Towards building a Bayesian Network COPD model

PMI RESEARCH & DEVELOPMENT

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Outline

- Context
  - Bayesian Networks and Disease Biology
  - Objectives
- Data
  - Sources and Processing
- Case Study (Human *in vivo* sub-model)
  - From Cigarette Smoke to FEV1
- Hugin Model
- Issues
- Next Steps

Context - Bayesian Networks (BN)

- A Bayesian network (or a belief network) is a probabilistic graphical model (directed acyclic graph) that represents a set of variables and their probabilistic independencies.

- Nodes can represent any kind of variable, be it a measured parameter, a latent variable, or a hypothesis. They are not restricted to representing random variables. Links, on the other hand, represent causal relationships.

- The network structure of a BN can either be learned from data (bottom-up) or specified by experts (top-down).

- In order to fully specify the Bayesian network and thus fully represent the joint probability distribution, it is necessary to specify for each node X the probability distribution for X conditional upon X's parents.

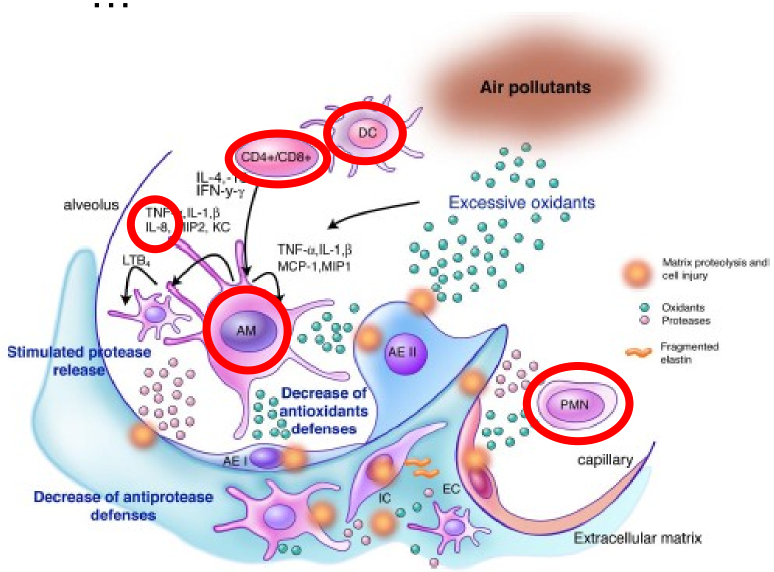
(adapted from Wikipedia)

Context - Disease Biology

- Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by airflow limitation that is poorly reversible with bronchodilators (unlike asthma). The airflow limitation usually gets progressively worse over time.
- COPD is strongly linked to exposure to noxious particles or gases, such as cigarette smoke, which trigger an abnormal inflammatory response in the lung.
- The inflammatory response in the larger airways is known as **chronic bronchitis**, whereas in the alveoli, the inflammatory response causes the progressive destruction of the lung tissue known as **emphysema**.
- The natural course of COPD is characterized by the occasional sudden worsening of symptoms called acute exacerbations, caused mainly by infections or air pollution.

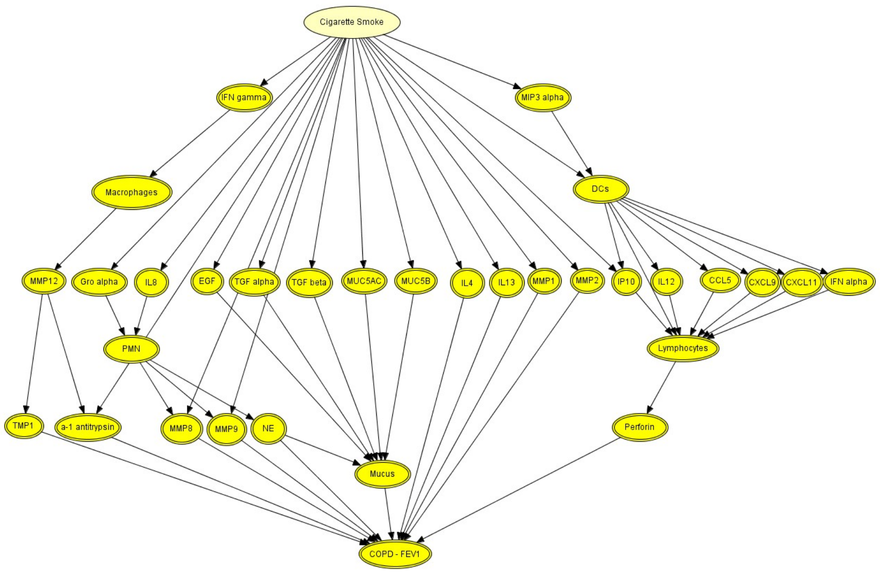
Context – From Disease to a BN COPD Model

- In-house COPD experts provided us with the main pathways involved in the development of COPD:
  - CS → Epithelium → IL-8 → PMNs → NE, MMP8, MMP9 → COPD/FEV1
  - CS → Macrophages → IL-8 → PMNs → NE, MMP8, MMP9 → COPD/FEV1
  - …



Yoshida & Tuder, 2007 (Fig. 2)

Main pathways



Context – Objectives

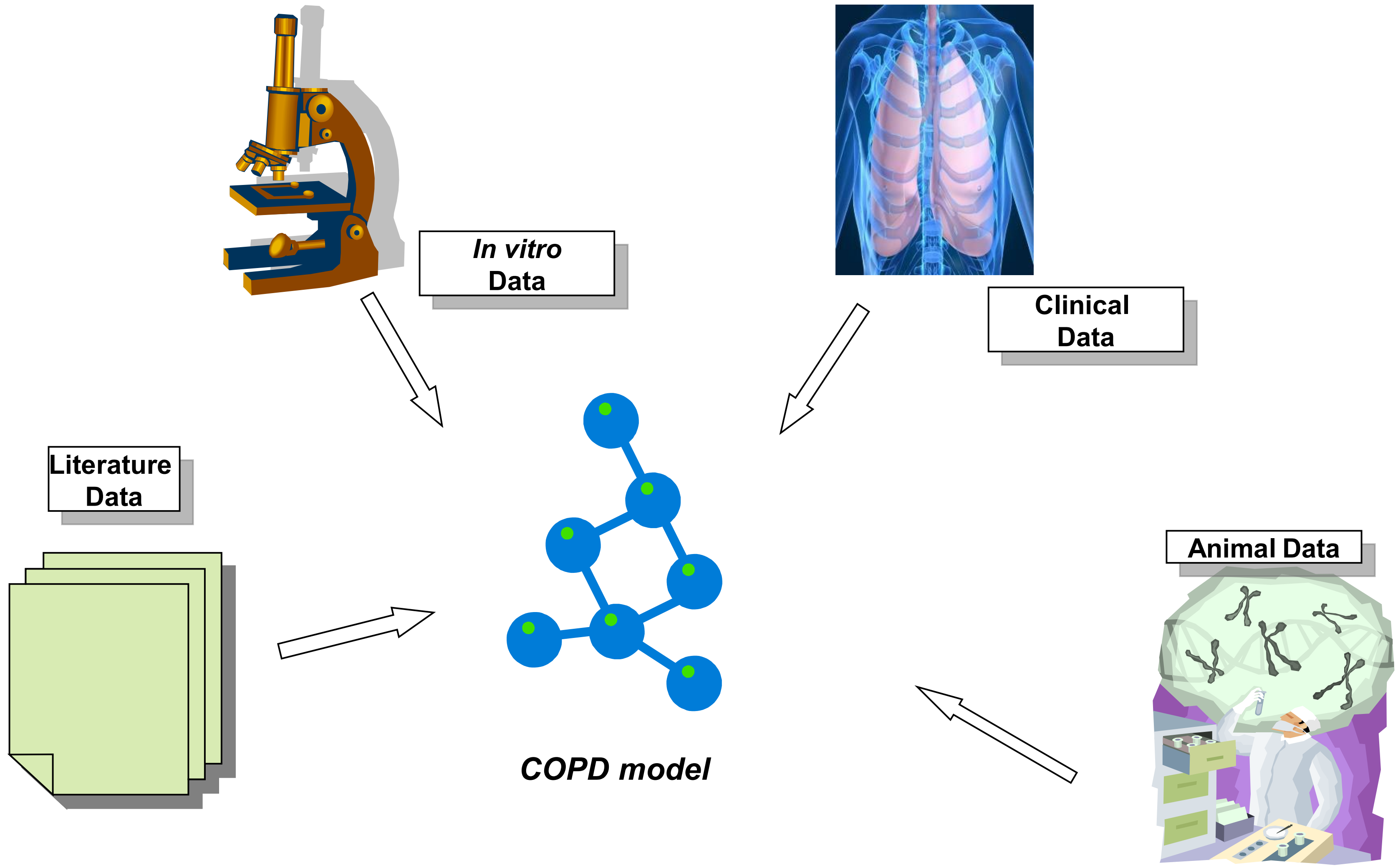
- Objectives of COPD modeling:

  - … predict the risk of COPD associated with cigarette smoke in the absence epidemiological studies

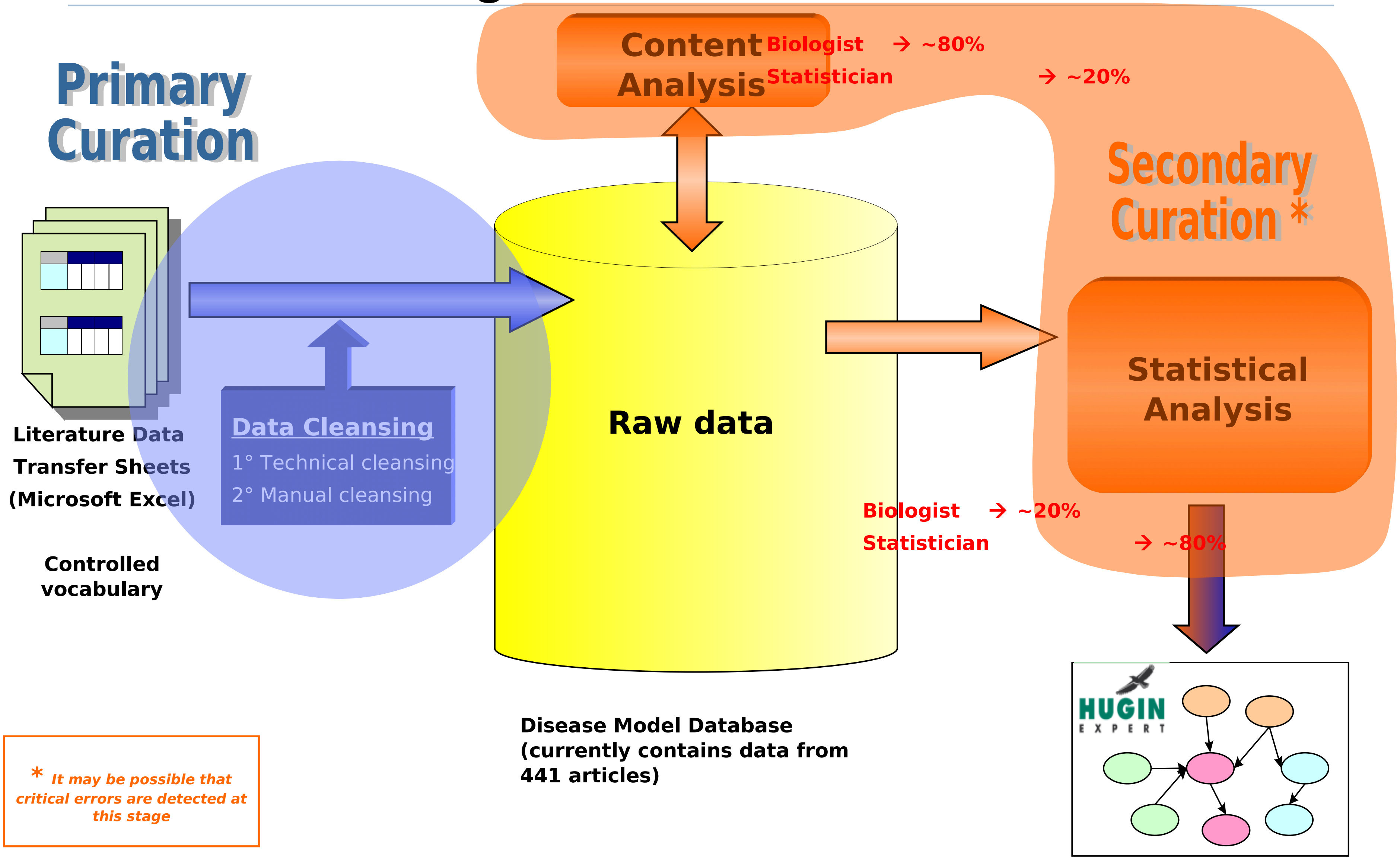
  - … better understand the disease mechanisms of COPD

  - … identify the most relevant biomarkers of COPD

Data - Sources



Data - Processing



Case Study - Strategy of Analysis

Case 1

Link categorical variable → continuous variable

Case 2

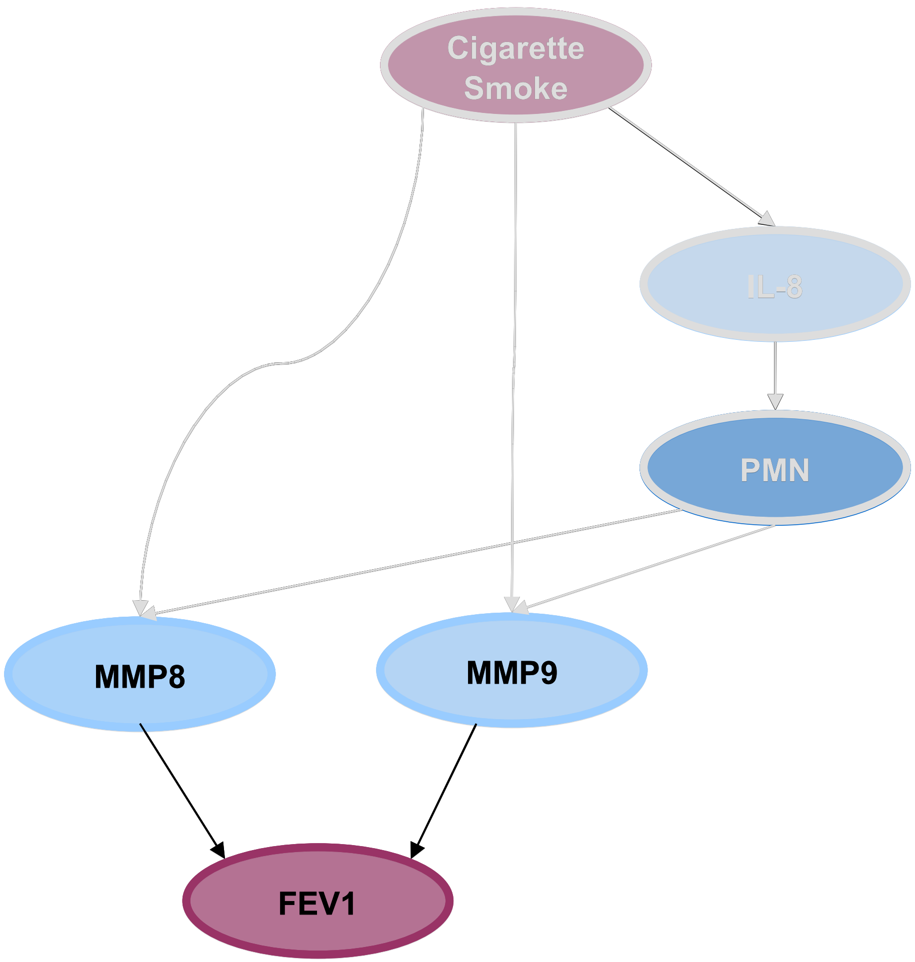
Link continuous variable → continuous variable

Case 3

Link categorical + continuous variables → continuous variable

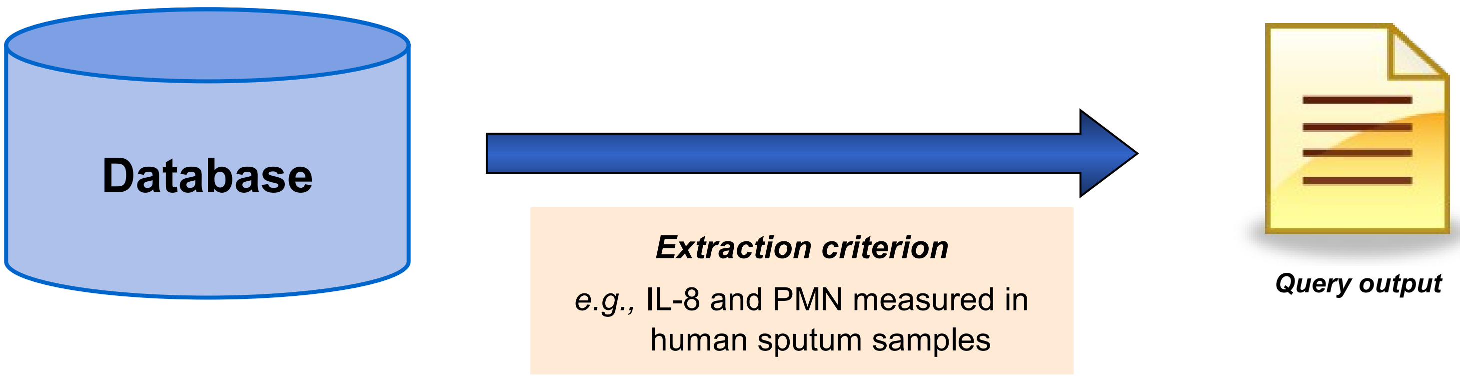
Case 4

Link (at least) 2 continuous variables → continuous variable



Case Study - Preliminaries

- Description of the data extraction process…



- Diversity in extracted data…
  - Different smoking status: *smoker, non-smoker, ex-smoker, smoker + no smoker, …*
  - Different groups: *healthy, COPD, chronic bronchitis, asthma, …*
  - Different units: *ng/mL, nMolar, nMol, %, pg/mL / mg albumin, …*
  - Different statistics: *mean, std, median, inter-quartile range, …*
  - Correlations and Regressions
  - Scatterplots of individual values

Case Study – Inclusion Criteria

- Human model
  - Whenever possible, use only human *in vivo* data

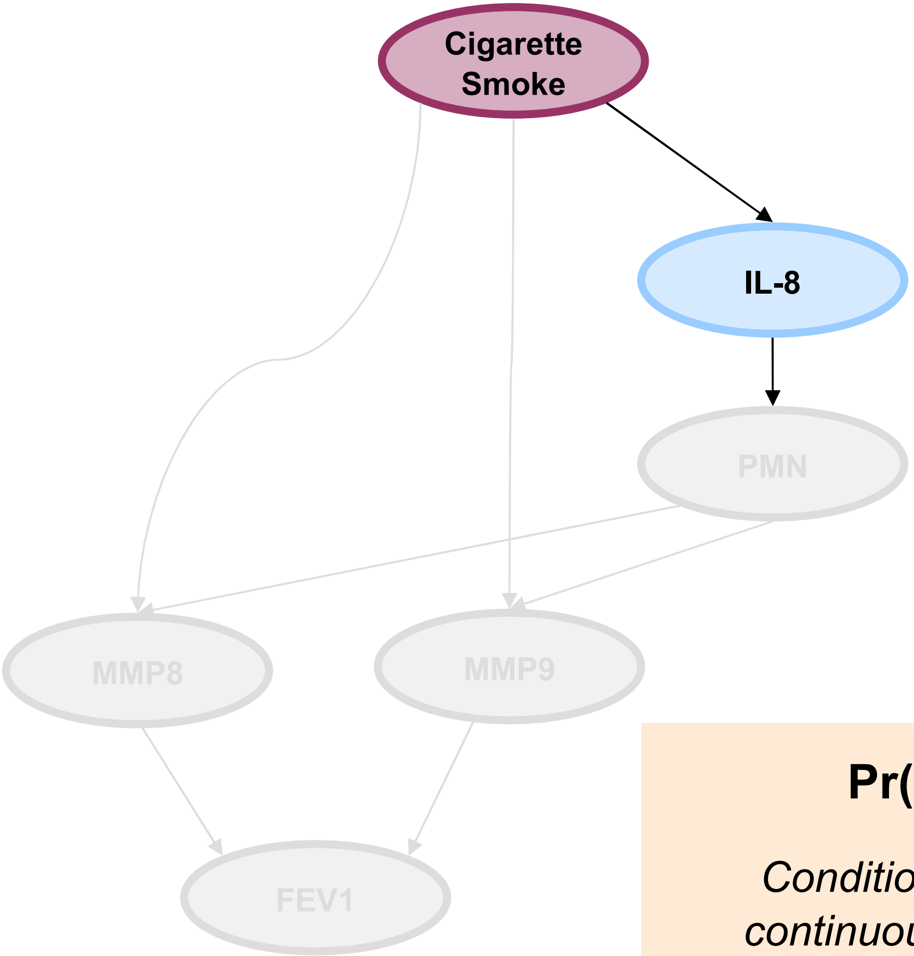
- Sputum samples
  - Whenever possible, use only data from sputum samples
  - Avoid standardization problems (e.g., concentration levels in BALF are quite different from concentration in sputum)
  - Clinical studies are more likely to use sputum samples (less invasive than BALF, etc.)

Case Study – Exclusion Criteria

- Data are excluded when…
  - … data refer to a group with a particular disease (e.g., asthma, cystic fibrosis, α1-AT deficiency, …)
  - … data have a unit that cannot be transformed to the same unit
  - … data are not biologically relevant
  - … smoking status is unknown or mixed when stratification by smoking status is required.

Case Study 1 (1/5)

Link Cigarette Smoke → IL-8



Pr(IL-8 | Cigarette Smoke) ???

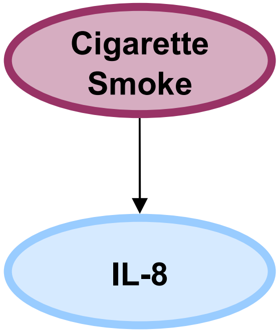
Conditional Probability Distribution (CPD) of a continuous variable given a categorical variable

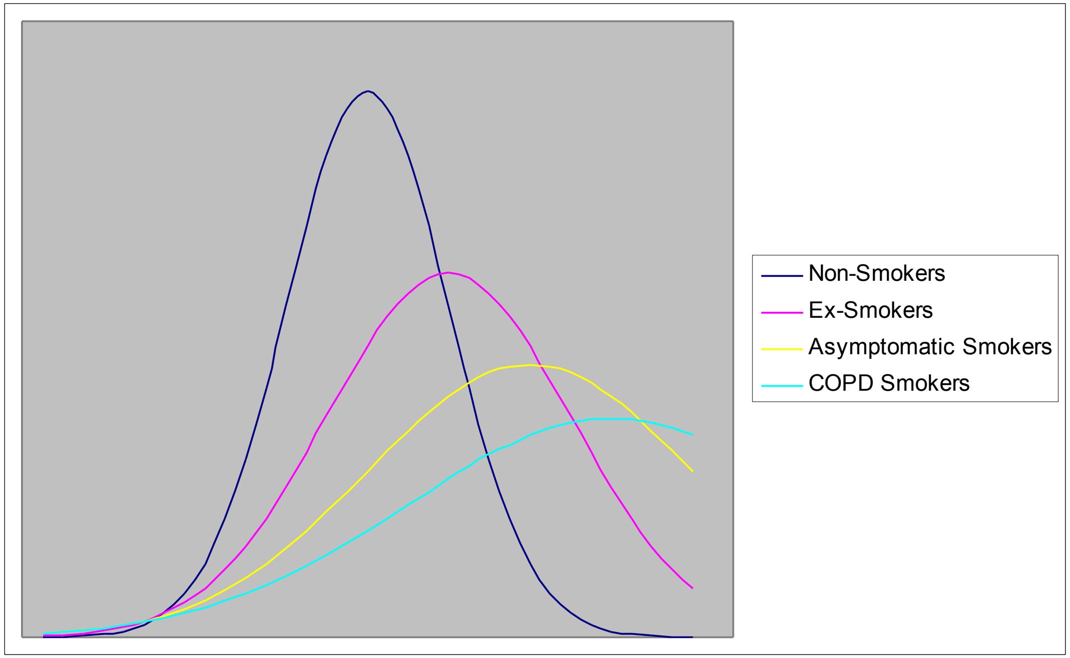
Case Study 1 (2/5)

Link Cigarette Smoke → IL-8

➢ Objective is to determine a probability distribution for each of the following categories…

- Non-Smokers
- Ex-Smokers
- Smokers without COPD
- Smokers with COPD





Case Study 1 (3/5)

Link Cigarette Smoke → IL-8

- Available data are rather limited
  - Usually low sample sizes
  - Frequently only aggregated data (means, SD, …)
  - Study context not always clearly specified
  - Outliers
- Data are heterogeneous
  - Very different populations: Age, gender, ethnic origin …

- However, a detailed analysis of the data is necessary…
  - … to include/exclude data
  - … to determine which data can be aggregated
  - … to decide whether an additional node (age, smoke-dose, …) needs to be added
- These points are also valid for all the other case studies!

Case Study 1 (4/5)

Link Cigarette Smoke → IL-8

- Values vary greatly in the literature.

- However, these variations cannot be attributed to anyone of the following confounders:
  - Age groups
  - Gender
  - Year of publication
  - Country of study
  - Smoke dose
  - Spirometric measurements (*e.g.*, FEV1)

Case Study 1 (5/5)

Link Cigarette Smoke → IL-8

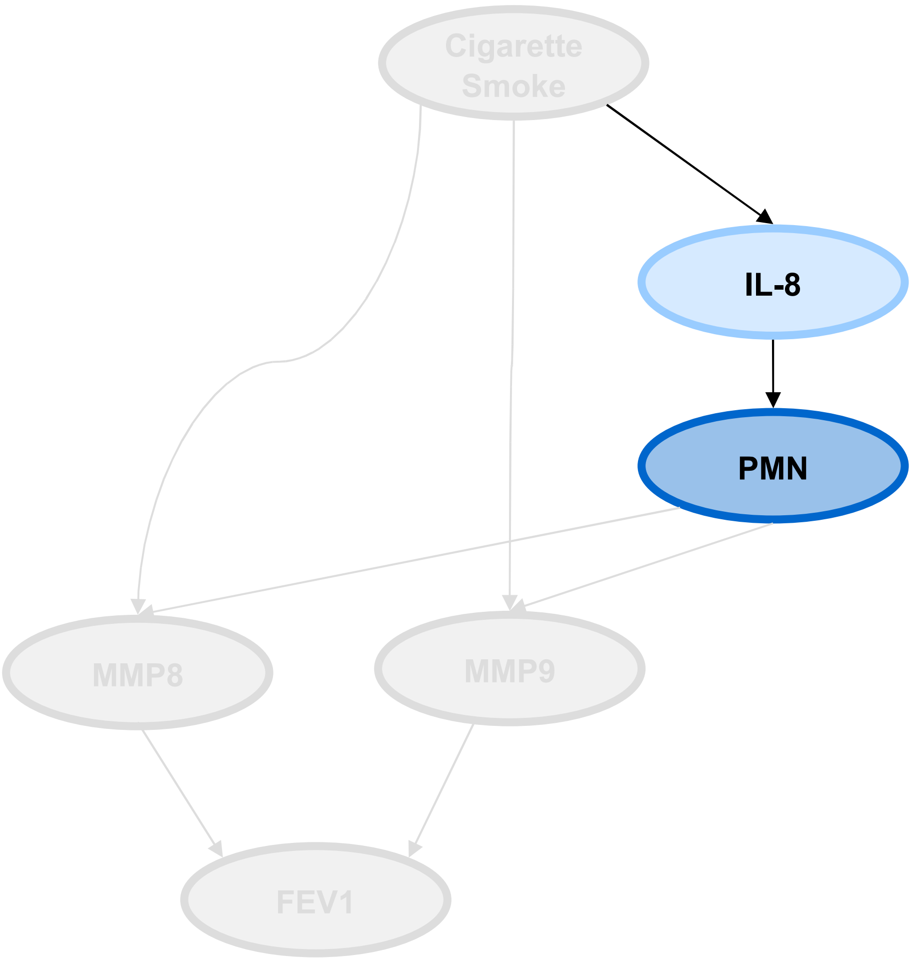
- We assume that the data are log normally distributed.

- For each observation, the parameters μ and σ of the underlying Log-Normal distribution are estimated using the summary statistics in the following order:
  - For μ:
    - Mean > Median > Geometric Mean > Interquartile Range > Range
  - For σ:
    - SD > SEM > Interquartile Range > Range

- Using ANOVA, we estimate an overall μ and σ, which represent the parameters of the CPD.

Case Study 2 (1/3)

Link IL-8 → PMN



Pr(PMN | IL-8) ???

CPD of a continuous variable given a continous variable

Case Study 2 (2/3)

Link IL-8 → PMN

- Data are not stratified by smoking status …
  - No link between *Cigarette Smoke* and *PMN* → Chemotactic activity of IL-8 towards neutrophils is *a priori* independent of the smoking status
    - First analysis will include all the data (independently of the smoking status)
    - In order to validate our assumption that chemotactic activity is independent of the smoking status, a second analysis will be performed on the data stratified by smoking status. These results will then be compared to the first analysis.
  - Same type of comment for healthy and COPD subjects
- Very difficult to find data where both variables (IL-8, PMN) are measured simultaneously.

Case Study 2 (3/3)

Link IL-8 → PMN

- In simple linear regression models, one assumes that the values of the regressor variable *x* are known constants, which is not the case for this example.

- The example shown here is a case where the regressor *x* is random. Therefore we treat the link of this type as a case where the two variables are jointly normally distributed:

$$f(y,x)=\frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}}\exp\left\{-\frac{1}{2(1-\rho^2)}\left[\left(\frac{y-\mu_1}{\sigma_1}\right)^2+\left(\frac{x-\mu_2}{\sigma_2}\right)^2-2\rho\left(\frac{y-\mu_1}{\sigma_1}\right)\left(\frac{x-\mu_2}{\sigma_2}\right)\right]\right\}$$

- The conditional distribution of *y* for a given value of *x* is:

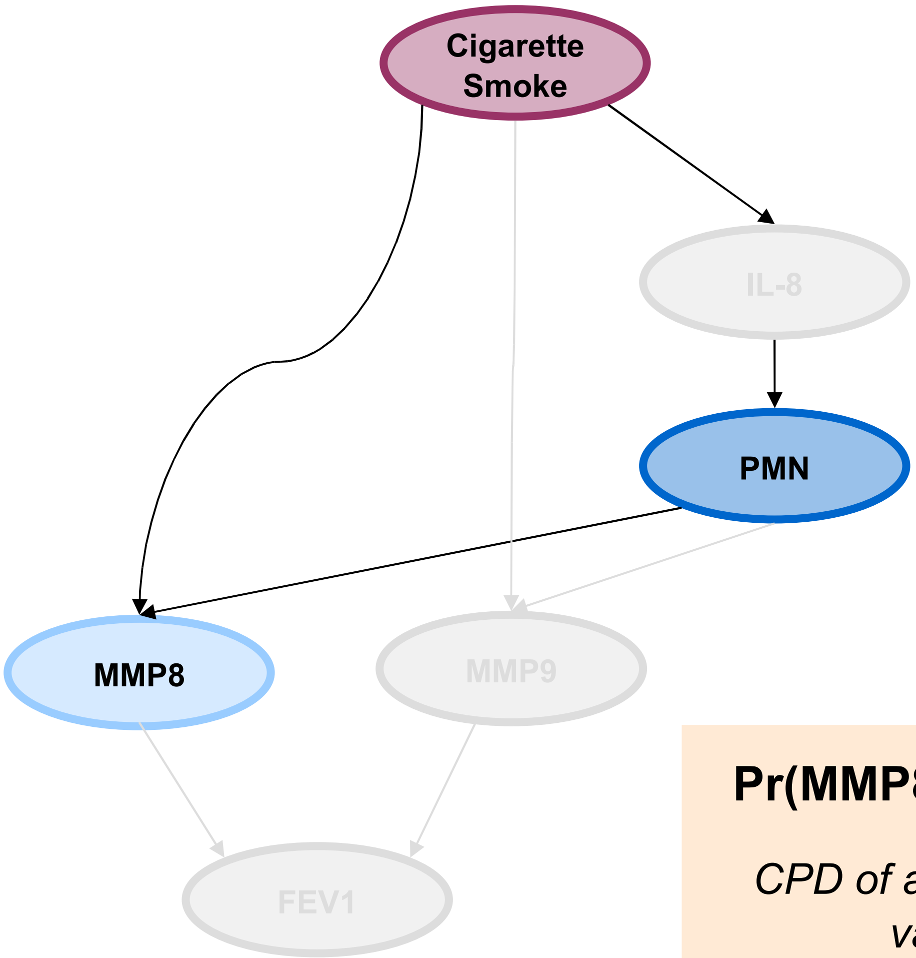
$$f(y|x)=\frac{1}{\sqrt{2\pi\sigma_{12}}}\exp\left[-\frac{1}{2}\left(\frac{y-\beta_0-\beta_1 x}{\sigma_{12}}\right)^2\right]$$

  - Where: , $\beta_1=\frac{\sigma_1}{\sigma_2}\rho$ and $\sigma_{1.2}=\sigma_1^2(1-\rho^2)$

- This conditional distribution would become the CPD of PMN.

Case Study 3 (1/2)

Link Cigarette Smoke + PMN → MMP8



Pr(MMP8 | Cigarette Smoke and PMN) ???

CPD of a continuous variable given a categorical variable and a continuous variable

Case Study 3 (1/2)

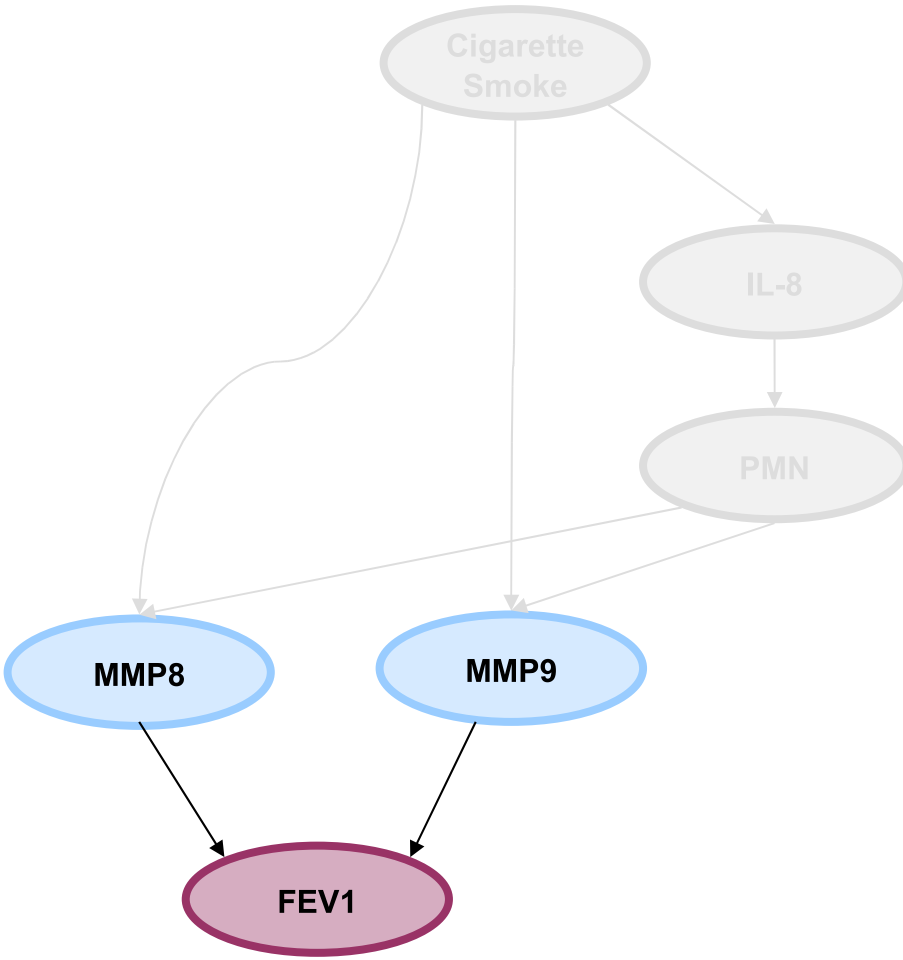
Link Cigarette Smoke + PMN → MMP8/MMP9

- Data are stratified by smoking status…
  - Link PMN → MMP8/MMP9 must be quantified for all categories of *Cigarette Smoke*

- Data analysis is similar to the case IL-8 → PMN, but it must be repeated for each category of *Cigarette Smoke* as for case study 1.

Case Study 4 (1/7)

Link MMP8 + MMP9 → FEV1



Pr(FEV1 | MMP8 and MMP9) ???

CPD of a continuous variable given (at least) 2 continuous variables

Case Study 4 (2/2)

Link MMP8 + MMP9 → FEV1

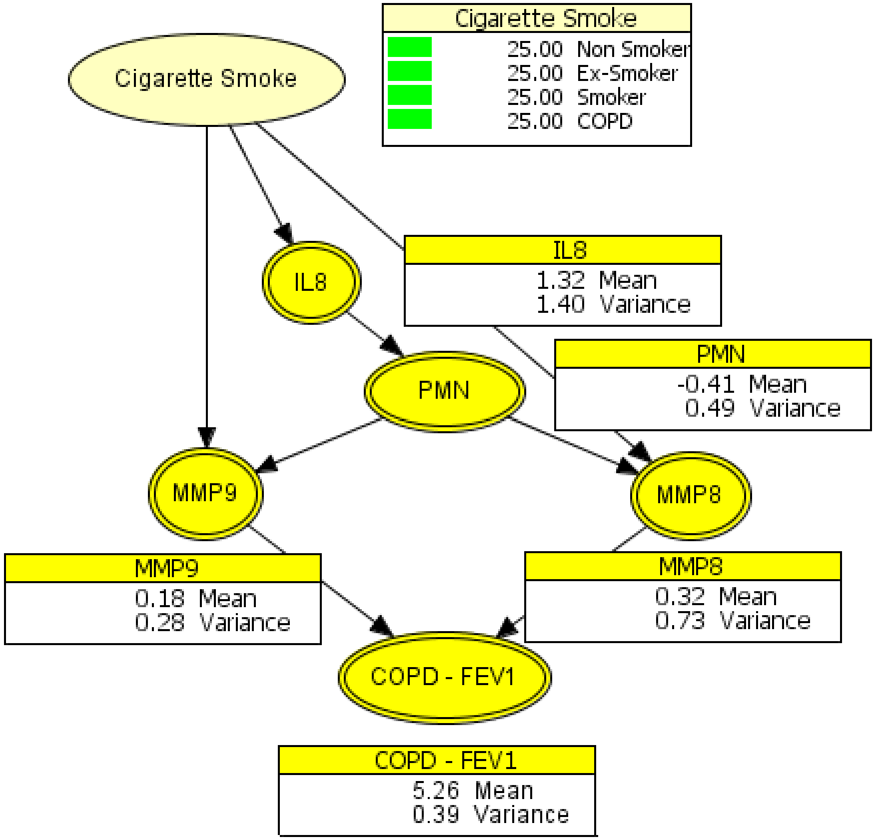
- Ideally, a regression equation of the type FEV1 = f (MMP8, MMP9) + ε and associated standard residual error is desired.

- Very difficult to find data where all 3 variables (MMP8, MMP9, FEV1) are measured simultaneously.

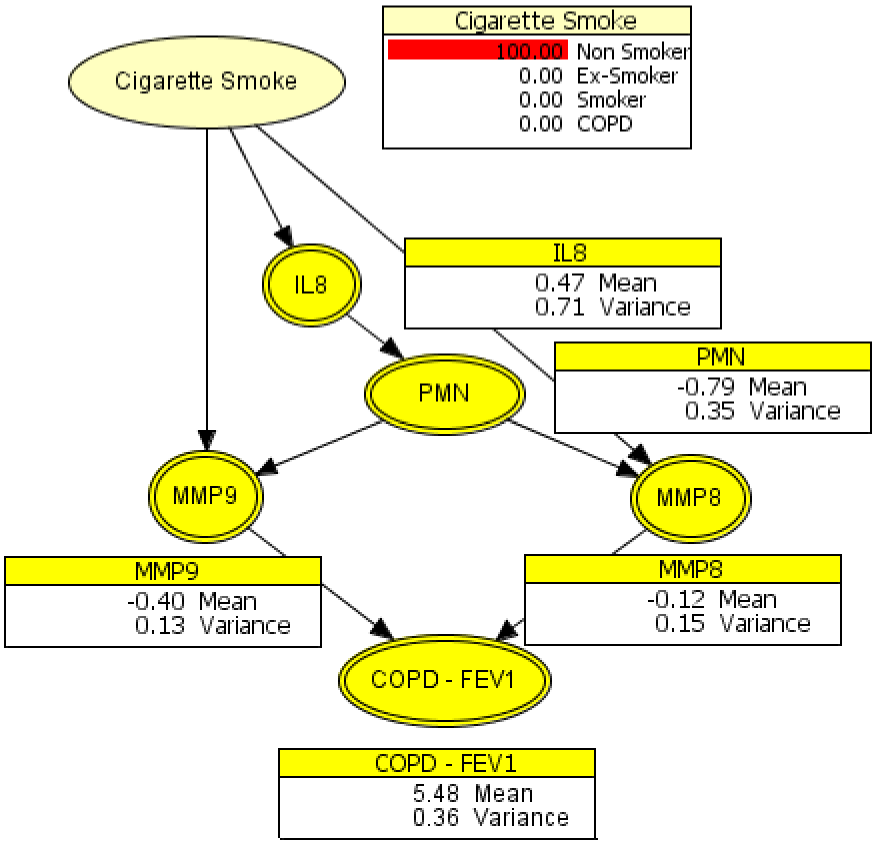
- Solution could be…
  - Treat the link MMP8 → FEV1 alone (as for the case IL-8 → PMN)
  - Treat the link MMP9 → FEV1 alone (as for the case IL-8 → PMN)
  - Compute a weighted average (weights could be chosen according to biological considerations)

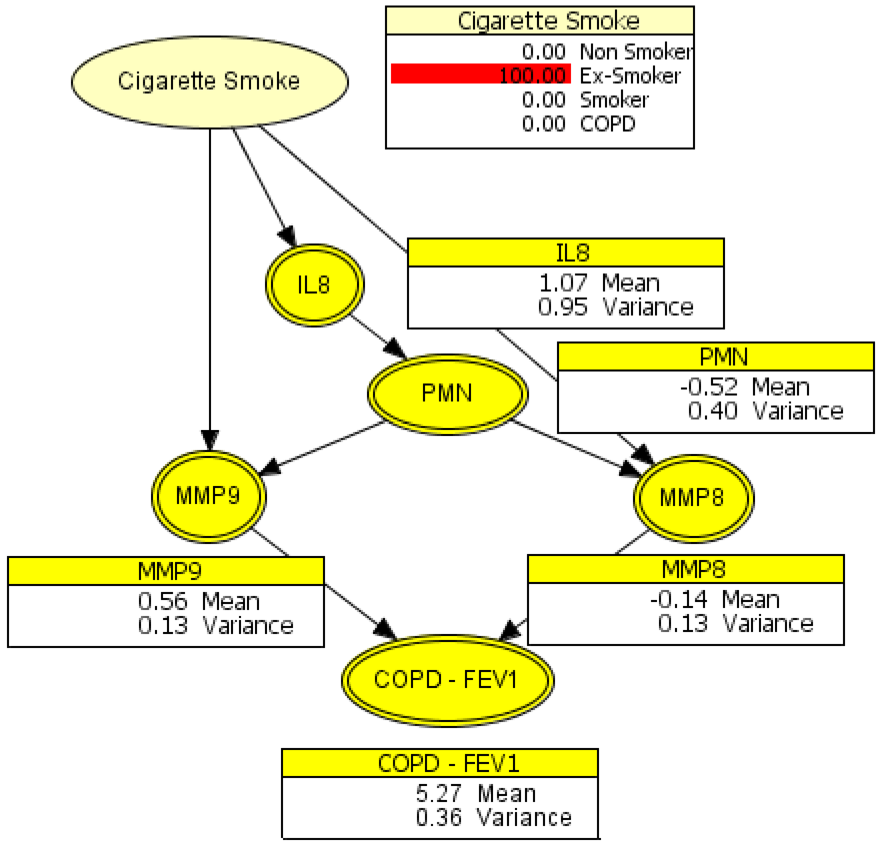
Hugin Model

- Population of 25% each for Non-Smokers, Ex-Smokers, asymptomatic Smokers, and Smokers with COPD:



Hugin Model

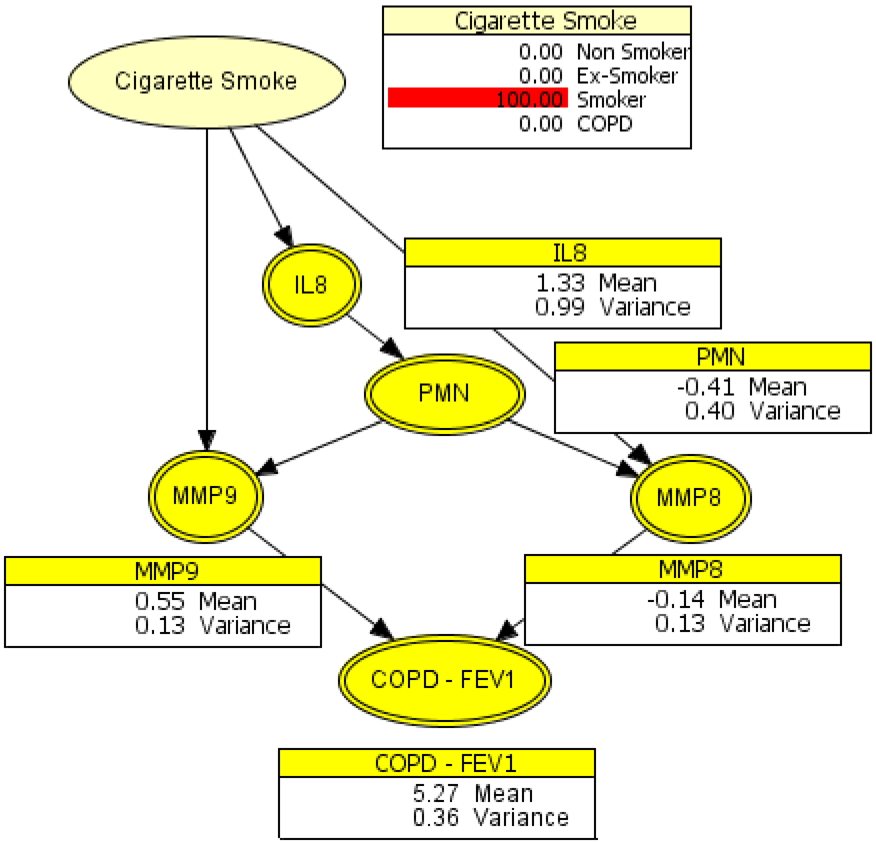


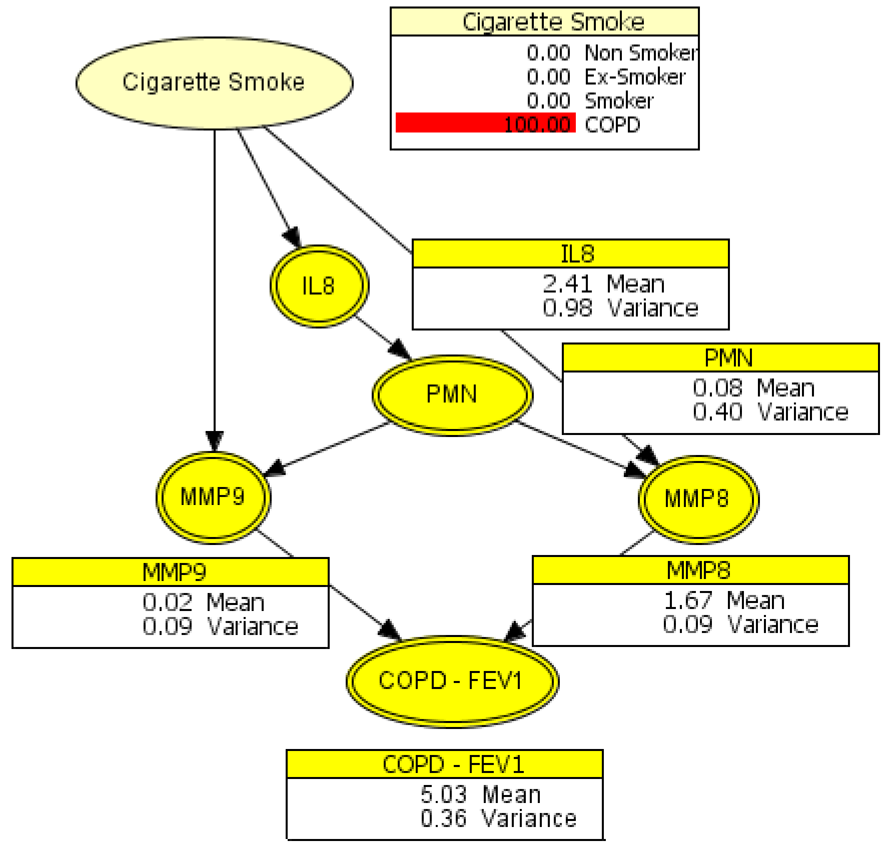


Population of 100% Non-Smokers

Population of 100% Ex-Smokers

Hugin Model





Population of 100% asymptomatic Smokers

Population of 100% Smokers with COPD

Issues

- Remaining issues:
  - Data gaps
    - Situation will improve with more articles in the database
    - New experiments will be required to fill these gaps
  - Data selection
    - Input from COPD experts is of prime importance
  - Mathematical analysis
    - Select better estimates for log-normal parameters
    - Test different distributions

- Data analysis may reveal patterns that are not currently represented in the model.

Next Steps

- Complete the human model
- Build an animal model
- Model Analysis & Validation
  - Conflict Analysis
  - Value of Information Analysis
  - Sensitivity Analysis
  - Cross-Validation on new data not used in the process of building the model

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