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## Why should prediction discrepancies be renamed Standardized VPC ?

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We have read the paper by Wang and Zhang<sup>1</sup>. We are pleased to see that other authors further illustrate and also find nice properties for an evaluation tool that we first used more than ten years ago<sup>2</sup>, presented at PAGE in 2000<sup>3</sup> and published extensively first in 2006<sup>4</sup>. However we disagree with some of the conclusions made by the authors, and we feel that an important reference should have been included in their manuscript.

As Wang and Zhang point out themselves, what they call SVPC is nothing other than the prediction discrepancies (pd) named that way, after being called pseudo-residuals by Mentré and Escolano in 2006<sup>4</sup>. It is therefore misleading to present SVPC as something novel when in fact it goes back on something that our group has published and presented in conferences.

Plots of SVPC versus time in the paper by Wang and Zhang<sup>1</sup> are very similar to plots of pd versus time in Mentré and Escolano<sup>4</sup>, therefore we disagree with the statement on page 2 that "Neither pd nor npde was intended/recommended for evaluation of model predictions over a time course". pd and npde were developed for their improved statistical properties over linearisation-based residuals but are used as visual diagnostic tools in a similar way.

Also the paper is not complete when it comes to the current state of literature. Wang and Zang<sup>1</sup> missed one important reference, in which we have compared pd, npde, VPC, as well as tests based on prediction intervals with or without decorrelation<sup>5</sup>. We have also proposed tests for covariate models illustrating how npde can be used to evaluate covariate models. Their paper is rather inaccurate when comparing the properties of the pd to those of the npde. The idea behind the npde, as recalled in the paper, is to decorrelate observations within individuals. In Mentré and Escolano<sup>4</sup>, it had been shown that the type I error of the test based on pd was inflated when subjects contribute several observations, because of the within-subject correlation between observations, and it was anticipated that the decorrelation would improve this feature. Indeed, in Brendel et al.<sup>5</sup> we have shown that the type I error of the npde is close to the expected 5% while the type I error for the pd or the test based on prediction intervals of the VPC was larger. In that paper, we performed a full simulation study, i.e. with several replications of the simulated data set, while in the manuscript of Wang and Zhang only one simulated dataset is given, from which it is very hard to draw meaningful conclusions. It is quite possible that for one simulated dataset the pd detects something that the npde does not, indeed, our simulations have shown that on a large number of simulated datasets, the tests with npde maintain type I error while the tests with pd have an increased type I error and hence a higher power. A discussion of the power to detect model misspecification should therefore take into account the increase in type I error under the null hypothesis. Also in their table V, there was a significant departure from 0 of the mean npde for the wrong model ( $p=0.03$  with a Wilcoxon test).

We would also like to take this opportunity to mention that more informative VPC graphs have been proposed by Wilkins<sup>6</sup> *et al* in 2006, which use prediction intervals around the simulated percentiles, and that we have adapted these graphs to pd and npde<sup>7</sup>. In that paper, we made a case

of using pd instead of npde to plot diagnostic graphs because the decorrelation tends to blur the relationship with time when used for visual diagnostics.

Finally, we join Wang and Zhang to stress the nice properties of simulation-based model evaluation tools such as pd (SVPC) over VPC and to encourage readers to use them.

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