

Statistical analysis of labelling patterns of mammary carcinoma cell nuclei on histological sections

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In diagnostic histopathology, it is a routine application to use immunohistochemical stains to study the labelled pattern of tumour cell nuclei. Using such methods, it is possible to classify observed tumour cell nucleus profiles on histological sections in a binary manner into two categories, i.e. stained vs. unstained nuclei (labelled vs. unlabelled, positive vs. negative nuclei). In the domain of mammary cancer, a relevant immunohistochemical marker is the MIB-1 stain, which decorates specifically the nuclei of proliferating (dividing) cells, whereas the nuclei of nondividing cells are negative.

It is of scientific interest to find out whether the labelled nuclei are compatible with a random thinning of all nuclei. In this case, they would be generated from the mother process of all nuclei simply by random labelling (see [1], pp. 48–49). The reduced second moment functions $K(r)$ of the labelled and the unlabelled points would then be identical. The same would hold for the pair correlation functions $g(r)$. The alternative hypothesis is, that the second-order properties of the processes of the labelled and unlabelled points are systematically different.

Twenty cases of invasive mammary ductal carcinomas were studied. The planar coordinates of the tumor cell nuclei from two rectangular visual fields per case were recorded (384–1387 points per field, of which 3–27% were labelled). Subsequently, for each visual field the following investigations were performed by using GeoStoch, a Java-based open-library system, and with the software package *spatstat* [2, 3]:

- Estimation of the explorative summary characteristics $K(r)$ and $g(r)$
- Fitting of the parameters of a stationary Strauss hard core model to the observed point patterns
- Estimation of two distance-dependent Simpson indices
- Monte Carlo tests on the null hypothesis of random labelling

Significant differences between the mean K -functions and the mean g -functions of the labelled and the unlabelled nuclei were found. Moreover, the mean interaction parameter γ of the stationary Strauss hard core model was significantly higher for the labelled nuclei than for the unlabelled nuclei. The estimates of the two distance-dependent Simpson indices showed a tendency of the points towards a positive spatial correlation. In the Monte Carlo tests, the null hypothesis of random labelling was rejected for the majority of the visual fields.

These four lines of investigation led to the concordant conclusion, that the labelling of mammary carcinoma nuclei by MIB-1 does not simply result from a random labelling of the nuclei. The data suggest that the second-order properties of the point process of the labelled nuclei are significantly different from those of the unlabelled nuclei. The process of the labelled nuclei shows a higher degree of clustering (increased strength of interaction) than the process of the unlabelled points.

References

- [1] DIGGLE, P.J. (2003). *Statistical Analysis of Spatial Point Patterns*. Second edition. London, Arnold.
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- [3] MATTFELDT, T., ECKEL, S., FLEISCHER, F. AND SCHMIDT, V. (2007) Statistical modelling of the geometry of planar sections of prostatic capillaries on the basis of stationary Strauss hard-core processes. *J. Microsc.* (in press).