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Measurement of genetic structure within populations using Moran's spatial autocorrelation statistics

(spatial patterns/population structure/dispersal/gene flow)

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ABSTRACT **Spatial structure of genetic variation within populations, an important interacting influence on evolutionary and ecological processes, can be analyzed in detail by using spatial autocorrelation statistics. This paper characterizes the statistical properties of spatial autocorrelation statistics in this context and develops estimators of gene dispersal based on data on standing patterns of genetic variation. Large numbers of Monte Carlo simulations and a wide variety of sampling strategies are utilized. The results show that spatial autocorrelation statistics are highly predictable and informative. Thus, strong hypothesis tests for neutral theory can be formulated. Most strikingly, robust estimators of gene dispersal can be obtained with practical sample sizes. Details about optimal sampling strategies are also described.**

Malécot (1) and Wright (2) originally demonstrated how limits to dispersal result in genetic isolation by distance within a continuous population. These results were expressed in terms of the *coefficients* of consanguinity and inbreeding, respectively, and they established many of the main features of how spatial structure depends on dispersal parameters. However, models that are directly applicable to spatial distributions of *genotypes* at a locus *per se* must also include the stochasticity inherent as individual genotypes successfully disperse, pair and mate, and reproduce. Inclusive modeling of these events in a (two-dimensional) continuous population is mathematically intractable (3–6); thus we must rely on Monte Carlo-type simulations that include this stochasticity, and which are expressed explicitly in terms of spatial and space–time distributions of genotypes. The dominant spatial features are large patches, areas containing mostly one homozygous genotype (7–10), and these features can be well characterized using spatial autocorrelation statistics. However, the statistical properties of spatial autocorrelation statistics in this context have not been characterized.

Genetic isolation by distance is a dynamic spatial—i.e., space–time—process that produces shifting patchworks of genotypes. To a large extent, population genetic processes should be treated in spatial or geographic contexts. Spatial structuring can strongly influence, and be strongly influenced by, most other important aspects of population genetics, including mating system, individual fitness, inbreeding, and the action of various forms of natural selection (see refs. 11 and 12). Spatial and geographic patterns of genetic variation have been a subject traditionally of great interest to genetics: recent major reviews include those by Endler (13), Bradshaw (14), and Nagylaki (6).

The resurgence of theoretical work on spatial structure has been coupled with experimental studies of spatial structure using spatial autocorrelation statistics (introduced primarily through the work of R. R. Sokal and colleagues; see refs. 11 and 15–17). Indeed, the numbers of experimental studies using spatial autocorrelation statistics to study the distributions of genetic variation within populations continue to increase (see refs. 18–25). Analyses based on spatial statistics have been highly powerful, even in cases where there is little structure (26, 27).

It has been recently suggested (28, 29) that the statistical power and utility of spatial autocorrelation statistics for inferring processes are minimal, and that the statistic F_{st} should be used instead. However, there are fundamental differences between spatial autocorrelations and F_{st}. Values of F_{st} measure the spatial *variance* in gene frequencies. Spatial autocorrelation statistics measure aspects of spatial *patterns*. F_{st} statistics require averaging or lumping together subpopulations at one or more hierarchical levels, but they do not utilize the genetic information from all pairs of locations, unlike spatial statistics. Moreover, population processes such as migration do not generally act through hierarchical pathways; rather they act through spatial proximity. In the few field studies where both statistics were calculated, F_{st} values for the data failed to indicate significant structure whereas spatial autocorrelation statistics did (25, 30). Slatkin and Arter (28) showed that when the spatial scale of sampling is near the scale of spatial patterns, the ability to make inferences based on Moran's *I*-statistics was limited in a system of discrete populations. However, Moran's *I*-statistics are especially useful in cases where the spatial scale of sampling is within the context of a larger spatial pattern (12)—indeed this is implicit in the definition of "spatial autocorrelation" (31). As noted by Sokal and Oden (32), Slatkin and Arter omitted first and second spatial order neighbor populations from their analysis, which means the scale they sampled on was too large (12). When smaller distances are considered, the *I*-statistics in systems of discrete populations are highly statistically powerful and have small standard deviations (33).

In this paper, we characterize for a broad range of conditions the statistical properties of spatial autocorrelation statistics as measures of spatial structure within populations. We focus on the "quasi-stationary" phase. Naturally, it is unwieldy to consider all contingencies in a single study. For example, one potentially important (here unstudied) factor may be heterogeneities in the distributions of individuals, although mild degrees of such heterogeneity are probably partially absorbed in the various sampling schemes in this study. Another possibly important factor is anisotropy in dispersal rates, which are not studied here (but see, for example, ref. 13). Previous studies (9) showed that patch structure develops within 50 generations and persists for very long periods, at least several thousand generations (10, 34, 35). Statistical power may depend on (*i*) the actual population structure, (*ii*) the size of the sample taken from such populations, and (*iii*) aspects of the spatial scale and orientation, or spatial distribution, of the sample points over the populational surface. In this paper we use a wide range of sampling methods that cover the range of

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virtually all cases that would be appropriate under field conditions—i.e., the minimum and maximum likely sample sizes with careful consideration of appropriate spatial scales of sampling (12).

METHODS

Simulations of Populations. The FORTRAN program detailed by Epperson (10) was used to conduct the simulations. The program uses standard Monte Carlo methods for stochastic models. A sequence of random numbers is used to actualize dispersal, mating, and Mendelian segregation. Each simulated population consists of 10,000 individuals, with diploid genotypes, located on a 100 × 100 square matrix or lattice. Simulation runs that share the same values of parameters were replicated in sets of 100. Each population was initially generated by randomly choosing genotypes with probabilities that were binomial square proportions of the input allele frequencies, which were set at 0.5. The life cycle was repeated 200 generations for each simulation. It has been demonstrated that for many cases the primary and long-persisting spatial features of population genetic spatial structures are repeated several times within the area covered by simulated populations with size 10,000 (8–10, 34, 35).

Sets with a wide range of dispersal levels were simulated. Either or both the female and male parents of an offspring were chosen at random [using two Uniform (0, 1) pseudorandom numbers to choose its two coordinates] generally from one of the nearest N_f and N_m (respectively) neighbors including self. Thus, here each individual within the group of size N_f and N_m had equal chances of being the female or male parent, respectively. We ran a total of 1300 simulations; 100 for each of 12 different dispersal models with different values of N_f and N_m (Table 1), plus the random case.

Sampling Simulated Populations. Characterizations of a single generation from about generation 50, to several thousand, are adequate, because of the quasi-stationarity phenomena (9); it is more meaningful to replicate over entire simulations rather than over generations. We arbitrarily chose generation 200. At generation 200, each simulated population was sampled in 23 different ways. The sampling schemes varied according to 14 different combinations of the total number of individuals in the population area sampled and the "porosity" of sampling (Table 2). Porosity is the proportion of the total number that are actually sampled from the population of individuals covered by a sample area (this is also the population density per unit area—in simulations this is 1.0—divided by the square of the physical distance between nearest sample lattice points). Thus a sample lattice was superimposed onto a simulated population surface of genotypes. Note that porosity affects the spatial scale of sampling as well as the total size of the sample (Table 2). This range of sampling schemes covers and extends beyond those delineated as rough guidelines for sampling for a realistic range of sample sizes and appropriate spatial scales (12). For porosity equal to 1, all individuals in the sample area are sampled. For the nine combinations of area and porosity where porosity was not equal to 1, the sampled individuals were chosen in two distinct manners: of these the first set of nine sampling schemes involved sampling in the form of a fixed regular sample lattice; for the second, exact sample sites were chosen stochastically from the neighbors of the fixed original "sample" lattice points (thus adding 9 sampling designs to the 14, for a total of 23).

Next for each of the sampling schemes the chosen individuals were grouped into quadrats. Three different quadrat sizes were used: 25 individuals (5 by 5); 9 individuals (3 by 3); and 4 individuals (2 by 2). Note that the size of the quadrat also affects the spatial scale as well as the number of sample quadrats. In total, then, 69 different quadrat sampling configurations were conducted (Table 2). However, results for the 27 with stochastic sampling are not listed because they were virtually identical to those with fixed lattice sampling.

For each set of samples of quadrats, the allele frequencies, q_i, in each quadrat i were calculated and recorded along with quadrat location in a matrix or lattice of quadrats, also referred to as a gene frequency surface. To calculate Moran's I-statistics, all pairs of quadrats were grouped by the Euclidean distances between the quadrat centers. Thus distance class k contained all pairs of quadrats that were separated by $k - 0.5$ to $k + 0.5$ quadrat lengths. Moran's I-statistics, I_k, were calculated for each distance class k. We calculated the test statistic $(I - u_1)/\sqrt{u_2}$ (where u_1 and u_2 are the expected value and variance under the randomization null hypothesis, H_o, that there is no spatial autocorrelation), which statistic has an approximate standard normal distribution under H_o (31). Results are not shown for tests of entire I-correlograms, because the appropriate maximum distance classes vary widely among sampling schemes, which makes comparisons among sampling schemes unwieldy. Moreover, the distribution of entire correlograms is complex and unknown when structure is present (36).

We also characterized observed values of the statistic, F_{st}, calculated in the traditional way, as well as the less-biased estimator θ (37), of the theoretical F_{st}, and the jackknife variances for θ, for the quadrat size 25 sampling schemes for the abovementioned I-statistic analysis. The statistical significance of values of θ was assessed by whether or not a 95% confidence interval, calculated directly from the distribution of the jackknife estimates (37) overlapped with zero.

RESULTS

Fig. 1 shows the means for Moran's I-statistics for the complete sampling scheme (porosity 1, fixed sampling, total population area) for quadrat sizes of four individuals. These values are very representative of the results. Decreases in the size of the populational area sampled—i.e., the numbers of quadrats—scarcely changed the mean values of I (Table 3). The only exceptions occurred where the total number of quadrats, and thus the population area sampled, was small relative to the spatial patch size; however, as noted, such samples are not expected to be useful. For example, for porosity 1 and quadrat size four, for set 1 the mean values are 0.56, 0.55, 0.54, 0.53, and 0.49 for sizes of sample areas 10,000, 5000, 2500, 1250, and 625, respectively. Moreover, the effect of porosity was to shift the value of I to the value for the analogous distance class on an absolute (i.e., equal to the square root of the product of quadrat size and porosity) scale (Table 3), as may be expected

Table 1. Dispersal parameters in the various sets of simulations

	Simulation dispersal model*											
	1	2	3	4	5	6	7	8	9	10	11	12
N_f	1	9	1	25	1	49	81	121	1	225	1	625
N_m	9	9	25	25	49	49	81	121	225	225	625	625
N_e	4.2	8.4	12.6	25.1	25.1	50.2	83.7	125.7	115.2	230.4	316.2	632.4

*N_f and N_m are the numbers of nearest female and male individuals from which parents of an offspring are randomly chosen, and N_e is Wright's neighborhood size.

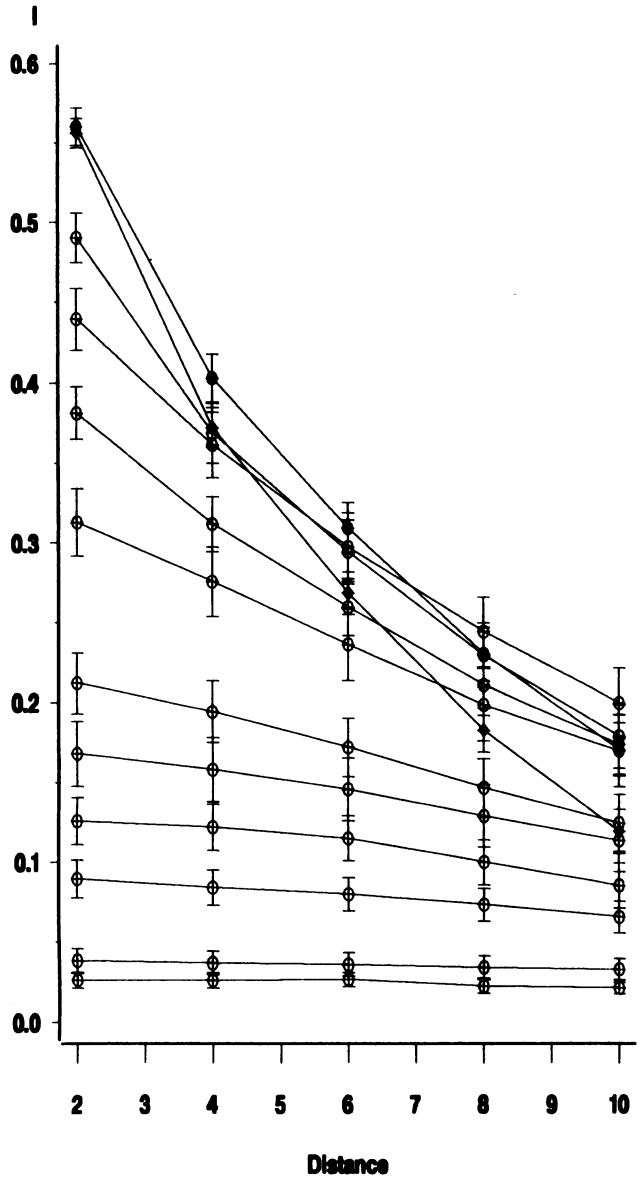

FIG. 1. Graphs of average Moran's autocorrelation statistics (I) for genetic correlations as a function of spatial distance, for sets of 100 replicate simulations. Each set had different amounts of dispersal (see Table 1). Unique symbols are assigned for sets 1 (◇) and 2 (●). All other sets are such that they have succeedingly smaller values for distance class one, except that sets 4 and 5 (same value of neighbor size) have switched ranks. Statistics were calculated for the finest sampling ("porosity" equal 1.0; see text), with each quadrat containing four individual genotypes at a locus. Error bars represent ± 1.0 standard errors, as calculated for 10 simulations (analogous to errors for the average I-statistic for 10 loci).

because of the corresponding increase in spatial scale of sampling. For example, for quadrat size four, mean values for I for the first distance class for set 3 for porosities 4, 9, and 25 (0.36, 0.27, and 0.18) correspond to those for porosity 1 with absolute distance classes 4, 6, and 10 (0.37, 0.29, and 0.18; Table 3 and Fig. 1), respectively. These effects of porosity and sample area were generally true for all distance classes (results not shown), for all dispersal models.

Moran's I-statistic for distances of one quadrat unit generally had small standard deviations (SDs) among the 100 simulations for each set, for each sampling scheme. For example, for full sampling at the first distance class, for quadrat size nine, the SDs were 0.037, 0.043, 0.057, 0.059, 0.065, 0.080, 0.082, 0.092, 0.076, 0.062, 0.044, and 0.029, respectively, for dispersal models 1–12, and for quadrat size 25 they were 0.049, 0.054, 0.072, 0.070, 0.074, 0.092, 0.093, 0.114, 0.101, 0.093, 0.086, and 0.060. Moreover, the SDs follow a simple relationship. For low-to-moderate amounts of dispersal, generally SDs for sampling schemes with smaller numbers of quadrats (but same porosity), n, fit very closely with the function: $SD_{full}\sqrt{n_{full}/n}$, where SD_{full} and n_{full} are the SD and number of quadrats for the full sampling scheme. As an example, consider set 1: for porosity 1, the SD for one-fourth of the total population was 0.064 or approximately twice that for full sampling, 0.030; the SD for one-sixteenth of the population was 0.0116, almost exactly four times that of the full sampling case. For higher amounts of dispersal, the SDs increased even more slowly with decreasing numbers of quadrats. These simple relationships also simplify expectations for application to field studies. In addition, Fig. 1 shows that the standard errors expected for an average I-statistic for 10 simulations (analogous to averaging over 10 loci in a real population) are small.

Table 2. The sample sizes in terms of sampled individuals for various sampling schemes from the simulated populations

	Area*		
Porosity†	10,000	5000	2500
1	10,000	5000	2500
1/4	2,500	1250	625
1/9	1,089	544	272
1/25	400	200	100

Samples of total populational numbers 1250 and 625 were taken for porosity equal to one. In addition, sampled individuals were grouped into quadrats of sizes 4, 9, or 25, depending on sampling schemes.
*The total number of individuals in the population that the entire sample lattice covered.
†Porosity is the proportion of total population individuals that were sampled (before forming quadrats).

Moran's I-statistic for distances of one quadrat unit generally had very high statistical power (usually 100% of sample statistics were significant at the 5% level) for population areas as small as 2500. The values decreased somewhat but were still at respectable rates (70–100%) for the smallest population area (625) for very high levels dispersal, N_e over 200. Moreover, I-statistics for short distances have small SDs. Naturally, the average values and the power dropped off as the distance of separation increased. However, it is only when the scale of the smallest distance class (roughly the square-root of porosity, on the quadrat scale) was near the x-intercept (the distances at which I-correlograms take the value zero) that the "statistical power" was low. Based on well-known theoretical results (see ref. 12), this was the sample scale situation for the I-statistics reported in Slatkin and Arter (28). Values for distances near the x-intercepts were also more variable.

We found very high positive biases of F_{st} over θ (results not shown), the latter being a "less biased" measure of the partition of genetic variation (37). Even θ was biased for 100 simulations and 23 sampling schemes of truly random sampling, where the expected value of F is zero. Moreover, we found that a standard method of constructing confidence intervals based on jackknifing over populations (37) (jackknifing is required for single locus estimates) rejected the null hypothesis from 4% to 47%, with an average of 21.5%, (if cases where there were only 4 sample quadrats are excluded, then the range is from 10% to 47%, with an average of 23.4%) of the samples even when the null hypothesis was true. This inflation invalidates the use of these tests. We obtained similarly high rejection rates for an approximately normal test statistic based on F_{st}. With these kinds of inflated "apparent" rejection rates it is meaningless to try to measure the statistical power function under alternative hypotheses: only upper bounds of the true rejection rates can be obtained. In contrast, Moran's I-statistics were very well-behaved, and over various

Table 3. Average value of Moran's *I*-statistics (×100) for different sampling schemes and the various dispersal levels

			Dispersal model											
Qsize*	Poro†	Area*	1	2	3	4	5	6	7	8	9	10	11	12
4	1	10,000	56	56	49	38	44	31	21	17	13	9	4	3
	4	10,000	40	41	36	29	35	27	19	15	12	8	3	2
	9	10,000	28	32	27	24	27	21	14	12	10	6	3	2
	25	10,000	14	20	18	16	19	15	10	8	8	5	2	1
	1	5,000	55	55	47	37	42	29	20	14	11	7	3	2
	4	5,000	40	39	34	28	33	24	17	12	10	6	2	2
	9	5,000	28	30	26	22	25	18	13	10	8	5	1	1
	25	5,000	12	16	16	14	16	12	7	5	4	4	0	0
	1	2,500	54	52	45	34	38	25	17	11	8	6	2	1
	4	2,500	38	35	29	25	28	19	13	8	7	4	1	1
	9	2,500	26	25	21	18	20	13	9	6	4	2	0	0
	25	2,500	9	9	9	8	10	6	1	0	0	−2	−4	−3
	1	1,250	53	50	43	31	34	23	14	10	6	4	2	1
	1	625	49	46	38	26	29	18	9	7	4	3	1	0
9	1	10,000	54	57	54	50	54	45	34	29	23	17	8	5
	4	10,000	35	39	38	36	40	34	26	23	19	14	7	4
	9	10,000	22	29	28	28	31	27	20	18	17	10	5	3
	25	10,000	7	11	12	13	17	14	10	8	7	4	3	−2
	1	5,000	53	55	52	48	52	42	32	25	20	14	6	5
	4	5,000	35	36	35	34	37	30	25	19	15	11	5	3
	9	5,000	21	24	25	24	27	22	16	14	12	7	1	2
	25	5,000	3	4	9	8	10	8	5	4	2	−1	0	−4
	1	2,500	51	51	49	44	46	36	27	19	14	10	4	3
	4	2,500	32	31	29	29	30	23	18	12	11	7	2	1
	9	2,500	14	16	15	14	17	12	7	5	4	2	−2	−3
	25	2,500	−7	−6	−7	−4	−5	−5	−7	−7	−10	−12	−10	−10
	1	1,250	48	48	46	39	40	33	24	17	11	7	2	2
	1	625	43	43	39	32	32	26	16	11	5	5	0	−1
25	1	10,000	45	51	53	54	56	54	48	45	40	32	18	13
	4	10,000	23	31	34	37	38	37	33	32	28	24	14	10
	9	10,000	10	15	18	22	24	22	19	18	16	12	5	3
	25	10,000	−3	0	3	4	7	10	6	6	6	3	1	−4
	1	5,000	45	49	49	52	54	50	45	39	35	27	15	11
	4	5,000	22	27	29	33	35	31	28	24	21	17	10	7
	9	5,000	7	7	12	15	16	15	12	11	6	6	−2	−1
	25	5,000	−10	−10	−5	−7	−3	−5	−3	−4	−5	−3	−8	−12
	1	2,500	42	44	45	47	46	43	38	30	27	19	9	7
	4	2,500	17	18	18	23	23	19	17	12	10	10	2	2
	9	2,500	−6	−5	−4	−3	0	−1	−6	−5	−6	−7	−12	−11
	25	2,500§	—	—	—	—	—	—	—	—	—	—	—	—
	1	1,250	38	38	40	40	38	39	32	26	21	14	5	5
	1	625	29	30	30	27	27	26	18	16	10	6	−1	−2

*The size of the quadrat samples in terms of number of sampled individuals in a quadrat.
†Porosity is the proportion of total population individuals that were sampled (before forming quadrats).
‡The total number of individuals in the population that the entire sample lattice covered.
§Values for this case are not valid because they are based on four quadrats, all pairs of which are in distance class one.

sampling schemes there was a range of 3–6% (with one exception at 10% which was based on only 4 quadrats) rejection rates, with an overall average of 4.89%. This is very near (and not statistically significantly different from) what the type I error should be, 5.0%. The average value of Moran's *I*-statistics was very near the expected values, $-1/(n-1)$, where n is the number of quadrats.

DISCUSSION

Our results are based on large numbers (1300) of simulations and sampling schemes (69 for each of the 1300 simulations, or 89,700 samples in total) for patterns of genetic variation within populations. We found that for most investigated cases of interest, *I*-statistics had high statistical power, and low stochastic and statistical variation. This was true even when sample sizes were quite small, as long as the spatial scale of sampling was smaller than the scale of spatial autocorrelation, as is typically advised (10–12, 15). The reason for this scale-dependency is that at large sampling scales the expected values of *I*-statistics are near zero. Slatkin and Arter's (28) result could be reproduced only when the scale of sampling was at least 50% of the scale of the spatial patterns. Moran's *I*-statistics are especially useful in cases where the spatial scale of sampling is within the context of a larger spatial pattern (10, 12); this is inherent in the definition of "spatial autocorrelation" (31). Slatkin and Arter sampled on too large a scale (12, 33). Results parallel to ours were found for systems of discrete populations (33).

The standard errors of *I*-statistics are small as long the total sample size (number of quadrats × number of individuals per quadrat) times the number of loci is on the order of 2000 (e.g., 125 four-individual quadrats for four loci), which is well within practical experimental ranges. Thus *I*-statistics provide two useful experimental tools. First, they provide robust expectations for neutral loci, if the amount of dispersal is known, and

thus a null hypothesis for neutrality; and the results also show that stochastic and sampling variation should result in minimal differences in autocorrelation statistics for all neutral loci in a multiple locus sample from a population (11, 38). Perhaps most strikingly, the results indicate that precise estimates of dispersal can be obtained from standing spatial genetic distributions within a population. With a properly designed sample of 2000 genotypes as discussed above, and using fairly small quadrats, estimates of standardized measures of dispersal (Wright's neighborhood sizes, N_e) can have precision to within a factor of 2 or less. This is quite precise compared with direct measures of gene dispersal, which are typically subject to many experimental errors that are difficult to control (39). Remarkably, this is true even when dispersal levels are very high (values of N_e of 600 or greater). Although the mean values of I-statistics decrease as N_e becomes large, the SDs are very small (high repeatability–low stochastic and statistical variation), which implies small standard errors in field studies.

An important issue is the size of quadrats. For small quadrats (e.g., four individuals), I-statistics for distance class one decrease monotonically with N_e, except for N_e in the range of 4–8. Completely monotonic decrease is observed for a quadrat size of one individual (34). This contrasts with earlier results based on quadrats of size 25 which decrease monotonically only when N_e exceeds 50 (40), and our results revealed intermediate behavior for quadrats of intermediate sizes. Experimentalists should choose the convenience of large quadrats only when dispersal is believed to be in the moderate to high range ($N_e > 50$).

Our results contribute methods for using I-statistics based on small numbers of individuals per quadrat, as providing robust and unbiased estimators of standardized measures of dispersal such as Wright's neighborhood sizes. Moreover, these should fit populations that have existed for more than a few dozen generations, because results demonstrate the quasi-stationarity phenomena (see refs. 10 and 40); a finding that reflects on Slatkin and Arter's hypothesis that such systems "are either at a stochastic equilibrium or they are not." Moreover, the size of quadrats can be decreased to arbitrarily small numbers of individuals, with beneficial effects on I-statistics; but not so for F_{st}. Join–count statistics and Moran's I-statistics for individual genotypes are the most powerful. In other work, we have found that total sample sizes must as much as 10 to 20 times as large in order for F-statistics to have power similar to autocorrelation measures based on individual genotypes, even though in these calculations we could use only the observed power of F_{st} as an upper bound, because it is inflated by biases toward rejecting H_o when H_o is true. The most efficient use of data for individual genotypes is join–counts or I-statistics, rather than combining individuals into subsamples, as required for the usual estimates of F_{st} or θ (which usually involves loss of information and statistical power). However, if it is necessary by experimental constraints to sample on a quadrat system, the smaller quadrat sizes perform better, especially considering constraints on total sample size. In sum, for studies of structure within populations, spatial autocorrelation statistics are more efficient and powerful than F_{st}. This is true for all of the cases studied, which cover the conditions of realistic sample size and recommended spatial scales based on logical considerations of the spatial scales of patterns produced by limited gene flow within populations.

Interestingly, our results also revealed some difficulties with using F_{st} in analyses of spatial structure and gene dispersal. The results showed that F_{st} is strongly biased (37). Slatkin and Barton (41) found that F_{st} was strongly biased also in systems of discrete populations, especially when dispersal is large. In addition, our results showed that, for the entire range of dispersal distances and sampling schemes, tests of significance of F_{st} rejected the null hypothesis at extremely high rates (up to 47%, with an average of 22%). In contrast, tests of significance of I-statistics based on the same simulated data rejected the null hypothesis at a rate (4.92%) not statistically different from the correct rate (i.e., the 5% level). The bias for the statistics F_{st} and θ is difficult to correct, because their distributions are unknown (37, 42). Moran's I-statistics have well-known actual and asymptotic distributions under the null hypothesis (31).

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