Bayesian Conditional Auto-regressive LASSO Models to Learn Sparse Networks with Predictors

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ABSTRACT

Microbiome data generated by next generation sequencing continue to flourish. There is a need for statistical models that can decode microbes’ reaction to the environment and interactions among microbes simultaneously. The model should have the ability to correctly incorporate prior knowledge from controlled experiments that are oftentimes conditioned on other responses. We introduce a novel Bayesian conditional auto-regressive (CAR) LASSO model to infer a sparse network structure with nodes for responses and for predictors and whose edges all represent conditional dependence, not conditional among responses and marginal between responses and predictors. We also propose an adaptive extension of the CAR LASSO model so that different shrinkage can be applied to different edges which allows the incorporation of edge-specific prior knowledge. Indeed, the conditional representation of our model coefficients and adaptivity allow us to adequately encode prior knowledge obtained by specific experimental interventions and agrees with the experimenter’s intuition on average behavior of nodes under experiments. In addition, our model is able to equally handle small and big data and is computationally inexpensive through an efficient Gibbs sampling algorithm. With hierarchical structure, we extend the model to binary, counting and compositional responses by adding an appropriate sampling distribution to the core Normal model. Finally, we apply our model to two real-life microbial composition datasets: one related to human gut and one related to soil.

Keywords Linear Regression · Compositional Data · Interaction Network · Microbiome

1 Introduction

Background. Recent years have seen explosion of microbiome research studies. As evidenced by The Human Microbiome Project [31], the microbes that live on the human body are key determinants of human health and disease [11]. In addition, microbial communities are among the main driving forces of all biogeochemical processes on Earth. On one side, many critical soil processes such as mineral weathering, and soil cycling of mineral-sorbed organic matter are governed by mineral-associated microbes [13, 34, 8, 21, 35]. On another side, plant and soil microbiome drive phenotype variation related to plant health and crop production [2, 29, 24, 23].

Understanding the composition of microbial communities and what environmental or experimental factors play a role in shaping this composition is crucial to comprehend biological processes in humans, soil and plants alike, and to predict microbial responses to environmental changes. However, the inter-connectivity of microbes-environment is still not fully understood. One of the reasons for this gap in knowledge is the lack of statistical tools to infer connections among microbial communities while simultaneously accounting for predictors in an unified framework. That is, a desirable model would allow us to identify how predictors affect multivariate responses that are also correlated with each other. Here, we introduce a novel model framework to infer a complex network structure that represents both interactions among nodes and effects of a set of predictors. Specifically, our model estimates a network that represents the dependence structure of a multivariate response (e.g. abundances of microbes) while simultaneously estimating the effect of a set of predictors that influence the network (e.g. diet, weather, experimental treatments). The model is represented by a graph with two sets of nodes: predictors and responses (Figure 1). Directed edges between a predictor and a response represent conditional links, and undirected edges among responses represent correlations.

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Current challenges. Learning this graphical structure from data can be challenging due to three main reasons: 1) simple correlations among responses can confound the mechanisms of dependence \[5\], 2) the nature of the responses can be varied (continuous, discrete, compositional or binary), and 3) we expect the network to be sparse.

First, the standard approach to reconstruct such a network is to compute simple correlations among responses. This approach is flawed because of the key distinction between marginal and conditional dependence. This distinction is particularly more important when we include predictors in the model. For instance, penicillin has no biological effect on Gram-positive bacteria, yet it might still promote the abundance of such bacteria by inhibiting their Gram-negative competitors. In this example, penicillin has no conditional effect on Gram-positive nodes (conditioned on all other microbes), but it may have a marginal effect on them by marginalizing over all other microbes (Figure 1 B). The inverse is also possible. A response can be conditionally dependent on a predictor, but marginally independent when another response has a similar dependence with that predictor (Figure 1 F). In this case, the different link between the responses could marginally cancel out the effect of the predictor. Our goal is thus to find a graph that best represents the conditional dependence structure observed in the data instead of marginal correlations (e.g. ideally to be able to distinguish between A and B in Figure 1).

Second, the nature of the data is diverse. Counts or compositional data are common in microbiome studies. However, our statistical approach does not need to be constraint to microbial communities. Indeed, ecological data where presence/absence of animals are recorded can also be utilized to infer a network. Thus, our model should be flexible and easy to extend to various types of responses: continuous, compositional, counts, or binary.

Third, we want the resulting network to be sparse. Biologically, we want to identify the important links that are driving the signal in the data, and we do not expect all links to have an impact. Traditional LASSO \[30\] has been used to find a sparse solution for regression coefficients, but this setup is restricted to independent data and univariate response. Graphical LASSO \[14\] extends traditional LASSO to find a sparse precision matrix. This matrix can be viewed as the adjacency matrix of the graph among responses where links represent conditional dependence. Our model allows for different types of responses where links represent conditional dependence. This setup, however, does not allow for the inclusion of predictors.

A combined approach of traditional LASSO and graphical LASSO could indeed yield sparse regression coefficients (predictor selection) and sparse precision matrix at the same time. However, in this approach, the graph would not encode conditional dependence in general unless responses are all independent (more details in Section 2.2). Thus, we want a unified sparse framework for the predictors and the precision matrix that does not violate the conditional dependence of the nodes.

Our novel model will achieve sparsity on the predictors and on the graph simultaneously without compromising the conditional dependence among the nodes. Furthermore, our novel model will be suitable for multiple types of responses, and hence, it will overcome the three main challenges of existing models.

Main contributions. Here, we introduce a novel conditional auto-regressive (CAR) linear regression model to infer a network structure with node types for responses and for predictors and whose edges indeed represent conditional dependence, not marginal dependence. Our model allows for different types of responses (continuous, discrete and compositional) and it is flexible to account for a unique parametrization for any covariance matrix \[32\]. Furthermore, our model guarantees sparsity on the predictor effects and on the precision matrix of the graph through LASSO penalty.

Additionally, our model is well-suited to account for biological prior knowledge. For example, a given microbe’s response to certain treatment could be known from a previous controlled experiment. To account for prior knowledge, we used a Bayesian framework which allows us to build a Bayesian hierarchical structure for a complex data structure \[15\] and the inclusion of prior knowledge.

While a standard combination of Bayesian LASSO \[28\] and Graphical LASSO \[33\] still produces networks where the conditional dependence is not satisfied \[25\] \[26\], our sparse Bayesian CAR model does encode the correct conditional dependence structure while allowing for the flexibility to extend to other types of responses and to incorporate prior knowledge. Finally, our model is able to equally handle small and big data and is computationally inexpensive through an efficient Gibbs sampling algorithm.

2 The (Bayesian) CAR-LASSO Model

2.1 Model specification

Let \( Y_i \in \mathbb{R}^k \) be a multivariate response with \( k \) entries for \( i = 1, \ldots, n \) observations. Let \( X_i \in \mathbb{R}^{1 \times p} \) be the row vector of predictors for \( i = 1, \ldots, n \) (i.e. the \( i^{th} \) row of the design matrix \( X \in \mathbb{R}^{n \times p} \)). We assume that the design matrix is standardized so that each column has a mean of 0 and same standard deviation (set to be 1 in the simulations).
Figure 1: Simple network with predictors. We use a triangle to represent a predictor $X$ and circles to represent the responses $Y_1$ and $Y_2$. Red edges correspond to positive links between nodes while blue edges correspond to a negative links. Networks A and B (likewise networks C and D) can produce a similar marginal correlation structure between any two nodes. Distinguishing edges in E can be difficult since all edges have the same direction. Finally, in network F, $X$ and $Y_2$ are conditionally correlated, yet they might not have a marginal correlation. For example, if $Y_1, Y_2$ had marginal variance 1 and covariance $\rho = -0.5$, while conditional regression coefficient between $Y_1$ and $X$ conditioned on $Y_2$ was $\beta_1 = 2 > 0$ and conditional regression coefficient between $Y_2$ and $X$ conditioned on $Y_1$ was $\beta_2 = 1 > 0$, we can show that the marginal regression coefficient between $Y_2$ and $X$ when integrating out $Y_1$ is $\rho \beta_1 + \beta_2 = 0$ (more in Section 2.2).

Let $Y_i$ follow a Normal distribution with mean vector $\Omega^{-1}(B^T X_i^T + \mu)$ and precision matrix $\Omega \in \mathbb{R}^{k \times k}$ (positive definite) where $B \in \mathbb{R}^{p \times k}$ corresponds to the regression coefficients connecting the responses ($Y_i \in \mathbb{R}^k$) and the predictors ($X_i \in \mathbb{R}^{1 \times p}$) scaled by the marginal variance and $\mu \in \mathbb{R}^k$ corresponds to the intercept. We use the transpose $B^T X_i^T \in \mathbb{R}^{k \times 1}$ because samples are encoded as row vectors in the design matrix while by convention multivariate Normal samples are column vectors.

The likelihood function of the model is:

$$p(Y_i | X_i, \mu, B, \Omega) \propto \exp\left( (B^T X_i^T + \mu)^T Y_i - \frac{1}{2} Y_i^T \Omega Y_i \right).$$  \hspace{1cm} (1)

Note that in this parametrization, $B$ encodes conditional dependence between $Y$ and $X$ because in the kernel of the density, $B_{ij}$ is the coefficient of product between $X_i$ and $Y_j$. Thus, if $B_{ij} = 0$, then $X_i$ and $Y_j$ are conditionally independent. This is analogous to the case of $\Omega$ whose off-diagonal entries encode the conditional dependence between responses $Y_i$ and $Y_j$.

From a graphical perspective, $B$ represents the adjacency matrix between response nodes ($Y$) and predictor nodes ($X$) while the off-diagonal entries of $\Omega$ represent the partial correlations which coincide with the adjacency matrix between response nodes.

**Correspondence to classical CAR.** The parameters in the proposed model corresponds to a scale transformation of the classical conditional auto-regressive (CAR) model [32], and both models share sparse solutions. We can re-parametrize our model to the classical CAR parametrization as follows. Let $B'$ denote the unscaled conditional regression coefficients between responses and predictors. Let $C$ denote the conditional regression coefficients between responses, and let $M$ denote the conditional variance. We can generate the three matrices by decomposing $\Omega$. Define diagonal matrix $D$ by $D_{ii} = \Omega_{ii}$ and $R = D - \Omega$. Then we can calculate $C = D^{-1} R, M = D^{-1}$ and $B' = D^{-1} B$ [32]. Though a sparse precision matrix ($\Omega$) guarantees a sparse conditional auto-regression coefficient ($C$), one needs to be careful about the negative sign in this transformation. Conditional auto-regression coefficients ($C$) has an opposite sign as those in the precision matrix ($\Omega$).
We can derive an efficient Gibbs sampler for all parameters in this model due to the scale mixture representation.

where \( \tau_{ij} \) (1 \( \leq \) i \( \leq \) p, 1 \( \leq \) j \( \leq \) k) be the latent scale parameters for \( \Omega \).

The full model specification is then:

\[
Y_i | X_i, \mu, B, \Omega \sim N(\Omega^{-1}(B^T X_i^T + \mu), \Omega^{-1})
\]

\[
B_{ij} | \tau_{ij} \sim N(0, \tau_{ij}^2)
\]

\[
\tau_{ij} \sim \frac{\lambda_j^2}{2} e^{-\lambda_j^2 \tau_{ij}}
\]

\[
p(\Omega | \eta, \lambda) = C_{\eta}^{-1} \prod_{m<l} \left[ \frac{1}{2 \sqrt{\pi \eta_{ml}}} \exp \left( -\frac{\omega_{ml}^2}{2 \eta_{ml}} \right) \right] \prod_{m=1}^{k} \left[ \frac{\lambda_{\Omega m}}{2} \exp \left( -\frac{\lambda_{\Omega m}^2}{2 \eta_{ml}} \right) \right] I_{\Omega \in M^+}
\]

\[
p(\eta | \lambda_{\Omega}) \propto C_{\eta} \prod_{m<l} \left( \frac{\lambda_j^2}{2} \eta_{ml} \right) \exp \left( -\frac{\lambda_j^2 \eta_{ml}}{2} \right)
\]

where \( I_{\Omega \in M^+} \) means that \( \Omega \) must be positive definite.

### 2.2 On conditional (in)dependence

In regression models for multivariate response, the regression coefficients linking a given response with the predictors can be conditional (conditioned on the other responses) or marginal (integrating out the other responses). In our model, the regression coefficients matrix \( B \) encode conditional dependence (scaled by marginal variance) between the responses and the predictors.

Biologically, conditional regression coefficients are more interpretable than marginal regression coefficients (e.g. the effect of penicillin effect on Gram positive microbes). In particular, given prior knowledge on the behavior of microbes (e.g. laboratory controlled experiments), it is crucial for the regression coefficients to encode conditional dependence between nodes and predictors or the biological prior knowledge would be misused.

Despite its biological interpretability, there are downsides to a conditional construction. For example, with conditional coefficients is not possible to do marginal predictions of nodes given that the marginal distribution depends on the regression coefficients of other nodes as well as on the covariance matrix.

In general, it is not possible to perform marginal prediction of single node and graphical selection simultaneously. That is, for \( \hat{B} = B \Omega^{-1} \), marginal prediction requires that \( \hat{B} \) encodes marginal dependence to predictors so that we can take a certain column and use it like the regression coefficient of that single node. On the contrary, graphical selection requires that \( \hat{B} \) encodes conditional dependence. Simultaneous marginal prediction and graphical selection is only possible when \( \Omega^{-1} \) is diagonal, i.e. when nodes are independent, and thus, \( B_{ij} = 0 \) implies \( \hat{B}_{ij} = 0 \) for any \( B \).

Our model focuses on graphical selection, yet we also implement a model for sparse marginal regression coefficient and sparse precision matrix by joining Gibbs sampling for precision matrix in [33] into the Gibbs sampler in [28]. We denote this model Simultaneous Regression and Graphical LASSO (SRG-LASSO) and we use it to compare to the CAR-LASSO in the simulation study (Section 5).

### 3 Estimation

#### 3.1 Sampling scheme

We can derive an efficient Gibbs sampler for all parameters in this model due to the scale mixture representation. Following [33], let \( 1_n \) be the column vector of ones with dimension \( n \), let \( S = YY^T \), let \( \hat{\mu} = XB + 1_n \mu^T \), and let \( U = \hat{\mu} \hat{\mu}^T \). Equation 3 shows the full conditional distribution of \( \Omega \) and \( \eta \) (the hyperparameters in Equation 2).

\[
p(\Omega, \eta | Y, \lambda_{\Omega}, \mu) \propto |\Omega|^{-\frac{1}{2}} \exp \left( -\frac{1}{2} \text{tr}(S\Omega) - \frac{1}{2} \text{tr}(U\Omega^{-1}) \right) \prod_{m<l} \left[ \frac{1}{\sqrt{2 \pi \eta_{ml}}} \exp \left( -\frac{\omega_{ml}^2}{2 \eta_{ml}} \right) \right] I_{\Omega \in M^+}
\]

\[
\times \prod_{m=1}^{k} \left[ \frac{\lambda_{\Omega}}{2} \exp \left( -\frac{\lambda_{\Omega} \omega_{mm}}{2 \eta_{ml}} \right) \right] I_{\Omega \in M^+}
\]

\[
(3)
\]
Following [33], we can update one row (column) at one iteration. Let $H$ be the symmetric matrix with $H_{ml} = H_{lm} = \eta_{ml}$ ($m < l$) on the off-diagonal entries and on the diagonal $H_{mm} = 0$. We take one column out and partition $\Omega$, $S$, $U$, and $H$. Without lose of generality, we show the sampling scheme for the last row (column). Let $\Omega_{11} \in \mathbb{R}^{(k-1) \times (k-1)}$, $\omega_{12} \in \mathbb{R}^{k-1}$, and $\omega_{22} \in \mathbb{R}$. We partition $S$, $U$ and $H$ in the same manner.

$$
\Omega = \begin{bmatrix}
\Omega_{11} & \omega_{12} \\
\omega_{12}^T & \omega_{22}
\end{bmatrix},
S = \begin{bmatrix}
S_{11} & s_{12} \\
S_{12}^T & s_{22}
\end{bmatrix},
U = \begin{bmatrix}
U_{11} & u_{12} \\
U_{12}^T & u_{22}
\end{bmatrix},
H = \begin{bmatrix}
H_{11} & \eta_{12} \\
\eta_{12}^T & \eta_{22}
\end{bmatrix}.
$$

By setting $\gamma = \omega_{22} - \omega_{12}^T \Omega_{11}^{-1} \omega_{12} \in \mathbb{R}$, $\Omega^{-1}$ can be written in a block form [37]:

$$
\Omega^{-1} = \begin{bmatrix}
\Omega_{11}^{-1} + \frac{1}{\gamma} \omega_{12}^T \Omega_{11}^{-1} \omega_{12} & -\frac{1}{\gamma} \Omega_{11}^{-1} \\
-\frac{1}{\gamma} \Omega_{11}^{-1} & \frac{1}{\gamma}
\end{bmatrix}.
$$

Given

$$
\text{tr}(U \Omega^{-1}) = \text{tr}(U \Omega_{11}^{-1}) + \frac{1}{\gamma} \left( \omega_{12}^T \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12} - 2 u_{12}^T \Omega_{11}^{-1} \omega_{12} + u_{22} \right),
$$

we have the full conditional distribution of $\omega_{12}$ and $\gamma$:

$$
p(\omega_{12}, \gamma | \Omega_{11}, \eta, \lambda) \propto \gamma^{\frac{\eta}{2}} \exp \left( -\frac{1}{2} (s_{22} + \lambda) \gamma - \frac{u_{22}}{2\gamma} \right) \times \exp \left\{ -[s_{12} - \frac{1}{\gamma} \Omega_{11}^{-1} u_{12}]^T \omega_{12} - \frac{1}{2} \omega_{12}^T D_0^{-1} + (s_{22} + \lambda \Omega_{11}^{-1} \omega_{12} + \frac{1}{\gamma} \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12}) \right\}.
$$

From the above equation, we get a closed form expression for the conditional distribution of $\gamma$:

$$
p(\gamma | \omega_{12}, \Omega_{11}, \eta, \lambda) \propto \gamma^{\frac{\eta}{2}} \exp \left( -\frac{1}{2} (s_{22} + \lambda) \gamma - \frac{u_{22} - 2 u_{12}^T \Omega_{11}^{-1} \omega_{12} + \frac{1}{\gamma} \omega_{12}^T \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12}}{2\gamma} \right) I_{\gamma \geq 0}
$$

which is a Generalized Inverse Gaussian (GIG) distribution [18,20] with parameters:

$$
\lambda = \frac{n}{2} + 1
$$

$$
\psi = s_{22} + \lambda \Omega_{11}^{-1}
$$

$$
\chi = u_{22} - 2 u_{12}^T \Omega_{11}^{-1} \omega_{12} + \frac{1}{\gamma} \omega_{12}^T \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12}.
$$

GIG has a positive support. Thus, the determinant and the $k^{th}$ principle minor of the updated $\Omega$ are positive, while the first $k - 1$ principle minors remain unchanged and positive. In this manner, the updated $\Omega$ always remains positive definite.

By denoting $D_{\eta} = \text{diag}(\eta_{12}) \in \mathbb{R}^{(k-1) \times (k-1)}$, the full conditional distribution of $\omega_{12}$ is a Normal distribution:

$$
p(\omega_{12} | \gamma, \Omega_{11}, \eta, \lambda) \propto \exp \left\{ -[s_{12} - \frac{1}{\gamma} \Omega_{11}^{-1} u_{12}]^T \omega_{12} - \frac{1}{2} \omega_{12}^T D_{\eta}^{-1} + (s_{22} + \lambda \Omega_{11}^{-1} \omega_{12} + \frac{1}{\gamma} \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12}) \right\}
$$

with parameters:

$$
\Sigma_{\omega_{12}}^{-1} = D_{\eta}^{-1} + (s_{22} + \lambda \Omega_{11}^{-1} \omega_{12} + \frac{1}{\gamma} \Omega_{11}^{-1} U_{11} \Omega_{11}^{-1} \omega_{12})
$$

$$
\mu_{\omega_{12}} = - \Sigma_{\omega_{12}} [s_{12} - \frac{1}{\gamma} \Omega_{11}^{-1} u_{12}].
$$

As in [33], the $z_{ij} = 1/\eta_{ij}$ are independent inverse Gaussians with parameters:

$$
\mu_{z_{ij}} = \sqrt{\lambda^2_{ij} / \omega^2_{ij}}
$$

$$
\lambda_{z_{ij}} = \lambda^2_{ij}
$$
and density:
\[ p(z_{ij} | \Omega, \lambda_\Omega) = \left( \frac{\lambda_{z_{ij}}}{2\pi \sigma_{z_{ij}}^2} \right)^{1/2} \exp \left( -\frac{\lambda_{z_{ij}} (z_{ij} - \mu_{z_{ij}})^2}{2(\mu_{z_{ij}})^2} \right) I_{z_{ij} > 0}. \]

The full conditional distribution of \( \text{vec}(B) \) can be represented using tensor product [28]. Let \( D_{\tau^2} = \text{diag}(\tau^2) \in \mathbb{R}^{kp \times kp} \) for \( \tau \) the scaling parameters in the prior density of \( B \) (Equation 2). Then, the conditional distribution of \( \text{vec}(B) \) has the following form:

\[
    p(\text{vec}(B)|D_{\tau^2}, \Omega, \mu, X, Y) \propto \exp \{ X^T (Y - 1_n \mu^T \Omega^{-1}) \}
    - \frac{1}{2} \text{vec}(B)^T (\Omega^{-1} \otimes X^T X + D_{\tau^2}) \text{vec}(B). \tag{6}
\]

Note that the information from data is encoded by \( \Omega^{-1} \otimes X^T X \) which differs from the canonical parameterization of the multivariate linear regression model in which the information from data is encoded by \( \Omega \otimes X^T X \). This is because in the kernel of the likelihood, the term involving \( B \) is \( X \Omega^{-1} \Omega^{-1} B^T X^T = X \Omega^{-1} B^T X^T \), instead of \( X \Omega \Omega^{-1} B^T X^T \) as in the canonical parametrization (see Section 3.2).

Finally, we update \( \tau_{ij}^2 \) using an Inverse Gaussian distribution with parameters \( \sqrt{\lambda^2_{\beta} / B_{ij}^2} \) and \( \lambda^2_{\beta} \), and we update \( \mu \) using a Normal distribution with mean \( (Y \Omega - XB)^T \) and variance \( \Omega / n \).

### 3.2 Choice of hyperparameters

The shrinkage parameters \( \lambda_{\Omega} \) and \( \lambda_{\beta} \) (Equation 2) are hyperparameters to be determined. Following [28, 33], we assume these shrinkage parameters have a hyperprior Gamma distribution with shape parameter \( r \) and rate parameter \( \delta \) which can be set to produce a relatively flat density for a non-informative prior scenario. Note that since the prior on \( \Omega \) is not a Laplacian but a graphical LASSO prior [33], the Gamma prior is on \( \lambda \), not on \( \lambda^2 \) as it would be under a LASSO prior.

\[
\lambda^2_{\beta} \sim \text{Gamma}(r_{\beta}, \delta_{\beta}) \quad \lambda_{\Omega} \sim \text{Gamma}(r_{\Omega}, \delta_{\Omega})
\]

The shrinkage parameters \( \lambda_{\Omega} \) and \( \lambda_{\beta} \) are included in the Gibbs sampler with full conditional distribution still Gamma with shape parameters \( r_{\beta} + kp, \delta_{\beta} + \sum \tau_i / 2 \) and rate parameters \( r_{\Omega} + k(k + 1) / 2, \delta_{\Omega} + ||\Omega||_{1}/2 \) respectively.

### 3.3 Graphical structure learning

Our model has a zero posterior probability for a parameter to be zero given the continuous priors. Yet, we still need to determine the cases when the edges of the graph will be considered "non-existent". Here, we infer the graph structure using the horseshoe method in [7, 33] which compares the LASSO estimate for the regression coefficient with the posterior mean of a standard conjugate (non-shrinkage) prior [19].

Let \( \pi = \frac{\hat{\theta}}{E_\theta(\theta|Y)} \) where \( \hat{\theta} \) represents the estimate of the parameter under the LASSO prior and \( E_\theta(\theta|Y) \) is the posterior mean of that parameter under non-shrinkage prior (e.g. Normal for \( B \) and Washart for \( \Omega \)). The statistics \( 1 - \pi \) characterizes the amount of shrinkage due to the LASSO prior. We use \( \pi > 0.5 \) as the threshold to decide that \( \theta \neq 0 \) as in [33].

### 4 Extensions

#### 4.1 Adaptive LASSO

One simple extension to LASSO was Adaptive LASSO, in which the shrinkage parameter \( \lambda \) can be different for all elements in \( B \) and \( \Omega \) [25, 33]. This extension is particularly useful when we have prior knowledge of independence among certain nodes.

As suggested in [25, 33], we set the hyperpriors on \( \lambda^2_{\beta,ij} \) as Gamma distributions with shape parameters \( r_{ij,\beta} \) and rate parameter \( \delta_{\beta,ij} \). We also set the prior suggested in [33] for \( \lambda_{ij,\Omega} \) (with \( i \neq j \)). While in [33] \( \lambda_{ij,\Omega} \) is a hyperparameter, we set it here to 0. That is, we are not shrinking the diagonal entries of \( \Omega \).
We set the hyperparameters as $r$.

The prior for $\Omega$ is

$$p(\Omega) \propto C^{-1}_{(\lambda_{ij}, \Omega)} \prod_{i<j} \lambda_{ij, \Omega} \exp(-\lambda_{ij, \Omega} | \omega_{ij}|)$$

$$p(\Omega) \propto C_{(\lambda_{ij}, \Omega)} \prod_{i<j} \frac{1}{\Gamma(r_{ij, \Omega})} \lambda_{ij, \Omega}^{r_{ij, \Omega} - 1} \exp(-\delta_{ij, \Omega} \lambda_{ij, \Omega}).$$

The full conditional distribution of the shrinkage parameters is then Gamma (shape and rate parametrization):

$$\lambda_{ij, \Omega} | \Omega \sim \text{Gamma}(r_{ij, \Omega} + 1, \delta_{ij, \Omega} + | \omega_{ij}|), i \neq j$$

$$\lambda_{ij, \beta} | \tau \sim \text{Gamma}(r_{ij, \beta} + 1, \delta_{ij, \beta} + \tau_{ij}/2).$$

We set the hyperparameters as $r = 10^{-2}$ and $\delta = 10^{-6}$ for both $\Omega$ and $B$ with a small value of $\delta$ selected to take advantage of the adaptiveness of the shrinkage.

### 4.2 Other types of responses

The model has been defined for continuous responses, yet there are different extensions for the case of binary data, counts and compositional data that we describe below.

#### 4.2.1 Probit model for binary data

For binary responses, we can use a Probit model with CAR in the core of the dependence structure. We denote the CAR latent variable as $Z_i \in \mathbb{R}^k$, and let $\Phi(Z_{ij})$ model the probability of observing a 1 where $\Phi$ is the cumulative distribution function of a standard Normal.

Equation (7) shows the alternative representation of the model:

$$Z_i \sim N(\Omega^{-1}(B^T X_i^T + \mu), \Omega^{-1})$$

$$Y_{ij}^* \sim N(Z_{ij}, 1)$$

$$Y_{ij} = 1_{Y_{ij}^* > 0}$$

Then, the full conditional probability of $Y_{ij}^*$ is a truncated Normal with mean $Z_{ij}$ and variance 1. By denoting $\tilde{\mu}_i = (B^T X_i^T + \mu)$, we have the full conditional distribution of $Z_i$:

$$Z_i | Y_{ij}^*, \tilde{\mu}_i, \Omega \sim N([\Omega + I]^{-1}(\tilde{\mu}_i + Y_{ij}^*), [\Omega + I]^{-1}).$$

#### 4.2.2 Log-normal Poisson model for counts

To model a response of multivariate counts, we use a Lognormal-Poisson model. Let $Z_i \in \mathbb{R}^k$ be the latent vector of log expected counts of the $i^{th}$ sample and let $Y_i \in \mathbb{N}^k$ be the observed counts. We use $Z_{i,-j} \in \mathbb{R}^{k-1}$ to denote the vector of log expected counts of the $i^{th}$ sample but without response $j$ and $Z_{ij}$ as the log expected counts of the $i^{th}$ sample and $j^{th}$ response.

The covariance matrix accounts for both over-dispersion and correlation of the counts:

$$Z_i \sim N(\Omega^{-1}(B^T X_i^T + \mu), \Omega^{-1})$$

$$\lambda_{ij} = \exp(Z_{ij})$$

$$Y_{ij} \sim \text{Poisson}(\lambda_{ij}).$$

Then, the density of $Y_{ij}$ is:

$$p(Y_{ij} | Z_{ij}) \propto \exp\{Y_{ij} Z_{ij} - e^{Z_{ij}}\}.$$  

Let $Z_{ij} | Z_{i,-j} \sim N(\tilde{\mu}_{ij}, \tilde{\sigma}_{ij}^2)$ be the conditional prior so that the log full conditional is:

$$\log[p(Z_{ij} | Z_{i,-j}, \tilde{\mu}, \Omega, Y)] = Y_{ij} Z_{ij} - \exp(Z_{ij}) - \frac{1}{2\tilde{\sigma}_{ij}^2}(Z_{ij} - \tilde{\mu}_{ij})^2 + C$$

CAR-LASSO
which is clearly concave.

This means that we can sample the full conditional distribution of the latent variables using adaptive rejection sampling (ARS) [16], and this can be done in parallel to further speed up the sampling.

4.2.3 Normal-Logistic for multinomial data

As in [36], we developed a Normal-Logistic model for multinomial compositional data. This type of data is very common in microbiome and ecology studies.

Assume that we have \( k + 1 \) responses in our sample and the last response serves as reference group. Let \( \mathbf{Z}_i \in \mathbb{R}^{k+1} \) denote the latent vector of logit transformed relative abundance for \( i \)th sample, and let \( \mathbf{Y}_i \in \mathbb{N}^k \) be the observed species counts. Denote as \( M \) the known total count (e.g. sequence depth in microbiome studies). Similarly we use \( \mathbf{Z}_{i,-j} \) to denote the vector logit transformed relative abundance of the \( i \)th sample but without response \( j \) and \( Z_{ij} \) as the log expected counts of the \( i \)th sample and \( j \)th response.

The six graphical structures are defined below. Note that model 1 and model 3 specify the entries of the covariance matrix \( \Sigma \) while the other models specify the entries of the precision matrix \( \Omega \) (\( \omega_{ij} \)).

- Model 1: An AR(1) model with \( \sigma_{ij} = 0.7^{\lfloor i-j \rfloor} \)
- Model 2: An AR(2) model with \( \omega_{ii} = 1, \omega_{i-1,i} = \omega_{i,i-1} = 0.5, \omega_{i-2,i} = \omega_{i,i-2} = 0.25 \) for \( i = 1, \ldots, k \)
- Model 3: A block model with \( \sigma_{ii} = 1 \) for \( i = 1, \ldots, k \), \( \sigma_{ij} = 0.5 \) for \( 1 \leq i \neq j \leq k/2 \), \( \sigma_{ij} = 0.5 \) for \( k/2 + 1 \leq i \neq j \leq 10 \) and \( \sigma_{ij} = 0 \) otherwise.
- Model 4: A star model with every node connected to the first node, with \( \omega_{ii} = 1, \omega_{1,i} = \omega_{i,1} = 0.1 \) for \( i = 1, \ldots, k \), and \( \omega_{ij} = 0 \) otherwise.
- Model 5: A circle model with \( \omega_{ii} = 2, \omega_{i-1,i} = \omega_{i,i-1} = 1 \) for \( i = 1, \ldots, k \), and \( \omega_{1,j} = \omega_{j,1} = 0.9 \) for \( j = 1, \ldots, k \).

The Normal-Logistic model has the following structure:

\[
\mathbf{Z}_i \sim N(\Omega^{-1}(\mathbf{B}^T \mathbf{X}_i^T + \mu), \Omega^{-1})
\]

\[
p_{ij} = \frac{\exp(Z_{ij})}{\sum_{i=1}^{k} \exp(Z_{ij}) + 1}
\]

\[
\mathbf{Y}_i \sim \text{Multinomial}(p_{i1}, \ldots, p_{ik}, M)
\]

Note that the normal latent variables take care of the over-dispersion, so a key part of the model is the sampling the latent variable.

Then, the likelihood of \( \mathbf{Y}_i \) is:

\[
p(\mathbf{Y}_i | \mathbf{Z}_i) = \frac{1}{\sum_{j=1}^{k} \exp(Z_{ij}) + 1} \prod_{j=1}^{k} \frac{\exp(Y_{ij}Z_{ij})}{\sum_{j=1}^{k} \exp(Z_{ij}) + 1}
\]

Let \( Z_{ij} | \mathbf{Z}_{i,-j} \sim N(\mu_{ij}, \sigma_{ij}^2) \) be the conditional prior so that the log full conditional is:

\[
\log[p(Z_{ij} | \mathbf{Z}_{i,-j}, \mu, \Omega, \mathbf{Y})] = Y_{ij}Z_{ij} - N \log \left( \sum_{j=1}^{k} \exp(Z_{ij}) + 1 \right) - \frac{1}{2\sigma_{ij}^2} (Z_{ij} - \mu_{ij})^2 + C
\]

This function is concave because the first term is an affine, the second term is the negative log sum of exponential of an affine function, and the last term is a concave quadratic form. Thus, ARS [16] can again be used during the Gibbs sampling, and this process can be parallelized for extra speed.

5 Simulations

We simulate data under the six graphical structures in [33] with two sample sizes: 1) \( k = 30, n = 50 \) and 2) \( k = 100, n = 200 \). We vary the sparsity of \( \mathbf{B} \) with 80% or 50% entries equal to zero (denoted beta sparsity of 0.8 and 0.5 in the figures) and a grand mean (i.e. intercept \( \mu \)) of 0. Each simulation setting was repeated 50 times.

The six graphical structures are defined below. Note that model 1 and model 3 specify the entries of the covariance matrix \( \Sigma \) while the other models specify the entries of the precision matrix \( \Omega \) (\( \omega_{ij} \)).
• Model 6: A full model with \( \omega_{ii} = 2 \) and \( \omega_{ij} = 1 \) for \( i \neq j \in \{1, \ldots, k\} \).

We compare the performance of eight models:

• CAR-LASSO: our proposed model
• Adaptive CAR-LASSO: our proposed model with different shrinkage parameters for \( B \) and \( \Omega \)
• SRG-LASSO: our model focused on marginal prediction described in Section 2.2
• Graphical LASSO in [33]
• Adaptive Graphical LASSO: adaptive version in [33]
• Multivariate regression: Bayesian multi-response regression with conjugate priors. Since this model does not really estimate the conditional regression coefficients \( B \) but the marginal regression coefficient \( \tilde{B} \), we get \( B = \tilde{B}\Omega \) (see Section 2.2)
• Multivariate regression with 0 mean: Bayesian multi-response regression with conjugate priors that assume the marginal mean is 0 (similar to Graphical LASSO)
• Calculate the empirical covariance matrix and take inverse (denoted ad-hoc in the figures)

As in [33, 25], we set the hyperparameters of the Gamma hyperprior for the shrinkage parameters of both \( B \) and \( \Omega \) as \( r = 0.01, \delta = 10^{-6} \) for the adaptive versions, and \( r = 1, \delta = 0.01 \) for the non-adaptive versions.

To evaluate the performance of the methods, we compute the L2-loss of the estimate of \( B \) and the Stein’s loss of the estimate of \( \Omega \). To our knowledge, there is no convention for which loss should be used. We use Stein’s loss for \( \Omega \) since it is the KL-divergence when the mean vector is 0.

In addition, we evaluate the reconstruction of the graphical structures based on the Matthews Correlation Coefficient (MCC) [12] which range from -1 to 1 with 1 representing a perfect prediction. Given that the covariance model 6 is a fully connected graph (and thus, there are no true negatives or false positives), we did not calculate the MCC in this case. In multivariate regression, we consider any edge with weight \( < 1 \times 10^{-3} \) to be 0.

Figure 2a shows the results on the Stein’s loss on the estimation of \( \Omega \). Our proposed models (CAR-LASSO and adaptive CAR-LASSO) outperform the other models in almost every covariance model and sparsity setting with the adaptive version outperforming the non-adaptive version in almost every setting.

Figure 2b shows the results on the L2-loss on the estimation of \( B \). Similarly, our proposed models (CAR-LASSO and adaptive CAR-LASSO) outperform the other models in almost every covariance model and sparsity setting. However, unlike in the case of \( \Omega \), the adaptive version did not outperform the non-adaptive version in some scenarios especially when \( B \) is not sparse. Graphical LASSO and Adaptive Graphical LASSO are not included in this plot because these models do not estimate the matrix of regression coefficients \( B \).

Figure 3a shows the MCC for \( \Omega \) and Figure 3b shows the MCC for \( B \). In all cases, adaptive CAR-LASSO had highest MCC, except for covariance model 4 where all models performed poorly. This might due to the difficulty of finding the center of the graph in this model.

5.1 Computational speed and scaling test

We test the scalability of our estimation procedure by simulating 500 and 1000 samples with 5, 10, 25, 50, 100 nodes. We sample 1000 generations with 100 burn-in on a machine with Core-i7 4790 CPU and Windows 7 operating system. We record CPU seconds in R.

Figure 4 shows that while our models are slower than Graphical LASSO or multivariate regression, running time is not severely impacted by sample size. Instead, speed is mostly influenced by the number of nodes and the number of predictors. However, even the case of 100 nodes and 10 predictors is successfully completed in less than 10 minutes.

6 Microbiota networks for soil and human gut data

We test our method on two microbial compositional datasets:

**Soil microbiota data.** The objective of this study [17, 4] is to examine soil microbial community composition and structure of both bacteria and fungi at a microbiologically-relevant scale. The researchers isolated soil aggregates from three land management systems in central Iowa to test if the aggregate-level microbial responses are related to plant
Figure 2: (a) Stein’s Loss of $\Omega$ and (b) L2 Loss of $B$ (Y-axis in logarithmic scale) for simulated datasets with 30 nodes and 50 samples under two levels of beta sparsity (red 0.8 and blue 0.5), two different number of predictors (10 in bottom row and 5 in top row) and six covariance models (columns). X-axis corresponds to the models compared. Our models (Adaptive) CAR-LASSO get the lowest loss in most cases.
Figure 3: Matthews Correlation Coefficients for (a) Ω and (b) B for simulated datasets with 30 nodes and 50 samples under two levels of beta sparsity (red 0.8 and blue 0.5), two different number of predictors (10 in bottom row and 5 in top row) and six covariance models (columns, fully connected covariance model was omitted from Ω result since MCC was not defined). X-axis corresponds to the models compared. MCC=1 means a perfect reconstruction. Our model Adaptive CAR-LASSO gets the highest MCC in most cases.
community and management practices. The clean dataset has 120 samples with 17 genus under consideration. We focus on the bacteria to further evaluate the partial association among them and the environmental factors.

**Human gut microbiota data.** The microbiota of older people displays greater inter-individual variation than that of younger adults. This study [10] collected faecal microbiota composition from 178 elderly subjects, together with subjects’ residence type (in the community, day-hospital, rehabilitation or in long-term residential care) and diet. Researchers studied the correlation between microbes and other measurements. We evaluate the partial correlation between environments and among microbes in those elderly subjects.

We use the MG-RAST server [27] for profiling with an e-value of 5, 60% identity, alignment length of 15 bp, and minimal abundance of 10 reads. Unclassified hits are not included in the analysis. Genus with more than 0.5% (human) or 1% (soil) relative abundance in more than 50 samples is selected as the focal genus and all other genus serve as the reference group.

We reconstruct the weighted graph using the conditional regression coefficient between any two nodes. The $\alpha$-centrality [6] is used to identify the importance of nodes. Weighted adjacency matrix is constructed with the posterior mean of the conditional regression coefficients of those that showed significance with the horseshoe method described in Section 3.3.

The soil microbiota (Figure 5b) results in a more dense network compared to the human gut (Figure 5a). In the human gut microbiota network, the edges with the most weight correspond to connections between genus nodes, not so much with predictors. The most important predictor is whether the patient’s residence was a long-term residential care which positively affected genus *Caloramator*. This results agrees with the original analysis that also separates elderly subjects based upon where they live in the community. Another important predictor was Diet Group 4 which corresponds to the high fat/low fiber group. This diet positively affected genus *Caloramator* as well. In the soil microbiota network, the most important link is between *Candidatus Solibacter* and *Candidatus Koribacter*. There are not important connections with predictors in this case. These results agree with the original research that indicated that core microbial communities within soil aggregates are likely driven by stable and long-term factors such as clay content rather than relative short time scaled land management as the ones considered as predictors in this study.

It is worth highlighting that our model can produce meaningful results from relative small sample sizes: 120 samples for the soil microbiota study and 178 samples for the human gut microbiota study.
Figure 5: **Reconstructed genus network for (a) human gut and (b) soil microbiota.** Triangle nodes correspond to predictors and circle nodes correspond to relative abundances of genus. The node size on the circle nodes correspond to the $\alpha$—centrality values [6]. The width of the edges correspond to the absolute weight, and the color to the type of interaction (red positive, blue negative).
7 Discussion

Importance of conditional dependence. It is crucial for any model dealing with predictors and multivariate responses to distinguish between marginal effects and conditional effects. A conditional construction coincides with the intuition that the marginal response of a node should be influenced by both its and others’ reaction to a common input. This distinction of marginal or conditional effect is particularly important when including biological prior knowledge. For example, species reactions to treatments can be measured under controlled experiments (e.g. [26]) and this knowledge would be properly encoded under a conditional dependence model. See more in the "Agreement with experimenter’s intuition on mean behavior" and "Optimal model-based design of experiments".

Flexibility of the Bayesian model. Compared with the frequentist method, the Bayesian method allows an easier extension of the core Normal model to different types of responses via hierarchical structures. As long as one can sample from the full conditional distribution of the (latent) Normal variable, the posterior sampling is a straight-forward extension of the Gibbs sampler we proposed. Though not presented here, other commonly encountered models in biology are also simple extensions e.g. zero-inflated Poisson and multinomial [22]. By using the Normal distribution as the core model, we can automatically take into account the over-dispersion because the model considers the variance parameters explicitly. In addition, one common complaint on the LASSO prior is that it does not put any mass on 0 for any edge. Though a spike-slab prior is possible, an efficient posterior sampling algorithm like the block Gibbs sampler in [23] and in this work is hard to derive due the intractable normalizing constant.

Challenges of graph learning. Graphical selection can be difficult because of the confounding in its own structure. For example, recall Figure 1A and B. These two graphs can produce a similar correlation between $Y_1$ and $Y_2$. One extreme example is when all links in A and B have no noise (e.g. $Y_1 = X$, $Y_2 = -Y_1$ versus $Y_1 = X$, $Y_2 = -X$). In this extreme example, it is impossible to distinguish graph A from B. Of particular difficulty are also cases like Figure 1E where all partial correlations are positive (or negative). Additionally, when $\Omega$ has bad condition numbers, then $\mathbf{B}$ might have large error in estimation since the marginal mean response and $\Omega$ inform the estimation of $\mathbf{B}$, and a small change in the marginal mean response can have a large influence in $\mathbf{B}$.

Agreement with experimenter’s intuition on mean behavior. Intuitively, an experimenter should be able to make inferences about the interactions among responses from the behavior of the mean structures under treatment. For example, in Figure 1D, an experimenter might knock out a gene as the treatment ($X_1 = 1$ for knock out and $X_1 = 0$ for not) and compare the gene expression levels of another gene ($Y_2$) via a t test. The result of this t test will provide information regarding the interaction between $Y_1$ and $Y_2$ because there are no other factors affecting $Y_1$ and $X_1$ is conditionally independent with $Y_2$. Thus, this experiment is specific to $Y_1$ and provides information on partial correlation between $Y_1$ and $Y_2$ by only affecting $Y_1$. That is, any change in $Y_2$ is due to the partial correlation with $Y_1$ rather than a reaction to $X_1$. It is precisely the fact that the mean of $Y_2$ in this experiment depends on the correlation between $Y_1$ and $Y_2$ that allows experimenters to test differences in means of $Y_2$ under the effect of the treatment ($X_1$) through standard t tests. However, this intuition is violated though under the standard linear regression setting. The vector $(Y_1, Y_2)$ is Normally distributed with mean $\mu = (X_1 \beta_1, 0)$ and covariance $\Sigma$ under the network in Figure 1D, and thus, the mean of $Y_2$ is always 0 regardless of the value of $X_1$. In contrast, in the CAR parametrization, the mean vector is $\Sigma \mu$ whose second entry is given by $\rho \beta_1 X_1$, i.e. the mean value of $Y_2$ depends on $\beta_1$ (the reaction of $Y_1$ to the treatment) as well as $\rho$ (the correlation between $Y_1$ and $Y_2$). Given that the experimenter’s intuition on specificity is based on the notion of conditional (in)dependence between $X_1$ and $Y_1, Y_2$, we conclude that it is desirable that the mean vector contains information on the correlation structure among responses and this is a characteristic of the CAR model that we propose.

Optimal model-based design of experiments. An experimenter should be able to design experiments that decode the links among response nodes when specific experimental interventions towards one node are possible. In practice, when possible, experimenters will always prefer experiments with better specificity. However, this preference is not evident in the linear regression setting since the Fisher information matrix of the mean vector and the precision matrix is block-diagonal, and thus, any information that we have on B will not affect estimation of $\Sigma$. In addition, the information of $\Sigma$ is not a function of design $(X)$ no matter whether we have prior knowledge about effect of such experiment (prior on B). Using the CAR parametrization avoids this disagreement because the Fisher information matrix is no longer block-diagonal and prior information about the treatment can flow into the estimation of $\Sigma$ via an optimal model-based experimental design [29]. We highlight that due to the confounding between the treatment effect and the interaction among responses, the prior knowledge on specificity of the treatment is necessary for such an optimal model-based experimental design.

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