# Exploratory and prospective model of stent restenosis after Percutaneous Coronary Intervention using Multivariate Gaussian Subspatial Regression

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## Abstract

A new methodology, "Multivariate Gaussian Subspatial Regression" (MGSR), has been applied to randomized clinical trial data collected from percutaneous coronary intervention (PCI) patients.

This model allows multiple variable combinations to be explained and predicted in a dynamic way by combining Gaussian Processes and Factorial Techniques virtues. We built our model from 3 different quantitative coronary angiographic core-lab measures of the same lesion from 2 separate angiograms (at baseline before PCI, at baseline immediately after PCI and at 12 months follow-up).

Using this new method, we were able to predict acute gain and late loss with certainty by mapping the predictions over a factorial plane. This representation allows physicians to better interpret the behavior of hypothetical patients and measured variables.

MGSR makes it possible to detect patients at risk of coronary stent restenosis or patients in whom ruling out the disease; avoiding unnecessary, costly and possibly risky treatments; in a graphical way. In addition, we can forecast missed values regardless of the variables. Once the MGSR model is fitted, it can easily correct itself when more dependent variables are included. MGSR software is freely available online at https://github.com/victorvicpal/MGSR.

## Introduction

Angioplasty and stenting are percutaneous coronary interventions (PCI) which have become routine practice for the revascularization of coronary vessels with significant

obstructive atherosclerotic disease [1, 2]. Furthermore, PCI with stent implantation immediately performed is the gold-standard of treatment in patients with acute myocardial infarction, reducing the rates of death and recurrent ischemia as compared to medical treatment [3].

The long-term success of these procedures may be limited by restenosis [4, 5], a pathological process leading to recurrent arterial narrowing at the site of PCI which may manifest as a new myocardial infarction or force new-target-vessel revascularization. There is no equation attempting to predict which patients will develop restenosis, since there are probably multiple risk factors responsible for restenosis with anatomical vessel features and coexisting medical conditions. Thus, developing a model to predict the risk of restenosis would be a valuable tool for improving the stratification of patients, providing individually tailored follow-up and treatment.

Gaussian distributions are quite common in the medical and biological field. Angiography data are no exception and Gaussian processes are suitable to use. Gaussian processes use lazy learning and a measure of the similarity between points to predict new values accurately. Nevertheless, Gaussian processes rely on continuous domains such as time or space, which are not present in this kind of data. We used a subspatial domain produced by dimensional reduction techniques to apply a Gaussian process such as cokriging. Thanks to this iteration we were able to forecast how PCI patients will behave after a PCI.

# Materials and methods

Stent Restenosis (SR) data were obtained from the previously published GRACIA-3 trial [6]. The GRACIA 3 trial is a randomized, open-label, multicenter, clinical trial that compares the efficacy of the paclitaxel-eluting stent with the conventional bare-metal stent. Patients with ST segment elevation acute myocardial infarction were enrolled from 20 Spanish hospitals.

To determine the incidence of SR, coronary angiography was performed at baseline and after 12 months of follow-up. All angiograms were analyzed at an independent angiography core laboratory (ICICOR, Valladolid, Spain) with a well-validated quantitative computer-based system (Medis, Leesburg, Va). The rate of SR was assessed by an experienced reader who was blinded to and not directly involved in the stent-implantation project.

Angiographic follow-up at 12 months was completed in 299 out of 346 (86%) randomized and eligible patients. SR was defined following the rate of binary restenosis after 12 months of angiographic follow-up. Binary angiographic restenosis was defined as a >50% narrowing of the lumen diameter in the target segment (defined as all portions of the vessel that received treatment within the stent zone, including the proximal and distal 5-mm margins) [7].

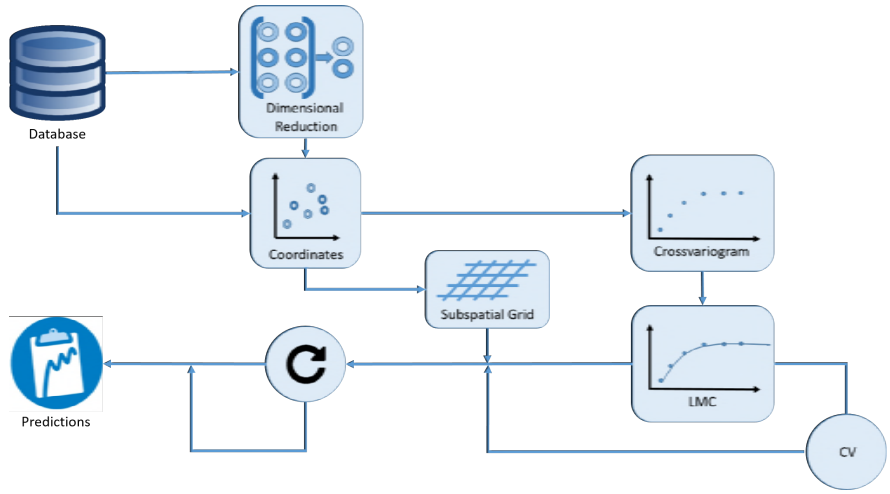
## 0.1 Statistical Analysis

We first briefly describe the Multivariate Gaussian Subspatial Regression (MGSR) [8] model(1) and summarize its statistical properties.

Let $\boldsymbol{X_{N\times P}}$ be the data matrix that is composed of $P$ variables and $N$ individuals. We chose a Classical Biplot [9] as a dimensional reduction technique. Biplot is a graphical representation of the data matrix $\boldsymbol{X}$ as $\boldsymbol{X} \approx \boldsymbol{R}\boldsymbol{C}^T$. $\boldsymbol{R}$ and $\boldsymbol{C}$ are the row and column coordinates respectively. From now on we will refer to $\boldsymbol{R}$ as the subspatial coordinates. On the basis of these coordinates, we propose a cokriging exploration.

Previous to applying cokriging we need to compose a suitable matrix that will be used later on. For this purpose, we proceed to standardize by columns the $\boldsymbol{X}_{N\times P}$ by

**Fig 1. MGSR algorithm**




removing the column means and dividing by its standard deviation. Then, we attach the coordinates $\boldsymbol{R}$ to the standardized matrix obtaining $\boldsymbol{Z}(u) = [\boldsymbol{X}(\boldsymbol{R})]$ where $u =< \boldsymbol{r_s} >, u \in S$ are the set of subspatial locations.

Subsequently, we built an experimental subspatial cross-variogram [10] $\Gamma_{i,j}(h)$, where $h$ is the distance between points and $i, j$ represent our features.

$$\boldsymbol{\Gamma_{i,j}(h)} = \frac{1}{2}\mathrm{E}[(\boldsymbol{Z}_i(u+h) - \boldsymbol{Z}_i(u)) \cdot (\boldsymbol{Z}_j(u+h) - \boldsymbol{Z}_j(u))]. \tag{1}$$

Therefore, we obtained $P(P+1)/2$ experimental cross-variograms that needed to be fitted. We chose the Linear Model of Coregionalization (LMC) to fit our set of cross-variograms. The LMC can be expressed as a multivariate nested semivariogram model [11].

$$\boldsymbol{\Gamma}(h) = \sum_{f=1}^{F} \boldsymbol{B_f} g_f(h) \tag{2}$$

where $\boldsymbol{\Gamma}(h)$ is the $P \times P$ matrix of semivariogram values at lag $h$, and $\boldsymbol{B_f}$ is the $P \times P$ matrix of sills [12] of the basic semivariogram function $g_f(h)$. $\boldsymbol{B_f}$ has to be positive semidefinite [12, 13] to ensure that the variance-covariance matrix is also positive semidefinite.

Although different approaches of LMC can be found in the literature, we use the algorithm defined by Pelletier et al. [14] owing to its clarity.

Unlike geostatistical analyses [15], there was no real field where boundaries restricted our study. However, this aspect was more positive than negative because we were able to create a simpler grid without losing information.

By establishing the interval between the maximum and minimum location in their different dimensions we created a frame, which could be extended if necessary. Subsequently, we built the grid choosing a suitable division.

Using simple cokriging [11] we were able to project our predictions onto the grid, and thus were able to compare the results within the variables.

Cokriging is the multivariate extension of kriging, whose main purpose is to compute a weighted average of the sample values in close proximity to the grid point. It searches for the best linear unbiased estimator, based on assumptions on covariances.

Simple cokriging is based on three assumptions: stationary, known means and known covariance functions.

The simple cokriging estimator is

$$\hat{\boldsymbol{Z}_{\boldsymbol{i_0}}}(u_0) = m_{i_0} + \sum_{i=1}^{P}\sum_{\alpha=1}^{N} w_\alpha^i(\boldsymbol{Z_i}(u_\alpha) - m_i) \tag{3}$$

where $u_0$ is the grid location and $u_\alpha$ the sample location, $w_\alpha^i$ is the weight and $m$ corresponds to the means of our variables.

# Results

Our aim was to develop an exploratory and prospective model of the obstructed diameter of the artery for two different conditions, post and follow-up PCI. For this matter we had 3 pre-PCI variables (Legth, obstructed diameter and reference diameter of the artery) and 2 post-PCI variables (immediately-post and 12-month follow-up PCI diameters).

Our starting matrix was composed of 337 patients and 5 variables; however, there were only 180 patients without missing values (Table 1), representing 53% of the total.

**Table 1. Stent data Summary (mm.)**

| | **Pre** | | | **Post** | **Follow-Up** |
|---|---|---|---|---|---|
| **Variables** | **Seg Length** | **Obs Diam** | **Ref Diam** | **Obs Diam** | **Obs Diam** |
| mean | 43.42 | 0.78 | 2.89 | 2.35 | 2.22 |
| S.E. | 1.16 | 0.03 | 0.04 | 0.04 | 0.04 |
| max | 111.98 | 1.91 | 4.32 | 3.68 | 3.53 |
| min | 8.86 | 0.00 | 1.55 | 1.09 | 0.46 |
| Fig. ref. | Seg_Length_PRE | Obs_Diam_PRE | Ref_Diam_PRE | Obs_Diam_POST | Obs_Diam_FU |

We chose classical Biplot [9] as the initial dimensional reduction procedure, in particular a Row Metric Preserving Biplot. Biplots represent matrix elements as points and variables as vectors (Fig. 2). The inertia absorption of the first two factor axes was 69%. In view of the minimum loss, we kept two first axes in order to simplify the cokriging iteration later on.

As seen in Fig.2 points represent our patient's cohort and vectors describe the behavior of the analyzed variables. These representations allows researchers to simply visualize and understand their sample data. Nevertheless if we need to look beyond and build a predictive model, biplots are limited.

To overcome this issue we applied a Gaussian Process over the resulting Biplot plane. We might consider our first factorial plane as if it were a mining region in which points would represent our exploratory drilling sample. Multivariate geostatistical procedures [11] would help us to forecast where it would be better to drill in the unknown region depending on the desired mineral we want to extract. In our case we do not aim to "drill" but to map and predict new possible patient's outcomes by applying similar techniques over our factorial plane. Therefore, our unknown region is represented as the blank space not covered by our sample data (Fig.2) where we intend to estimate new hypothetical patients.

Once we got our Biplot coordinates, we calculated the experimental cross-variogram which describes the degree of subspatial dependence of the calculated factorial plane. Experimental cross-variograms are represented in Fig. 3 as a set of scatter-plots. The distribution of the experimental cross-variograms follows a power distribution $g_f(h) = h^a$, which has been the chosen function for the Linear Model of Coregionalization (LMC) fitting ($a = 1.83$). Table 2 displays the results of the LMC.

**Fig 2. JK-Biplot**

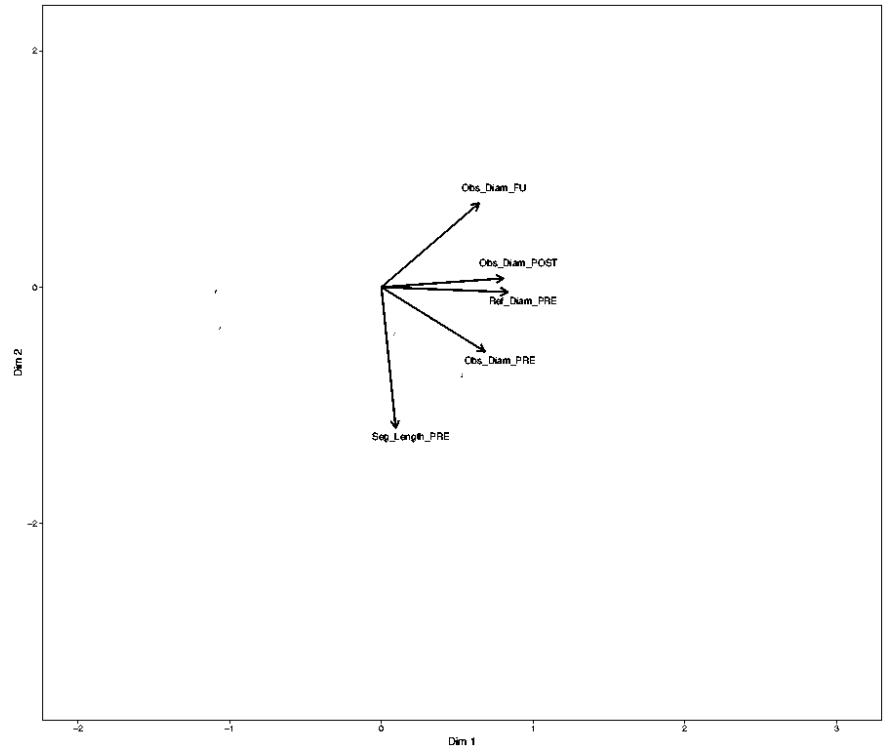
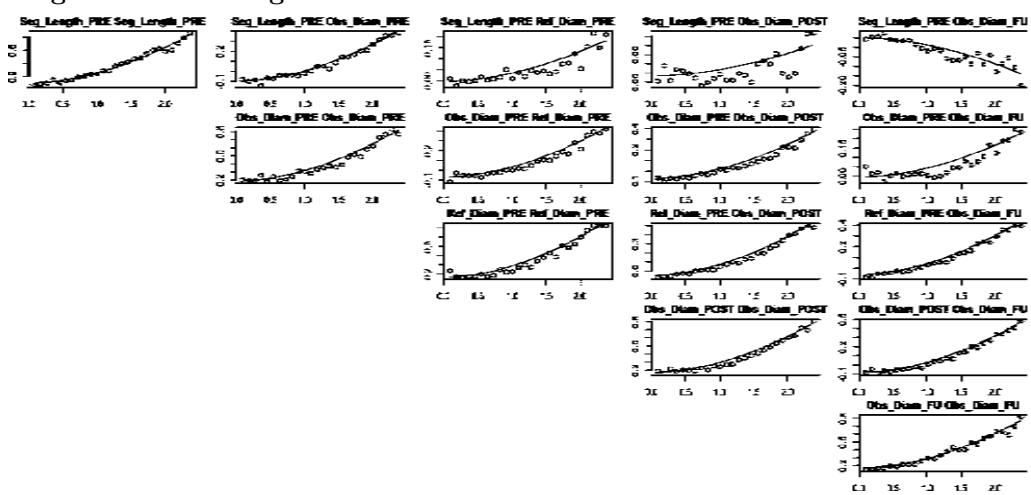



**Fig 3. Cross-Variogram**



In addition, we calculated the root mean square error (RMSE) of our model [11].

The cross-validation method was based on a common resampling. Each sample value $\boldsymbol{Z}(u_\alpha)$ was removed in turn from the data set and a value $\hat{\boldsymbol{Z}}(u_{[\alpha]})$ was estimated at that location using the $N-1$ other samples.

As a result we determined the residuals $\boldsymbol{Z}(u_\alpha) - \hat{\boldsymbol{Z}}(u_{[\alpha]})$ of our model and in addition, we compared our results with classical Multivariate Regression (MVR) models.

To be able to compare MGSR and MVR we needed to fit 10 different multivariate models. All of these models had 3 input variables and 2 output variables in such a manner that each variable was considered as a dependent variable 6 times and as

**Table 2. Summary of LMC results**

| Variogram | Variables | Nug | Pow |
|---|---|---|---|
| Direct | Seg. Len. - Seg. Len. | 0.10 | 0.15 |
| | Obs. D. PRE - Obs. D. PRE | 0.19 | 0.13 |
| | Ref. D. - Ref D. | 0.16 | 0.13 |
| | Obs. D. POST - Obs. D. POST | 0.17 | 0.13 |
| | Obs D. FU - Obs D. FU | 0.17 | 0.12 |
| CrossVar | Seg. Len. - Obs. D. PRE | -0.10 | 0.10 |
| | Seg. Len. - Ref. D. | -0.00 | 0.04 |
| | Seg. Len. - Obs. D. POST | 0.01 | 0.01 |
| | Seg. Len. - Obs. D. FU | 0.05 | -0.04 |
| | Obs D. PRE - Ref D. | -0.07 | 0.10 |
| | Obs D. PRE - Obs. D. POST | -0.07 | 0.09 |
| | Obs D. PRE - Obs. D. FU | -0.01 | 0.05 |
| | Ref D. PRE - Obs. D. POST | -0.05 | 0.12 |
| | Ref D. PRE - Obs. D. FU | -0.06 | 0.10 |
| | Obs. D. POST - Obs. D. FU | -0.08 | 0.11 |
| | | Range 1.83 | |

independent, 4 times. Table 3 shows the RMSE of MGSR and the 10 MVR models. Empty values on the table 3 correspond to input variables.

**Table 3. RMSE MGSR and Multivariate Regression**

| | PRE | | | POST | FU |
|---|---|---|---|---|---|
| Algorithm | Seg. Length | Obs. Diam. | Ref. Diam. | Obs. Diam. | Obs. Diam. |
| **MGSR** | 0.19 | 0.40 | 0.33 | 0.35 | 0.32 |
| **MVR1** | - | - | - | 0.43 | 0.50 |
| **MVR2** | - | 0.38 | - | 0.43 | - |
| **MVR3** | - | 0.38 | - | - | 0.49 |
| **MVR4** | - | 0.38 | 0.43 | - | - |
| **MVR5** | - | - | 0.46 | 0.46 | - |
| **MVR6** | - | - | 0.44 | - | 0.50 |
| **MVR7** | 14.47 | - | 0.42 | - | - |
| **MVR8** | 14.97 | 0.39 | - | - | - |
| **MVR9** | 14.40 | - | - | 0.42 | - |
| **MVR10** | 14.89 | - | - | - | 0.50 |

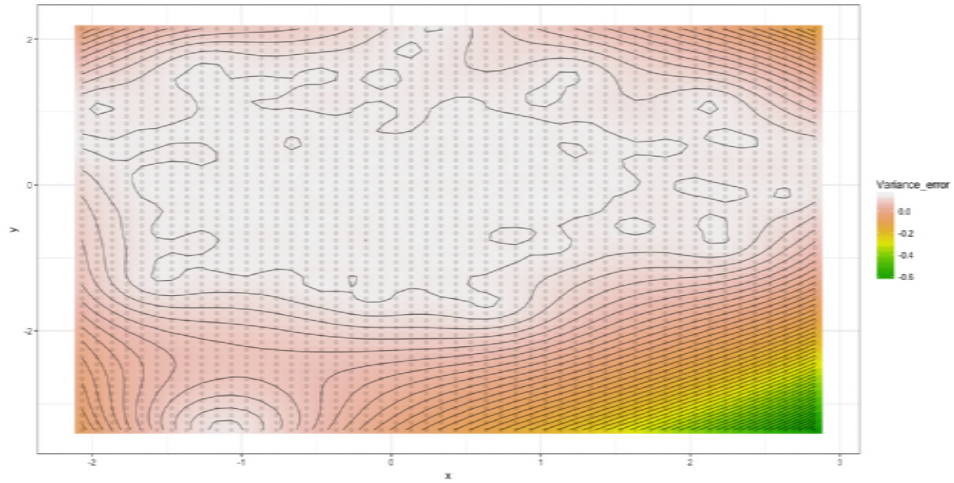
We then built a rectangular grid containing all the Biplot projections. Grey points in Figs. 4 and 5 show the grid distribution where we applied a Cokriging iteration. Owing to computational issues, we chose a 0.1 distance between grid points. A tighter choice would not improve results.

Variance errors were also calculated. In Fig. 4 we can see that the predicted points near the origin of the coordinate system are less accurate than the surrounding points [9]. This effect corroborates the Biplot quality of rows representation theory [16].

We illustrate our model as if it were a map of elements (Fig. 5). Each point represent an hypothetical patient with different characteristics. Patients nearby tend to be more similar than those that are farther apart. To illustrate how MGSR can be used, we present a couple of examples.

In patient number 1, pre-PCI MGRS predicts that the development of stent restenosis (red area) is uncommon to happen. This is confirmed in the post-PCI MGRS model predicting an optimal evolution, which is corroborated at the 12 months

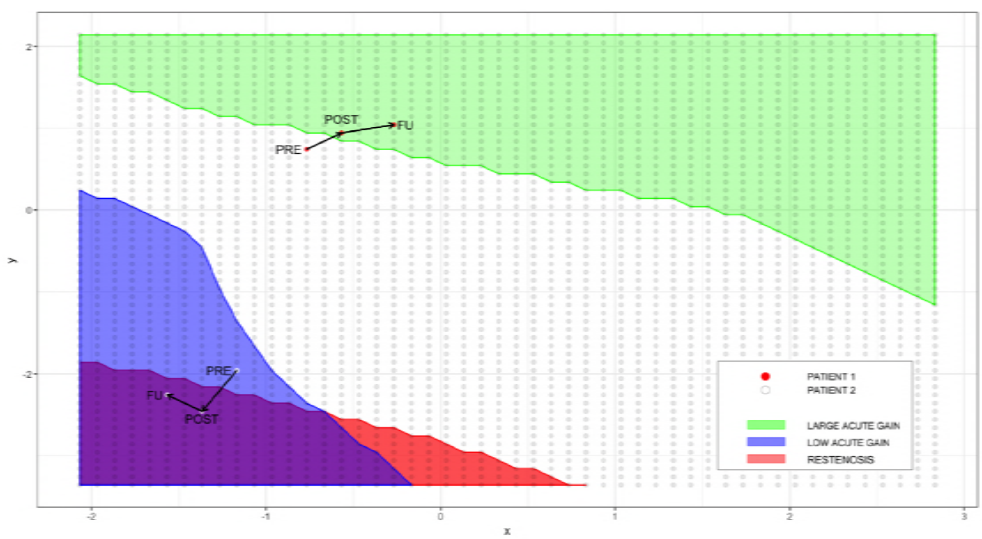
**Fig 4. Variance error**




angiographic follow-up. In patient number 1, we could avoid repeated clinical visits to the doctor as optimal evolution is predicted. Furthermore, we could also avoid double antithrombotic therapy continuation after 12 months, as no stent complications are predicted.

In contrast, patient number 2 pre-PCI prediction is closed to the red area of stent restenosis. The risk of stent restenosis MGRS prediction is even worse immediately post-PCI and stent restenosis is confirmed at the 12 months angiographic follow-up. In patient number 2, we should have optimize the post-PCI result; we should recommend a close clinical follow-up; a 12 month coronary angiography should be performed and; double antiaggregation should not be discontinued as we predict future adverse events.

**Fig 5. MGSR model**




This estimations can be done not only in a chronological way, as seen in Fig. 5 but also to calculate missing values. For instance, if the reference diameter of the artery was not measured on a patient, we could estimate its value without fitting a new model. By searching over our model (Fig. 5) the more similar hypothetical patient based on the real patient's known values.

**Table 4. Examples of prediction**

| | | Pre | | | Post | Follow-up |
|---|---|---|---|---|---|---|
| Patient | | Seg. Len. | Obs. Diam. | Ref. Diam. | Obs. Diam | Obs. Diam. |
| 1 | PRE | 84.95 | 0.86 | 2.24 | **1.72** | **1.09** |
| | POST | 84.95 | 0.86 | 2.24 | 1.62 | **0.86** |
| | FU | 84.95 | 0.86 | 2.24 | 1.62 | 0.85 |
| 2 | PRE | 25.47 | 0.37 | 2.66 | **2.10** | **2.18** |
| | POST | 25.47 | 0.37 | 2.66 | 2.21 | **2.34** |
| | FU1 | 25.47 | 0.37 | 2.66 | 2.21 | 2.50 |

Almost half of our dataset contains missing values which can be calculated as we explained above. A summary of our outcomes are shown in Table 5.

**Table 5. Missing Values**

| Intervention | Pre | | | Post | Follow-Up |
|---|---|---|---|---|---|
| Variables (mm.) | Seg Length | Obs Diam | Ref Diam | Obs Diam | Obs Diam |
| mean | 44.19 | 0.84 | 2.93 | 2.35 | 2.25 |
| S.E. | 0.90 | 0.02 | 0.03 | 0.03 | 0.03 |
| max | 106.40 | 2.00 | 4.19 | 3.55 | 3.88 |
| min | 8.87 | 0.00 | 1.96 | 1.35 | 1.00 |

# Discussion

Currently, PCI is the most common procedure to treat coronary atherosclerotic obstructions. The total number of PCI performed in Spain in 2015, with approximately 45 million inhabitants, were 67,671 procedures, with a ratio of 1,466 per million inhabitants. In addition, 18,418 were carried out during the acute phase of myocardial infarction (21.7%) [17].

The Achilles tendon of PCI is restenosis, which leads to recurrent arterial narrowing at the site of intervention. Restenosis is caused by chronic inflammatory disease featuring the activation of immune cells and excessive growth of vascular smooth muscle cells within the injured vessel wall. When PCI was initially carried out, in the late 1970s, angioplasty was limited to isolated balloon inflations. However, and although the artery would initially be opened successfully using a balloon, approximately 30% of all coronary arteries began to close up some months after balloon angioplasty owing to restenosis [18]. By the mid-1980s professionals began to design new devices to improve the durability of PCI procedures, avoiding restenosis. One such device was the stent, a metal tube that is inserted after balloon inflation, thus preventing negative remodeling of the treated vessel, the major cause of restenosis after conventional balloon angioplasty. But, while metal stents eliminated many abrupt artery closures, restenosis persisted in about 20% of cases [19]. In the early part of this century, the solution to restenosis moved away from mechanical devices towards the use of pharmaceuticals. Professionals started to test a variety of drugs that were known to interrupt the biological processes that cause restenosis. Stents were coated with immunosuppressive and anti-proliferative drugs, clinical trials began, and the era of the drug-eluting stents commenced. We are now in the second generation of drug eluting stents and restenosis has been reduced to 10%. However, and considering the increasing numbers of PCI performed worldwide and the widespread use of drug eluting stents, restenosis is still a health care problem of magnitude and identification of patients at risk is an important undertaking [20].

In this regard, the model to predict the risk of restenosis for improved stratification of patients proposed in our study is of clinical and economic relevance. Following this model, we could prescribe bare metal stents and decrease costs for patients at low-moderate risk of restenosis and improve outcomes in patients at high-risk of restenosis by implanting drug-eluting stents and performing established 12 month follow-up catheterization to rule out restenosis and avoid adverse clinical outcomes. Although restenosis may be associated with a recurrence of stable angina symptoms, it is recognized that up to 1 out of 3 patients present with myocardial infarction or unstable angina amenable to repeat catheter intervention [21].

The GRACIA-3 trial is unique in developing this predictive model for several reasons. First of all, it provides the opportunity to compare bare metal stents versus drug eluting stents in a clinical context, ST elevation acute myocardial infarction, where the benefit of new drug eluting stents is still discussed and under comparison [22]. Thus, our predictive model would be specifically useful in this specific scenario. Second, it is important to put into perspective the number of paired angiographic studies performed in the GRACIA-3 trial (70%), which surpasses surveillance studies in large cohorts of patients [23]. Thus, it will be difficult to find a cohort of patients so well characterized to develop and test a predictive model. Finally, the data come from a randomized clinical trial where all angiograms were analyzed at an independent angiographic core laboratory (ICICOR, Valladolid, Spain) with a gold-standard validated quantitative computer-based system (Medis, Leesburg, Va). Angiographic restenosis defined as binary angiographic restenosis $> 50\%$ narrowing of the lumen diameter in the target segment was assessed by an experienced reader who was blinded to treatment assignment and clinical outcome. Thus, the methodology used to define the presence of restenosis was of maximum rigor and quality.

The proposed model is very versatile and flexible for studying variables from an exploratory and prospective point of view. These variables can be combined according to the needs of the researcher.

We proved that, by combining two different procedures we could obtain interesting outcomes. Factorial techniques benefit from Gaussian Processes without losing their exploratory attributes and Gaussian Processes can be applied over a non continuous field. We can also reproduce our model in a visual way letting researchers better understand their data.

In addition, missing values, no matter which variable, can be estimated. This makes it possible to recover lost information from the trial.

Nevertheless, MGSR needs to be improved in several aspects. For instance, models with a large set of variables can be time consuming. This is an inherited problem of spatial Gaussian Processes. Also, to fit a MGSR model we need to follow a series of steps that can be tedious for users. In order to improve both issues we intend to better automate the LMC fitting to be more user-friendly and try different matrix factorizations or bayesian approaches to reduce time on the cokriging iteration.

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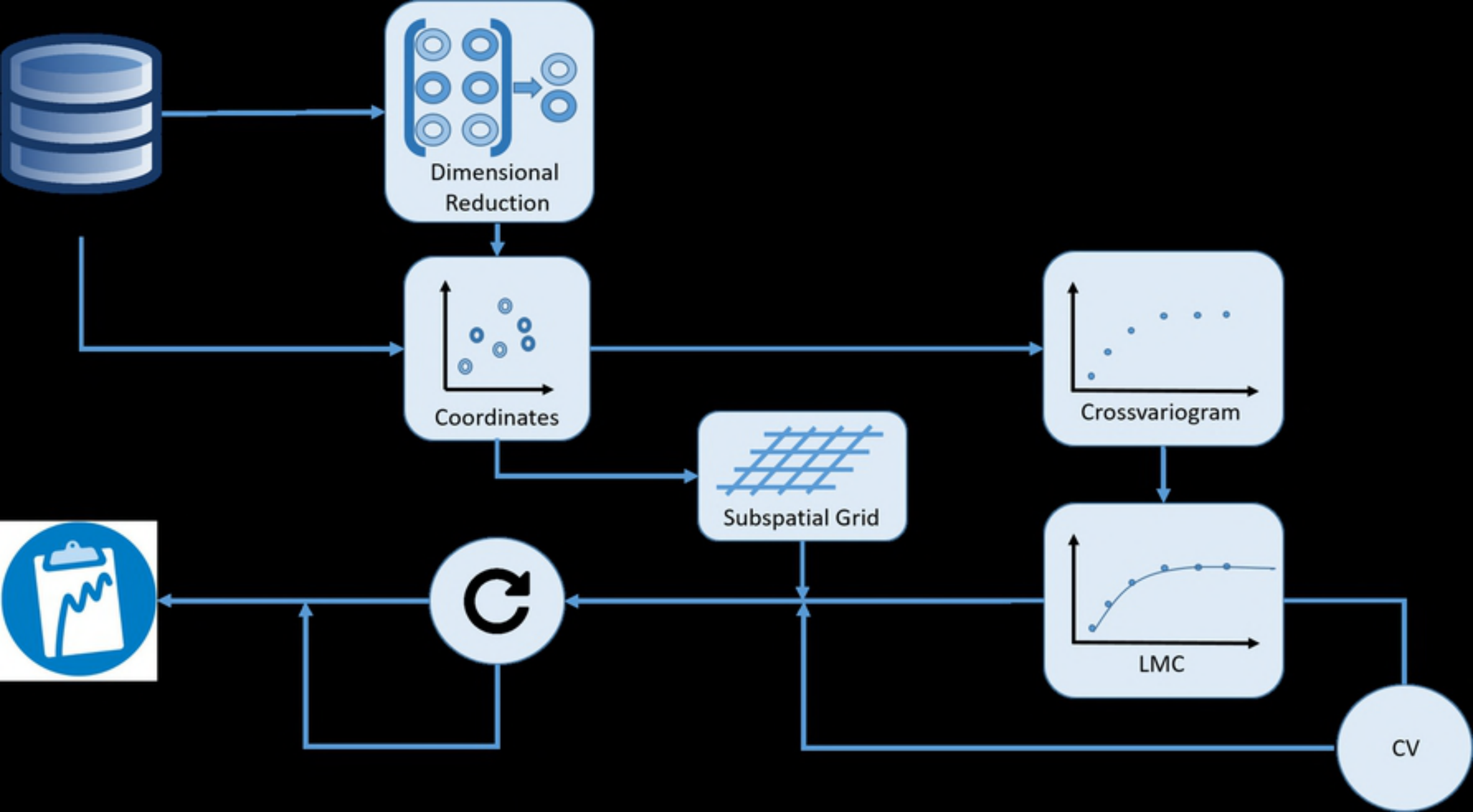
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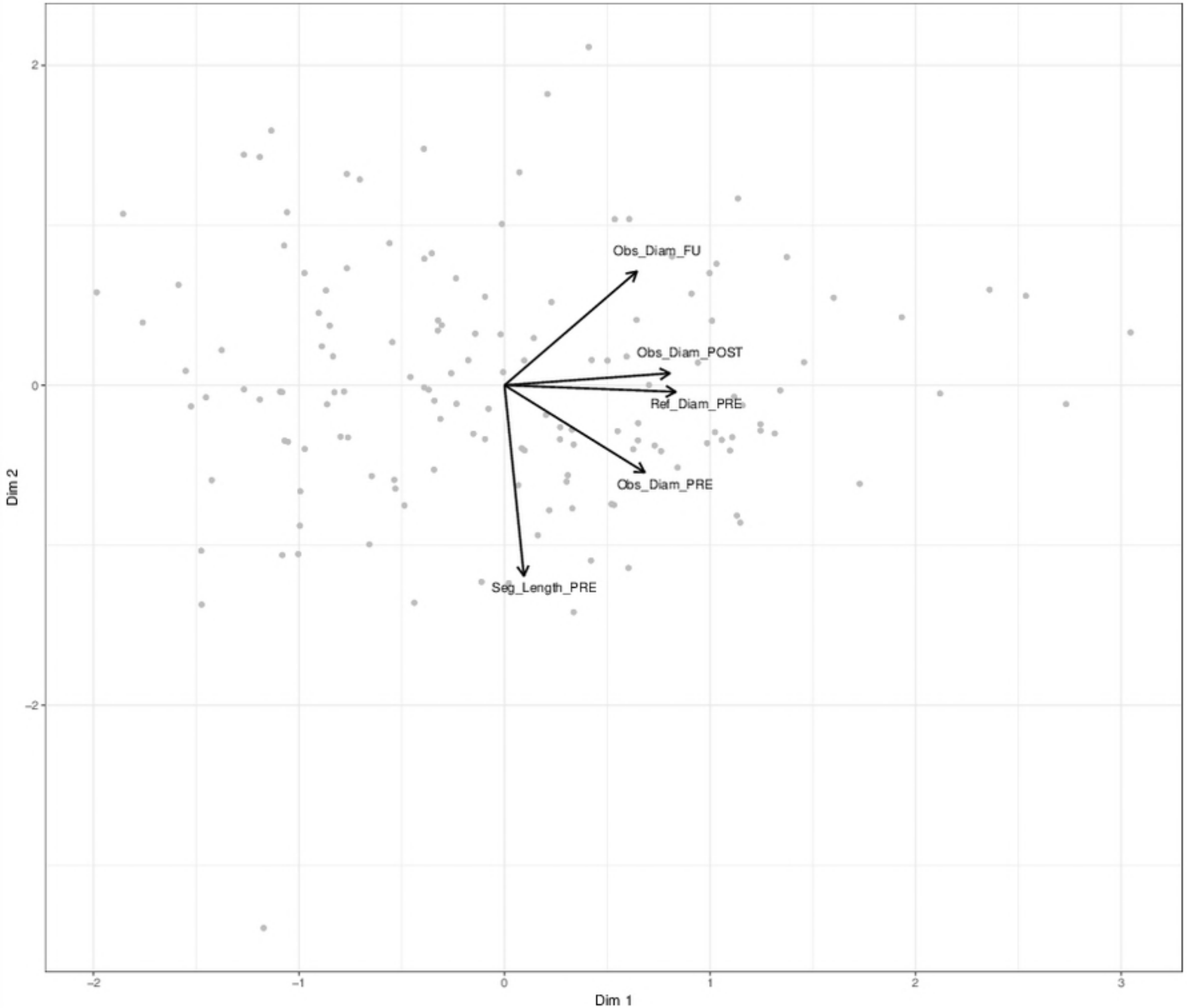
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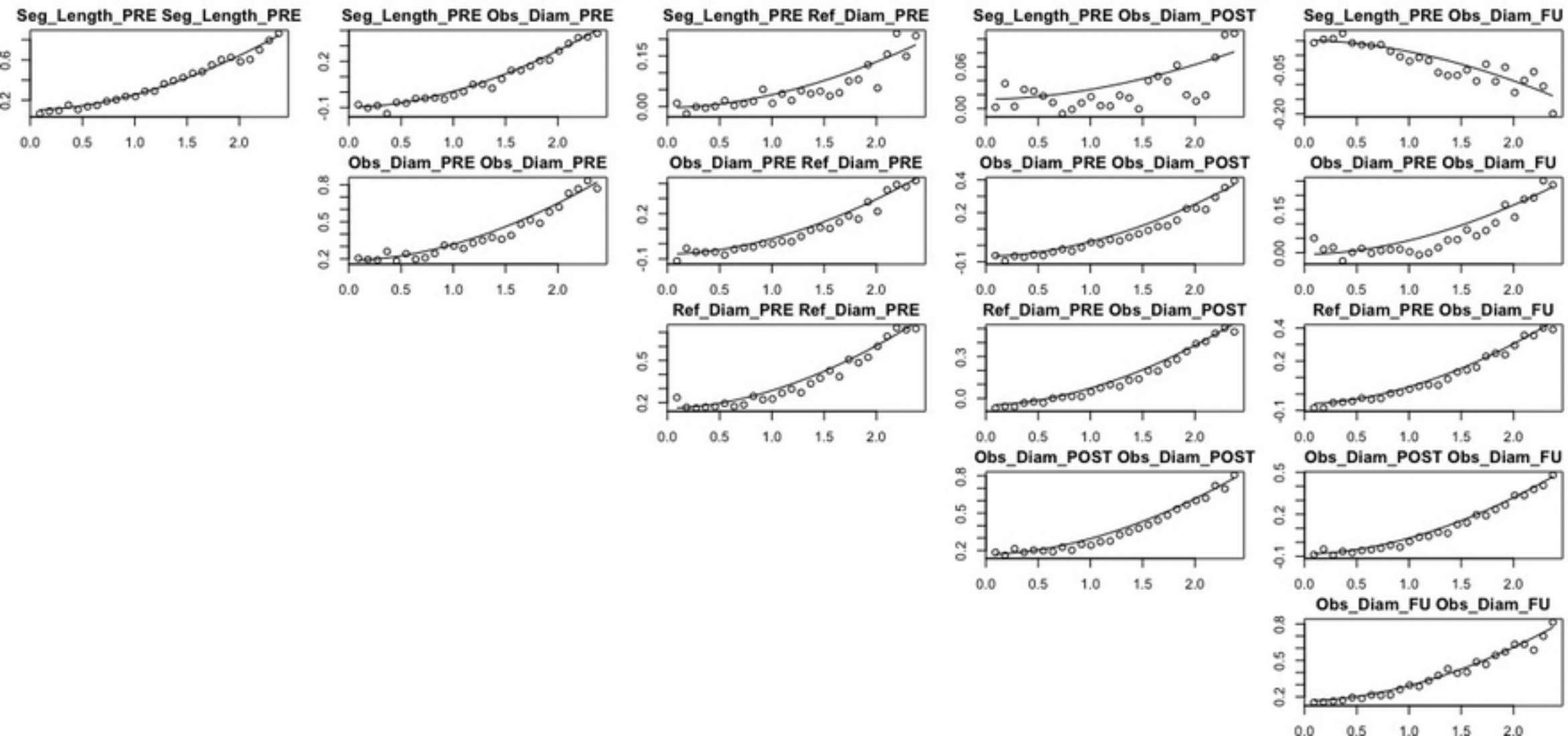
2
3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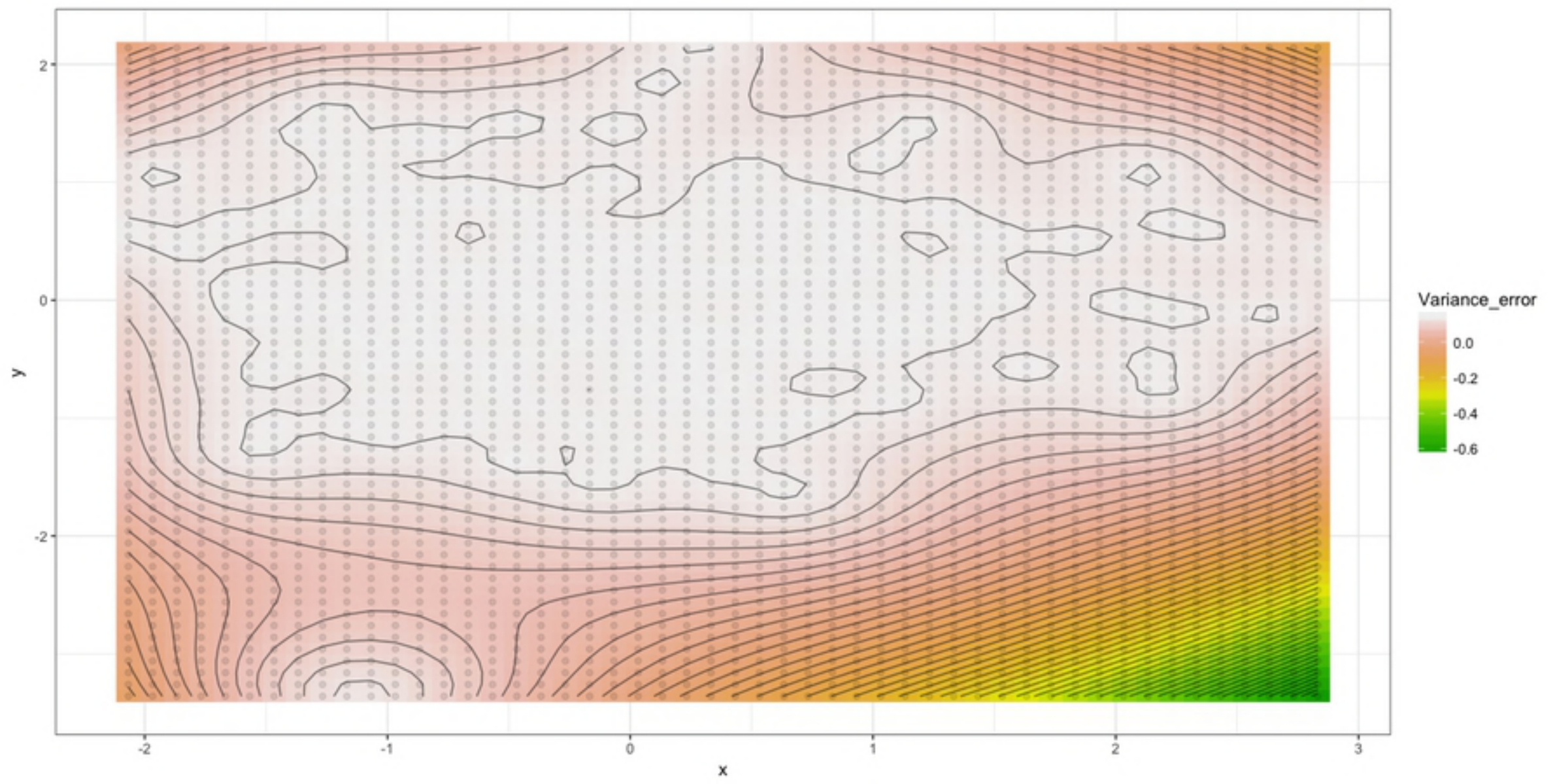
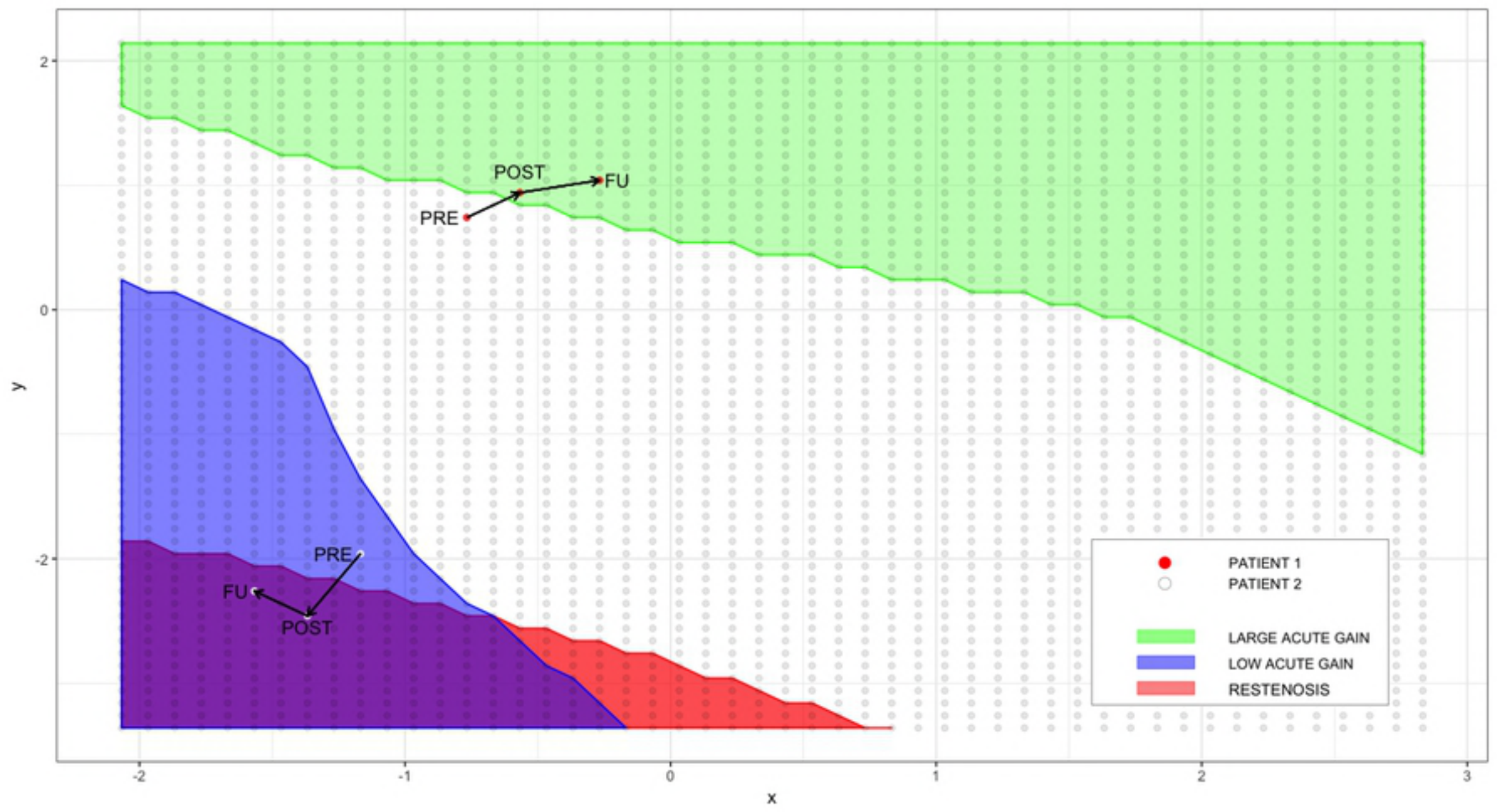
Seg_Length_PRE Obs_Diam_PRE
Seg_Length_PRE Ref_Diam_PRE
Seg_Length_PRE Obs_Diam_POST
Seg_Length_PRE Obs_Diam_FU
Obs_Diam_PRE Obs_Diam_PRE
Obs_Diam_PRE Ref_Diam_PRE
Obs_Diam_PRE Obs_Diam_POST
Obs_Diam_PRE Obs_Diam_FU
Ref_Diam_PRE Ref_Diam_PRE
Ref_Diam_PRE Obs_Diam_POST
Ref_Diam_PRE Obs_Diam_FU
Obs_Diam_POST Obs_Diam_POST
Obs_Diam_POST Obs_Diam_FU
Obs_Diam_FU Obs_Diam_FU


Variance_error
0.0
-0.2
-0.4
-0.6
y
2
0
-2
x
-2
-1
0
1
2
3


POST
FU
PRE
PRE
FU
POST
PATIENT 1
PATIENT 2
LARGE ACUTE GAIN
LOW ACUTE GAIN
RESTENOSIS
y
x
2
0
-2
-2
-1
0
1
2
3