, with m the number of observations

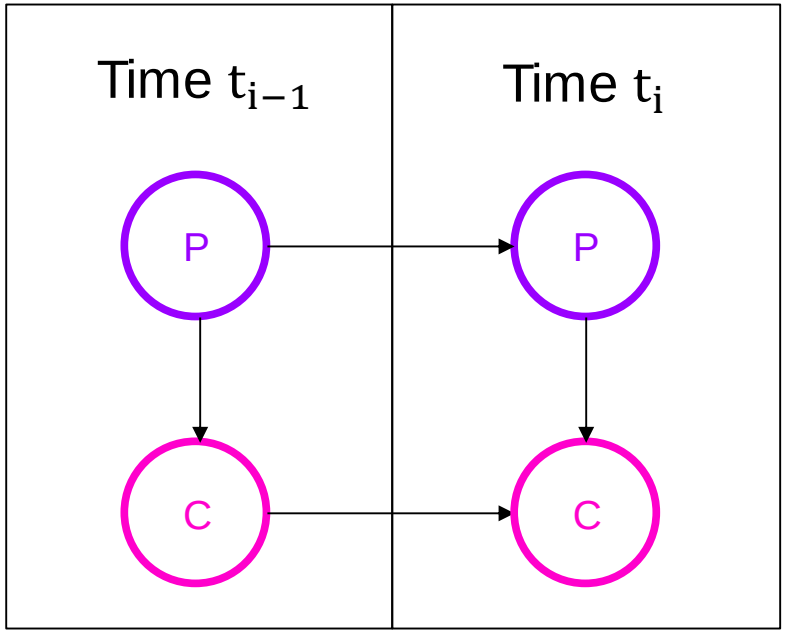
- Markov assumption for a dynamic system over the template variables X : $\forall\, i \in \mathbb{N}^+$

$$X^{(t_{i+1})} \perp X^{(t_0:(t_{i-1}))} | X^{(t_i)}$$

Two types of dependency :

- Inter time-slice dependency (between time-slices)

- Intra time-slice dependency (in the same time-slice)



C child node : C_t child node at time t
P parent node : P_t parent node at t

DBN : Dynamic Bayesian Networks

Markov assumption :

$$X^{(t_{i+1})} \perp X^{(t_0:(t_{i-1}))} | X^{(t_i)}$$

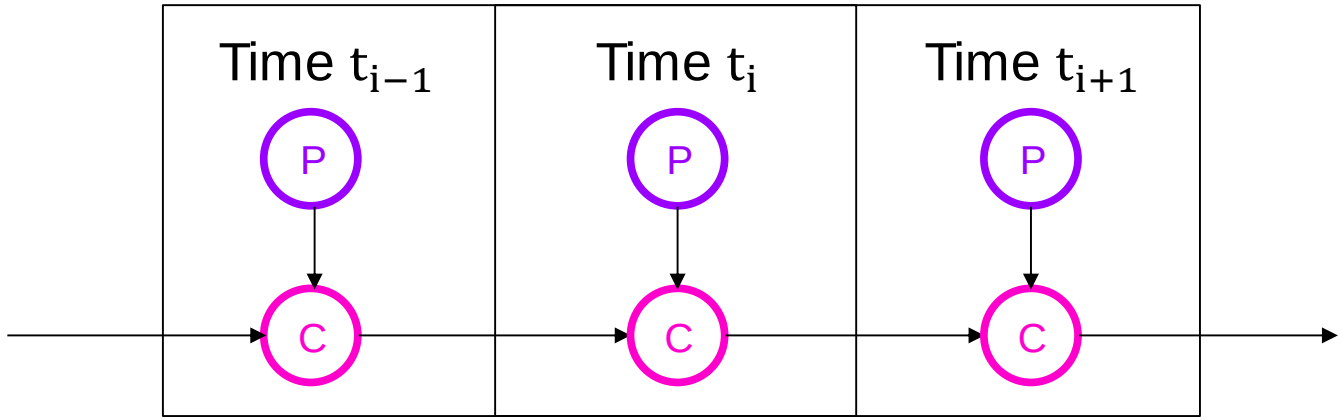
Compact definition of the joint probability distribution in DBN

$$P\left(X^{(t_0:t_m)}\right) = P\left(X^{(t_0)}\right) \prod_{i=1}^{m} P\left(X^{(t_i)} | X^{(t_{i-1})}\right)$$

Example : Linear Dynamic System

Classic linear DBN

$$\mathbb{E}[C_{t_i}] = \alpha + \beta_{prev} C_{t_{i-1}} + \beta_{curr} P_{t_i}$$



Insights about qAOP

Data visualization DEMO : Real data for kidney disease case study

Dynamic 3D plot GSH-DCF-Time (online) (local)

- S_C : Stationary state (Saturation level) of child node, denote :
- $S_C = f(P_t)$: Dependence of S_C on P_t
- C_t : Child node activity at time t
- C_t converges to S_C over time

II.3. Model family for qAOP : Embryonic form

$$S_C[P_t] - \mathbb{E}[C_t] = (S_C[P_t] - C_{t-h})e^{-\nu h}$$

- C_t : Child node activity at time t, (observed)
- P_t : Parent node(s) activity at time t, I could be a vector (observed)
- $S_C[P_t]$: stationary state of child node given its parent(s) (unobserved)

Questions :

$S_C[P_t] = ?$

$h \in \mathbb{R}^+$: non regular observation ?

$\nu > 0$: to ensure the convergence of C_t towards $S_C(P_t)$

Model family for qAOP : Linear model

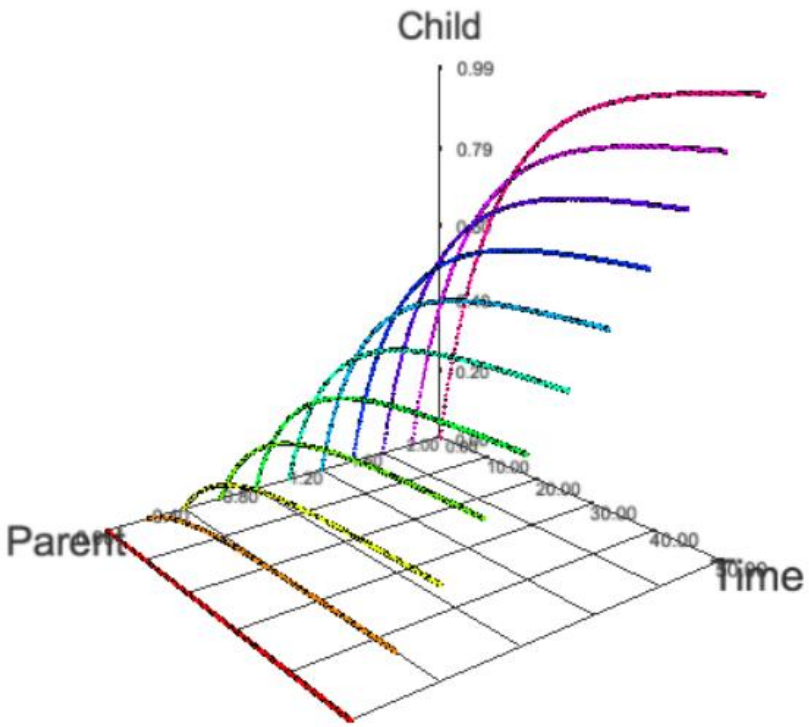
$$\begin{cases} S_C[P_t] - \mathbb{E}[C_t] = (S_C[P_t] - C_{t-h})e^{-\nu h} \\ S_C[P_t] = \beta P_t + \beta_0 \\ h \in \mathbb{R}^+ \end{cases} \qquad (\mathcal{M}_L)$$

Assumption : Stationary stat of Child node is a **linear function** of parent node(s)

Remark : The classic linear DBN model is a special case of $(\mathcal{M}_L)$

- $S_C[P_t] = \frac{\beta_{curr}}{1-\beta_{prev}} P_t + \frac{\alpha}{1-\beta_{prev}}$
- $h = 1$
- $e^{-\nu h} = e^{-\nu} = \beta_{prev}$

$$\mathbb{E}[C_{t_i}] = \alpha + \beta_{prev} C_{t_{i-1}} + \beta_{curr} P_{t_i}$$



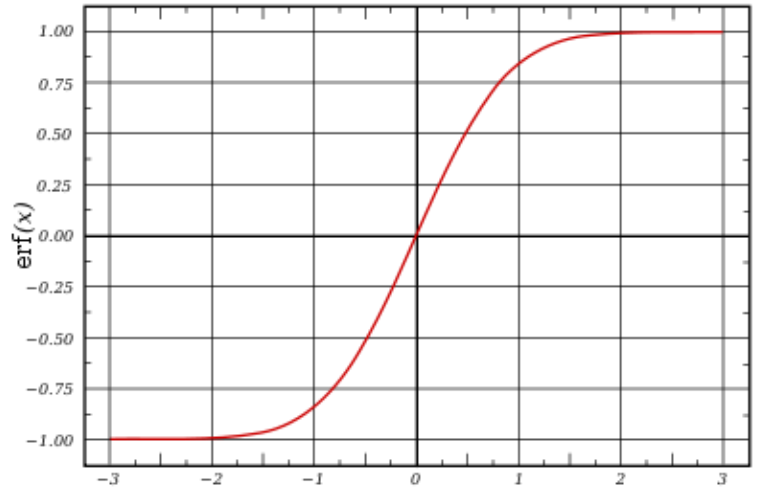
Demo (online)

Model family for qAOP : Sigmoid model

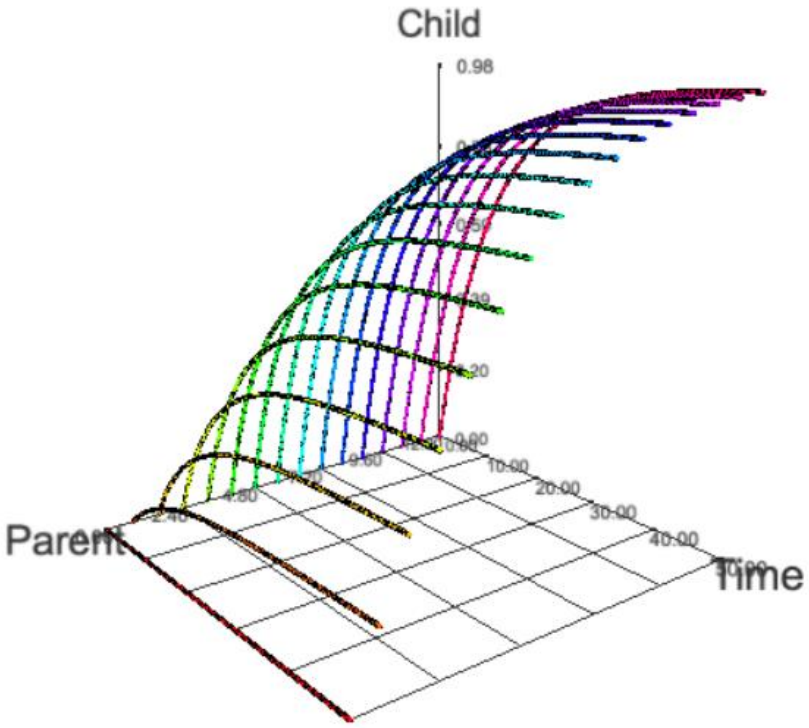
$$\begin{cases} S_C[P_t] - \mathbb{E}[C_t] = (S_C[P_t] - C_{t-h})e^{-\nu h} \\ S_C[P_t] = \alpha_{\max}\,\mathrm{Sigmoid}[\beta P_t + \beta_0] \\ h \in \mathbb{R}^+ \end{cases} \qquad (\mathcal{M}_S)$$

With

- $\mathrm{Sigmoid}[x] = \frac{1}{1+e^{-x}} - \frac{1}{2}$
  - Odd
  - Bounded $[-1,1]$



Assumption : The stationary stat of Child node is a **sigmoid function** of parent node(s)



Demo (online)

III. Inference

III.1. Input – **Steatosis** (real)

Real public domain databases (available before my thesis)

- ToxCast
- TG-Gate

DEMO : Steatosis real data (use online DEMO link)

Problems :

The experiments are not designed for qAOP modelling.

- Very few number of data : 3 endpoints
- Discretization assumption may fail because the measurements of the system state taken at intervals that are regularly spaced with a predetermined time granularity Δt
- observations on time $t = 2h\ 8h$ and $24h$

Input – **Steatosis** (simulated)

Data simulated from pharmacokinetics models based on ODE

Three virtual experimentation conditions:

- One injection of chemical X, without dicreasing feature $\forall i \in I,\ \mathrm{C}_X^{(t_i)} = \mathrm{C}_X^{(0)}$

- One injection of chemical X, with decreasing feature. $\forall i \in I,\ \mathrm{C}_X^{(t_i)} < \mathrm{C}_X^{(t_{i-1})}$

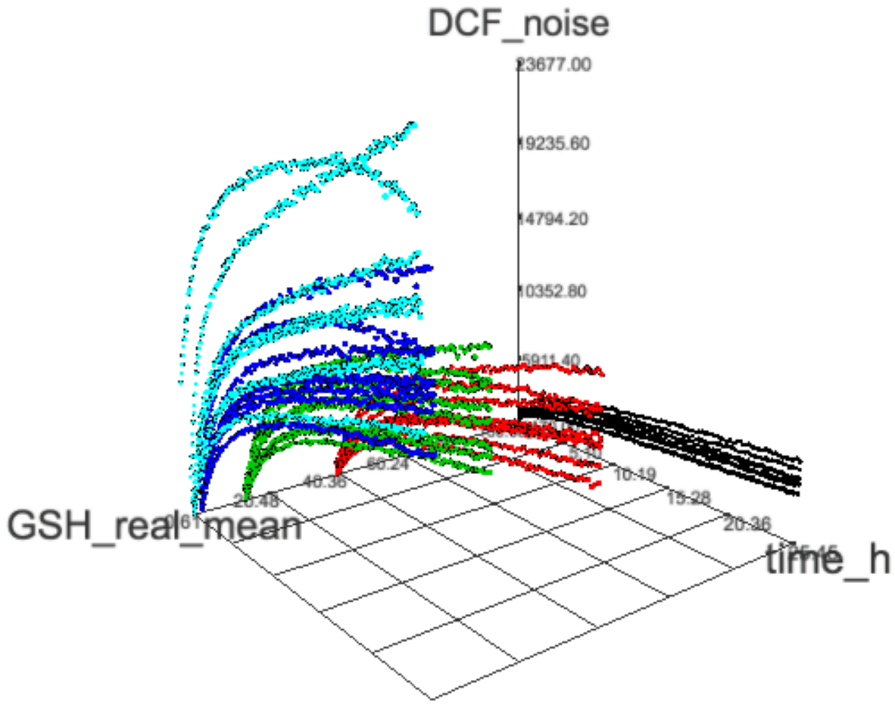
- Four injection of chemical X, with decreasing feature : $\frac{\mathrm{C}_X^{(0)}}{4}$ each time

[online DEMO : Steatosis Generated data]

Input – **Kidney disease** (real)

Data of kidney disease from Eu-ToxRisk21

- 5 doses
- 8 replicates
- 103 observations endpoints
  - measured on time $t_i = 1 + 15 \times (i - 1)$ minutes $\forall i \in 1:10$



III.2. Parameters learning : linear model

$$\begin{cases} S_C[P_t] - \mathbb{E}[C_t] = (S_C[P_t] - C_{t-h})e^{-\nu h} \\ S_C[P_t] = \beta P_t + \beta_0 \\ h \in \mathbb{R}^+ \end{cases} \qquad (\mathcal{M}_L)$$

Parameter estimation based on observations

Frequentist approach

$$\hat{\theta}_{ML} = \underset{\theta \in \Theta}{\operatorname{argmax}} L(\theta|\mathcal{D}) = \underset{\theta \in \Theta}{\operatorname{argmax}} P(\mathcal{D}\,|\theta)$$

Bayesian approach

$$\hat{\theta}_{MAP} = \underset{\theta \in \Theta}{\operatorname{argmax}} P(\mathcal{D}\,|\theta)\pi(\theta)$$

- Algorithm MCMC under the probabilistic programming language "**stan**"

III.3. Implementation: Simulated data

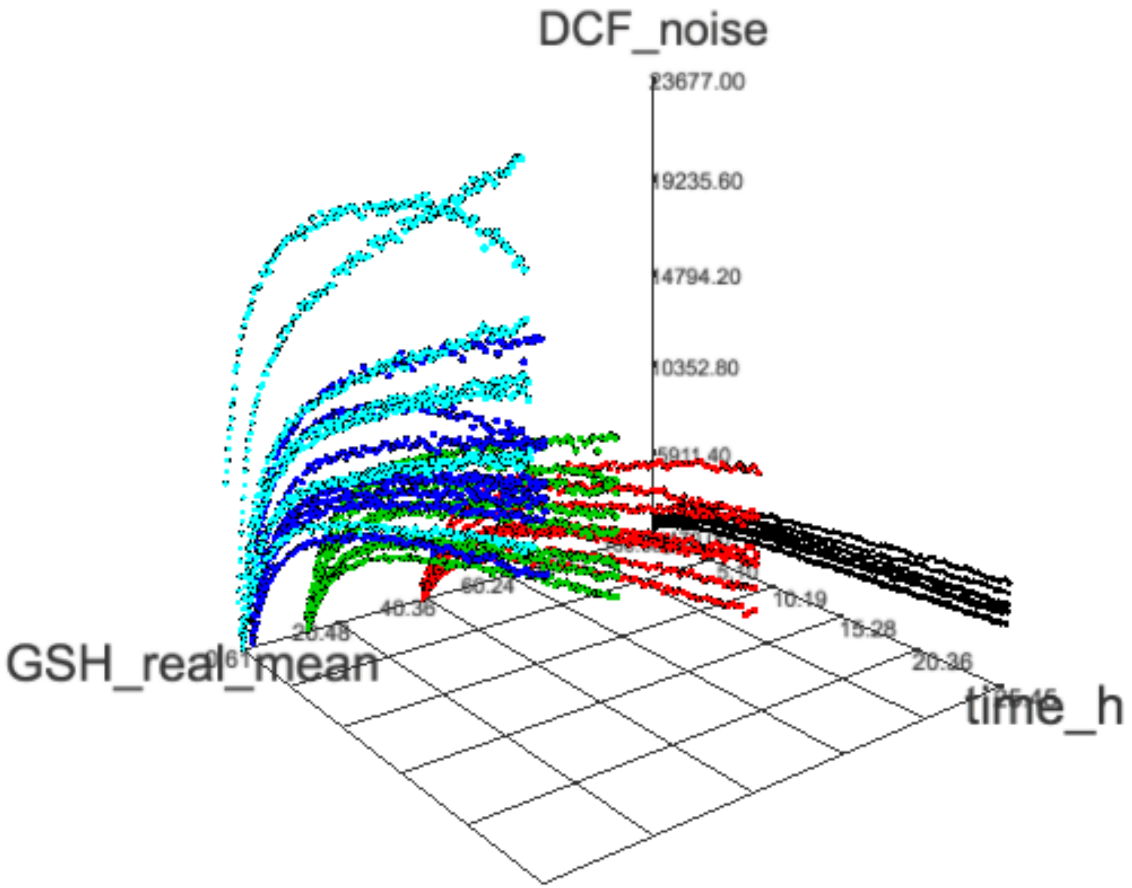
Parameter learning for a local conditional model :

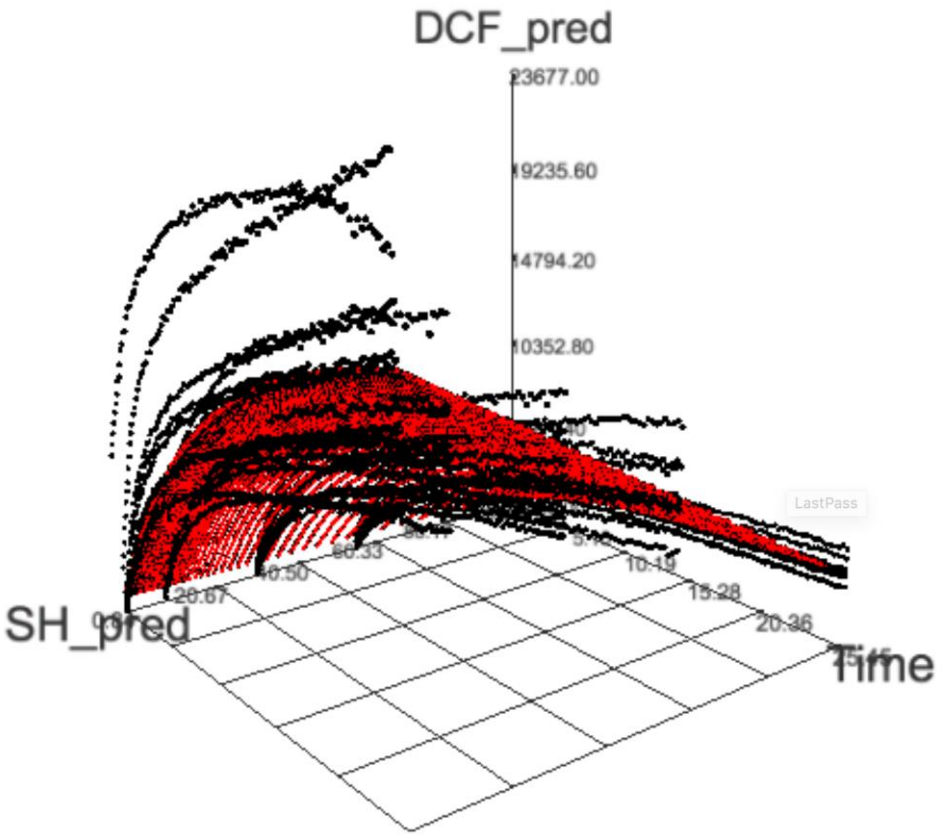
$$P(FAS \mid LXR, t)$$

Result :

- Sigmoid model works significantly better with small set of data
- The linear model works as well as Sigmoid with large set of data

Implementation : Kidney disease (real)





[3D Plot (online)]

IV. Conclusion

Conclusion

- Proposition of qAOP model family: Linear model, Sigmoid model
- Application on Steatosis (real), steatosis (simulated), kidney disease (real).
  - Steatosis (real): Not fit well, not enough data.
  - Steatosis (simulated):
    - The sigmoid model fits better when only few data are available
    - The Linear model fits as well as the sigmoid model when more data are available
  - Kidney disease (real):
    - Linear models can well fit the database.

Future steps:

- Test sigmoid model on Kidney disease data
- Test model performance (behaviour) on simulated data with more nodes in AOP
- qAOP network problems: hierarchical DBN.

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Thank you for your attention