Inferring the presence of metabolites

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1 Idea and concept

We seek to infer the presence or absence of M metabolites in S species. We denote by x_{sm} whether metabolite $m = 1, \ldots, M$ is present ($x_{sm} = 1$) or absent ($x_{sm} = 0$) in species $s = 1, \ldots, S$. To infer the full vector $\boldsymbol{x} = (x_{11}, \ldots, x_{1M}, \ldots, x_{SM})$, we assume that related species share a similar set of metabolites and that metabolites related in their synthesis share a similar distribution across species. Let $\mathbb{P}(x_{sm} = 1|y_{sm}) = y_{sm}$ be the probability with which metabolite m is present in species s. We then assume that

$$\operatorname{logit} y_{sm} = \mu_m + \epsilon_{sm}$$

where μ is a metabolite-specific intercept and ϵ_{sm} is normally distributed with mean 0 and co-variance $\operatorname{cov}(\epsilon_{sm}, \epsilon_{s'm'}) = \alpha\sigma_{ss'} + \beta\sigma_{mm'}$ between each combination of species and metabolite. Here, $\sigma_{ss'}$ and $\sigma_{mm'}$ are known measures of covariance between species s and s' and between metabolites m and m', respectively, and α and β are positive scalars.

We consider two sets of data informative about $\boldsymbol{x}$: i) Presence-absence data obtained with mass-spectrometry and ii) presence-only reports of specific metabolites in specific specie. Let $\boldsymbol{d}_{sj} = (d_{sj1}, \ldots, d_{sjM})$ be the presence-absence vector of each metabolite m obtained with mass-spectrometry run $j = 1, \ldots, J_s$ performed on species s. Assuming a false-positive and false-negative error rates ϵ_{01} and ϵ_{10}, respectively, we have

$$\mathbb{P}(\boldsymbol{d}_{sj}|\boldsymbol{x}, \epsilon_{01}, \epsilon_{10}) = \prod_m \left[x_{sm} \left(\epsilon_{10}^{1-d_{sjm}} (1-\epsilon_{10})^{d_{sjm}} \right) + (1 - x_{sm}) \left(\epsilon_{01}^{d_{sjm}} (1-\epsilon_{01})^{1-d_{sjm}} \right) \right].$$

To model the presence only data, it must be put in relation to the expected research effort. Let p_{sm} denote the known number of presence-only reports for metabolite m in species s and n_{sm} the unknown number of research projects that aimed at discovering metabolite m in species s. Assuming a false-positive and false-negative error rates π_{01} and π_{10}, respectively, we have

$$\mathbb{P}(p_{sm}|n_{sm}, \pi_{01}, \pi_{10}) =$$

We would have the covariance matrix such as :

$$\operatorname{cov}(\epsilon_{smt}, \epsilon_{s'm't'}) = \alpha\sigma^P_{ss'} + \beta\sigma^M_{mm'} + \gamma\sigma^E_{ss'} + \ldots \tag{1}$$

With P the phenotype between two species, E an environment factor between two species and M the TODO

2 DAG scratch

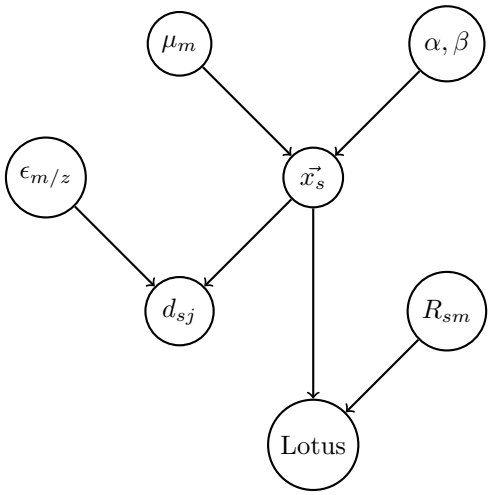
2.1 Test 1

We assume that the probability of having a molecule in a species is the average presence of that molecule across all species μ_m plus a normally distributed error that depends on certain parameters $\alpha, \beta, \ldots$.

From there, the LOTUS database and any result of MS depends on the set of molecules present in a species $\vec{x_s}$. However we still have to take into account the fact that there can be an error of analysis on the MS $\epsilon_{m/z}$ that where $\epsilon_{m/z} = f(\epsilon_{01}, \epsilon_{10})$.

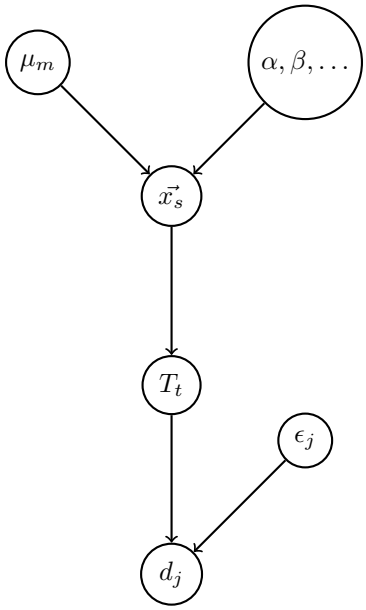
Could we assume that as $j \to \infty$, then $d_{sj} \to \vec{x_s}$? TODO

According to Pierre-Marie LOTUS database is highly dependent on the research effort accorded to the specific molecule. He also said that error rate in the majority of LOTUS database is very low since most data is an actual isolation of the specific compound. Error rate of LOTUS database should then have little effect on the model.



2.2 Test 2

2.2.1 MS data



With μ_m the average presence of a molecule across all species. $\alpha, \beta, \ldots$ the environmental variables (the error that is normally distributed across the mean). x_s the molecule x in species s. T the tissue of species s. d_j the mass spec data. The previous DAG can then be derived as the following.

$$P(\boldsymbol{d}|\mu_m, \alpha, \beta, \ldots) = \prod_{s=1}^{s} P(x_s|\mu_m, \alpha, \beta \ldots.) \prod_{t=1}^{t} \prod_{j=1}^{j} P(d_j|T_t, \epsilon_j) P(T_t|x_s) \tag{2}$$

This is for one molecule. If we want to have for all the molecules we would have :

$$P(\boldsymbol{d}|\boldsymbol{\mu}, \alpha, \beta, \ldots) = \prod_{m=1}^{m} \prod_{s=1}^{s} P(x_s|\mu_m, \alpha, \beta \ldots) \prod_{t=1}^{t} \prod_{j=1}^{j} P(d_j|T_t, \epsilon_j) P(T_t|x_s) \tag{3}$$

Where do we go from here ? We search the probability of a molecule in a species give the data. We thus have $P(x|d) = \frac{P(x,d)}{P(d)}$.

Where do we use Lotus DB ? Should it be our prior probability $P(x|d)$?

2.2.2 Error rate of MS

We could have either a false positive meaning that the MS detects something that is not truly present in the species $0 \rightarrow 1$ or a false negative meaning that a molecule is present in the sample but is not present in the data $1 \rightarrow 0$.

Could this be viewed as a birth and death process ? If yes, this could be modelled with Kolmogorov forward-master equation:

$$\frac{dP_{ij}(t)}{dt} = \lambda_{j-1} P_{ij-1}(t) + \mu_{j+1} P_{ij+1}(t) - (\lambda_j + \mu_j) P_{ij}(t) \tag{4}$$

- With a Poisson process for birth $(0 \rightarrow 1)$ TODO ...
- HMM process ?

2.2.3 Error on Lotus DB

Since the Lotus DB supposedly contains little to "no" errors, maybe we should also model as a Poisson process since error might occur but on rare occasions.

The fact that Lotus doesn't contain many error is that each molecule present in the database, was isolated and analysed with either NMR or X-ray crystallography. Moreover, the latter techniques need to have a high amount of chemical extract so the probability that a compound is not present in the organism is close to 0 if not 0. However, not all entries in the database are made with these techniques so that is why we still need to account for that error in the model.

3 Formulation

We seek to infer the presence or absence of M metabolites in tissue T in S species. We denote by x_{smt} whether metabolite $m = 1, \ldots, M$ is present ($x_{smt} = 1$) or absent ($x_{smt} = 0$) in tissue $t = 1, \ldots T$ in species $s = 1, \ldots, S$. We denote $\vec{x_{st}} = (x_{st1}, \ldots, x_{stM})$ the vector of molecules present in a tissue T of a specific species S.

Let us further denote $\vec{x_s} = (\vec{x_{s1}}, \ldots, \vec{x_{sT}}) = (x_{s11}, \ldots, x_{s1M}, x_{s21}, \ldots, x_{sTM})$ the vector of presence/absence of all molecules across all tissues for species s.

We have two origins of data, mass spectrometry data and the Lotus database. We denote d_{sj} the j^{th} mass spectrometry run for species s and $\vec{L_s}$ all molecules assigned to species s present in the LOTUS database. Finally we define R, a function representing the research effort produced for either a species s or a specific molecule m. We also define $\vec{\epsilon_j}$ a vector of error that is specific for each mass-spectrometry run.

A DAG of the model can be seen in Figure 1. $\vec{\mu}$ being the vector of the average presence/absence of each molecule across all species and $\vec{\alpha}$ represents the vector of all known measures of covariates between species and molecules.

Since the tissue specific origin of a molecule is not known in the LOTUS database [1], we denote

$$P(\vec{L_S}|\vec{x_s}, R) = P(\vec{L_s}|\vec{\xi_s}, \vec{R}),$$

with $\vec{\xi_s} = (\xi_{s1}, \ldots, \xi_{sM})$ the vector of presence/absence of all molecules M in species s. Furthermore, $\xi_{sm} = min(1, \sum_t^T x_{smt})$ the minimum between 1 and the sum of presence or absence of a molecule across all tissues.

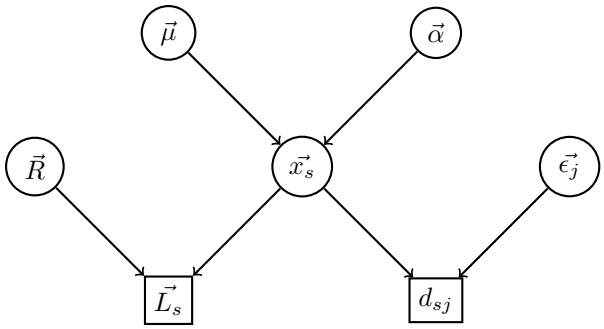


Figure 1: Potential DAG of the model.

We can also denote $\vec{R} = (R_{11}, \ldots, R_{1M}, R_{21}, \ldots, R_{SM})$ the vector of *research effort* of all molecules across all species.

The probability of having a molecule present in the LOTUS database not only depends on the presence/absence of that molecule in a species but also on the research effort done for a specific molecule or species. We thus have $R_{sm} = f(n_s, n_m)$ with $R_{sm} \in [0, 1]$ and where n_s and n_m are the number of scientific papers that relate respectively the species and the molecules of interest. We thus have the following matrix :

$$\begin{array}{c} \\ x_{sm} = 0 \\ x_{sm} = 1 \end{array} \begin{array}{c} \begin{array}{cc} L_{sm} = NA & L_{sm} = 1 \end{array} \\ \begin{pmatrix} 1 & 0 \\ 1 - R_{sm} & R_{sm} \end{pmatrix} \end{array}$$

Tissue of origin is usually known in mass spectrometry analysis. From Figure 1, we have, $P(d_{sj}|\vec{x_s}, \vec{\epsilon_j}) = P(d_{sj}|x_{st\vec{(d_{sj})}}, \vec{\epsilon_j})$ where $t(d_{sj})$ reflects the tissue from which mass spectrometry run j in species s was sampled.

We thus have:

$$P(\boldsymbol{d}, \boldsymbol{x}, \boldsymbol{\mu}, \boldsymbol{\alpha}) = P(\boldsymbol{\mu})P(\boldsymbol{\alpha}) \prod_{s=1}^{S} P(\vec{x_s}|\boldsymbol{\mu}, \boldsymbol{\alpha}) \prod_{j=1}^{J} P(d_{sj}|x_{st\vec{(d_{sj})}}, \vec{\epsilon_j}) \tag{5}$$

Similarly, for LOTUS database we have :

$$P(\mathbb{L}, \boldsymbol{x}, \boldsymbol{\mu}, \boldsymbol{\alpha}) = P(\boldsymbol{\mu})P(\boldsymbol{\alpha})P(\mathbf{R}) \prod_{s=1}^{S} P(\vec{x_s}|\boldsymbol{\mu}, \boldsymbol{\alpha})P(L_s|\vec{x_s}, \mathbf{R}) \tag{6}$$

The likelihood is then :

References

[1] Adriano Rutz, Maria Sorokina, Jakub Galgonek, Daniel Mietchen, Egon Willighagen, Arnaud Gaudry, James G Graham, Ralf Stephan, Roderic Page, Jiří Vondrášek, Christoph Steinbeck, Guido F Pauli, Jean-Luc Wolfender, Jonathan Bisson, and Pierre-Marie Allard. The LOTUS initiative for open knowledge management in natural products research. *eLife*, 11:e70780, May 2022. doi:10.7554/eLife.70780.