Letter to the Editor

Goodness-of-fit of the fractal dimension as a prognostic factor

To the Editor,

One of the most important tasks in quantitative pathology is to elaborate methods which help to improve diagnosis [2,3,6,7,9,12,16,20] or prognosis [1,3–5,8–11,14,15,17,19,21].

In a previous investigation we found that the fractal dimension (based on the Minkowski–Bouligand method extended to three dimensions) of nuclear chromatin was not a prognostic factor in patients with acute precursor B lymphoblastic leukemia [1]. When looking at the log–log plots (area versus ε) containing 30 points used to calculate the regression line, we noticed that in most of the cases the real values were not located very closely to the calculated linear regression. This prompted us to investigate, whether the goodness-of-fit of the regression line could be of prognostic value. Therefore we calculated the coefficient of determination, i.e., the R^2 value of the regression between the real and the estimated values on the y-axis. R^2 characterizes the goodness-of-fit of the regression line and is therefore an estimate of the "quality of fractality". It could be demonstrated that this goodness-of-fit is an independent prognostic factor for overall survival when applied to the chromatin texture of MGG-stained routine bone marrow smears of patients with acute precursor B lymphoblastic leukemia [1]. Furthermore, it could be shown that this variable is relatively robust against variations of the staining process [13].

We agree with the arguments of Prof. Albregtsen. Therefore we reanalyzed the data [1] in the following way: The fractal dimension (FD) was determined as described earlier: FD was estimated by the volume$/2\varepsilon$ (being ε the radius, varying between 1 and 30 pixels) of the non-planar structuring element in form of a ball. The linear regression was calculated in a log–log plot (area versus ε) containing 30 points. The difference between the "real" y value and its corresponding "$\hat{Y}$" on the regression line was called "res".

The square value of the correlation coefficient between "y" and "$\hat{Y}$" was called R^2 (the coefficient of determination).

Now we calculated the sum of the square values of the 30 residuals per case "Sum res^2". In a second step we determined the perpendicular residuals "res p", calculating in analogy the variable "Sum res p^2". In a third step the above mentioned point distribution was rotated so that the slope was at 45 degrees and then we calculated the coefficient of determination between "y" and "$\hat{Y}$", now called "R^2_{45}".

Finally the prognostic relevance of all these parameters was analyzed in univariate and multivariate Cox regressions ($p = 0.05$ for input and $p = 0.1$ for output, backward conditional step-wise selection), comparing them with established prognostic factors such as age, white blood cell count and MFI of CD45 (MFICD45).

Each of the new values entered as the mean value of 100 nuclei per case. "Sum res^2" was highly correlated with R^2 ($r = 0.99$; $p < 0.0001$), and also "Sum res p^2" with "R^2_{45}" ($r = 0.99$; $p < 0.0001$). In a linear multivariate regression R^2 could be calculated from the sum of the square values of perpendicular residuals, "Sum res^2" and the slope of the fractal dimension.

The coefficient of determination between R^2 and the slope was 0.337, and between R^2 and "Sum res p^2" it was 0.974. In a multivariate linear regression both slope and "Sum res p^2" entered the regression as independent significant variables the regression and together explained 99.1% of the variance of R^2. When combining slope and "R^2_{45}" in a multivariate linear regression, its coefficient of determination reached 0.9996.

Thus in our data set the influence of the slope (fractal dimension) on R^2 is very small. When recalculating the prognostic relevance regarding survival, in the univariate Cox-regressions, R^2 ($p = 0.049$), "R^2_{45}" ($p = 0.05$), "Sum res^2" ($p = 0.047$) and "Sum res p^2" ($p = 0.048$) were all significant prognostic factors. In the multivariate Cox regression, when tested together with well known prognostic factors, the final model was composed of "R^2_{45}", white blood cell count and MFICD45, whereas "Sum res p^2" and age had been eliminated. These results, obtained with an improved methodology, indicate that the "goodness-of-fit" of the regression line may be an interesting new variable for

the evaluation of the chromatin texture and thus are in agreement with our previous publication [1]. Yet confirmatory studies based on an independent data set are necessary in order to validate this new variable for the evaluation of texture [18].

In summary, the differences between our previous results and those obtained with the improved methodological approach as suggested by Prof. Albregtsen are small, nevertheless we cannot exclude that they could be important when analyzing another data set. Therefore we suggest that the "R_{45}^2" should be used in future investigations on the goodness-of-fit of the fractal dimensions.

Konradin Metze[a,*]
Irene Lorand-Metze[a]
Neucimar J. Leite[b]
Randall L. Adam[b]

[a]*Departments of Pathology and Internal Medicine Faculty of Medicine, University of Campinas – UNICAMP, 13081-970 Campinas-SP, Brazil*
[b]*Institute of Computing, University of Campinas – UNICAMP, 13081-970 Campinas-SP, Brazil*

[*]Corresponding author. E-mail: kmetze@pq.cnpq.br.

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