

SVEMnet: An R package for Self-Validated Elastic-Net Ensembles and Multi-Response Optimization in Small-Sample Mixture–Process Experiments

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Abstract

SVEMnet is an R package for fitting Self-Validated Ensemble Models (SVEM) with elastic-net base learners and for performing multi-response optimization in small-sample mixture–process design-of-experiments (DOE) studies with numeric, categorical, and mixture factors. **SVEMnet** wraps elastic-net and relaxed elastic-net models for Gaussian and binomial responses from `glmnet` in a fractional random-weight (FRW) resampling scheme with anti-correlated train/validation weights; penalties are selected by validation-weighted AIC- and BIC-type criteria, and predictions are averaged across replicates to stabilize fits near the interpolation boundary. In addition to the core SVEM engine, the package provides deterministic high-order formula expansion, a permutation-based whole-model test heuristic, and a mixture-constrained random-search optimizer that combines Derringer–Suich desirability functions, bootstrap-based uncertainty summaries, and optional mean-level specification-limit probabilities to generate scored candidate tables and diverse exploitation and exploration medoids for sequential fit–score–run–refit workflows. A simulated lipid nanoparticle (LNP) formulation study illustrates these tools in a small-sample mixture–process DOE setting, and simulation experiments based on sparse quadratic response surfaces benchmark **SVEMnet** against repeated cross-validated elastic-net baselines.

Keywords: SVEM; design of experiments; relaxed lasso; LNP; formulation optimization; desirability functions;

1. Introduction

Formulation optimization experiments in chemistry and biopharmaceutics often operate with limited runs, complex factor spaces (interactions, curvature, mixtures), and multiple responses of interest. In such small- N regimes, flexible models can be unstable: small changes in the construction of the training sample (for example, different train/validation splits or cross-validation folds) may yield noticeably different predictions and selected penalties [1]. Self-Validated Ensemble Models (SVEM) were proposed by Lemkus et al. [2] to mitigate this instability by drawing fractional random-weight (FRW) [3] bootstraps paired with anti-correlated validation weights and averaging predictions across resampled fits. The idea was first presented under the name “autovalidation” by Gotwalt and Ramsey [4] and has since been extended with a permutation-based whole-model testing heuristic [5] and nonlinear base learners such as neural networks in

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mixture experiments [6]. SVEM is primarily intended as a predictive surrogate-modeling tool rather than a hypothesis-testing procedure, in line with the broader “to explain or to predict” distinction of Shmueli [7].

This paper introduces **SVEMnet**, an R package that implements SVEM with elastic-net and optional relaxed elastic-net base learners [8, 9, 10, 11]. In a relaxed fit, `glmnet` computes a penalized solution path indexed by the penalty parameter λ , identifies the active set at each λ , and then refits an unpenalized least-squares (or GLM) model on that active set, interpolating between penalized and unpenalized coefficients via a relaxation parameter $\gamma \in [0, 1]$. In the sparse Gaussian linear model studied by Meinshausen [10], the relaxed lasso reduces the shrinkage of non-zero coefficients and can achieve lower prediction error than the standard lasso. Simulations in Section 4 indicate that combining relaxed base learners with the SVEM FRW ensemble can further reduce out-of-sample prediction error for Gaussian responses, plausibly because the ensemble averages over the additional variance introduced by relaxation.

In place of the validation-weighted sum of squared errors criterion (denoted `wSSE`) used in earlier SVEM work by Lemkus et al. [2], **SVEMnet** standardizes on heuristic, validation-weighted AIC/BIC-like criteria—`wAIC` for Gaussian responses and `wBIC` for binomial responses [12, 13, 14]. Flexible fits such as the lasso are known to behave poorly near the interpolation boundary, where the number of runs n approaches the full expansion dimension p_{full} (the total number of coefficients in the “full” linear model expansion, including the intercept), with “peaking” in out-of-sample error documented in small-sample classification and regression problems [15] and in lasso model selection [16]. In the simulations reported in Section 4, `wAIC` and `wBIC` avoid this peaking, whereas the loss-only `wSSE` selector exhibits a pronounced spike at $n \approx p_{\text{full}}$.

Self-Validated Ensemble Models have already seen practical use in industrial DOE and chemometric settings, including mixture–process workflows for lipid nanoparticle (LNP) formulations and other pharmaceutical and analytical applications [17, 18, 6, 19, 20, 21, 22, 23, 24]. These applications motivate an implementation tailored to chemometric DOE. In particular, **SVEMnet** is designed to automate many of the steps in the SVEM-based mixture–process workflow for LNP formulation optimization described by Karl et al. [17]. **SVEMnet** supplies an open-source SVEM implementation over `glmnet` with validation-weighted AIC/BIC selectors, deterministic high-order full model expansions, a permutation-based whole-model test heuristic, and a mixture-constrained random-search scoring tool for multi-response desirability and candidate generation.

SVEMnet is intended for round-by-round iteration in small- N DOE: fit SVEM models on the current data; use the random-search optimizer to generate and score a feasible candidate set under mixture and process constraints; select a small number of high-score exploitation medoids and high-uncertainty exploration medoids; then run those settings, append the new data, and refit the models. The lipid nanoparticle (LNP) formulation example below illustrates this workflow [17, 5]. The sequential workflow is an iterate–append loop that alternates exploitation and exploration based on predictive uncertainty, rather than a full Gaussian-process-based Bayesian optimization scheme, which remains the standard choice when richer covariance structures and acquisition strategies are desired [25, 26].

SVEMnet can be used with any single-error-stratum experimental design in which individual runs can be treated as independent. However, the predictive performance of **SVEMnet** will naturally depend on design

quality. For physical experiments we recommend optimal designs [27, 28], fast flexible space-filling designs [29], or U-Bridge designs [30] rather than the simple Latin hypercube samples [31] that are employed for computational expediency in the simulations in Section 4. Because the FRW bootstrap treats runs as the resampling units, split-plot and other multi-stratum designs with hierarchical variance components are not currently accommodated; blocking factors may only be treated as fixed effects.

The remainder of the paper is organized as follows. Section 2 details the **SVEMnet** modeling engine: SVEM background, the **glmnet** wrapper (including relaxed refits), deterministic expansion tools, the validation-weighted wAIC/wBIC selector, and the multi-response random-search optimizer. Section 3 illustrates the workflow on a lipid nanoparticle (LNP) formulation example. Section 4 reports simulations, and the paper concludes with a summary and outlook. Technical specifics of the validation-weighted criterion and mixed-model multiple-comparison tables for simulation results appear in Appendix A and Appendix B.

2. SVEMnet modeling and multi-response optimization

2.1. Software overview

SVEMnet takes a user-specified model formula and dataset, generates fractional random-weight (FRW) train/validation splits, fits elastic-net or relaxed elastic-net paths with **glmnet** within each FRW replicate, selects a penalty (and, when applicable, a relaxed refit) via a validation-weighted information criterion, and averages predictions across replicates. The same deterministic expansion of the right-hand side can be reused across responses so that all models share a common design matrix. The package additionally provides a permutation-based whole-model test heuristic and a mixture-constrained random-search optimizer that scores and selects candidates for additional experimental runs.

The main exported functions are:

- **SVEMnet()**: fit Gaussian or binomial SVEM models under a specified formula and dataset, with optional relaxed base learners and FRW control;
- **bigexp_terms()** and **bigexp_formula()**: build and reuse deterministic high-order factorial and polynomial linear model expansions from a single list of main-effects;
- **svem_wmt_multi()**: run the permutation-based whole-model test (WMT) and obtain approximate *p*-values and importance multipliers for multiple responses;
- **svem_score_random()** and **svem_select_from_score_table()**: generate feasible candidate settings, score them via multi-response desirability, and select diverse optimal and exploration candidates;
- **svem_export_candidates_csv()**: export collections of candidate tables for laboratory execution or documentation.

The remainder of this section explores these functions in more detail. Worked Gaussian and binomial examples are provided in the CRAN help pages (e.g., `?SVEMnet`).

2.2. SVEM background

SVEM draws B replicates using FRW sampling. For each replicate b and observation $i = 1, \dots, n$, training weights w_i^{train} and an anti-correlated validation copy w_i^{valid} are constructed from a shared $U_i \sim \text{Uniform}(0, 1)$ via

$$w_i^{\text{train}} = -\log U_i, \quad w_i^{\text{valid}} = -\log(1 - U_i),$$

following the FRW scheme for univariate analysis introduced by Xu et al. [3], which underpins the original SVEM extensions to penalized regression by Gotwalt and Ramsey [4] and Lemkus et al. [2]. For each FRW replicate we then rescale both the training and validation weights to have mean one, $w_i \leftarrow w_i / \bar{w}$ for $w \in \{w^{\text{train}}, w^{\text{valid}}\}$, matching `glmnet`'s internal normalization of observation weights.

Given $(w^{\text{train}}, w^{\text{valid}})$ for replicate b , **SVEMnet** fits an elastic-net or relaxed elastic-net base learner on (X, y) under w^{train} , evaluates a collection of path points by a validation-weighted information criterion computed with w^{valid} (Section 2.4), and stores predictions from the selected path point. Overall SVEM predictions are obtained by averaging these member predictions across $b = 1, \dots, B$. Lemkus et al. [2] tuned penalties by validation-weighted SSE (`wSSE`); **SVEMnet** adopts the same FRW-and-ensemble structure but standardizes on validation-weighted AIC/BIC analogs—`wAIC` default for Gaussian responses; `wBIC` default for binomial responses.

Although we focus on Gaussian responses in the exposition and case study, the software also implements a binomial (logistic) variant. In that case, the elastic-net base learner is fit under an FRW-weighted logistic log-likelihood, penalties are selected on the deviance scale, and ensemble predictions are formed by averaging member-predicted probabilities; Appendix A gives the corresponding criteria.

2.3. Implementation note: a SVEM wrapper over `glmnet`

SVEMnet implements SVEM by wrapping the standard and relaxed elastic-net paths in `glmnet` [8, 32, 9, 11] with FRW train/validation weights (Section 2.2). For each FRW replicate b and each α in a user-specified grid (default $\alpha \in \{0.5, 1\}$), **SVEMnet** calls `glmnet` with training weights w^{train} , an intercept, and predictor standardization enabled. By default, **SVEMnet** uses relaxed paths for Gaussian responses and standard elastic-net paths for binomial responses.

Within each replicate, **SVEMnet** treats each combination of α and penalty λ (and, when relaxed fits are enabled, each relaxed refit value γ) as a candidate path point. For a given `glmnet` fit, the λ path is traversed and, for relaxed fits, a small grid of γ values is considered. Each candidate $(\alpha, \lambda, \gamma)$ is evaluated on the FRW validation copy using the chosen validation-weighted criterion (`wAIC`, `wBIC`, or `wSSE`; Appendix A), and the combination that minimizes this criterion determines the selected coefficients for replicate b . These selected coefficients populate a bootstrap-by-parameter coefficient matrix.

For new data, the design matrix is rebuilt to match training, each replicate's coefficients are applied, and the resulting member predictions are averaged—on the response scale for Gaussian models and, by default, on the probability scale for binomial models.

In this sense, penalized optimization is delegated to `glmnet`; **SVEMnet** contributes the FRW-based self-validation and ensembling, the validation-weighted AIC/BIC analogs with effective-validation-size guardrails, and the DOE-oriented expansion, testing, and candidate-generation tools used in the workflows of Section 3.

For Gaussian models, an optional *debias* step fits a linear calibration $\text{lm}(y \sim \hat{y})$ on the training data and applies the resulting intercept and slope to ensemble predictions. Debiasing is off by default and is included mainly to match the JMP implementation, where it is always applied [33].

2.3.1. Deterministic expansion utilities

A practical convenience in **SVEMnet** is that the user lists main-effect predictors only once and lets the expansion utilities (`bigexp_terms()` and `bigexp_formula()`) deterministically build interaction and polynomial columns. The same specification can be reused across responses, guaranteeing identical design matrices, stable column order, and reproducible comparisons. With `factorial_order = 2` and `polynomial_order = 2`, for example, the generated right-hand side includes all two-way interactions and quadratic terms (and, optionally, partial-cubic terms of the form $I(X^2):Z$) without hand-writing products or powers; categorical factors are handled using the contrasts recorded for the training data. When blocking or covariate factors (e.g., Operator, day, plate, ambient temperature) are supplied via `blocking` in `bigexp_terms()`, these factors make an additive adjustment to the response surface and do not interact with the other study factors.

2.4. Selection criterion

At each candidate path point within an FRW replicate—indexed by the elastic-net mixing parameter α , the penalty λ , and, when relaxed fits are used, a relaxation parameter γ —**SVEMnet** evaluates a validation loss on the anti-correlated FRW copy: a weighted sum of squared errors for Gaussian responses and a deviance-style loss (weighted negative log-likelihood) for binomial responses. We then add a penalty of the form $g k_\lambda$, where k_λ is the number of nonzero coefficients (including the intercept). Choosing $g = 0$ recovers the historical loss-only selector (`wSSE`); $g = 2$ and $g = \log(n_{\text{eff}}^{\text{adm}})$ give validation-weighted analogs of AIC (`wAIC`) and BIC (`wBIC`), respectively. Because the FRW validation weights are random rather than fixed design weights, these scores are used heuristically for relative model comparison inside the FRW replicate rather than as exact AIC/BIC. For binomial models we retain the label `wSSE` for backward compatibility even though the selector operates on the deviance scale rather than squared error. Appendix A records the full expressions and defines the effective-size guardrail $n_{\text{eff}}^{\text{adm}}$ used with `wAIC` and `wBIC` to avoid near-interpolating path points.

2.5. Random-search scoring and candidate selection for multi-response design

The built-in stochastic optimizer implements the desirability-based generate-and-rank strategy sketched in the introduction. Starting from fitted **SVEMnet** models, it generates feasible candidate settings under the observed factor ranges and user-specified mixture constraints, evaluates each setting via a multi-response desirability score, and returns shortlists of high-score (exploitation) and high-uncertainty (exploration) candidates. The following subsections describe candidate generation and mean-level specification probabilities, construction and weighting of desirability scores, the uncertainty measure used to target exploration, and the medoid-based selection of diverse recipes.

2.5.1. Sampling and specification limits

Candidate settings are generated by `svem_random_table_multi()`, which samples feasible combinations under any supplied mixture groups (sum-to-constant constraints with bounds) together with bounds on process variables taken from the factor ranges in the training data. When specification limits are provided for a response, **SVEMnet** uses the SVEM bootstrap to estimate, at each candidate, the probability that the *process mean* lies inside those limits and adds per-response and joint mean-level specification probabilities (e.g., `prob_in_spec` and `p_joint_mean`) as additional columns in the scored table. These mean-level probabilities are used only as ranking proxies: formal specification limits apply to individual observations, not to the process mean.

2.5.2. Scoring and response weighting

For each response r , we map predictions to unit-interval desirabilities $d_r(x) \in [0, 1]$ using Derringer–Suich curves and form a multi-response score as a weighted geometric mean of the per-response desirabilities,

$$S(x) = \exp\left(\sum_r w_r \log(d_{r,\varepsilon}(x))\right), \quad d_{r,\varepsilon}(x) = (1 - \varepsilon)d_r(x) + \varepsilon,$$

using a small ε (default 10^{-6}) to avoid $\log(0)$ [34, 35, 27].

User-specified goal weights \tilde{w}_r are first normalized to \bar{w}_r with $\sum_r \bar{w}_r = 1$. When `reweight_by_wmt = FALSE`, we set $w_r = \bar{w}_r$ and report a single column `score` based on $S(x)$. When `reweight_by_wmt = TRUE` for Gaussian responses, we further reweight the normalized user weights by a monotone function of the permutation whole-model p -values from [5] (for example $-\log_{10}(p_r)$), renormalize to obtain WMT-adjusted weights w_r^{WMT} , and compute a second geometric-mean score `wmt_score` by using $w_r = w_r^{\text{WMT}}$ in $S(x)$. These WMT-adjusted weights are diagnostic and do not alter the underlying SVEM fits.

Thus the output table always contains `score`, based purely on the user-specified weights \tilde{w}_r , and, when applicable, an additional `wmt_score` column that augments those weights using the WMT results. Gaussian and binomial outcomes are handled on the same scale by applying desirability functions to predicted means and predicted probabilities, respectively.

For candidate scoring, `blocking` variables are held fixed at a single reference setting while the controllable factors are varied over the feasible region. Categorical blocking factors are evaluated at the most common observed level; continuous blocking covariates are evaluated at the midpoint of their modeled range. Under the additive-only blocking assumption this induces only an additive offset in the predicted responses and therefore does not change the ranking of candidate recipes.

2.5.3. Uncertainty and exploration

For each response r we compute a percentile prediction interval $[\ell_r(x), u_r(x)]$ at level $1 - \alpha$ from the SVEM bootstrap and define the interval width $W_r(x) = u_r(x) - \ell_r(x)$. To place uncertainty on a comparable scale across responses, we normalize $W_r(x)$ using the empirical 2%–98% range for that response and aggregate the normalized widths using the original normalized goal weights \bar{w}_r :

$$U(x) = \sum_r \bar{w}_r \text{Norm}_{0,1}(W_r(x); q_{r,0.02}, q_{r,0.98}),$$

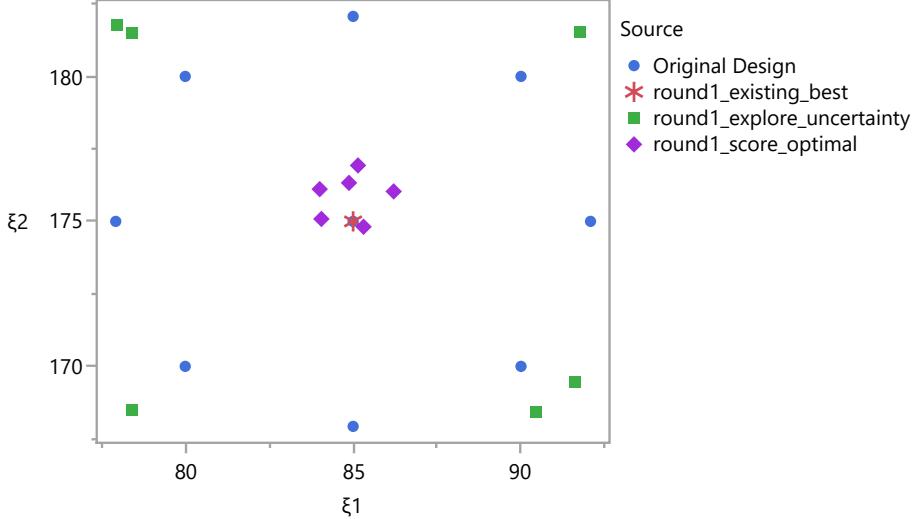


Figure 1: Original CCD runs from Table 6.8 of Myers et al. [27] (blue circles), SVEMnet-selected optimal candidates (purple diamonds), and high-uncertainty exploration runs (green squares) for the y_1 response, which attains its maximum near the center of the design region.

where $\text{Norm}_{0,1}(\cdot; q_{r,0.02}, q_{r,0.98})$ denotes a rescaling to $[0, 1]$ based on the empirical 2% and 98% quantiles $q_{r,0.02}$ and $q_{r,0.98}$ for response r . Large values of $U(x)$ correspond to regions of higher predicted uncertainty. We report the single exploration target $\arg \max_x U(x)$ and also use $U(x)$ to construct exploration shortlists in the next subsection.

2.5.4. Diverse candidates via medoids and practical defaults

Score and uncertainty surfaces often exhibit ridges of near-equivalent values across a broad range of factor settings. To capture this range of feasible recipes with similar predicted performance, the user may choose a number k of candidates by ranking the scored table on a scalar objective (typically $S(x)$ or $U(x)$, corresponding to the `score` and `uncertainty_measure` columns, but also, for example, `wmt_score`, `p_joint_mean`, or any other numeric column), retaining either the top fraction or the top n rows, and clustering this subset using Gower distance on the predictor columns with partitioning-around-medoids (PAM) [36, 37]. The medoids are existing feasible rows and summarize diverse “exploitation” and “exploration” recipes, and the functions `svem_score_random()` and `svem_select_from_score_table()` additionally return the single best row under the chosen objective. Figure 1 illustrates this strategy for the central composite design from Table 6.8 of Myers et al. [27].

3. Example LNP Application

We illustrate the workflow using the bundled simulated LNP formulation screening data, which include four mixture components (PEG, Helper, Ionizable, Cholesterol), a categorical ionizable lipid type, two continuous process factors (`N_P_ratio` and `flow_rate`), a categorical Operator factor, and three responses: Potency, Size, and PDI. This example parallels the SVEM-based mixture–process LNP workflow of Karl et al. [17].

We first build a single deterministic right-hand-side expansion and reuse it across all three models. We treat Operator as a blocking variable that enters additively and does not interact with other study factors.

```

1 library(SVEMnet)
2 data(lipid_screen)
3 spec <- bigexp_terms(
4   Potency ~ PEG + Helper + Ionizable + Cholesterol +
5     Ionizable_Lipid_Type + N_P_ratio + flow_rate,
6   blocking      = "Operator", # additive blocking factor
7   data          = lipid_screen,
8   factorial_order = 3, # up to 3-way interactions
9   polynomial_order = 3, # up to cubic terms I(X^2), I(X^3)
10  include_pc_2way = TRUE
11 )
12 form_pot <- bigexp_formula(spec, "Potency")
13 form_siz <- bigexp_formula(spec, "Size")
14 form_pdi <- bigexp_formula(spec, "PDI")

```

Using this shared expansion for a third-order model, we fit Gaussian SVEM models for each response with default settings and collect them in a named list. Multi-response goals are set so that Potency is maximized, while Size and PDI are minimized, and mixture constraints reflect practical bounds and a unit-sum constraint on the four composition variables:

```

1 set.seed(1)
2 fit_pot <- SVEMnet(form_pot, lipid_screen)
3 fit_siz <- SVEMnet(form_siz, lipid_screen)
4 fit_pdi <- SVEMnet(form_pdi, lipid_screen)
5
6 objs <- list(Potency = fit_pot, Size = fit_siz, PDI = fit_pdi)
7
8 goals <- list(
9   Potency = list(goal = "max", weight = 0.6),
10  Size    = list(goal = "min", weight = 0.3),
11  PDI     = list(goal = "min", weight = 0.1)
12 )
13
14 mix <- list(list(
15   vars  = c("PEG", "Helper", "Ionizable", "Cholesterol"),
16   lower = c(0.01, 0.10, 0.10, 0.10),
17   upper = c(0.05, 0.60, 0.60, 0.60),
18   total = 1.0
19 )))

```

3.1. Whole-model reweighting and permutation tests

To assess which responses show the strongest relationship with the study factors, we apply the permutation-based whole-model test heuristic (WMT) of Karl [5] to each SVEM model. WMT-based multipliers can optionally reweight the user-specified response weights, prioritizing responses with stronger predictive signal and down-weighting weaker ones. If utilized, WMT-reweighted candidate sets should be secondary to those formed without the WMT reweighting, since the heuristic may have limited power in

Table 1: Permutation whole-model test results for the three responses (SVEMnet).

Response	Approx. whole-model p -value
Size	1×10^{-16}
Potency	3×10^{-7}
PDI	0.78

Notes. Values are permutation-based and subject to Monte Carlo error.

some situations [5]. Because WMT is permutation-based with finite simulation budgets, these p -values are approximate.

The helper `svem_wmt_multi()` runs the permutation test for each response under the shared deterministic expansion and mixture constraints, and returns approximate p -values and multipliers:

```

1 set.seed(123)
2 wmt_out <- svem_wmt_multi(
3   formulas      = list(Potency = form_pot,
4                         Size    = form_siz,
5                         PDI     = form_pdi),
6   data         = lipid_screen,
7   mixture_groups = mix,
8   wmt_control   = list(seed = 123)
9 )
10 wmt_out$p_values
11 wmt_out$multipliers

```

The approximate whole-model p -values are summarized in Table 1: Size and Potency show strong global signal, whereas PDI does not (although lack of signal in this heuristic alone should not be used to conclude that there is no relationship between the study factors and PDI [5]). Figure 2 shows the associated whole-model significance diagnostic, generated by `svem_wmt_multi()` under the shared expansion and mixture constraints. Clear separation between the “Original” and permutation-based distance distributions indicates strong global factor signal, as in Figure 3 of Karl [5].

3.2. Random-search scoring, candidate selection, and sequential use

To illustrate the optional specification-limit handling, we impose mean-level requirements on the three responses—limits on the predicted process means rather than on individual unit-level measurements: $Potency > 78$, $Size < 100$, and $PDI < 0.25$. Only the bounded side of each limit needs to be supplied:

```

1 specs_ds <- list(
2   Potency = list(lower = 78),
3   Size    = list(upper = 100),
4   PDI     = list(upper = 0.25)
5 )

```

The random-search scoring step then evaluates a large number of feasible settings (here 25,000). For each candidate, `svem_score_random()` evaluates the SVEM models, computes per-response Derringer–Suich desirabilities, aggregates them into a single multi-response score via a weighted geometric mean, constructs a scalar uncertainty measure $U(x)$ from bootstrap percentile intervals, and, when specifications are supplied,

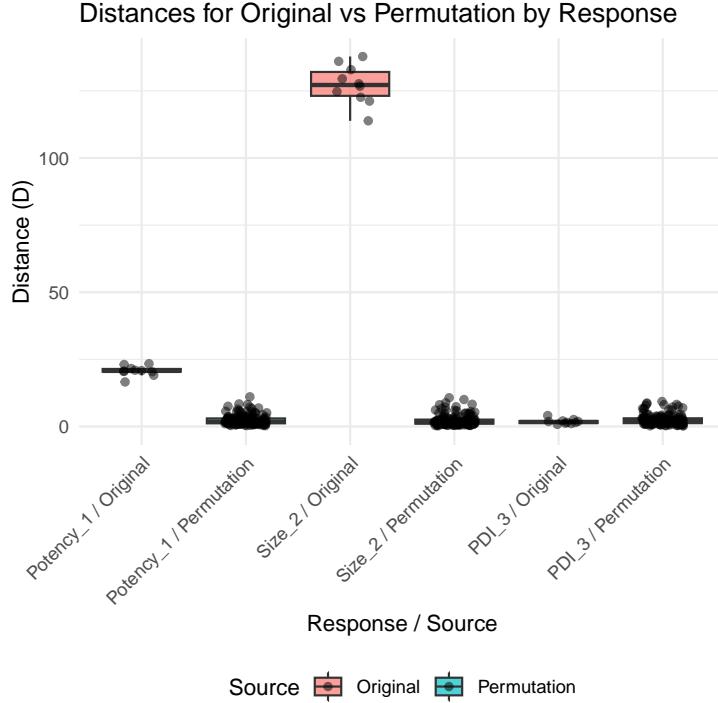


Figure 2: Whole-model significance diagnostic for Potency, Size, and PDI: distributions of Mahalanobis-like distances for the original data versus permuted replicates under the shared deterministic expansion and mixture constraints; cf. Figure 3 in [5].

computes mean-level probabilities that each candidate's modeled mean lies inside the user limits. Supplying `wmt = wmt_out` adds a WMT-adjusted score column `wmt_score` in addition to the user-weighted `score`:

```

1 set.seed(3)
2 scored <- svem_score_random(
3   objects      = objs,
4   goals        = goals,
5   data         = lipid_screen,
6   mixture_groups = mix,
7   wmt          = wmt_out,    # optional: NULL for no WMT
8   specs        = specs_ds  # optional: NULL for no design-space columns
9 )

```

From the resulting scored table we extract high-score, exploration, and design-space candidates using `svem_select_from_score_table()`. For example, the following call selects five near-optimal score medoids, in addition to the single highest scored recipe from the candidate set of 25,000:

```

1 # Score-optimal medoids (user-weighted score)
2 opt_sel <- svem_select_from_score_table(
3   score_table = scored$score_table,
4   target      = "score",
5   direction   = "max",
6   k           = 5,
7   top_type    = "frac",
8   top         = 0.1,
9   label       = "round1_score_optimal"
10 )

```

Analogous calls with `target = "uncertainty_measure"` and `target = "p_joint_mean"` (and `score_table` set to either the random-search candidates or the original screening runs) were used to obtain the candidates summarized in Tables 2 and 3. The replication script contains the full set of `svem_select_from_score_table()` calls [38].

In routine use these tools are embedded in a simple sequential loop: fit SVEM on the current data under a fixed deterministic expansion; use `svem_score_random()` and `svem_select_from_score_table()` to generate optimal, exploration, and mean-in-spec medoids; run those settings and append the new rows; then refit and repeat. Candidate tables for laboratory use can be exported with `svem_export_candidates_csv()`; the Supplementary CSV file was generated using this function and is included in the Mendeley Data archive [38].

Tables 2 and 3 show four SVEM candidates from the simulated first-round lipid screening. The first row corresponds to the best existing screened run by multi-response score and provides a baseline. This row displays the original level of the `blocking` factor, Operator, which may differ from the level shown for the random-search candidates; the latter are evaluated at the reference Operator level used for scoring. The additive offsets for the Operator levels are visible in the fitted coefficients (e.g., `coef(fit_pot)`), and predictions for other Operator levels can be obtained via `predict(fit_pot, newdata = ...)`. The score-optimal run from the random search trades a modest reduction in predicted Potency for a large improvement in Size, yielding an overall desirability of one. In this example, the `wmt_score` optimum coincides with the score-optimal run, so no additional row is shown. The “In-spec” optimum illustrates a candidate that lies comfortably inside the specification region. The exploration target has the highest uncertainty measure $U(x)$ and sits near the edge of the feasible mixture region, with poor predicted Potency.

Table 2: Representative SVEM candidate recipes from the lipid screening example. Mixture components are proportions on the 0–1 scale; process factors are in their native units. All random-search candidates arbitrarily set Operator to A.

Scenario	PEG	Helper	Ionizable	Cholesterol	Ionizable Type	N:P	flow rate	Operator
Best screened	0.047	0.430	0.140	0.383	H101	6.0	2.5	B
Max Score	0.048	0.596	0.101	0.256	H102	11.9	2.9	A
In-spec	0.040	0.415	0.193	0.352	H101	9.2	2.5	A
Exploration	0.012	0.593	0.209	0.185	H103	6.3	2.7	A

Table 3: Predicted behavior for the candidate recipes in Table 2. Responses are SVEM point predictions. The columns `score` and `wmt_score` are scalar desirability measures, $p_{\text{joint},\text{mean}}$ is the estimated probability that the mean responses satisfy the specification limits (Potency ≥ 78 , Size ≤ 100 , PDI ≤ 0.25), and `uncert.` is the dimensionless uncertainty measure $U(x)$.

Scenario	Potency	Size	PDI	score	wmt_score	$p_{\text{joint},\text{mean}}$	uncert.
Best screened	91.5	88.2	0.21	0.83	0.91	0.93	0.77
Max Score	89.4	47.7	0.17	1.00	1.00	1.00	0.50
In-spec	86.3	89.8	0.20	0.81	0.83	1.00	0.18
Exploration	71.0	49.4	0.21	0.29	0.29	0.05	0.92

3.3. Computational environment and runtime

All timings were obtained on a Windows 11 x64 desktop with an Intel Core Ultra 7 265 CPU (20 cores, 2.4 GHz) and 64 GB RAM, running R 4.5.2 with **SVEMnet** 3.1.4 and **glmnet** 4.1-10 and parallel execution enabled for the WMT. Users should note that on Windows, the parallelization of the WMT will trigger a one-time Windows Firewall prompt for R when worker processes are created; this is due to local socket connections between R processes and does not involve external network access.

For the lipid screening example (23 experimental runs, three Gaussian responses, shared third-order deterministic expansion, and a 25 000-point random candidate set), a single end-to-end run of the workflow required about 260 seconds: roughly 92 seconds to fit **SVEMnet** for the three responses, 156 seconds for the optional permutation-based whole-model tests, and 9 seconds for the random-search scoring, candidate selection, and CSV export. Thus most of the computational cost lies in SVEM model fitting and the WMT; the optimization layer is comparatively light.

4. Simulation study

We carried out simulations comparing **SVEMnet** to repeated cross-validated elastic-net baselines over grids of sample sizes and signal strengths, where “signal strength” refers to the proportion of variance in the data explained by the underlying model (target R^2). The baselines use a thin wrapper `glmnet_with_cv()` around `cv.glmnet`, matching the α grid and penalty path to the **SVEMnet** settings. For each configuration we ran both the default two-point grid $\alpha \in \{0.5, 1\}$ and a lasso-only grid $\alpha = 1$, which behaved indistinguishably in these simulations. All simulation scripts and CSV result files are provided in the replication bundle of Karl [38].

4.1. Design and metrics

Each replicate uses a sparse quadratic response surface in four continuous factors $X_1:X_4 \in [-1, 1]$ and one three-level factor $X_5 \in L1, L2, L3$ (sum-to-zero coding). Training data are Latin hypercube samples for $X_1:X_4$ with balanced X_5 levels [31], with $n_{\text{total}} \in \{15, 20, \dots, 50\}$. As noted in the introduction, we use Latin hypercubes here for simulation convenience; in practice, more sophisticated optimal or space-filling designs are typically preferable when constructing the initial experimental design in applied settings [39, 27, 29, 30, 28].

The quadratic model has $p_{\text{full}} = 25$ coefficients (including the intercept), so $n_{\text{total}} = p_{\text{full}} = 25$ is the interpolation boundary. To induce sparsity, in each simulation replicate and for each coefficient j , draw $\pi_j \sim \text{Beta}(0.5, 0.5)$, $Z_j \sim \text{Bernoulli}(\pi_j)$, and E_j from a mean-zero Laplace distribution, and set $\beta_j = Z_j E_j$. This produces many exact zeros with Laplace-distributed nonzero effects.

For the Gaussian case, we evaluate the noiseless surface on a large grid to estimate its standard deviation σ_f , add Gaussian noise to the training responses so that the expected domain R^2 matches a target $R^2 \in \{0.5, 0.9\}$, and score all methods on a separate noiseless 10 000-point holdout. Performance is summarized by log-normalized RMSE (log-NRMSE), where RMSE on the holdout is normalized by the empirical standard deviation of the noiseless surface on that grid.

To probe under- and over-specification, we fit three right-hand-side expansions against the same data-generating mechanism (whose true order is quadratic): *Order 1* = main effects only (underspecified), $p_{\text{full}} = 7$; *Order 2* = quadratics and two-way interactions (correct order), $p_{\text{full}} = 25$; and *Order 3* = Order 2 plus all three-way interactions and pure cubic terms (overspecified), $p_{\text{full}} = 45$. Within each expansion, we compare **SVEMnet** objectives (`wSSE`, `wAIC`, `wBIC`) with and without relaxed base learners, and repeated $5 \times CV$ elastic-net baselines using the same α grids.

The binomial study uses the same latent quadratic surface $\eta(x)$ but treats the binary outcome as a discretized analog. We define $p(x) = \text{logit}^{-1}(s \eta(x))$ with $s = \sqrt{R^2/(1 - R^2)}$ for $R^2 \in \{0.5, 0.9\}$, draw training labels $Y \sim \text{Bernoulli}\{p(x)\}$ once per replicate, and score models on a large noiseless holdout using the true probabilities $p(x)$. Here R^2 serves as a convenient signal-strength parameter (an approximate analog of the Gaussian-domain R^2 rather than an exact GLM coefficient of determination). Performance is measured by holdout log-loss. Methods again include **SVEMnet** with `{wAIC, wBIC, wSSE}` and repeated cross-validated baselines matched on α and relaxation.

To reduce Monte Carlo error, the summary curves in Figures 3, 4, and 5 average over 900 independent simulation replicates for each combination of n_{total} , target R^2 , model order, and fitting method (**Setting**). In these overview plots we fix a common set of tuning defaults. For Gaussian responses, `cv.glmnet` uses standard (non-relaxed) elastic-net paths (`relax = FALSE`) and **SVEMnet** uses relaxed base learners (`relax = TRUE`); post-hoc debiasing is disabled for all methods and the elastic-net mixing grid is held at $\alpha \in \{0.5, 1\}$. For binomial responses, all methods use non-relaxed paths (`relax = FALSE`) with the same default α grid. These settings are used for all model orders shown in the figures.

For the mixed-model multiple-comparison summaries in Tables B.4 and B.5 we focus on the correctly specified quadratic expansion (Order 2) and explore a richer grid of SVEM and `cv.glmnet` configurations. Separate simulation runs with 250 (Gaussian) and 200 (binomial) independent replicates for each combination of n_{total} , `Target_R2`, and `Setting` are used to fit linear mixed models with `Setting` as the primary fixed effect, n_{total} , `Target_R2`, and their interaction as additional categorical fixed effects, and a random intercept for replicate (`RunID`). Pairwise differences in log-NRMSE and log-loss are summarized via Tukey–Kramer all-pairs comparisons of the model-based least-squares means. The loss-only `wSSE` selector is included in the simulation runs and overview figures but excluded from the mixed-model datasets to avoid inflating the number of clearly noncompetitive comparisons. The resulting connecting-letter displays appear in Tables B.4 and B.5 and in the Supplement.

4.2. Gaussian results

Several consistent patterns emerge across R^2 levels, sample sizes, and model orders.

- **Information criteria versus loss-only selectors.** Across the grid, **SVEMnet** with validation-weighted information criteria (`wAIC`, `wBIC`) dominates the historical loss-only `wSSE` selector in terms of mean log-NRMSE on the noiseless holdout. `wAIC` often slightly improves on the repeated `cv.glmnet` for Order 2 and 3. The best overall configuration in these simulations is **SVEM-wAIC** with relaxed elastic-net base learners and no debias step; `wBIC` is close behind (Figure 3 and Appendix Table B.4).

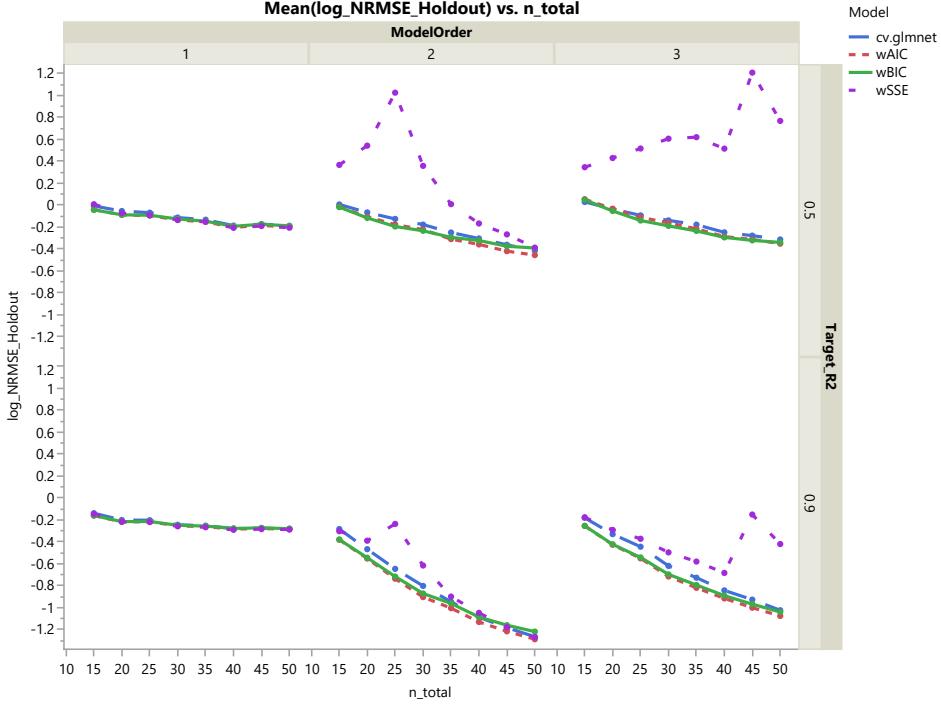


Figure 3: Effect of expansion order on mean log-NRMSE (lower is better) on a noiseless holdout. Panels: target $R^2 \in \{0.5, 0.9\}$. Columns: model order used in fitting. Curves compare repeated `cv.glmnet` baselines (standard, non-relaxed paths) to `SVEMnet` with relaxed elastic-net base learners using the default mixing grid $\alpha \in \{0.5, 1\}$; no debiasing is applied. Underspecification (Order 1) consistently harms accuracy; modest overspecification (Order 3) degrades far less than underspecification, with Order 2 best as expected.

- **Relaxation and debiasing.** For the SVEM information-criterion selectors, relaxed base learners improve performance relative to non-relaxed fits, while relaxation degrades `cv.glmnet` performance. The best-performing overall configuration in these simulations is `SVEM-wAIC` with relaxed base learners and no debias step; `wBIC` is close behind (Figure 3 and Table B.4).
- **Effect of expansion order.** Underspecification (Order 1, main effects only) substantially degrades accuracy. The correctly specified quadratic expansion (Order 2) performs best, and mild overspecification with additional three-way interactions and pure cubic terms (Order 3) degrades far less than underspecification (Figure 3).
- **Peaking near the interpolation boundary.** For each simulation run we recorded k_{median} , the median number of active parameters k_λ across SVEM bootstrap replicates; Figure 4 shows the mean of these medians over simulation replicates. The `wsSE` selector shows a pronounced spike in both mean log-NRMSE (Figure 3) and median selected model size k_λ (Figure 4) when n_{total} equals the expansion dimensions: $p_{\text{full}} = 25$ for Order 2 and $p_{\text{full}} = 45$ for Order 3 ($p_{\text{full}} = 7$ for Order 1 is not included in the range of the graph). This is the “peaking” phenomenon near the interpolation boundary in small-sample regression [16]. In contrast, `wAIC` and `wBIC` remain smooth in both error and k_λ .

Overall, the simulations support the default configuration used in `SVEMnet` for Gaussian responses: validation-weighted `wAIC`, relaxed elastic-net base learners, `debias = FALSE`, and $\alpha \in \{0.5, 1\}$.

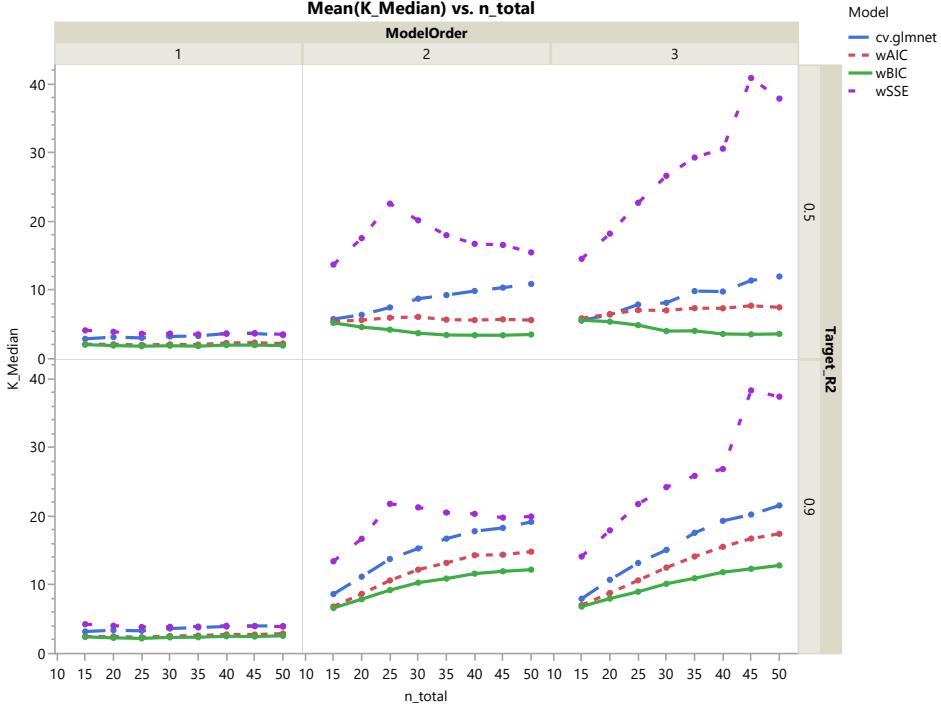


Figure 4: Mean median-selected size k_λ versus n_{total} for Gaussian simulations, stratified by target R^2 and model order. Colors denote selector (`cv.glmnet`, `wAIC`, `wsSE`, `wBIC`); line type denotes $\alpha \in \{0.5, 1\}$. Simulation settings match Figure 3 (non-relaxed `cv.glmnet`, relaxed `SVEMnet`, no debiasing). `wsSE` exhibits a localized spike in k_λ near $n = p_{\text{full}}$.

4.3. Binomial results

Across $n_{\text{total}} \in \{15, \dots, 50\}$ and $R^2 \in \{0.5, 0.9\}$, non-relaxed fits dominate their relaxed counterparts on the holdout log-loss scale. For the correctly specified quadratic expansion (Order 2), `SVEMnet` with `wBIC` and the non-relaxed repeated-`cv.glmnet` baselines attain essentially indistinguishable performance: Tukey–Kramer comparisons based on the mixed-effects model place these configurations in the same best-performing group (Table B.5). However, Figure 5 suggests that `SVEMnet` with `wBIC` may outperform `cv.glmnet` in the overspecified case.

Relaxed refits are systematically worse: for each objective and α grid the `relax = TRUE` versions have larger least-squares means, with the relaxed cross-validated baselines forming the worst group in Table B.5. The degradation from relaxation is especially pronounced for the repeated-`cv.glmnet` fits, where the increase in mean log-loss is roughly twice as large as for the corresponding `SVEMnet` selectors.

Allowing $\alpha \in \{0.5, 1\}$ has no material impact relative to lasso-only fits ($\alpha = 1$): default two-point grids and pure lasso grids are indistinguishable within each selection method. As in the Gaussian case, the loss-only `wsSE` selector (included only in the overview plots) exhibits a pronounced error spike at $n_{\text{total}} = p_{\text{full}}$, now on the log-loss scale (Figure 5). `SVEMnet` with `wAIC` underperforms `wBIC` in the binomial setting. These simulations support the default configuration used in `SVEMnet` for binomial responses: validation-weighted `wBIC`, no relaxation, and $\alpha \in \{0.5, 1\}$.

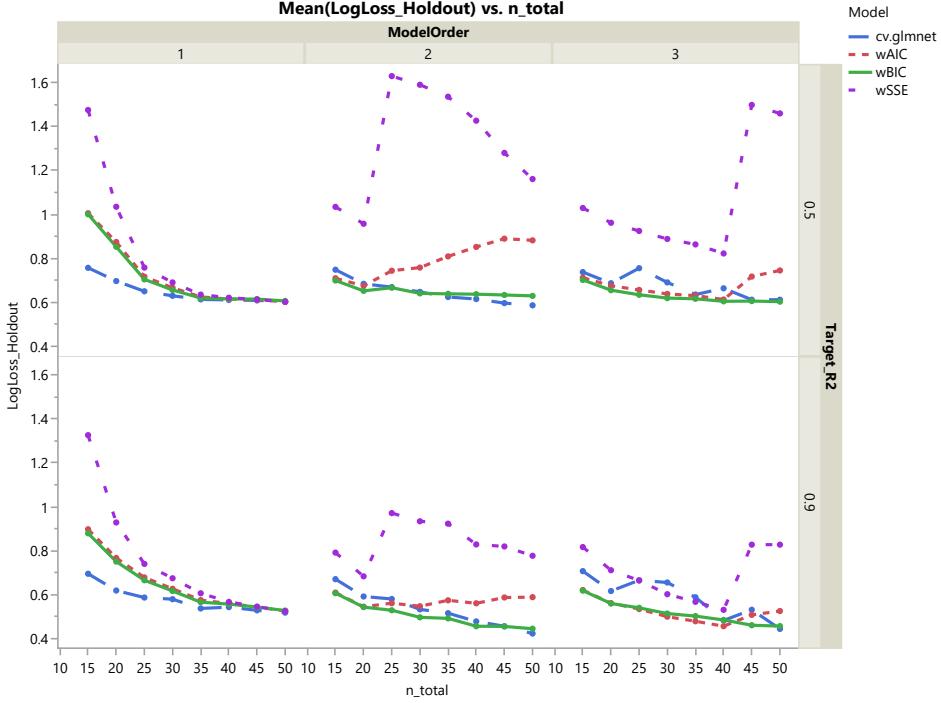


Figure 5: Binomial simulation summary (response: `LogLoss_Holdout` versus true probabilities). Mean log-loss on a large holdout versus n_{total} , stratified by target R^2 and model order. All methods use non-relaxed paths (`relax = FALSE`) with the default mixing grid $\alpha \in \{0.5, 1\}$. `wSSE` spikes at $n = p_{\text{full}}$.

5. Conclusion

SVEMnet provides an open-source implementation of Self-Validated Ensemble Models for small-sample DOE and chemometric applications, with (relaxed) elastic-net base learners for Gaussian and binomial responses built on `glmnet` using validation-weighted information-criterion analogs.

Together with the permutation whole-model test and the random-search desirability scoring and candidate-selection tools, **SVEMnet** offers an end-to-end workflow for mixture-constrained multi-response optimization in a single toolchain. The software is aimed at practitioners running small-sample (*e.g.*, tens of runs) chemometric, pharmaceutical, and industrial DOE studies for formulation optimization, often involving mixture factors alongside numeric and categorical process factors. SVEM-based elastic-net surrogates provide a practical alternative or complement to Gaussian-process-based Bayesian optimization, particularly when the number of runs is too small to support rich covariance structures or when full BO tooling is unavailable. A head-to-head comparison with Gaussian-process Bayesian optimization is beyond the scope of this software-focused paper; here our comparisons focus on repeated CV elastic-net baselines that reflect common penalized-regression workflows in small-sample DOE.

Appendix A. Validation-weighted criterion and guardrails

This appendix records the validation-weighted selection criteria used in **SVEMnet**.

Appendix A.1. Gaussian criterion

Within each FRW replicate, let λ index a point on the elastic-net path, let k_λ denote the number of nonzero coefficients (including the intercept), and let w_i^{valid} be the FRW validation weights, rescaled to have mean one so that $\sum_i w_i^{\text{valid}} = n$. Write $r_{\lambda,i} = y_i - \hat{y}_{\lambda,i}$ for the residual at observation i under λ , and define the weighted sum of squared errors

$$\text{SSE}_w(\lambda) = \sum_i w_i^{\text{valid}} r_{\lambda,i}^2.$$

For Gaussian responses we consider three selectors: a loss-only rule based on $\text{SSE}_w(\lambda)$ and two information-criterion analogs. The loss-only selector wSSE minimizes $\text{SSE}_w(\lambda)$ over the path. The validation-weighted AIC and BIC analogs minimize

$$C_g(\lambda) = n \log\left(\frac{\text{SSE}_w(\lambda)}{n}\right) + g k_\lambda, \quad g \in \{2, \log(n_{\text{eff}}^{\text{adm}})\}, \quad (\text{A.1})$$

which yield, respectively, a validation-weighted AIC analog (wAIC , $g = 2$) and a validation-weighted BIC analog (wBIC , $g = \log(n_{\text{eff}}^{\text{adm}})$) [12, 13, 14]. In the unweighted case, $w_i^{\text{valid}} \equiv 1$ and $\text{SSE}_w(\lambda)$ reduces to the usual residual sum of squares $\text{RSS}(\lambda)$. In that case $C_g(\lambda)$ reduces to $n \log\{\text{RSS}(\lambda)/n\} + g k_\lambda$, which is the standard Gaussian AIC/BIC form (up to an additive constant independent of λ).

Following Kish [40], we summarize the variability of the validation weights via an effective sample size

$$n_{\text{eff}} = \frac{(\sum_i w_i^{\text{valid}})^2}{\sum_i (w_i^{\text{valid}})^2}$$

and use the bounded quantity

$$n_{\text{eff}}^{\text{adm}} = \min\{n, \max(2, n_{\text{eff}})\}$$

when forming the BIC-style penalty $\log(n_{\text{eff}}^{\text{adm}}) k_\lambda$. With mean-one FRW weights, $2 \leq n_{\text{eff}}^{\text{adm}} \leq n$.

For the information-criterion selectors (wAIC , wBIC) we additionally impose

$$k_\lambda - 1 < n_{\text{eff}}^{\text{adm}},$$

so that the number of non-intercept coefficients is strictly smaller than the effective number of validation observations. Path points violating this inequality are treated as inadmissible when evaluating $C_g(\lambda)$. This guardrail helps stabilize model selection near the interpolation boundary $n = p_{\text{full}}$ [41, 32, 16, 42].

Appendix A.2. Binomial (logistic) criterion

For binomial responses we minimize a deviance-style quantity plus a complexity penalty. Let $\ell_{\text{valid}}(\lambda)$ denote the weighted log-likelihood on the FRW validation copy under path point λ , and let $\text{NLL}(\lambda) = -\ell_{\text{valid}}(\lambda)$ be the corresponding weighted negative log-likelihood. The AIC- and BIC-style selectors minimize

$$C_g^{(\text{bin})}(\lambda) = -2 \ell_{\text{valid}}(\lambda) + g k_\lambda = 2 \text{NLL}(\lambda) + g k_\lambda, \quad g \in \{2, \log(n_{\text{eff}}^{\text{adm}})\},$$

which differs from the usual binomial deviance only by an additive constant independent of λ . In the implementation we work directly with $\text{NLL}(\lambda)$ and form $C_g^{(\text{bin})}(\lambda)$ as $2 \times \text{NLL} + g k_\lambda$ for these selectors. For wAIC and wBIC the same effective-size quantity $n_{\text{eff}}^{\text{adm}}$ and guardrail $k_\lambda - 1 < n_{\text{eff}}^{\text{adm}}$ are used as in the Gaussian case.

When $g = 0$ the selector is a loss-only rule based on the weighted negative log-likelihood; for consistency with historical SVEM tooling we retain the label `wSSE` for this case even though it is based on negative log-likelihood rather than squared error. Ensemble predictions are formed by averaging member-predicted probabilities on the response scale.

Appendix B. Supplementary multiple-comparison tables

For completeness we provide Tukey–Kramer multiple-comparison summaries for the Gaussian and binomial simulations. These tables correspond to the mixed-model analyses described in Section 4, based on 250 (Gaussian) and 200 (binomial) independent simulation replicates for each combination of n_{total} , `Target_R2`, and `Setting` at the quadratic expansion (Order 2); full CSV outputs are included in the replication bundle [38].

For all Tukey–Kramer analyses we fixed the expansion at the correctly specified quadratic order (Order 2) and fit linear mixed models with `Setting` as the primary factor of interest, n_{total} , `Target_R2`, and their interaction as categorical fixed effects, and simulation run ID as a random intercept. Pairwise differences between settings were assessed using Tukey–Kramer honestly significant difference comparisons of the model-based least-squares means, controlling the familywise error rate at $\alpha = 0.05$. Settings that do not share a letter differ significantly, and smaller least-squares means correspond to better performance (lower log-NRMSE or log-loss). Here `relaxTRUE/False` indicates whether relaxed base learners are used, `lasso/default` indicates the pure lasso case ($\alpha = 1$) versus the mixed- α grid $\alpha \in \{0.5, 1\}$, and in Table B.4 the suffix `dbTRUE/False` indicates whether the post-hoc debiasing step is applied. In Table B.5 all configurations use `dbFALSE`.

To avoid inflating the number of pairwise comparisons with a clearly noncompetitive method, the loss-only `wSSE` selector was omitted from the Tukey–Kramer analyses. The overview plots in Figures 3 and 5 show `wSSE` performing uniformly poorly across the simulation grid.

Table B.4: Tukey–Kramer HSD connecting letters for the Gaussian simulation (response: log-NRMSE on a noiseless holdout; smaller least-squares means are better; rows are sorted from worst to best).

Setting	Least-squares mean	Group
CV_relaxTRUE_lasso_dbTRUE	-0.4550838	A
CV_relaxTRUE_default_dbTRUE	-0.4568168	A
CV_relaxTRUE_lasso_dbFALSE	-0.4784299	B
CV_relaxTRUE_default_dbFALSE	-0.4795369	B
SVEM_wBIC_relaxFALSE_lasso_dbFALSE	-0.4872574	BC
SVEM_wBIC_relaxFALSE_default_dbFALSE	-0.4873671	BC
CV_relaxFALSE_lasso_dbTRUE	-0.4890622	C
CV_relaxFALSE_default_dbTRUE	-0.4955437	C
CV_relaxFALSE_lasso_dbFALSE	-0.5125708	D

Setting	Least-squares mean	Group
SVEM_wBIC_relaxFALSE_default_dbTRUE	-0.5153720	DE
SVEM_wBIC_relaxFALSE_lasso_dbTRUE	-0.5154061	DE
SVEM_wAIC_relaxFALSE_lasso_dbTRUE	-0.5173612	DE
SVEM_wAIC_relaxFALSE_default_dbTRUE	-0.5173877	DE
CV_relaxFALSE_default_dbFALSE	-0.5182228	DE
SVEM_wBIC_relaxTRUE_lasso_dbTRUE	-0.5202504	DE
SVEM_wBIC_relaxTRUE_default_dbTRUE	-0.5205100	DE
SVEM_wAIC_relaxTRUE_default_dbTRUE	-0.5240749	E
SVEM_wAIC_relaxTRUE_lasso_dbTRUE	-0.5243519	E
SVEM_wAIC_relaxFALSE_default_dbFALSE	-0.5429558	F
SVEM_wAIC_relaxFALSE_lasso_dbFALSE	-0.5436361	F
SVEM_wBIC_relaxTRUE_lasso_dbFALSE	-0.5495013	F
SVEM_wBIC_relaxTRUE_default_dbFALSE	-0.5501097	F
SVEM_wAIC_relaxTRUE_default_dbFALSE	-0.5745804	G
SVEM_wAIC_relaxTRUE_lasso_dbFALSE	-0.5746790	G

Table B.5: Tukey–Kramer HSD connecting letters for the binomial simulation (response: `LogLoss_Holdout`; smaller least-squares means are better; rows are sorted from worst to best).

Setting	Least-squares mean	Group
CV_relaxTRUE_default	0.938427	A
CV_relaxTRUE_lasso	0.896920	A
SVEM_wAIC_relaxTRUE_default	0.808413	B
SVEM_wAIC_relaxTRUE_lasso	0.800409	B
SVEM_wBIC_relaxTRUE_default	0.735577	C
SVEM_wBIC_relaxTRUE_lasso	0.724202	C
SVEM_wAIC_relaxFALSE_default	0.683151	D
SVEM_wAIC_relaxFALSE_lasso	0.683002	D
CV_relaxFALSE_lasso	0.602811	E
CV_relaxFALSE_default	0.593384	E
SVEM_wBIC_relaxFALSE_default	0.575261	E
SVEM_wBIC_relaxFALSE_lasso	0.575050	E

CRediT authorship contribution statement

Andrew T. Karl: Software; Writing - original draft;

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The author developed the **SVEMnet** package and the related JMP add-in. The author has no other competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the manuscript and software preparation process

During the preparation of this manuscript *and* the accompanying software, the author used OpenAI GPT models as assistive tools. Under the author's direction, these models were used (i) to revise and proofread prose and (ii) to draft the majority of the initial **SVEMnet** R code and associated documentation. All AI-generated text and code were reviewed, edited, and validated by the author before inclusion. All algorithmic design choices, statistical methodology, simulation design, and final implementation decisions were made by the author, who takes full responsibility for the content of the manuscript, the software, and all reported results.

Data and software availability

Data and replication. The R scripts, configuration files, and CSV outputs required to reproduce the simulations, figures, and LNP case study are available in the Mendeley Data repository [38].

Software. **SVEMnet** is available on CRAN: <https://doi.org/10.32614/CRAN.package.SVEMnet>. The version used in this paper is 3.1.4. Documentation includes a reference manual shipped with the package. The package is written in R 4.5.2 and licensed under GPL-2 | GPL-3.

JMP add-in. An optional JMP add-in, “Relaxed Elastic Net and Lasso SVEM using R” (<https://marketplace.jmp.com/appdetails/Relaxed+Elastic+Net+and+Lasso+SVEM+using+R>), is available via the JMP Marketplace. The add-in lets JMP users install **SVEMnet** in R, call the package for a saved Fit Model table script with Gaussian responses, and obtain prediction and standard error formula columns. It provides a convenience front-end to **SVEMnet** but is not required to reproduce the results in this paper.

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