Selection and Estimation of Conditional Graphical Models

Stephen Salerno, MS and Yi Li, PhD
Department of Biostastics · University of Michigan

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Outline

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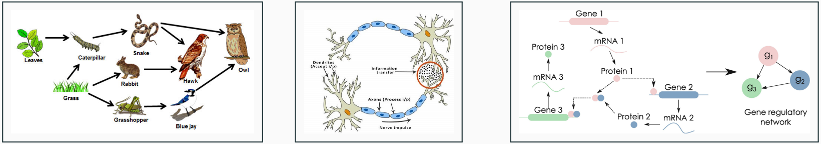
Background and Motivation

Biological Networks

Network-based structures appear everywhere in nature throughout various **biological systems**:



(a) Ecological **(b)** Neural **(c)** Gene Co-Regulation

Figure 1: Example biological networks.

(a) https://link.springer.com/protocol/10.1007/978-1-4939-8882-2_1;//

(b) https://medium.com/predict/artificial-neural-networks-mapping-the-human-brain-2e0bd4a93160;//

(c) https://ontrack-media.net/gateway/science7/g_s7m1l2s3.html

Biological Networks

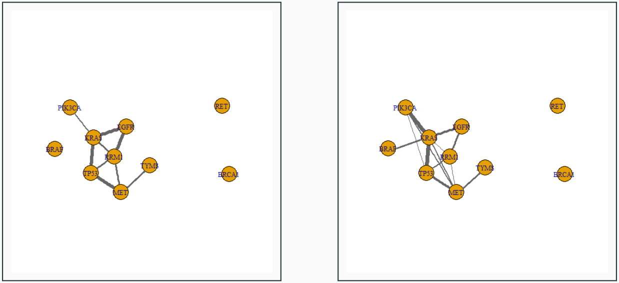
Modeling biological networks provides a **mathematical representation** of the **unit-to-unit connections** in these systems[1]

These network connections may **differ** by **important factors**

In particular, gene co-regulated networks may differ by **individual DNA profiles**[2–4] or characteristics such as **sex**[5–9]

Boston Lung Cancer Survival Cohort Example

Figure 2 shows that the network structure of lung cancer-related genes depends on the heterozygous or homozygous status of SNP chr1:1792215.



(a) Homozygous Subgroup

(b) Heterozygous Subgroup

Figure 2: Networks with eight lung cancer genes differing by SNP chr1:1792215 genotype among Boston Lung Cancer Survival Cohort (BLCSC) study patients.

Graphical Models

Graphical models provide a means of quantifying the relationship between nodes of a network through **conditional co-dependence** (edges)

- Let $\boldsymbol{X} = (X_1, \ldots, X_p)$ be a p-dimensional random vector
- The tuple $\mathcal{G}_{\boldsymbol{X}} = \{\mathcal{G},\ \mathcal{P}(\boldsymbol{X})\}$ defines a graphical model for $\boldsymbol{X}$ where $\mathcal{G}$ is a graph and $\mathcal{P}(\boldsymbol{X})$ is a given probability

An edge between two nodes is defined by a **non-zero partial correlation**

Conditional Gaussian Graphical Models

The **Gaussian distribution** is a natural choice for jointly modeling conditional independences, encoded by $\mathcal{G}$, for continuous outcomes

Conditional Gaussian graphical models (CGGMs) reparametrize the multivariate linear regression model to **explicitly exhibit**:[10]

- Partial correlations between predictors and responses
- Partial correlations among responses

Current CGGM Formulations

For observed $\{(\boldsymbol{x}_i, \boldsymbol{y}_i)\}_{i=1}^n$ where $\boldsymbol{x}_i$ is a p-vector of predictors and $\boldsymbol{y}_i$ is a q-vector of responses, CGGMs **currently** take the form:

$$\boldsymbol{y}_i = \boldsymbol{A}'\boldsymbol{x}_i + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Psi}), \quad \forall i = 1, \ldots, n$$

where $\boldsymbol{A}$ is a $p \times q$ matrix of regression coefficients, $\boldsymbol{\Psi}$ is a $q \times q$ covariance matrix of Gaussian noise, and $\mathcal{N}(\cdot)$ denotes the Normal distribution

Existing CGGM Literature

Existing CGGMs typically only allow the mean structure, not the network structures, to vary with predictors[11–13]

- Precision matrix, $\boldsymbol{\Psi}^{-1}$, specifies a 'covariate-adjusted' Gaussian graph
- The conditional dependence structure is estimated after taking into account confounding effects on the mean structure
- Regression coefficients $\boldsymbol{A}$ relate to associations in the mean (e.g. gene expression level) structure

A Baysian Gaussian Graphical Model

A related work in the context of Bayesian **directed acyclic graphs** allows **network structures**, not means, to vary with predictors[14]

- Models the conditional independence function as the product of a smooth function and a thresholding function
- Accounts for functional nonlinearity in edge-covariate relationships
- Allows the structure of the graph to vary with multiple covariates

Our Proposal

We propose a **new class** of conditional (undirected) graphical models, where **both** the mean and network structures depend on covariates

- Jointly model the mean and covariance functions given covariates
- Parsimonious representation of these sources of variation
- Accomodates low- and high-dimensional settings

Model

Notation and Assumptions

Let $\boldsymbol{x} = (x_1, \ldots, x_p)^T$ be an observed p-vector of covariates and $\boldsymbol{y} = (y_1, \ldots, y_q)^T$ be an observed q-vector of outcomes. We assume:

$$\boldsymbol{y}|\boldsymbol{x} \sim \mathcal{N}_q\left(\boldsymbol{\mu}(\boldsymbol{x}), \boldsymbol{\Theta}^{-1}(\boldsymbol{x})\right) \tag{1}$$

where $\boldsymbol{\mu}(\boldsymbol{x})$ is a q-dimensional mean vector and $\boldsymbol{\Theta}(\boldsymbol{x})$ is a $q \times q$ positive-definite precision matrix, both of which depend on $\boldsymbol{x}$, and $\mathcal{N}_q(\cdot)$ denotes the q-dimensional multivariate Normal distribution

Parameterizing the Mean and Covariance

We seek to achieve a **parsimonious**, interpretable representation of the mean and covariance structures:

- We parameterize the mean vector by $\boldsymbol{\mu}(\boldsymbol{x}) = \boldsymbol{A}\boldsymbol{x}$, where $\boldsymbol{A}$ is a $q \times p$ regression coefficient matrix
- We further parameterize $\boldsymbol{\Theta}^{-1}(\boldsymbol{x})$ as $\boldsymbol{\Theta}^{-1}(\boldsymbol{x}) = \boldsymbol{\Psi} + \boldsymbol{B}\boldsymbol{x}\boldsymbol{x}'\boldsymbol{B}'$ where $\boldsymbol{\Psi}$ is a $q \times q$ positive-definite matrix and $\boldsymbol{B}$ is a $q \times p$ matrix
- Since $\boldsymbol{\Psi}$ is positive-definite and $\boldsymbol{B}\boldsymbol{x}\boldsymbol{x}'\boldsymbol{B}'$ is a rank-1 matrix that depends on $\boldsymbol{x}$, then $\boldsymbol{\Theta}^{-1}(\boldsymbol{x})$ is also positive-definite

Dimensionality and Sparsity

Given the context of the scientific question, the **dimensionality** of the data may vary greatly:

- This approach accomodates both the **low-** $(p, q << n)$ and **high-dimensional** $(p, q >> n)$ settings
- When $p, q >> n$, we impose **sparsity conditions** on the selection and estimation of $\boldsymbol{A}$, $\boldsymbol{B}$, and $\boldsymbol{\Psi}$ through **regularization**
- In the **special case** when $p, q << n$ and $\boldsymbol{A}$, $\boldsymbol{B}$, and $\boldsymbol{\Psi}$ are dense, the problem reduces to Hoff and Niu's covariance regression[15]

Random Effects Model Representation

We can conveniently express this formulation as a **random effects** model:

$$\boldsymbol{y} = \boldsymbol{A}\boldsymbol{x} + \gamma \cdot \boldsymbol{B}\boldsymbol{x} + \boldsymbol{\varepsilon} \tag{2}$$

where $\gamma \sim N(0,1)$, $\boldsymbol{\varepsilon} \sim \mathcal{N}_q\left(\boldsymbol{0}, \boldsymbol{\Psi}\right)$, and $\gamma \perp \boldsymbol{\varepsilon}$. Thus:

- $\mathrm{E}\left[\boldsymbol{y}\right] = \boldsymbol{A}\boldsymbol{x} = \boldsymbol{\mu}(\boldsymbol{x})$
- $\mathrm{E}\left[\left(\boldsymbol{y} - \boldsymbol{\mu}\left(\boldsymbol{x}\right)\right)\left(\boldsymbol{y} - \boldsymbol{\mu}\left(\boldsymbol{x}\right)\right)'\right] = \boldsymbol{B}\boldsymbol{x}\boldsymbol{x}'\boldsymbol{B}' + \boldsymbol{\Psi} = \boldsymbol{\Theta}^{-1}\left(\boldsymbol{x}\right)$

Note: We have $\boldsymbol{\mu}(\boldsymbol{x})$ and $\boldsymbol{\Theta}^{-1}(\boldsymbol{x})$ where $\boldsymbol{x}$ is a common set of predictors. We can consider $\boldsymbol{\mu}(\boldsymbol{x})$ and $\boldsymbol{\Theta}^{-1}(\boldsymbol{x}^*)$ where $\boldsymbol{x}^* \subseteq \boldsymbol{x}$ or $\boldsymbol{x}^* \not\subset \boldsymbol{x}$.

Log-Likelihood Function

Given n i.i.d. samples, $\{(\boldsymbol{x}_i, \boldsymbol{y}_i)\}_{i=1}^{n}$, and with the γ_i are known, we consider the **complete data** log-likelihood function:

$$
\begin{aligned}
\ell\left(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B}, \gamma\right) &= \log \left[\prod_{i=1}^{n} (2\pi)^{-\frac{q}{2}} \, |\boldsymbol{\Psi}|^{-\frac{1}{2}} \exp\left\{ -\frac{1}{2} \left[\boldsymbol{y}_i - \left(\boldsymbol{A} + \gamma_i \cdot \boldsymbol{B} \right) \boldsymbol{x}_i \right]' \boldsymbol{\Psi}^{-1} \left[\boldsymbol{y}_i - \left(\boldsymbol{A} + \gamma_i \cdot \boldsymbol{B} \right) \boldsymbol{x}_i \right] \right\} \right] \\
&\propto \frac{1}{2} \sum_{i=1}^{n} \log |\boldsymbol{\Psi}|^{-1} - \left[\boldsymbol{y}_i - \left(\boldsymbol{A} + \gamma_i \cdot \boldsymbol{B} \right) \boldsymbol{x}_i \right]' \boldsymbol{\Psi}^{-1} \left[\boldsymbol{y}_i - \left(\boldsymbol{A} + \gamma_i \cdot \boldsymbol{B} \right) \boldsymbol{x}_i \right]
\end{aligned} \tag{3}
$$

In reality, the γ_i are **unknown** random effects, thus there is added computational difficulty, as we cannot observe $\boldsymbol{B}$ and $\boldsymbol{\Psi}$, only $\boldsymbol{\Theta}^{-1}$

Algorithm

Our Problem

Our Problem

Maximize: $\ell(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B})$ subject to: $\|[\boldsymbol{A}|\boldsymbol{B}]\|_1 \leq \lambda_1$ and $\|\boldsymbol{\Psi}\|_1 \leq \lambda_2$

- λ_1 and λ_2 are **tuning parameters** and $\|\cdot\|_1$ is the ℓ_1 norm
- Constraints **control sparsity** in the mean/covariance coefficients and our 'baseline' heterogeneity, respectively
- Exploiting the random-effects representation in (2), we establish a penalized expectation-maximization **(EM) algorithm**

Estimation via Penalized EM-Algorithm

E-Step

As γ_i are **unobserved**, we replace them in the likelihood with their:

- Conditional Expectation: $\mathrm{E}[\gamma_i | \boldsymbol{y}_i, \boldsymbol{x}_i, \boldsymbol{\Psi}, \boldsymbol{B}]$
- Conditional Variance: $\mathrm{Var}[\gamma_i | \boldsymbol{y}_i, \boldsymbol{x}_i, \boldsymbol{\Psi}, \boldsymbol{B}]$

M-Step

We formulate two ℓ_1-constrained optimization problems to iteratively obtain estimates for our parameters $\{\boldsymbol{A}, \boldsymbol{B}\}$ and $\boldsymbol{\Psi}$

- These problems can be expressed in their **primal-dual** form
- And solved with straight-forward **linear programming** approaches

Penalized EM-Algorithm: E-Step

In the **low-dimensional** setting, $\gamma_i | \boldsymbol{y}_i, \boldsymbol{x}_i, \boldsymbol{\Psi}, \boldsymbol{B} \sim \mathcal{N}(m_i, v_i)$ where:

$$v_i = \mathrm{Var}[\gamma_i | \boldsymbol{y}, \boldsymbol{x}, \boldsymbol{\Psi}, \boldsymbol{B}] = (1 + \boldsymbol{x}_i' \boldsymbol{B}' \boldsymbol{\Psi}^{-1} \boldsymbol{B} \boldsymbol{x}_i)^{-1}$$

$$m_i = \mathrm{E}[\gamma_i | \boldsymbol{y}, \boldsymbol{x}, \boldsymbol{\Psi}, \boldsymbol{B}] = v_i (\boldsymbol{y}_i - \boldsymbol{A} \boldsymbol{x}_i)' \boldsymbol{\Psi}^{-1} \boldsymbol{B} \boldsymbol{x}_i$$

In the **high-dimensional** setting, these integrals are intractable. Conditional means/variances are approximated with **Laplace's method**

E-Step: Complete Data Log Likelihood

We utilize the expressions derived for the conditional means and variances of γ_i in the **expected complete-data log likelihood** as follows:

$$
\begin{aligned}
&Q(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B} | \hat{\boldsymbol{A}}, \hat{\boldsymbol{\Psi}}, \hat{\boldsymbol{B}}) = -2 \cdot \mathrm{E}[\ell(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B}) | \hat{\boldsymbol{A}}, \hat{\boldsymbol{\Psi}}, \hat{\boldsymbol{B}}] \\
&\qquad \propto n \log |\boldsymbol{\Psi}| + \sum\nolimits_{i=1}^{n} \mathrm{E}\left[\left(\boldsymbol{y}_i - \hat{\boldsymbol{A}}\boldsymbol{x}_i - \gamma_i \cdot \boldsymbol{B}\boldsymbol{x}_i \right)' \boldsymbol{\Psi}^{-1} \left(\boldsymbol{y}_i - \hat{\boldsymbol{A}}\boldsymbol{x}_i - \gamma_i \cdot \boldsymbol{B}\boldsymbol{x}_i \right) | \hat{\boldsymbol{A}}, \hat{\boldsymbol{\Psi}}, \hat{\boldsymbol{B}} \right] \\
&\qquad = n \log |\boldsymbol{\Psi}| + \sum\nolimits_{i=1}^{n} \left\{ \left(\boldsymbol{y}_i - \hat{\boldsymbol{A}}\boldsymbol{x}_i - m_i \boldsymbol{B}\boldsymbol{x}_i \right)' \boldsymbol{\Psi}^{-1} \left(\boldsymbol{y}_i - \hat{\boldsymbol{A}}\boldsymbol{x}_i - m_i \boldsymbol{B}\boldsymbol{x}_i \right) + s_i \boldsymbol{x}_i' \boldsymbol{B}' \boldsymbol{\Psi}^{-1} \boldsymbol{B}\boldsymbol{x}_i s_i \right\}
\end{aligned}
$$

where $s_i = \sqrt{v_i}$

E-Step: Alternative Notation

We then construct the following **augmented matrices**:

$$\boldsymbol{X}^* = \begin{bmatrix} \boldsymbol{x}_1' & \cdots & \boldsymbol{x}_n' & \boldsymbol{0}_1' & \cdots & \boldsymbol{0}_p' \\ m_1\boldsymbol{x}_1' & \cdots & m_n\boldsymbol{x}_n' & s_1\boldsymbol{x}_1' & \cdots & s_n\boldsymbol{x}_n' \end{bmatrix}_{2n\times 2p}'$$

$$\boldsymbol{Y}^* = \begin{bmatrix} \boldsymbol{Y}_{n\times q}' \\ \boldsymbol{0}_{n\times q}' \end{bmatrix}_{2n\times q} \qquad \boldsymbol{C}^* = \begin{bmatrix} \boldsymbol{A}_{p\times q} \\ \boldsymbol{B}_{p\times q} \end{bmatrix}_{p\times 2q}'$$

and write the expected value of the complete data log-likelihood as:

$$\begin{aligned} Q(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B}|\hat{\boldsymbol{A}}, \hat{\boldsymbol{\Psi}}, \hat{\boldsymbol{B}}) &= -2 \cdot \mathrm{E}[\ell(\boldsymbol{A}, \boldsymbol{\Psi}, \boldsymbol{B})|\hat{\boldsymbol{A}}, \hat{\boldsymbol{\Psi}}, \hat{\boldsymbol{B}}] \\ &\propto n \log|\boldsymbol{\Psi}| + [\boldsymbol{Y}^* - \boldsymbol{X}^*(\boldsymbol{C}^*)']' \, \boldsymbol{\Psi}^{-1} \, [\boldsymbol{Y}^* - \boldsymbol{X}^*(\boldsymbol{C}^*)'] \end{aligned}$$

Penalized EM-Algorithm: M-Step

In the **low-dimensional setting**, we have convenient, closed-form updates for both $\hat{\boldsymbol{C}}^*$ and $\hat{\boldsymbol{\Psi}}$:[15]

- $\hat{\boldsymbol{C}}\boldsymbol{*} = (\boldsymbol{Y}^*)'\boldsymbol{X}^*\left[(\boldsymbol{X}^*)'\boldsymbol{X}^*\right]^{-1}$
- $\hat{\boldsymbol{\Psi}} = \frac{1}{n}\left[\boldsymbol{Y}^* - \boldsymbol{X}^*(\boldsymbol{C}^*)'\right]'\left[\boldsymbol{Y}^* - \boldsymbol{X}^*(\boldsymbol{C}^*)'\right]$

In the **high-dimensional setting**, we iteratively update $\hat{\boldsymbol{C}}^*$ and $\hat{\boldsymbol{\Psi}}$ using linear programming approaches for constrained ℓ_1 minimization[13,16,17]

M-Step: Notation

Let:

- $\bar{y^*} = (2n)^{-1} \sum_{i=1}^{2n} y_i^*$
- $\bar{x^*} = (2n)^{-1} \sum_{i=1}^{2n} x_i^*$

and define:

- $S_{x^* y^*} = (2n)^{-1} \sum_{i=1}^{2n} \left(y_i^* - \bar{y^*} \right) \left(x_i^* - \bar{x^*} \right)'$
- $S_{x^* x^*} = (2n)^{-1} \sum_{i=1}^{n} \left(x_i^* - \bar{x^*} \right) \left(x_i^* - \bar{x^*} \right)'$
- $S_{y^* y^*} = (2n)^{-1} \sum_{i=1}^{2n} \left(y_i^* - \hat{\boldsymbol{C}}^* x_i^* \right) \left(y_i^* - \hat{\boldsymbol{C}}^* x_i^* \right)'$

M-Step: Updating C^*

We estimate $\boldsymbol{C}^*$ by solving the constrained optimization problem:

$$\hat{\boldsymbol{C}}^* \in \underset{\boldsymbol{C}^* \in R^{p \times 2q}}{\arg\min} \left\{ |\boldsymbol{C}^*|_1 : |S_{x^*y^*} - \boldsymbol{C}^* S_{x^*x^*}|_\infty \leqslant \lambda_1 \right\}$$

where λ_1 is the tuning parameter

- Exploiting the **separability** of the penalty function, this this is equivalently carried out as p separate optimization problems
- Expressing this minimization problem in its **primal-dual** form, we utilize a multivariate variation on the **Dantzig selector**[13,16]

M-Step: Updating $\boldsymbol{\Psi}$

Given $\boldsymbol{C}^*$, we estimate $\boldsymbol{\Psi}$ by solving the constrained optimization problem:

$$\hat{\Psi} \in \underset{\Psi \in R^{q\times q}}{\arg\min} \left\{ |\Psi|_1 : \left| I_{q\times q} - S_{y^* y^*} \Psi \right|_\infty \leqslant \lambda_2 \right\}$$

where λ_2 is the tuning parameter:

- We again exploit the **separability** of the penalty function and solve q separate optimization problems
- Expressing this minimization problem in its **primal-dual** form, we utilize a variation on the **CLIME algorithm**[17]

Symmetry Conditions on $\hat{\Psi}$

We impose a **symmetry condition** on $\hat{\Psi}$ as in Cai et al. (2013):[13]

$$\hat{\boldsymbol{\Psi}} = \left(\hat{\psi}_{ij}\right)$$

$$\hat{\psi}_{ij} = \hat{\psi}_{ji} = \hat{\psi}^1_{ij} \cdot \mathbb{I}\left(\left|\hat{\psi}^1_{ij}\right| \leqslant \left|\hat{\psi}^1_{ji}\right|\right) + \hat{\psi}^1_{ji} \cdot \mathbb{I}\left(\left|\hat{\psi}^1_{ij}\right| > \left|\hat{\psi}^1_{ji}\right|\right)$$

where $\mathbb{I}(\cdot)$ is the indicator function

Tuning λ_1 and λ_2

- We run the EM-Algorithm over a **grid** of candidate λ_1 and λ_2 values
- Tuning of λ_1 and λ_2 is carried out via *k*-fold **cross-validation**
- Optimal λ_1 and λ_2 are evaluated **jointly** using the Bayesian Information Criterion

Conclusions

Future Work

- Work through several computational considerations, including parallelization and converting `R` code to `C++`
- Run simulations comparing the selection and estimation accuracy and performance time of our method to existing methods
- Develop an `R` package and submit to the Comprehensive `R` Archive Network (CRAN)
- Analyze data from the Boston Lung Cancer Study Cohort

(brief) Simulated Case

We simulate $\boldsymbol{A}$ and $\boldsymbol{B}$ to form complex, though *not* biologically plausible coefficient matrices for the mean and covariance functions:

- $p = 70,\ q = 100,\ n = 50$
- $\boldsymbol{x}_i = (x_1, \ldots, x_p)' \sim \mathrm{Bin}(p, 1/q);\ i = 1, \ldots, n$

(brief) Simulated Case

Example results are given in Figure (3) below:

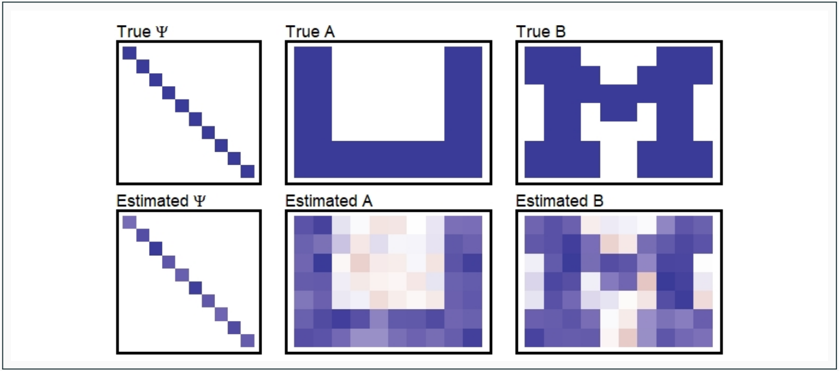


Figure 3: Recovery of complex mean and covariance coefficient structures

Conclusions

We have proposed a **novel method** for the selection and estimation of conditional Gaussian graphical models:

- We jointly model the mean and covariance structure of our Gaussian graph conditional on low- or high-dimensional covariates
- We offer a parsimonious random-effects model representation with computationally efficient and straightforward estimation techniques
- Parameters of $\boldsymbol{A}$, $\boldsymbol{B}$, and $\boldsymbol{\Psi}$ have a direct interpretation in terms of how heteroscedasticity co-occurs in $\boldsymbol{y}$

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