Group Variable Selection in Cardiopulmonary Cerebral Resuscitation Data for Veterinary Patients

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Abstract

Cardiopulmonary cerebral resuscitation (CPCR) is a procedure to restore spontaneous circulation in patients with cardiopulmonary arrest (CPA). While animals with CPA generally have a lower success rate of CPCR than people do, CPCR studies in veterinary patients have been limited. In this paper, we construct a model for predicting success or failure of CPCR, and identifying and evaluating factors that affect the success of CPCR in veterinary patients. Due to reparametrization using multiple dummy variables or close proximity in nature, many variables in the data form groups, and thus a desirable method should take this grouping feature into account in variable selection. To accomplish these goals we propose an adaptive group bridge method for a logistic regression model. The performance of the proposed method is evaluated under different simulated setups and compared with several other regression methods. Using the logistic group bridge model we analyze data from a CPCR study for veterinary patients and discuss their implications on the practice of veterinary medicine.

Key words: Bridge regression; Cardiopulmonary Cerebral Resuscitation; Group variable selection; Logistic regression; Veterinary patients

1 Introduction

Cardiopulmonary cerebral resuscitation (CPCR) is the attempt to return spontaneous circulation (ROSC) to a patient who has suffered cardiac arrest (Henik, 1992). A typical CPCR procedure involves establishment of an airway, provision of intermittent positive pressure ventilation and provision of circulatory support by mechanical and pharmacological means in addition to a variety of treatments (Figure 1). CPCR is also conducted in veterinary patients, particularly dogs and cats, which are hospitalized and suffering from a variety of diseases. Cardiac arrest can occur from a variety of severe disease states, and the exact incidence in hospitalized animals is unknown. When cardiac arrest occurs, significant resources in terms of manpower, drugs, and energy are dedicated to CPCR efforts. Furthermore, CPCR efforts are stressful to those administering CPCR (Scott et al., 2003).

Fig. 1 about here.

Although several publications about CPCR in animals exist (Rush and Wingfield, 1992; Wingfield and Van Pelt, 1992; Kass and Haskins, 1992; Waldrop et al., 2004; Gilroy et al., 1987), only one applies statistical modeling to identify variables which may predict success or failure of CPCR (Hofmeister et al., 2009). Predicting this outcome is important so that veterinarians can dedicate resources to those patients who are most likely to be successfully resuscitated. Time, energy, and resources may be spent on interventions which have not been evaluated for effectiveness. Identifying interventions which are most likely to be beneficial is important so that veterinarians can focus on useful interventions and not pursue interventions of questionable efficacy.

In Hofmeister et al. (2009), factors affecting the success of CPCR on animals having cardiac arrest were studied. During the 5-year study period from February 2003 till February 2008, data were collected via a standard survey form (Appendix) designed for dogs and cats which suffered cardiac arrest and for whom CPCR was performed in the Veterinary Teaching Hospital of the University of Georgia. The data collected included demographic factors, health status, CPCR therapies, and events leading to ROSC or death (see Section 4 for more details). To predict the successful ROSC, they used a logistic regression model and applied a stepwise selection method to identify variables in the model which have significant effects on the successful ROSC. Subset selection methods including stepwise procedures have been popular for the purpose of variable selection since they produce an interpretable model, may have lower prediction error than the full model, and wide availability of computer software. However, their weaknesses also have been well documented as stated in the subsequent paragraphs. Recent development in the statistical methods for variable selection offers better alternatives which we pursue in this work.

Variable selection is ubiquitous in modern scientific problems due to the high dimensional nature of many current data sets where the data dimension is large in comparison to sample size. Examples include the analysis of micro-array data in Biology, feature selection in spam email classification, cloud detection through analysis of satellite images composed of many sensory channels, and many others.

Subset selection such as backward, forward, and stepwise procedures is a traditional way of choosing important predictors for a response variable. It can be done incrementally, starting with all or none of the available variables, and based on some information criterion remove or add a variable at each step. Subset selection provides interpretable models but can be unstable because it is a discrete process, and thus it could yield completely different models with one observation dropped or added. The prediction capability of the model may change significantly if a variable is preserved or discarded.

Regularization methods are a continuous process and provide a flexible technique for reducing the complexity involved in the estimation procedure. Recent developments in the statistical literature offer promising new approaches to variable selection, which include the bridge (Frank and Friedman, 1993), lasso (Tibshirani, 1996), scad (Fan and Li, 2001), elastic net (Zou and Hastie, 2005), adaptive lasso (Zou, 2006; Zhang and Lu, 2007), Bayesian lasso (Park and Casella, 2008), and sica (Lv and Fan, 2009). Fan and Lv (2010) provided an overview of recent developments of theory, methods, and implementations in high dimensional variable selection.

The main interest of this paper is to construct a logistic regression model for the aforementioned data in Hofmeister et al. (2009), predict success or failure of CPCR and identify relevant variables. Since some predictors are categorical or naturally forms a group, variable selection should be done groupwise rather than individually. Hence, we develop a logistic bridge regression model with adaptive L_q penalty for group variable selection. The proposed method can handle a binary response, select variables as a group, and adaptively estimate the penalty from the data. Section 2 reviews bridge regression and proposes logistic group bridge regression.

Meier et al. (2008) also proposed logistic regression with a group selection procedure using the lasso penalty. The comparisons of finite sample performance between the proposed and several other methods including stepwise selection, ridge regression (Hoerl and Kennard, 1970), group lasso and group smoothly clipped absolute deviation (Wang et al., 2007) are thoroughly done using simulated examples in Section 3. There, we conclude that the proposed method outperforms the other existing methods in terms of predictability and selection of relevant variables and groups. We present the analysis of the CPCR data and discuss the implication of the result in the practice of veterinary medicine in Section 4. It is shown that the proposed method provides more accurate prediction and a more interpretable model compared to other methods including stepwise selection used in Hofmeister et al. (2009).

2 Logistic group bridge regression with adaptive L_q penalty

In this section we review bridge regression and group bridge regression proposed by Park and Yoon (2011) in Section 2.1 and propose logistic group bridge regression with adaptive L_q penalty in Section 2.2.

2.1 Bridge regression

We consider a linear regression model with p predictors and n observations:

$$\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon},$$

where $\boldsymbol{Y} = (Y_1, \cdots, Y_n)^{\mathrm{T}}$, $\boldsymbol{\beta} = (\beta_1, \cdots, \beta_p)^{\mathrm{T}}$, $\boldsymbol{\epsilon} = (\epsilon_1, \cdots, \epsilon_n)^{\mathrm{T}}$, and $\boldsymbol{X} = (\mathbf{x}_1, \cdots \mathbf{x}_p)$ where $\mathbf{x}_i$ is a $n \times 1$ vector. Here the ϵ_i's are independently and identically distributed (i.i.d.) as normal with mean 0 and variance σ^2. Assume that the Y_i's are centered and the covariates $\mathbf{x}_i$'s are standardized.

Bridge regression is a broad class of the penalized regression method proposed by Frank and Friedman (1993). The bridge estimate can be obtained by

$$\hat{\boldsymbol{\beta}} = \arg\min_{\boldsymbol{\beta}} \left\{ \sum_{i=1}^{n} (Y_i - \mathbf{x}_i^{\mathrm{T}} \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{p} |\beta_j|^q \right\},$$

where the tuning parameter $\lambda \geq 0$ controls the amount of regularization and $q > 0$ is the order of the penalty. Bridge regression includes the ridge ($q = 2$) and lasso ($q = 1$) as special cases. Note that bridge estimators produce sparse models when $0 < q \leq 1$.

Since the proposal by Frank and Friedman (1993), several related works have been proposed regarding bridge regression. Fu (1998) studied the structure of bridge estimators and developed a general algorithm to solve for $q \geq 1$. Knight and Fu (2000) showed asymptotic properties of bridge estimators with $q > 0$ when p is fixed. Huang et al. (2008) studied the asymptotic properties of bridge estimators in sparse, high dimensional, linear regression models when the number of covariates p may increase along with the sample size n. Park and Yoon (2011) thoroughly investigated the properties of bridge estimators by treating q as another tuning parameter. They also proposed group bridge regression and applied it to varying coefficient models. Independently, Huang et al. (2009) developed a group bridge method that allows variable selection within a group as well as group selection. Liu et al. (2007) and Tian et al. (2009) considered logistic bridge regression for binary responses and established individual variable selection procedures.

Of interest in this paper is when some predictors are represented by a group of derived input variables. In this case, the selection of important variables should be done on groups of variables rather than on individual variables. For example, the goal of a multifactor ANOVA problem is often to select important main effects for accurate prediction. Yuan and Lin (2006) proposed a group lasso procedure that is capable of selecting meaningful blocks of covariates or categorical variables. Its extension to blockwise sparse regression was done by Kim et al. (2006), and Nardi and Rinaldo (2008) established estimation and model selection consistency, prediction and estimation bounds and persistence for the group lasso estimator. Other recent regularization methods concerning categorical data include Bondell and Reich (2009); Breheny and Huang (2009); Gertheiss and Tutz (2010); Huang et al. (2009). The group lasso penalty has been applied to logistic regression by Meier et al. (2008).

In what follows we briefly introduce group bridge regression with adaptive L_q penalty proposed by Park and Yoon (2011), and extend it to logistic regression in the next subsection. Let m be the number of groups which is assumed to be known in advance and d_j is the size of the jth group so that $\sum_{j=1}^{m} d_j = p$. Then, the estimate can be obtained by minimizing

$$S_\lambda^{linear}(\boldsymbol{\beta}) = \sum_{i=1}^{n} (Y_i - \mathbf{x}_i^{\mathrm{T}} \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{m} \tau_j ||\boldsymbol{\beta}_j||^q \quad (1)$$

where $\lambda,\ \tau_j \geq 0$, $\boldsymbol{\beta} = (\boldsymbol{\beta}_1^{\mathrm{T}}, \cdots \boldsymbol{\beta}_m^{\mathrm{T}})^{\mathrm{T}}$, and $||\boldsymbol{\beta}_j||^q = \left(\sum_{k=1}^{d_j} {\beta_{j,k}}^2\right)^{q/2}$. Here $\beta_{j,k}$'s are the regression coefficients in the jth group. The use of τ_j allows the estimator to give different weights to the different coefficients. Note that if $q = 1$ in the equation (1), the estimator is reduced to the group lasso proposed by Yuan and Lin (2006).

Park and Yoon (2011) allowed q to be estimated from the data to gain more flexibility, which automatically adapts to either a sparse situation or multicollinearity. In the presence of noise or redundant variables, q is expected to be less than or equal to 1 for the automatic selection of important variables. In the presence of multicollinearity between variables, it may be more desirable to use $q > 1$ to avoid unnecessary variable deletion and also achieve more accurate prediction. Because our main interest lies in variable selection in this paper, we restrict the range of the order to $0 < q \leq 1$ in our analysis.

2.2 Group bridge regression for a binary response

In this subsection we explain our logistic group bridge regression method under the setting and notations in Meier et al. (2008). Let us consider a two-class classification problem in which a training dataset $\{\mathbf{x}_i, Y_i\}_{i=1}^n$, i.i.d. realizations from $\mathrm{P}(\boldsymbol{X}, Y)$, is given. Here Y_i indicates its class label from $\{0, 1\}$ and we assume that the covariates $\mathbf{x}_i$'s are standardized. Also, let $\eta_{\boldsymbol{\beta}}(\mathbf{x}_i) = \sum_{j=1}^m \mathbf{x}_{i,j}^{\mathrm{T}} \boldsymbol{\beta}_j$ where $\mathbf{x}_i = (\mathbf{x}_{i,1}^{\mathrm{T}}, \ldots, \mathbf{x}_{i,m}^{\mathrm{T}})^{\mathrm{T}}$.

In a linear logistic regression model the conditional probability $p_{\boldsymbol{\beta}}(\mathbf{x}_i) = \mathrm{P}_{\boldsymbol{\beta}}(Y = 1|\mathbf{x}_i)$ is given as

$$\log\left\{\frac{p_{\boldsymbol{\beta}}(\mathbf{x}_i)}{1 - p_{\boldsymbol{\beta}}(\mathbf{x}_i)}\right\} = \eta_{\boldsymbol{\beta}}(\mathbf{x}_i).$$

Then, the logistic group bridge estimator $\hat{\boldsymbol{\beta}}$ is given by the minimizer of the objective function

$$S_\lambda^{logistic}(\boldsymbol{\beta}) = -l(\boldsymbol{\beta}) + \lambda \sum_{j=1}^m \tau_j ||\boldsymbol{\beta}_j||^q \tag{2}$$

where $l(\cdot)$ is the log-likelihood function given as

$$l(\boldsymbol{\beta}) = \sum_{i=1}^n Y_i \eta_{\boldsymbol{\beta}}(\mathbf{x}_i) - \log\left[1 + \exp\{\eta_{\boldsymbol{\beta}}(\mathbf{x}_i)\}\right].$$

We use $\tau_j = \sqrt{d_j}$ in our analysis as suggested by Yuan and Lin (2006).

Since we only consider the cases $0 < q \leq 1$, the optimization problem in the equation (2) becomes nonconvex. The local quadratic approximation (LQA) procedure proposed by Fan and Li (2001) provides a flexible solution to this. Given an initial value of $\boldsymbol{\beta}_j^0$, $p_\lambda(||\boldsymbol{\beta}_j||) = \lambda\tau_j||\boldsymbol{\beta}_j||^q$ can be approximated by a quadratic form

$$p_\lambda(||\boldsymbol{\beta}_j||) \approx p_\lambda(||\boldsymbol{\beta}_j^0||) + \frac{1}{2} p'_\lambda(||\boldsymbol{\beta}_j^0||) \frac{(\boldsymbol{\beta}_j^{\mathrm{T}}\boldsymbol{\beta}_j - \boldsymbol{\beta}_j^{0\mathrm{T}}\boldsymbol{\beta}_j^0)}{||\boldsymbol{\beta}_j^0||}.$$

Then, the minimization problem of (2) is reduced to a quadratic minimization problem, and thus the Newton-Raphson algorithm can be used.

We summarize the proposed algorithm as follows. For given q and λ,

(i) initialize $\hat{\boldsymbol{\beta}}^{(0)} = (\hat{\boldsymbol{\beta}}_1^{(0)}, \cdots, \hat{\boldsymbol{\beta}}_m^{(0)})^{\mathrm{T}}$.

(ii) until ($\hat{\boldsymbol{\beta}}^{(b)}$ converges)

$$\hat{\boldsymbol{\beta}}^{(b)} = \hat{\boldsymbol{\beta}}^{(b-1)} + \left\{\boldsymbol{X}^{\mathrm{T}}\boldsymbol{W}\boldsymbol{X} + \boldsymbol{\Sigma}_\lambda(\hat{\boldsymbol{\beta}}^{(b-1)})\right\}^{-1}\left\{\boldsymbol{X}^{\mathrm{T}}(\boldsymbol{Y} - \boldsymbol{p}(\hat{\boldsymbol{\beta}}^{(b-1)})) - \boldsymbol{\Sigma}_\lambda(\hat{\boldsymbol{\beta}}^{(b-1)})\hat{\boldsymbol{\beta}}^{(b-1)}\right\},$$

where $\boldsymbol{\Sigma}_\lambda(\hat{\boldsymbol{\beta}}^{(b-1)}) = \text{diag}\{(p'_\lambda(||\hat{\boldsymbol{\beta}}_1^{(b-1)}||)/||\hat{\boldsymbol{\beta}}_1^{(b-1)}||)I_{d_1}, \cdots, (p'_\lambda(||\hat{\boldsymbol{\beta}}_m^{(b-1)}||)/||\hat{\boldsymbol{\beta}}_m^{(b-1)}||)I_{d_m}\}$ with I_{d_j} a d_j dimensional identity matrix, $\boldsymbol{W}$ is $N \times N$ diagonal matrix of weights with ith diagonal element $p(\mathbf{x}_i; \hat{\boldsymbol{\beta}}^{(b-1)})(1 - p(\mathbf{x}_i; \hat{\boldsymbol{\beta}}^{(b-1)}))$, $\boldsymbol{p}(\hat{\boldsymbol{\beta}}^{(b-1)})$ is the vector of fitted probabilities with ith element $p(\mathbf{x}_i; \hat{\boldsymbol{\beta}}^{(b-1)})$, and $p(\mathbf{x}_i; \hat{\boldsymbol{\beta}}^{(b-1)}) = \exp(\mathbf{x}_i\hat{\boldsymbol{\beta}}^{(b-1)})/\{1 + \exp(\mathbf{x}_i\hat{\boldsymbol{\beta}}^{(b-1)})\}$.

The choice of the tuning parameters λ and q will be discussed in Sections 3 and 4 for simulated and real data, respectively. Since the LQA algorithm is a backward deletion procedure, it is desirable for an initial estimate to keep all the original groups, in addition to providing a precise guess. We use the bias reduction method of binary response (Firth, 1993) as an initial value. It removes the first-order bias term of maximum likelihood estimates by modifying the score function. The simulation in the next section shows that this method provides more accurate prediction than the logistic regression estimate, and thus it is more appropriate for an initial estimate. The ridge estimate is also a good candidate, but we do not use it in our analysis to avoid another fine tuning at the initial stage.

3 Simulation

In this section we compared the group bridge method (abbreviated as **gb** in Figures 2 and 3 and **gBRIDGE** in the description below and the tables in the supplemental materials) with the ordinary logistic regression (**ls**, **Logistic**), bias reduction method of binary response GLM (**br**, **BR**), ridge regression (**ri**, **Ridge**), stepwise selection (**sw**, **Stepwise**), group lasso (**gl**, **gLASSO**) and group smoothly clipped absolute deviation penalty (**gs**, **gSCAD**) using simulated data. We considered two simulation settings; the idea for the first setting was borrowed from Meier et al. (2008).

1. Setting I : Nine factors $Z_1, \cdots, Z_9$ were first generated from a centered multivariate normal distribution with correlation between Z_s and Z_t being ρ. Each component Z_t was transformed into a four-valued categorical random variable using the quartiles of the standard normal distribution. In other words, each Z_t was divided into 4 groups having 0, 1, 2, or 3 if it was smaller than $\Phi^{-1}(\frac{1}{4})$, between $\Phi^{-1}(\frac{1}{4})$ and $\Phi^{-1}(\frac{2}{4})$, between $\Phi^{-1}(\frac{2}{4})$ and $\Phi^{-1}(\frac{3}{4})$, or larger than $\Phi^{-1}(\frac{3}{4})$, respectively. The sum to zero constraint was used for dummy variables. The corresponding response Y_i was generated from a Bernoulli distribution with model based probabilities. The coefficient vector $\boldsymbol{\beta}_j$ was generated as follows. The intercept (β_0) was generated from the standard normal variable. For the rest, we generated four independent

standard normal variables, say $\tilde{\beta}_{j,1}, \cdots \tilde{\beta}_{j,4}$ and obtained $\beta_{j,l}$ by

$$\beta_{j,l} = \tilde{\beta}_{j,l} - \frac{1}{4}\sum_{k=1}^{4}\tilde{\beta}_{j,k} \tag{3}$$

for $l = 1, 2, 3$. The coefficient vector $\boldsymbol{\beta}$ was rescaled to adjust the empirical Bayes risk r at the desired level, where

$$r = \frac{1}{n}\sum_{i=1}^{n}\min\{p_{\boldsymbol{\beta}}(\mathbf{x}_i), 1 - p_{\boldsymbol{\beta}}(\mathbf{x}_i)\}$$

for some large n.

2. Setting II : We added ten continuous variables to Setting I; $X_1, \cdots, X_{10}$ were generated from a centered multivariate normal distribution with covariance between X_s and X_t being ρ.

Note that, in Setting I, we considered only categorical variables to evaluate the performance of the proposed method. In Setting II, both categorical and continuous variables were considered to mimic the CPCR study data. The features that systematically varied in these simulation studies were as follows: the size of the training set (n), the correlation among the predictors (ρ), the empirical Bayes risk (r), and the fraction of relevant variables (frv=(number of meaningful predictors)/(total number of predictors)). We considered $n = 100$ and 300, $\rho = 0.5^{|s-t|}$, 0.5 (weak vs. strong correlation), $r = 0.15$ and 0.25 (large vs. small magnitude of the coefficients), and frv=9/27 and 18/27 for Setting I and frv=14/37 and 23/37 for Setting II. In Setting I, for frv=9/27, the coefficients of the first two and the fifth categorical variables were generated from (3) and the others were set to zero. Therefore, the true model contained 9 nonzero coefficients, and 18 zero coefficients. For frv=18/27, the coefficients of the first, second, fifth, sixth, eighth and ninth categorical variables were generated from (3) and the others were set to zero. In Setting II, the coefficients of the first five continuous variables were generated from the standard normal distribution and the other five were set to zero. The same coefficients were used for the categorical variables. Therefore, the number of nonzero coefficients in the true model were 14 and 23, respectively, out of a total of 37 predictors. The combinations of the four simulation factors are summarized in Table 1.

Table 1 about here.

The tuning parameters were selected according to the log-likelihood score on an validation set which had the same size as the training set. In the two settings, we considered $\lambda = 2^{k-6}$ for $k = 1, 2, \cdots, 20$ for Ridge, gLASSO, gSCAD, and gBRIDGE, and $q = 0.1, 0.2, \ldots, 1$ for gBRIDGE.

Stepwise utilized the BIC for its model selection. In each simulation setting, we repeated 100 times and compared the prediction capability using the average of the estimated model errors $ME = \mathrm{E}\{\mathrm{E}(Y|\mathbf{x}) - \hat{\mu}(\mathbf{x})\}^2$ where $\mathrm{E}(Y|\mathbf{x}) = p(\mathbf{x}) = \exp(\mathbf{x}\boldsymbol{\beta})/\{1 + \exp(\mathbf{x}\boldsymbol{\beta})\}$ and $\hat{\mu}(\mathbf{x}) = \hat{p}(\mathbf{x}) = \exp(\mathbf{x}\hat{\boldsymbol{\beta}})/\{1+\exp(\mathbf{x}\hat{\boldsymbol{\beta}})\}$, and the estimated mean squared errors of the parameter estimates $MSE = E(||\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}||^2)$, on a test set of size of 500. Additionally, we compared the fraction of noise variables that were excluded (fnve), and the fraction of relevant variables that were selected (frvs) in the estimated models. An ideal variable selection method would produce the values close to 1 for both fractions. The tables that report the complete analysis are available in the supplemental materials and we summarize those results here using plots to save space.

Figure 2 about here.

Figure 2 summarizes the results for Setting I when only categorical variables are present. It reports the mean values of ME, MSE, fnve, and frvs for 100 repetitions. Since two different levels of correlation among categorical variables yielded similar results, we leave their effects out of discussion for Setting I. In terms of ME, all the methods performed well for a larger sample size. The performance of Logistic depended on the Bayes risk r; larger values of r, i.e. the small magnitudes of βs, produced lower ME values. Stepwise, gLASSO, gSCAD and gBRIDGE performed better than the others for small frv, which is expected because their main intention is variable selection. The overall performances of gBRIDGE, gLASSO and Ridge were superior to those of the other methods. For MSE, we discuss only Ridge, gLASSO and gBRIDGE because the other methods produced very large values in some cases, which made them not competitive. These three methods performed better for large n and r, and small frv. The prediction performance of Ridge was competitive to the variable selection methods, which is often found in various simulation settings (e.g. see Park and Yoon (2011)). However, it did not identify important variables. While the MSE values of the three methods were similar, those of gBRIDGE produced the lowest values in most cases considered.

In terms of variable selection (fnve and frvs), we focused only on Stepwise, gLASSO, gSCAD and gBRIDGE because the other methods do not produce sparse models. Figures 2 (c) and (d) suggest that gBRIDGE showed a balanced performance between fnve and frvs. Its fnve values were always high (≥ 0.90), indicating that it tended to correctly set the coefficients of the noise variables to zero. Its frvs values were relatively high (0.47–0.90) compared to the other variable selection methods, indicating that it tended to correctly include the relevant predictors in the model. Since the proposed gBRIDGE selects the order of penalty from the data, it is more flexible and can be adapted to various situations. Stepwise and gSCAD yielded large values for fnve (≥ 0.80) but not for frvs (0.16–0.47 and 0.10–0.81, respectively), suggesting that they tended to set more coefficients than necessary to zero. Since the BIC tends to produce a simple model (Hastie et al., 2009), Stepwise with the BIC eliminated more variables than necessary in the simulation studies. The gSCAD performed better than Stepwise, but was not as flexible as gBRIDGE because it utilizes a fixed penalty. On the contrary, gLASSO yielded the smallest fnve values (0.09–0.57) but the largest frvs values (≥ 0.76), suggesting that its model tended to be less sparse compared to the ones produced by the other variable selection methods. This phenomenon can be explained by the fact that gLASSO utilizes the LARS algorithm (Yuan and Lin, 2006); LARS selects individual variables first and then includes all the factors with at least one selected variable in the model. Hence, it frequently produces a unnecessarily large model.

Figure 3 about here.

Figure 3 presents the results for Setting II. This setting is more challenging because ten additional continuous variables were augmented to Setting I. For ME, all the methods performed well when n is large. They also tended to yield slightly small values for large r and small frv with a few exceptions. In terms of MSE, the main findings were similar to those of Setting I; Ridge and gBRIDGE were the two best performers. In Setting II with the addition of continuous variables, the performance of gBRIDGE was improved in some cases when extending the range of q to greater than 1 which addresses multicollinearity. For instance, when $n = 100$, $\rho = 0.5$, $r = .25$ and frv=14/37, gBRIDGE with $q = 1.05$ slightly reduced both ME and MSE compared to gBRIDGE with $0 < q \leq 1$. However, we do not include the results with extended q values because they were similar to the ones reported in the paper. If we increased the number of continuous variables and the level of correlation, a bigger difference was expected. We refer to Park and Yoon (2011) for this issue where they thoroughly studied the impact of correlation on several penalized regression methods. For variable selection, while a general trend remained similar to that in Setting I, gBRIDGE revealed their limitation especially when $n = 100$, $r = 0.25$ and frv=23/37 where the frvs value fell to 0.25–0.28.

Table 3 about here.

Based on a referee's suggestion, we conducted another simulation study to compare the performance of our proposed method with the other group selection methods in the presence of outliers. When the class labels are contaminated by some unusual data points, which is often the case in many real examples, it is desirable to use a robust method to these outliers. In this simulation study, we added random classification noises and set $n = 300$, $\rho = 0.5^{|s-t|}$, $r = 0.25$ and frv=9/27 for Setting I and 14/37 for Setting II. Under this scenario, we chose randomly 10 or 20% of the data and changed their class labels to be incorrect. Table 3 summarizes the results of the three group selection methods: gLASSO, gSCAD and gBRIDGE. As expected, the performances of the three methods with the increases of the noise rate were not as good as the ones under the original settings with no classification noises (see Tables 3 and 7 in the supplemental materials). In the comparison of the three methods, we observed the same phenomena as the original settings; gBRIDGE outperformed gSCAD and gLASSO in terms of ME and MSE. For variable selection, gBRIDGE tended to correctly exclude the noise variables with high fnve and chose the relevant variables with reasonably large frvs. On the other hand, gLASSO produced a relatively larger model with high frvs and low fnve. These simulation results demonstrated that the proposed method gBRIDGE is more robust to data contamination compared to the other group selection methods.

4 Analysis of the CPCR data

In this section, we analyzed the CPCR data for dogs only using the logistic group bridge method and compared the results with those using the stepwise regression method employed in Hofmeister et al. (2009).

4.1 Data

During the 60 months of study, data were collected on 161 dogs. From each of the patients, information on a total of 51 variables were obtained for demographic factors, health status, CPCR therapies, and events to the ROSC. Among them, 8 were continuous variables, 2 were categorical variables, and 41 were binary variables. The two categorical variables, gender with 3 levels and supervisor with 5 levels, were transformed into 2 and 4 binary variables, respectively. Forty-one binary variables were organized into the following 5 groups according to their characteristics: medical problem (8 variables), suspect cause of CPA (8 variables), mean of CPA identification (7 variables), initial arrhythmia (6 variables), and treatment (16 variables). The list of variables is available in Tables 4–6.

4.2 Prediction

We compared the prediction accuracy of Logistic, BR, Ridge, Stepwise, gLASSO, gSCAD and gBRIDGE using the CPCR data. The performance for each method was evaluated by the K-fold cross validation. Hastie et al. (2009) recommended to use $K = 5$ or 10 , and Mahmood and Khan (2009) proposed an approach to estimate K from data. In our analysis, we tried both $K = 5$ and 10 and found that the results were very similar to each other. Therefore, we report the results with the 10-fold cross validation in this subsection. As in the simulation studies, the tuning parameters were selected according to the log-likelihood score on a validation set with $\lambda = 2^{k-6}$ for $k = 1, 2, \cdots, 20$ for Ridge, gLASSO, gMCP, and gBRIDGE, and $q = 0.1, 0.2, \ldots, 1$ for gBRIDGE. We classified each dog based on the estimated probability for successful ROSC status. If this probability was greater than 0.5, this dog's status was classified as a successful ROSC status. Then, we calculated the misclassification error rate for each method.

Table 2 about here.

Table 2 reports the misclassification error of each method. In general, the misclassification error did not vary much from method to method (0.27–0.36). However, the performance of Ridge and gBRIDGE was better than the other methods, which was consistently observed in other various attempts of the 10-fold cross validation (results not shown).

4.3 Variable selection

A logistic regression model was considered with the response variable being the ROSC status. We used the group bridge method for variable selection and obtaining the estimates of the regression coefficients.

The tuning parameters λ and q were selected by minimizing GCV (generalized cross validation) which is defined as

$$GCV = \frac{-l(\hat{\boldsymbol{\beta}})}{\left\{n\left(1 - e(\lambda)/n\right)^2\right\}},$$

where $e(\lambda) = tr\left[\left\{\nabla^2 l(\hat{\boldsymbol{\beta}}) + \boldsymbol{\Sigma}_\lambda(\hat{\boldsymbol{\beta}})\right\}^{-1} \nabla^2 l(\hat{\boldsymbol{\beta}})\right]$ and $\nabla^2 l(\hat{\boldsymbol{\beta}}) = \left\{\partial^2 l(\boldsymbol{\beta}) / \left(\partial\boldsymbol{\beta}\partial\boldsymbol{\beta}^{\mathrm{T}}\right)\right\}_{\boldsymbol{\beta}=\hat{\boldsymbol{\beta}}}$ (Fan and Li, 2002). The estimated q for the group bridge method was 0.1, which allows a selection of important variables.

In Tables 4–6, the estimated coefficients obtained from gBRIDGE and Stepwise are presented. For gBRIDGE, the following variables were chosen: age, under anaesthesia at time of arrest, dead on arrival, medical problem, suspect cause of CPA, initial arrhythmia, number of people actively participating in CPCR attempt, duration of CPCR attempt, rounds of epinephrine, body position for external compression and treatment included.

Tables 4–6 about here.

The results showed that dogs were more likely to be resuscitated if they have been under anaesthesia at the time of CPA, had more people actively participated in CPCR attempt, had initial arrhythmia with ventricular tachycardia, and had chest compressions performed while in lateral recumbency. Among treatments given, mannitol, atropine, lidocaine, fluids, dopamine, steroids, vasopressin, and others were positively associated with the successful ROSC in dogs. A multi-organ dysfunction syndrome (MODS) and cause of arrest other than hemorrhage/anemia, shock, hypoximia, MODS, cerebral trauma, malignant arrhythmia, or anaphylactoid reaction seemed to be associated with the successful ROSC in dogs. These variables showed strong relevant effects with the estimated odds of resuscitation being 2.6 or higher. While age, and treatments with epinephrine with both high (HDEPI) and low (LDEPI) dose, and electrical defibrillation also increased the odds of being resuscitated, their effects were relatively weak with the estimated odds ranging from 1.0 to 1.7.

On the other hand, the following variables appeared to decrease the odds of being resuscitated in dogs: dead on arrival (DOA), all medical problems cause of arrest including hemorrhage/anemia, shock, cerebral trauma, malignant arrhythmia, or anaphylactoid reaction, initial arrhythmia with asystole, bradycardia, electromechanical dissociation, ventricular fibrillation, or atrial tachyarrhythmia, duration of CPCR attempt, rounds of epinephrine, and treatments with hydroxyethyl starch, naloxone, abdominal compressions, dobutamine CRI, and sodium bicarbonate. Variables such as weight, gender, body condition score, multiple medical problem, means of identifying CPA, type of supervisor, rounds of atropine, and route of drug administered during resuscitation were all removed from the model, and thus they all have estimated log odds of 0.

We also tried the group lasso method for a comparison purpose and the result was quite different from the results of the two previous methods: no variables (and groups) were excluded. This is consistent with our observations in Section 3 that the final model produced by the group lasso tends to be less sparse than it should be. A detailed result is not shown here.

4.4 Discussion

A comparison between the results from using the group bridge method and those from using the stepwise regression method in Hofmeister et al. (2009) can be summarized in two folds; first, the group bridge method selected more variables than the stepwise regression method did. Treatments with mannitol, lidocaine, fluids, dopamine, steroids, and vasopressin, duration of resuscitation, under anesthesia at time of arrest, number of rounds of epinephrine, chest compressions in lateral recumbency, multiple disease condition, and cause of arrest other than hemorrhage/anemia, shock, hypoximia, MODS, cerebral trauma, malignant arrhythmia, or anaphylactoid reaction were selected by the stepwise regression method. In addition to these variables, for the group bridge method, age, under anaesthesia at time of arrest, DOA, medical problems, cause of CPA other than listed above, initial arrhythmia, number of people actively participating in CPCR attempt, and treatments other than listed above were also selected for the group bridge method. The only exception was multiple disease condition which was selected for the stepwise method only. Second, although there were differences in the magnitude of the estimated odds ratios for the variables commonly selected by the both methods, directions of the estimates from one method agreed with those from the other.

For animals presenting to a hospital or already hospitalized, the new analysis revealed variables which veterinarians can use to determine who would benefit most from aggressive CPCR efforts. Although only 11% of the animals who were DOA had ROSC, the effect of DOA was not able to be determined using the stepwise method. With the bridge method, a strong negative effect of DOA was documented, which gives veterinarians evidence that performing CPCR on DOA cases is not likely to be fruitful.

For the medical problem, the stepwise model did not produce a significant result. The bridge model illustrated that patients with an unknown disease diagnosis, cardiovascular disease, other systemic disease, and pulmonary disease had the worst odds of resuscitation with hemolymphatic and gastrointestinal disease patients also having fairly poor odds of resuscitation. These results will help guide veterinarians faced with patients suffering from these diagnoses. Resuscitation efforts may not begin in patients with one of these disease diagnoses, thus conserving resources for patients more likely to be resuscitated.

The suspected cause of cardiac arrest was excluded from the model in the stepwise but was selected in the bridge. Patients with a spontaneous fatal arrhythmia were believed to be more likely to be resuscitated, but the bridge model demonstrated that this is not the case. Also surprising was the finding that patients with MODS had a better odds of resuscitation. Patients suffering a spontaneous fatal arrhythmia may not benefit from CPCR but patients suffering cardiac arrest due to MODS should have additional resources dedicated to the resuscitation effort.

In people, ventricular fibrillation carries a relatively good prognosis (Robinson and Hess, 1994). While the stepwise model showed no significant effect of arrhythmia on outcome, it was selected by the bridge model and, specifically, within arrhythmia, ventricular fibrillation and atrial tachyarrhythmia carry a poorer prognosis. This suggests that treatments designed to return a patient to ventricular fibrillation from asystole may be misguided, and ventricular fibrillation is not as successfully treated as in people.

Various standard-of-care treatments, which did not show any significant effect using the stepwise method, demonstrated a small effect but were selected via the bridge method. In particular, atropine and epinephrine are given to virtually all CPA cases; having evidence that supports their use is important to ensure that practitioners are making medical decisions based on the evidence available. Performing simultaneous abdominal compressions during CPCR has been theorized to prove helpful based on simulations (Xavier et al., 2003). In the stepwise model, no significant effect was found with abdominal compressions, but in the bridge method, they were selected with a harmful effect, which is consistent with one of the authors' clinical experience. This suggests that abdominal compressions, which may confuse the resuscitation team and complicate the resuscitation, should not be pursued.

Given the information derived from using the bridge method, veterinarians would make numerous different choices in CPCR events which may influence ultimate patient outcome. If this data had been published in lieu of the data using the stepwise method, it would dramatically affect the practice of veterinarians throughout the United States, which may result in more patients being successfully resuscitated or in resources being utilized in a more effective fashion.

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Appendix

A. Survey form

Survey – Cardiopulmonary Cerebral Resuscitation

Type of Animal: CAT DOG

Age:_______________ *Date:*__________________________

Weight:________________Kg

Sex: M/C M/I F/S F/I

Body Condition Score: ________/ 9

Patient Number:________________________________ *Under anaesthesia at time of arrest?* Yes No

ASA Status (See Back): 1 2 3 4 5

DOA? Yes No *If so, approximately how long?*:____________________

Medical Problem(s):____

Suspected Cause of CPA: Hemorrhage/Anemia Hypoxemia MOD Cerebral Trauma
Spontaneous Fatal Arrhythmia Anaphylactoid Reaction
Shock/Hypoperfusion
Other (Describe):____

CPA Identified by: Agonal Gasps Malignant Arrhythmia on Continuous ECG
Collapse Apnea Fixed gaze
Other (Describe):____

Initial Arrhythmia: EMD Asystole Vfib Vtac Bradycardia
Other (Describe):____

Individual Supervising
Majority of Arrest: Name:____

Number of People Actively Participating in CPCR Attempt Including Supervisor: ____________________

Time of CPA: _____________________

Duration of CPCR Attempt:_________________________

Treatment Included: Epinephrine 0.01mg/kg # Doses:_____ Epinephrine 0.1mg/kg # Doses:______
Atropine # Doses:_____ Lidocaine # Doses:_______
Electrical Defibrillation _____ Attempts at _______ J _____ Attempts at _______ J
_____ Attempts at _______ J _____ Attempts at _______ J
Fluids External Compressions Internal Compressions
Abdominal Compressions Abdominal Wrap Dopamine Dobutamine
Solu-Medrol Solu-Delta DexSP Sodium Bicarbonate
Other (Describe):____

Drugs Given (circle all that apply) IV Central Line IV Peripheral IT IO IC

Body Position for External Compressions: Dorsal Lateral

Highest End-Tidal CO_2:_______________________

CPCR Successful? – Return of audible heart sounds,ECG activity with heartbeat, spontaneous ventilation, palpable pulses Yes No

Arrhythmia at Time of Death: EMD Asystole Vfib N/A

Animal Discharged from Hospital? Yes No

- PI to fill out –

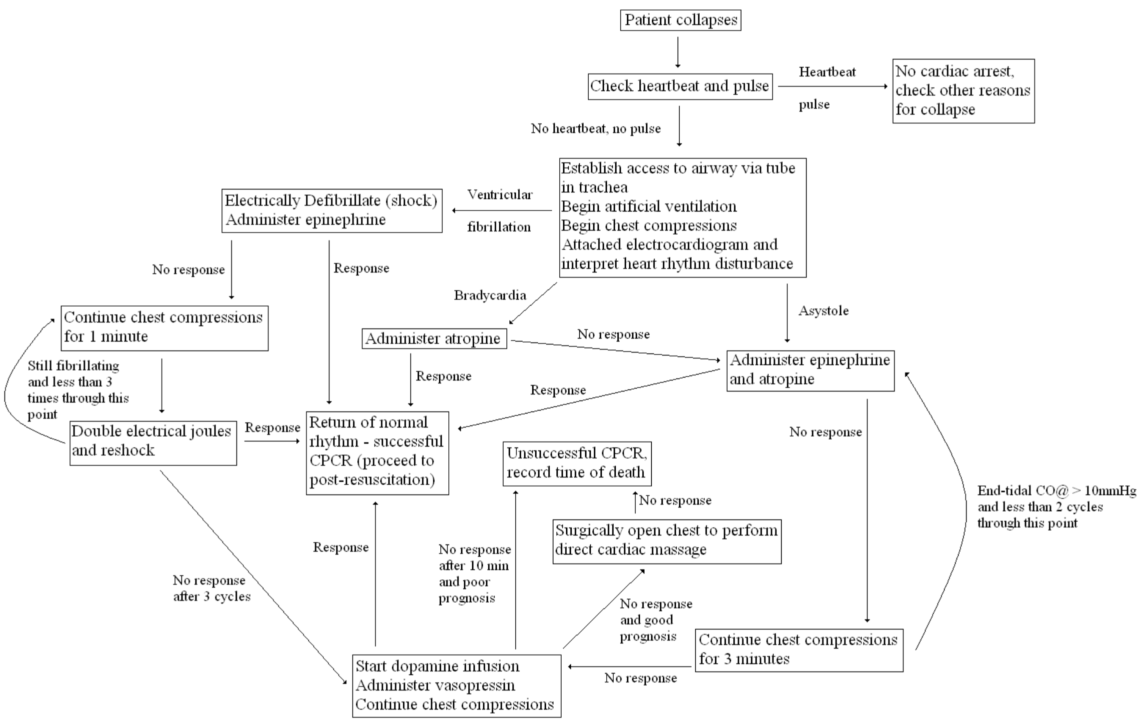
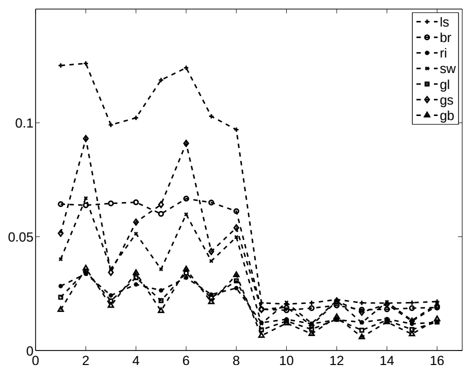


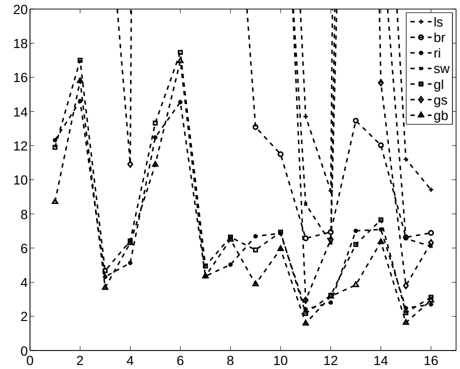
Figure 1: A flowchart for the CPCR procedure

Table 1: Simulation factors and their combinations

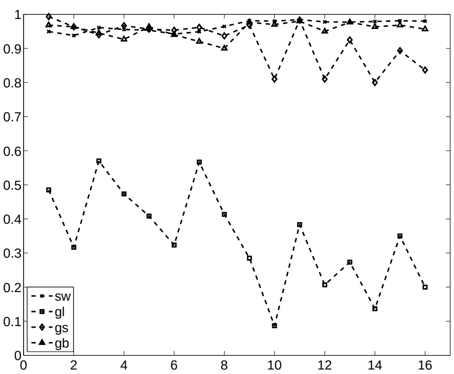
id	n	ρ	r	frv (Setting I, Setting II)
1	100	$0.5^{\|s-t\|}$	0.15	(9/27, 14/37)
2	100	$0.5^{\|s-t\|}$	0.15	(18/27, 23/37)
3	100	$0.5^{\|s-t\|}$	0.25	(9/27, 14/37)
4	100	$0.5^{\|s-t\|}$	0.25	(18/27, 23/37)
5	100	0.5	0.15	(9/27, 14/37)
6	100	0.5	0.15	(18/27, 23/37)
7	100	0.5	0.25	(9/27, 14/37)
8	100	0.5	0.25	(18/27, 23/37)
9	300	$0.5^{\|s-t\|}$	0.15	(9/27, 14/37)
10	300	$0.5^{\|s-t\|}$	0.15	(18/27, 23/37)
11	300	$0.5^{\|s-t\|}$	0.25	(9/27, 14/37)
12	300	$0.5^{\|s-t\|}$	0.25	(18/27, 23/37)
13	300	0.5	0.15	(9/27, 14/37)
14	300	0.5	0.15	(18/27, 23/37)
15	300	0.5	0.25	(9/27, 14/37)
16	300	0.5	0.25	(18/27, 23/37)



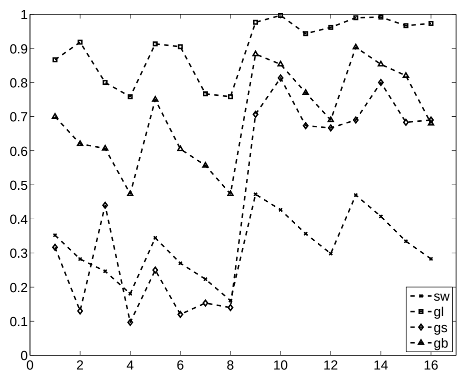
(a) ME



(b) MSE

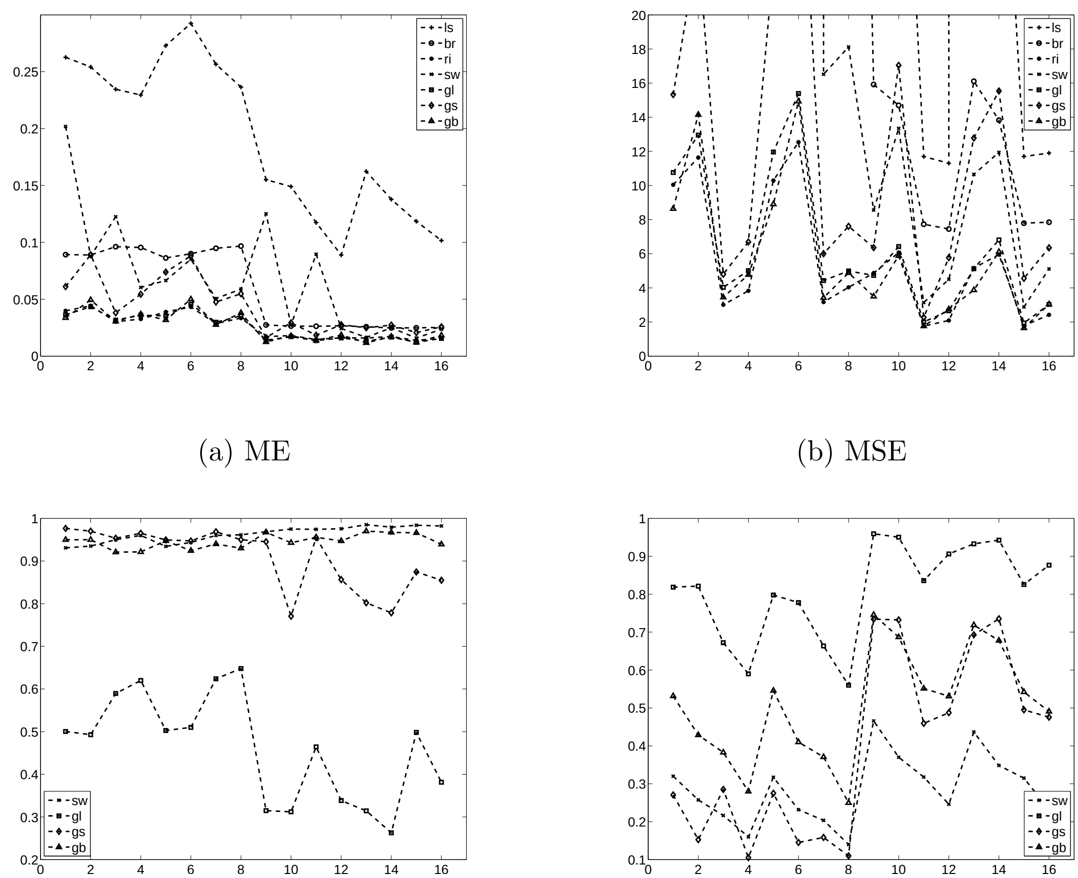


(c) fnve



(d) frve

Figure 2: Summary for Setting I: ME, MSE, the fraction of noise variables that are excluded (fnve), and the fraction of relevant variables that are selected (frvs).



(a) ME

(b) MSE

(c) fnve

(d) frve

Figure 3: Summary for Setting II: ME, MSE, the fraction of noise variables that are excluded (fnve), and the fraction of relevant variables that are selected (frvs).

Table 2: Misclassification errors of the various methods for the CPCR data.

Method	Logistic	BR	Ridge	Stepwise	gLASSO	gSCAD	gBRIDGE
Error	0.32	0.34	0.27	0.32	0.36	0.31	0.28

Table 3: Simulation with classification noise rate 10% or 20%: summary with $n = 300$ and $\rho = 0.5^{|s-t|}$, Bayes risk $r = 0.25$ and frv=9/27 (Setting I) and 14/37 (Setting II): ME, MSE, the fraction of noise variables that are excluded (fnve), and the fraction of relevant variables that are selected (frvs). Their standard errors are in the parentheses.

Method	gLASSO	gSCAD	gBRIDGE
	Setting I, rate=10%		
ME	0.02 (0.00)	0.02 (0.00)	0.01 (0.00)
MSE	3.48 (0.15)	4.31 (0.24)	2.71 (0.13)
fnve	0.23 (0.03)	0.91 (0.01)	0.96 (0.01)
frvs	0.94 (0.02)	0.60 (0.03)	0.71 (0.03)
	Setting I, rate=20%		
ME	0.03 (0.00)	0.04 (0.00)	0.03 (0.00)
MSE	5.03 (0.24)	5.74 (0.28)	4.50 (0.23)
fnve	0.23 (0.03)	0.92 (0.01)	0.93 (0.01)
frvs	0.91 (0.02)	0.41 (0.03)	0.56 (0.03)
	Setting II, rate=10%		
ME	0.02 (0.00)	0.03 (0.00)	0.02 (0.00)
MSE	2.96 (0.15)	3.95 (0.24)	2.44 (0.11)
fnve	0.30 (0.02)	0.88 (0.01)	0.95 (0.01)
frvs	0.84 (0.02)	0.43 (0.02)	0.46 (0.02)
	Setting II, rate=20%		
ME	0.04 (0.00)	0.04 (0.00)	0.04 (0.00)
MSE	3.80 (0.18)	4.59 (0.23)	3.37 (0.18)
fnve	0.30 (0.04)	0.89 (0.01)	0.94 (0.01)
frvs	0.81 (0.02)	0.32 (0.02)	0.33 (0.02)

Table 4: Estimated coefficients of group bridge and stepwise models.

Variable	Category	gBRIDGE	Stepwise
AGE		0.026	0.000
Weight		0.000	0.000
Gender	male/castrated	0.000	0.000
	male/intact	0.000	0.000
	female/spayed	0.000	0.000
Body condition score		0.000	0.000
Under anaesthesia at the time of CPA	Yes	4.980	2.103
Dead on arrival	Yes	-2.885	0.000
Multiple medical problem	Yes	0.000	-1.648
Medical problem	multi-organ dysfunction syndrome	-1.500	0.000
	cardiovascular	-7.447	0.000
	neurologic	-3.463	0.000
	pulmonary	-6.175	0.000
	hemolymphatic	-5.706	0.000
	gastrointestinal	-5.211	0.000
	others	-6.861	0.000
	unknown	-9.255	0.000
Suspect Cause of CPA	hemorrhage/anemia	-1.514	0.000
	hypoxemia	-0.258	0.000
	multi-organ dysfunction syndrome	6.219	0.000
	cerebral trauma	-6.472	0.000
	spontaneous fatal arrhythmia	-8.723	0.000
	anaphylactoid reaction	-1.054	0.000
	shock/hypoperfusion	-1.706	0.000
	others	2.486	1.359

Table 5: Estimated coefficients (continued)

Variable	Category	gBRIDGE	Stepwise
CPA Identified by	agonal gasps	0.000	0.000
	malignant arrhythmia on continuous ECG	0.000	0.000
	collapse	0.000	0.000
	apnea	0.000	0.000
	fixed gaze	0.000	0.000
	others	0.000	0.000
	lost pulse	0.000	0.000
Initial Arrhythmia	asystole	-1.801	0.000
	electromechanical dissociation	-4.019	0.000
	ventricular fibrillation	-8.614	0.000
	ventricular tachycardia	11.179	0.000
	bradycardia	-1.767	0.000
	atrial tachyarrhythmia	-10.139	0.000
Supervisor	veterinary technician	0.000	0.000
	veterinary intern	0.000	0.000
	veterinary resident - 2nd year	0.000	0.000
	veterinary resident - 3rd year	0.000	0.000
	veterinary resident - 4th year	0.000	0.000
Number of people actively participating in CPCR attempt		0.932	0.000
Time of CPA		0.000	0.000
Duration of CPCR attempt		-0.469	-0.092
Rounds of Epinephrine		-1.878	-0.7123
Rounds of Atropine		0.000	0.000
Body Position for External Compression	Lateral	12.058	3.842
Drugs Given	IV Central Line or IV Peripheral	0.000	0.000

Table 6: Estimated coefficients (continued)

Variable	Category	gBRIDGE	Stepwise
Treatment Included	low dose epinephrine	0.302	0.000
	mannitol	4.468	2.915
	hydroxyethyl starch	-0.666	0.000
	naloxone	-3.463	0.000
	high dose epinephrine	0.501	0.000
	atropine	7.425	0.000
	lidocaine	10.510	4.053
	electrical defibrillation	0.525	0.000
	fluids	3.765	1.535
	abdominal compression	-1.275	0.000
	dopamine	7.766	2.958
	dobutamine	-5.677	0.000
	steroids	6.863	5.608
	sodium bicarbonate	-2.033	0.000
	vasopressin	5.939	2.579
	others	1.980	0.000