Simulations using real population data and known spatial distributions are required and we are already running some appropriate to (b) and (c).

Julian Besag (University of Durham): The authors are somewhat dismissive of other *ad hoc* methods concerned with spatial clustering in inhomogeneous populations. As regards the GAM of Openshaw *et al.* (1988), I have described elsewhere (Besag, 1989) an alternative that may have a more acceptable statistical basis. Note that the aim of such methods is to monitor a very large expanse of small administrative zones for evidence of particular clusters that may merit detailed investigation by case–control or other techniques, rather than as an end in itself.

The authors also mention traditional tests of spatial dependence (e.g. Moran (1948)) between quantities q_i calculated for each zone i. However, when the q_i depend on the populations at risk, as with observed-to-expected ratios, such tests are generally inappropriate. The standard reference or null distribution assumes either that the q_i are realizations of independent and identically distributed random variables or that any permutation of the q_i among the zones is equally probable. Neither assumption is relevant to a common underlying risk if, as is usual, the populations at risk differ substantially from zone to zone in a spatially structured manner. Suppose, for example, that rural zones generally have smaller populations than urban zones. Then the rural q_i are inherently more variable and will tend to include the most extreme observed values. Thus, the result of a significance test may merely reflect or be confounded with the urban–rural pattern of zones. As an example, see Kemp *et al.* (1985), where the q_i are ranks of observed-to-expected ratios, though it is perhaps unfair to quote a single reference. Note that analogous tests based on $q_i=0$ or $q_i=1$, according to whether zone i passes or fails a fixed level significance test for a prescribed common risk, are not invalidated for the same reason but may be inappropriate in practice because discreteness does not allow exact attainment of the significance level in each zone.

A more satisfactory reference distribution for tests of spatial dependence is obtained simply by allocating at random the total number of observed cases to zones according to their respective populations at risk; allowance for known demographic differences between zones can sometimes be included. Exact significance tests can be implemented using Monte Carlo sampling.

In regard to the authors' treatment of bivariate point patterns, I wonder whether Monte Carlo tests of association based on Voronoi neighbourhoods would be more powerful against the alternatives of interest.

Dr M. K. Clayton and Dr B. S. Yandell (University of Wisconsin, Madison): How do we check for clustering of cases when the population might be clustered or otherwise non-uniform? The authors' solution to this problem is neat and appealing. It has prompted several questions which we pose for further thought.

The authors have suggested that the method proposed is superior to fitting a compound Poisson process in part because it does not require advance knowledge of the age- and sex-specific density of the population. However, if we must find $3n_0$ or $4n_0$ suitably matched controls, is this really saving much effort over fitting a compound Poisson process? We ask this recognizing that, even if the answer is no, the technique proposed might still be preferred.

The primary focus of the paper is on the detection of clustering, but to what extent can the approach proposed be used to detect regularity generated by an inhibitory process? Is it as simple as declaring a sufficiently negative Z statistic as evidence of regularity? Which of the statistics T_k, T_{run} or T^{inv} would the authors recommend, if any? If indeed there is regularity in the spatial process, as well as clustering, each at a different scale, then can the tools proposed be used to detect this? Can other complex processes be detected, e.g. clustering at several 'scales'? Perhaps the latter can be studied by examining T_k over a range of k, but if the scales of the spatial process are related according to a Euclidean metric, rather than a nearest neighbour metric, then problems can arise.

Graphical techniques for identifying clusters can be developed using more computationally intensive methods. We could estimate the intensity of a general inhomogeneous Poisson process with Dirichlet tesselations and penalized likelihoods (Green and Sibson, 1978; Green and Yandell, 1985). Separate intensity estimates for cases $\mu(\cdot)$ and controls $\lambda(\cdot)$ would allow graphical comparison of the two surfaces, or regression of $\log \mu$ on $\log \lambda$. Covariates such as age and sex could be included in a natural way in a semiparametric model. Graphical aids based on this could augment the more efficient tests proposed by the authors.

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