Translating biomarkers between multi-way time-series experiments from multiple species

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Abstract. Translating potential disease biomarkers between multi-species 'omics' experiments is a new direction in biomedical research. The existing methods are limited to simple experimental setups such as basic healthy-diseased comparisons. Most of these methods also require an a priori matching of the variables (e.g., genes or metabolites) between the species. However, many experiments have a complicated multi-way experimental design often involving irregularly-sampled time-series measurements, and for instance metabolites do not always have known matchings between organisms. We introduce a Bayesian modelling framework for translating between multiple species the results from 'omics' experiments having a complex multi-way, time-series experimental design. The underlying assumption is that the unknown matching can be inferred from the response of the variables to multiple covariates including time.

Keywords: Cross-species translation, Data integration, Hidden Markov Model, Multi-way experimental design, Time-series, Translational medicine

1 Introduction

Cross-species analysis of biological data is an increasingly important direction in biological research. The analysis calls for multivariate methods, since 'omics' technologies, such as transcriptomics and metabolomics, enable studying the dynamic response of biological organisms in various conditions, including various time points during disease progression. An important research problem of translational medicine is translating potential biomarkers for disease between species.

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This would ultimately allow mapping phenotypes between model organisms and actual human experiments.

The basic experimental design in searching for disease biomarkers is the one-way comparison of healthy and diseased populations. At the simplest, biomarkers can be translated between species by comparing lists of $p$-values of simple differential expression. Most existing cross-species analysis methods are limited to such simple designs [8]. A further limitation of most existing methods is that they require an \textit{a priori} matching of variables (genes) between the organisms. Such orthology information is not always available, especially in metabolomics where the mapping of metabolites between organisms has barely started, and is an interesting research problem in itself.

Most biological experiments have a multi-way experimental design, where healthy and diseased populations are further divided into subpopulations according to additional covariates such as gender, treatment groups, age, measurement times etc. A usual approach for dealing with the additional covariates is stratifying the diseased-healthy comparison; a typical example is comparing healthy and diseased males and females separately. The standard statistical methods for properly dealing with multi-way designs, are Analysis of Variance (ANOVA) and its multivariate generalization (MANOVA). While studying the effects of all the covariates on the data makes the analysis slightly more complicated, more information can be gained from each species to be used in the translation. Unfortunately, there exist no earlier proper tools for utilizing the information of the effects of multiple covariates on the data in cross-species analysis.

Furthermore, time-series experiments are becoming more and more common in clinical studies searching for disease biomarkers. Whereas in some cases the measurement times of such experiments are regular and allow a “neat and easy” data analysis, this is often not the case. In clinical follow-up studies, such as [13], measurement times are often irregular due to practical reasons of data collection, and there are missing time points. Also, in follow-up studies spanning timescales of years, individuals have been shown to develop into metabolic developmental states at an individual pace [12]. In addition, life spans of different organisms, such as man and mouse, are very different resulting in very different measurement times. These complications call for a possibility to align the time-series. All of these factors combined cause remarkable challenges for cross-species data analysis.

Instead of searching for single molecule biomarkers, which have a high risk of false positives, we concentrate on finding combinations of similarly-behaving biomarkers, which is a way towards treating a transcriptomic or a metabolic profile as a fingerprint of the clinical status of the organism. For this, multivariate statistics is needed. In this paper, we will now show how the data analysis problem can be formulated as a new multivariate ANOVA-type model in the case where data comes from multiple sources (species) and one of the variables, namely the time, has a previously unknown structure (alignment).

In this paper, we will present a formal framework for cross-species analysis of ‘omics’ data in the case of a multi-way, time-series experimental design. This
methodology can be directly used for finding previously unknown matching of
groups of variables between the species based on the data. In contrast to many-
step approaches, the whole modelling is done in a single, unified, multivariate
Bayesian model. The framework has estimation of uncertainty and dimension-
ality reduction built-in to overcome the main challenge: high dimensionality and
small sample-size. The central underlying assumption is that the actual link be-
tween the variables of the different species can be inferred from a similar response
of the variables to multi-way covariates.

**Previous work in cross-species analysis**

Until now, meta-analysis of microarray data has been the major approach to
cross-species studies in biology [8]. Plenty of meta-analyses have been done by
either comparing lists of differentially expressed genes between several species, or
by comparing expression levels of known gene orthologs between the species. So
far, mainly highly-controlled cell cycle studies have been analyzed across several
species and no attention has been paid to multi-way designs.

One step towards translational analysis has been taken by Lucas et al. [10,11].
To help finding biomarkers from an *in vivo* experiment, they incorporated prior
knowledge from results of an *in vitro* study analyzed with the same method.
Like ours, their approach is based on generative Bayesian modeling of factors
and can handle multiple covariates. Their approach does not, however, consider
time-series cases with unaligned time nor the case without any *a priori* matching
between the variables.

A probabilistic model based on Gaussian random fields has been applied
to two-species expression data [9]. This work combined differential expression
scores from different species, cell types, and pathogens utilizing homology infor-
mation. In [6] the task was to query large databases of micro-array experiments
to identify similar experiments in different species, by utilizing partially known
orthology information. In [7] time-series micro-array data from multiple species
was used to discover causal relations between genes to discover conserved regu-
latory networks. Also this approach naturally needs *a priori* known matching of
orthologous genes.

A standard method for finding similarities between several data sets is canon-
ical correlation analysis (CCA)[2]. CCA assumes paired samples over the data
set and thus is not directly applicable for the translation problem, where the
samples (patients) are different over species. A simple iterative method for pair-
ing genes has been developed in [14,15]. In the case the genes are samples in the
data matrix, optimal pairing of genes is sought by maximizing the dependency
between the data sets estimated by CCA. A very similar method was recently
used for regulatory network inference [1]. No prior matching of variables or sam-
ple is assumed, and the method attempts to find both iteratively by alternating
between matching of variables and matching of samples using a closely related
method Co-Inertia analysis. These methods do not, however, take into account
covariate information (including measurement time) of the samples, nor different
time resolution of the covariates.
In summary: none of the existing approaches can take into account a multi-way time-series covariate structure or exploit it to find previously unknown matchings between the variables without any a priori known matching information.

2 Model

Our method addresses the problem of translating biomarkers between multiple species from multi-way time-series experiments with previously unknown matchings between the variables (metabolites). We do not assume the samples have a pairing but our main assumption is that there is a similar multi-way time-series experimental design in both experiments.

A simple data analysis procedure towards this goal would be doing the univariate multi-way ANOVA analysis separately on the two data sets of the two species, and comparing the lists of $p$-values afterwards as a meta-analysis step.

In the two-way case, to explain the covariate-related variation in one species, say $x$, the following linear model is usually assumed:

$$x_j | (a, b) = \mu_x + \alpha^x_a + \beta^x_b + (\alpha \beta)^x_{ab} + \epsilon_j.$$

Here $x_j$ is a continuous-valued data vector, observation number $j$, the $\mu_x$ is the overall (grand) mean, the $a$ and $b$ ($a = 0, \ldots, A$ and $b = 0, \ldots, B$) are the two independent covariates, such as disease and treatment. The $\alpha^x_a$ and $\beta^x_b$ are parameter vectors describing the covariate-specific effects, called main effects. The $(\alpha \beta)^x_{ab}$ is a parameter vector describing the interaction effect.

Instead of searching for single-molecule biomarkers, that have a high risk of false positives, our approach is multivariate, concentrating on finding combinations of biomarkers.

In order to tackle high dimensionality and scarcity of observations, we assume that there are groups of similarly behaving variables (metabolites) in each species. We then search for correlated groups of metabolites sharing a similar response to external covariates. These correlated groups (clusters) are therefore assumed to be shared between the species. Underlying this process is the assumption that similarity of multi-way behavior of groups of metabolites indicates a cross-species mapping of the metabolites.

We have taken an ambitious goal by building a unified Bayesian model that integrates the separate multi-way experiments from multiple species. The model can be learned jointly by Gibbs sampling.

From the point of view of ANOVA-type modelling the question is how to do multi-way modelling when the data comes from different sources with different variables (e.g., man and mouse having different metabolites). The solution is to consider data “source” as an additional covariate in the multi-way analysis [5]. From the data integration point of view the task is to find dependencies between the data sets when neither the variables nor the samples have been paired. There is, however, a shared multi-way covariate structure in the data sets, and it is utilized to find the mapping of groups of variables. We study additionally
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the case where one of the covariates, time, has a previously unknown structure due to unknown time alignments. It will be shown that the alignments can be found simultaneously within the whole unified model.

The model we develop for this task is an extension of our recently published multi-way modelling methods [4,5]. In [4], we presented a method for multi-way ANOVA-type modelling in “small sample-size n, high dimensionality p”-conditions in the case of standard covariates, such as disease, treatment, and gender. The solution is to use regularized factor analysis for dimensionality reduction, such that each variable is assumed to come from one factor only. The effects of multi-way covariates $\alpha_a, \beta_b, (\alpha \beta)_{ab}$ are then estimated in the low-dimensional latent factor space. Each latent factor represents a group of correlated variables. The model is

$$x_j^{\text{lat}} \sim N(\alpha_a + \beta_b + (\alpha \beta)_{ab}, \mathbf{I})$$

$$x_j \sim N(\mu + Vx_j^{\text{lat}}, \Lambda).$$

Here $x_j$ is a $p$-dimensional data vector, $V$ is the projection matrix, and $x_j^{\text{lat}}$ is the low-dimensional latent variable, $\Lambda$ is a diagonal residual variance matrix with diagonal elements $\sigma_i^2$.

In [3], we further extended this framework into integrating data sources with paired samples, such as having measurements from multiple tissues of each individual. In [5], we first extended [4] into time-series cases with unknown alignments, such that these alignments can be learned simultaneously with the multi-way modelling task. In [5], we also presented the basic principle and a simplified model of how the multi-way modelling framework can be extended into translational modelling. This case is much more difficult than [3], because samples have not been paired between the data sources; For example, the pairing of one time-point of an individual test mouse and a time-point from one of the human patients cannot be assumed. In [5] we concentrated on finding a shared response of the variables to one covariate only; the aligned time. In this paper we now proceed by presenting the full translational model where, in addition to aligned time, there are other covariates, such as disease. Also, in this paper we separate the time- and disease behavior into shared and species-specific effects.

2.1 Modelling time-series measurements from multiple populations with regular measurement times

Let us now consider modelling data from time-series measurements from diseased and healthy populations in one species. If the measurement times are fixed and individuals can be assumed to have similar aging development, the data analysis can be seen as a two-way design and modelled with a linear model. When modelling the effects of time and other covariates on low-dimensional latent factors, each factor representing one correlated group of variables [4], we can use the model

$$x_j^{\text{lat}}_{(t,b)} = \alpha_t + \beta_b + (\alpha \beta)_{tb} + \text{noise}.$$
We denote from now on the time-point by $t$, the disease status by $b = \{0, 1\}$, the effect of time by $\alpha_t$, the effect of disease by $\beta_b$, and the interaction of time and disease $(\alpha\beta)_{tb}$. The last one is the most interesting, denoting the time-dependent disease effects.

### 2.2 Modelling time-series measurements from multiple populations with irregular measurement times

This work is motivated by the fact that in many real-world sparsely collected time-series datasets, especially from large-cohort human clinical studies, measurement times can be irregular within and between individuals; one particular state-of-the-art clinical lipidomic study is [13], on which we now concentrate. This study followed a set of patients; some of them remained healthy, some developed into type 1 Diabetes. Furthermore, it was shown in [12] that individuals progress into different age-related metabolic states at their individual pace. This phenomenon can be modelled by assuming that there are underlying latent metabolomic development states and individuals progress into these states in their individual pace [12]. The underlying states were modelled by Hidden Markov Models (HMM), where the observed metabolic profiles are assumed to be emitted by the underlying states. This modelling assumption also deals with the problem of aligning irregular measurements.

The important problem now is how to separate the effects of disease from the individual aging changes. In [12] the HMM model was trained separately for the healthy population and the diseased population, and such an approach cannot fully answer this question.

The model [5] that can separate these two effects is

$$x_{j,t}^{\text{lat}} | \text{state}(j,t) = s,b \sim \mathcal{N} (\alpha_s + \beta_b + (\alpha\beta)_{sb}, I),$$

where $s$ is the latent development state (HMM-state), $\alpha_s$ is the effect of aligned HMM-time and $(\alpha\beta)_{sb}$ is the most interesting effect, the interaction of “HMM-time” and disease. We showed in [5] that it is possible to simultaneously estimate the terms in the model (4) and learn the alignments of the time-series into the HMM development states. We assume a linear HMM-chain, allowing only self-transitions and transitions into the next state. The probability of the $t$:th time-point of individual $j$ being in state $s$ is

$$p(s(j, t) = s) = p(s(j, t)|s(j, t - 1)) p (x_{j,t}^{\text{lat}} | \alpha_s + \beta_b + (\alpha\beta)_{sb}) p (s(j, t + 1)|s(j, t)).$$

If more covariates are present in the study, it is straightforward to extend the model (4) by additional terms.

### 2.3 Translating biomarkers between species from time-series measurements from multiple populations with irregular measurement times

We now propose that translation of results between multiple species, from multi-way time-series experiments, should be done by finding groups of similarly behav-
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ing variables (metabolites) in both species that respond similarly into multi-way covariates. A data matrix representation of the data analysis problem and plate diagram of the Bayesian model are shown in Figure 1. We introduce a modeling framework that can do this task, even in the complicated case of having irregular time-series measurements that require alignment into hidden metabolic states.

The model makes the very flexible assumption \[ \theta = \{ \alpha_s, \beta_b, (\alpha \beta)_{sb}, (\alpha \beta)_{xsb}, (\alpha \beta)_{ysb} \} \] contains all latent variables describing the corresponding HMM state. The state of each sample is determined by an observed covariate \( b \) and an unobserved covariate \( s \).

\[ \begin{align*}
x &= \mu_x + f^x (\alpha_s + \beta_b + (\alpha \beta)_{sb}) + f^x (\alpha_x^s + \beta_b^x + (\alpha \beta)_{xsb}^x) + \epsilon, \\
y &= \mu_y + f^y (\alpha_s + \beta_b + (\alpha \beta)_{sb}) + f^y (\alpha_y^s + \beta_b^y + (\alpha \beta)_{ysb}^y) + \epsilon,
\end{align*} \] (6)

where \( \alpha_s, \beta_b, (\alpha \beta)_{sb} \) are the shared effects of HMM-time, disease and interaction of HMM-time and disease, respectively, \( \alpha_x^s, \beta_b^x, (\alpha \beta)_{xsb}^x \) and are the species-specific effects of HMM-time, disease and interaction of HMM-time and disease, respectively, and likewise for species \( y \). The variable-spaces of \( x \) and \( y \) are different, and therefore also the dimensions of the latent variables of \( x_{lat} \) and \( y_{lat} \) representing groups of correlated variables in both species, need not match. For this reason, the latent effects of the covariates have to be projected into the actual observed data spaces \( x \) and \( y \) through previously unknown projections \( f^x \) and \( f^y \), that will be learned jointly with the model.

The translational problem now becomes: Does some dimension of \( x_{lat} \) respond to the covariates \( s \) and \( b \) similarly as one of \( y_{lat} \). If it does, one can represent this behavior with shared effects \( (\alpha_s, \beta_b, (\alpha \beta)_{sb}) \). The interpretation is that a cluster of correlated variables in \( x \) represented by the dimension of \( x_{lat} \) matches with a cluster of correlated variables in \( y \). Such dimensions can be considered as multi-species biomarkers. If there is no match, the response to
the external covariates is modelled by species-specific effects \((\alpha_s^x, \beta_b^x, (\alpha\beta)_{sb}^x)\).

With this framework, we are able to estimate confidence of the shared effects.

2.4 Matching problem

We propose the following measure for quantifying the quality of the match between two clusters from different datasets: whether the matching is better than an average matching (over other pairs). On a meta-level the measure is intuitively appealing in the spirit of permutation tests, and it can be formulated more exactly by specifying what we mean by “better.” We will use probabilistic modeling to measure relative goodness below.

The matching problem of the clusters is a combinatorial problem, where possible configurations of pairs need to be evaluated, judging for each pair how similarly they respond to multi-way covariates. We resort to an iterative algorithm that attempts to change the matching of one cluster at a time. Choosing a candidate pair, we compare its goodness to an average pair (uniformly selected having one same endpoint), and accept forming a link between them by a Metropolis criterion that compares the likelihoods of the two pairings. A reverse operation is to attempt to break a link by comparing an existing link between two clusters to an average (random) pair. The goodness (likelihood) of a pair is evaluated by a shared multi-way model between the clusters. Clusters with no pairs are modelled as specific effects. Averaging over the iterations, we can estimate the probability for matchings and the “shapes” of the multi-way effects. A high probability of a specific pair indicates a found matching. A high probability for being modelled as a specific effect indicates the cluster has no pair.

3 Results

We illustrate the method with generated data and lipidomic time series data with a two-way, time-series experimental design. In the experiments, we neglect the static disease effects \(\beta_b\) and assume all the disease effects are due to HMM-state-specific disease effects \((\alpha\beta)_{sb}\).

3.1 Generated data

We generated from the model two data sets \(X\) and \(Y\) with no pairing of samples but only a shared two-way design. There are 11 separate time-series (“patients”) in both of the two data matrices, each series consisting of 5 to 15 time points. This results in 108 and 115 samples, and data matrices are 200- and 210-dimensional. The latent factors \(x_{ij}^{lat}\) and \(y_{ij}^{lat}\) are 3- and 4-dimensional, respectively. The data in each population is generated from a shared HMM-chain with 5 states. We generate three covariate effects into the data: (i) a shared temporal effect \(\alpha_s\) as 0, +0.5, +1, +1.5, +2 in one cluster of data set \(X\) and one cluster of data set \(Y\), (ii) a shared interaction effect \((\alpha\beta)_{sb}\) as 0, −0.5, −1, −1.5, −2 in another cluster of \(X\) and another cluster of \(Y\), (iii) a specific temporal effect \(\alpha_y^s\) as 0, −0.5, −1,
Patterns (i) and (ii) are the only behavior that is shared between the two data sets representing the two species, and the model should be able to learn the correct pairing of variable clusters based on this similarity. We use the proposed model to jointly align the samples into HMM states, learn the clusters of variables, search for the possible pairing of the clusters between the two data sets, and model the ANOVA-type effects acting on the found clusters. We choose a priori a model with 5 HMM states. For the analysis we discarded the first 5 000 samples from the Gibbs sampler as a burn-in period and after this ran the model for another 5 000 Gibbs samples of which we saved every 5th sample to obtain a total of 1 000 Gibbs samples to approximate the underlying posterior distribution.

Our model finds the previously generated clusters without mistakes (see Fig. 2). It also connects the X-cluster 1 to Y-cluster 3 and X-cluster 3 to Y-cluster 2 by estimating them to be linked in 89.9 % and 47.9 % of posterior samples, respectively. The generated shared and specific effects are detected as expected and no false positive effects are found.

### 3.2 Lipidomic time-series data

We then validate the model with a real lipidomic data set, consisting of time-series measurements from a recently published type 1 diabetes (T1D) follow-up study [13]. In the data, there are 71 healthy patients and 53 patients that later developed into T1D. For each time-series, there are 3–29 time points from irregular intervals. For this validation study, we randomly divide the individuals into two non-overlapping data sets X and Y. We then study, whether we can find a similar response to the covariates disease and HMM-time, and a matching between those clusters from the two data sets that respond to these covariates.

Again, we a priori chose a model with 5 HMM states. We learned a two-way model for the data, where the first way is “HMM-time” and the second way is “disease”. Lipids were assigned into 6 clusters. We discarded 10 000 burn-in samples and collected 10 000 Gibbs samples of which we saved every 10th sample to obtain a total of 1 000 Gibbs samples approximating the posterior distribution.

The model integrates the datasets X and Y by learning the HMM-time effects $\alpha_s$ and interaction effects $(\alpha\beta)_{sb}$. Clusters of lipids and effects found (Fig. 3) were similar as in our previous publication [5]. The model finds three matching clusters between X and Y responding similarly to the external covariates, thus linking the same lipids between the two subsets of data without prior knowledge. The corresponding clusters were paired in 10–12 % of posterior samples, which is higher than for other combinations of pairing (0–11 %). Naturally the method does not find matchings for clusters that do not respond to external covariates.

A group of triglycerol (TAG) and two groups of glycerophosphocholine (Gp-Chol) were strongly paired to their counterparts. On real data, the result is naturally not as good as on generated data, since the effects are weaker.
Fig. 2. Pairing results from generated time-series data. Shown are the main effects (HMM-time; left) and interaction effects (right). Topmost, the generated effects are illustrated. Lower, the table of estimated effects shows shared (top-right area) and specific (left column and bottom row) effects for both types of effects. Rows and columns in the area of shared effects correspond to clusters in data sets X and Y, respectively. The found true pairing is highlighted by a red box. Value on top of each plot shows the percentage of posterior samples where the effect is found. An effect above or below zero is considered significant.
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Fig. 3. Pairing results from lipidomic time-series data. Only the main effects $\alpha_s$ are shown. The true pairings found are highlighted by red boxes. The table shows shared (top-right area) and specific (left column and bottom row) effects estimated by the model. Rows and columns in the area of shared effects correspond to clusters in data sets X and Y, respectively. An effect (boxplot) consistently above or below zero is considered significant. Value on top of each plot shows the percentage of iterations where the clusters were matched.

4 Discussion

We presented a novel method for translating biomarkers between multiple species from multi-way, time-series experiments. The case we addressed is when there are no a priori known matching between the variables in the two datasets, but only a similar experimental design. The method estimates ANOVA-type multi-way covariate effects for clusters of variables, and identifies and separates effects that are shared between the species and effects that are species-specific.

For biological data, the task is harder than for generated data. Probabilities of matched shared effects were lower for biological data, which is caused by the fact that the covariate effects in a biological experiment are weaker, making it more challenging for the method to find the similarity between the data sets. The study with lipidomic T1D data showed, however, that the method is able to extract similarities between non-paired biological data sets. The approach presented can be naturally extended to multiple ways (covariates) and to multiple species.

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