Bayesian modeling of the placebo response in neuropathic pain.

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Introduction and Motivations

In analgesia randomized clinical trials (RCTs), the magnitude and the variability of the placebo response have a negative influence when testing the statistically significant superiority of active compounds compared to placebo.

The individual characterization of the placebo response is thus an important challenge.

Study Design and Patients

Two similar studies:

- Total 87 Peripheral Neuropathic Pain patients (30 + 57);
- Randomized patient-blind studies;
- 4 weeks of placebo treatment b.i.d. as add-on therapy;
- Placebo presented as new investigational drug named T4P1001.

Baseline patient data (X):

- Baseline pain measurements;
- Demographics;
- Medical history and concomitant medication;
- Psychological traits.

Placebo response (y):

- Reduction from baseline of the weekly mean of daily average pain score (APS).

Bayesian Modeling with Gaussian Process

A Gaussian process is a generalization of a multivariate Gaussian distribution to infinitely many variables.

$$f(x) \sim \mathcal{GP}(m(x), k(x, x'))$$

We modeled the placebo response y as a Gaussian Process:

$$y = f(x) + \epsilon, \quad \epsilon \sim \mathcal{N}(0, \sigma^2)$$

The joint distribution of the observed response y and the prediction targets f_* became:

$$\begin{bmatrix} y \\ f_* \end{bmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} K(X,X) + \sigma^2 I & K(X,X_*) \\ K(X,X_*) & K(X_*,X_*) \end{bmatrix}\right)$$

The posterior distribution of the placebo responses of new patients was estimated with:

$$f_* | X_*, X, y \sim \mathcal{N}\left(K(X_*,X)\left[K(X,X)+\sigma^2 I\right]^{-1} y, \; K(X_*,X_*) - K(X_*,X)\left[K(X,X)+\sigma^2 I\right]^{-1} K(X,X_*)\right)$$

To keep the interpretability of the model, a linear kernel was used as covariance function, k(x, x').

Model Validation

The model was tested in Monte Carlo cross-validation (or repeated random sub-sampling). We repeated 200 times the following steps:

1. Draw 90% of the samples uniformly at random (w/o replacement) as a training set $\{X_t, y_t\}$.
2. On the training data $\{X_t, y_t\}$:
   - Perform a recursive feature elimination (RFE).
   - Learn a gaussian process model.
3. Test the model on the 10% remaining samples (validation set).
4. Compare the actual placebo responses with the model predictions.

The average performances on the validation sets are reported.

Results

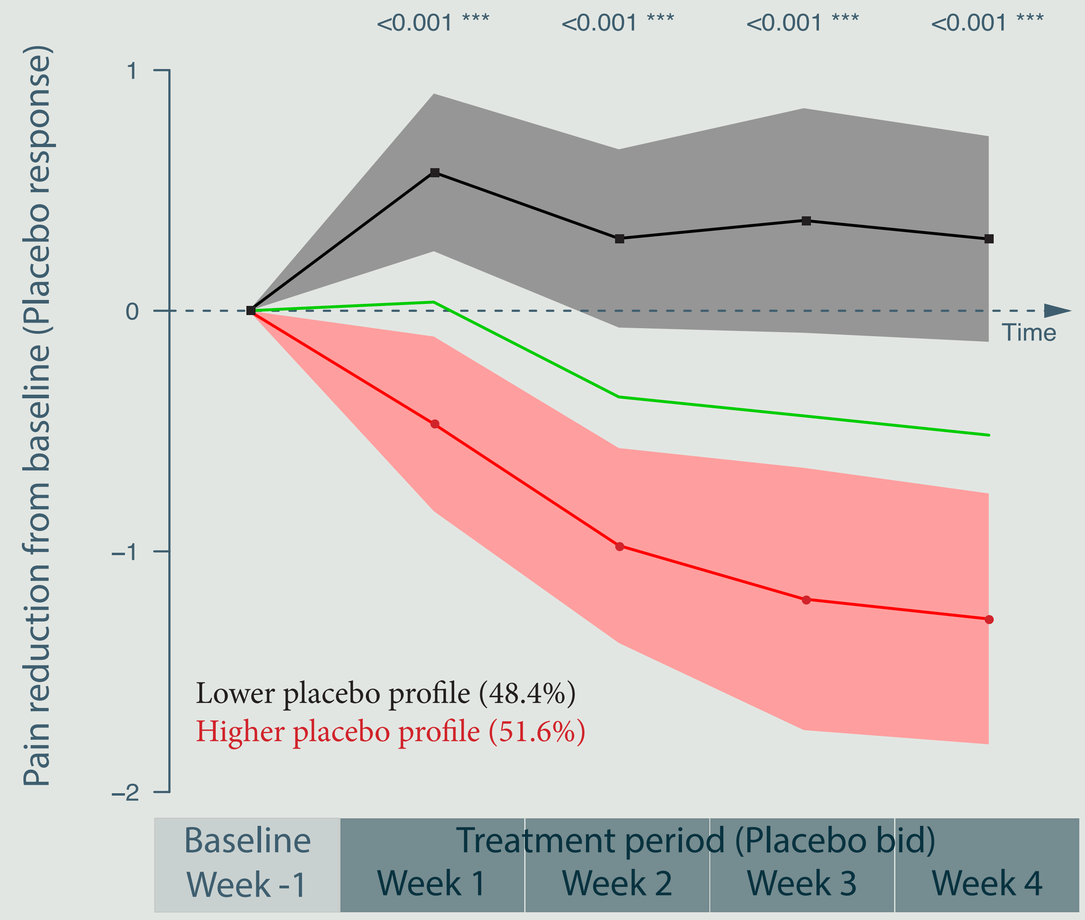
The model predictions were significantly correlated with the observed placebo responses:

	Estimate	95% CI	p-value
Nb features	9	-	-
Pearson's correlation	53.9%	[0.370,0.673]	<0.001
R-squared	29.0%	[0.137,0.453]	<0.001
Kuncheva Index	0.84	-	<0.001

On the test data, we defined two **predicted** placebo profiles:

- f (x) < mean(y) : Lower Placebo
- f (x) ≥ mean(y) : Higher Placebo

The pain evolution of those two groups was significantly different.



Conclusion

We were able to predict the placebo analgesia response on peripheral neuropathic pain patients.

The prediction was performed with baseline data only.

A significant difference was observed in the pain evolution of the predicted placebo responders.

We were able to explained almost 30% of the placebo variance.

Perspectives of the placebo modeling in RCTs

In peripheral neuropathic pain, the individual placebo response predicted at baseline could be used as a covariate in the statistical analyses.

The use of this covariate could reduce the impact of the placebo variance leading to :

- 20% increase in effect size;
- increased study power;
- or 30% reduced sample size.

This predicted covariate could also be used to stratify patients from their placebo profiles. This stratification may reduce the impact of this major confounding factor.