RESEARCH ARTICLE

The effect of genotyping errors on the robustness of composite linkage disequilibrium measures

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Abstract

We conclude that composite linkage disequilibrium (LD) measures be adopted in population-based LD mapping or association mapping studies since it is unaffected by Hardy–Weinberg disequilibrium. Although some properties of composite LD measures have been recently studied, the effects of genotyping errors on composite LD measures have not been examined. In this report, we derived deterministic formulas to evaluate the impact of genotyping errors on the composite LD measures Δ'_{AB} and r_{AB}, and compared the robustness of Δ'_{AB} and r_{AB} in the presence of genotyping errors. The results showed that Δ'_{AB} and r_{AB} depend on the allele frequencies and the assumed error model, and show varying degrees of robustness in the presence of errors. In general, whether there is HWD or not, r_{AB} is more robust than Δ'_{AB} except some special cases and the difference of robustness between Δ'_{AB} and r_{AB} becomes less severe as the difference between the frequencies of two SNP alleles A and B becomes smaller.

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Introduction

Linkage disequilibrium (LD) plays a fundamental role in genetic studies as a tool for gene mapping, delineation of the demographic history of populations, and testing hypotheses of human evolution (Pritchard and Przeworski 2001; Stephens *et al.* 2001). However, the level of linkage disequilibrium is often influenced by a number of factors, including genetic linkage, selection, the rate of recombination and mutation, genetic drift, nonrandom mating, population structure, and other nonbiological forces. For example, genotyping errors limit the full utility of LD-based methods (Akey *et al.* 2001). The measurement of LD, often based on pairs of loci, measure the departure of the joint frequency of pairs of alleles from two loci of a haplotype from their random pairing expectation. There are five commonly used measures of LD for disequilibrium mapping: the correlation coefficient r (Hill and Weir 1994), Lewontin's D' (Lewontin 1964), the robust formulation of the population attributable risk d (Levin and Bertell 1978), Yule's Q (Olson and Wijsman 1994), and Kaplan and Weir's proportional difference d (Kaplan and Weir 1992). A wide variety of studies have been performed for the property of the commonly used LD measures (Devlin and Risch 1995). For example, Akey *et al.* (2001) systematically investigated the effect that genotyping errors have on four commonly used LD measures—Δ', r, Q, and d—in studies of background LD. It should be noted that the classical LD measure rests on the assumption of Hardy–Weinberg equilibrium (HWE) (Weir and Cockerham 1979). But, in the local region with disease variants, Hardy–Weinberg disequilibrium (HWD) is generally expected in case and control samples (Wittke-Thompson *et al.* 2005). Therefore, some geneticists (Weir 1979; Schaid 2004; Zaykin *et al.* 2006) recommended using composite LD measures, which avoid the assumption of HWE. Although some properties of composite LD measures have been studied (Zaykin 2004), there has been no studies of the properties of composite LD measures in the presence of genotyping errors. Therefore, the purpose of this report is to demonstrate the impact of genotyping errors on composite LD measures, and compare the robustness of these measures when there is genotyping error.

Methods

Composite LD measures

Here we consider two SNPs '1' and '2' with codominant alleles A and a for locus 1, and, B and b for locus 2, respectively. The frequencies of alleles A, a, B, and b are given by

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P_A, P_a, P_B, and P_b, and the frequencies of genotype AA, Aa, aa, BB, Bb and bb are given by P_{AA}, P_{Aa}, P_{aa}, P_{BB}, P_{Bb}, and P_{bb}, respectively. Let P_{AB}, P_{Ab}, P_{aB}, and P_{ab} be the haplotype frequencies of AB, Ab, aB, and ab, respectively. Let $P_{/}$ be the joint frequency of alleles for loci 1 and 2 in two different gametes, for example, $P_{A/B}$ is the joint frequency of alleles A and B in two different gametes. The classical LD coefficient is $D = P_{AB} - P_A P_B$. The composite LD coefficient is defined as $\Delta_{AB} = P_{AB} + P_{A/B} - 2P_A P_B$. Let $P_{\dot{-}}$ be the sum of the allele frequencies for loci 1 and 2 in two different gametes and in two same gametes. For the sake of discussion, we also say $P_{\dot{-}}$ haplotype frequency, for example, we say $P_{\overline{AB}} = P_{AB} + P_{A/B}$ is the haplotype frequency of AB. Then, the composite LD coefficient is $\Delta_{AB} = P_{\overline{AB}} - 2P_A P_B$. The composite correlation is,

$$r_{AB} = \frac{\Delta_{AB}}{\sqrt{(P_A P_a + D_A)(P_B P_b + D_B)}}, \qquad (1)$$

where $\Delta_A = P_{AA} - P_A^2$ and $\Delta_B = P_{BB} - P_B^2$ are the HWD coefficients for loci 1 and 2, respectively. Zaykin (2004) gives the bounds for abs(Δ_{AB}) as:

$$\left\{\begin{array}{l} \max \Delta_{AB} = \dfrac{d-s}{2} + \dfrac{1}{2}(1-2P_A)(1-2P_B) \\ \text{where } d = \min(P_{AA}, P_{bb}) + \min(P_{aa}, P_{BB}) \end{array}\right\}, \quad \Delta_{AB} < 0,$$

$$\left\{\begin{array}{l} \max \Delta_{AB} = \dfrac{d-s}{2} - \dfrac{1}{2}(1-2P_A)(1-2P_B) \\ \text{where } d = \min(P_{AA}, P_{BB}) + \min(P_{aa}, P_{bb}) \end{array}\right\}, \quad \Delta_{AB} > 0,$$

and $s = 1 - d - \min(1-d, P_{Aa} + P_{Bb})$.

Then, the standardized composite LD measure is,

$$\Delta'_{AB} = \frac{\Delta_{AB}}{\max \Delta_{AB}} \qquad (2)$$

Genotyping-error model

Following Akey *et al.* (2001), we consider two models for genotyping errors: a stochastic-error model (SEM) and a directed-error model (DEM). In SEM, there is an equal probability u for alleles at a locus to be erroneously genotyped. On the other hand, in DEM, there is a greater probability for one allele to be consistently misgenotyped, here, A and B are misgenotyped as a and b respectively with probability u, and, a and b are misgenotyped as A and B respectively with probability 0.

Composite LD measures in the presence of genotyping errors

Let d denote the change in frequencies in the presence of errors, for example, the change in haplotype frequency of $P_{\overline{AB}}$ is: $dP_{\overline{AB}} = P'_{\overline{AB}} - P_{\overline{AB}}$, where $P'_{\overline{AB}}$ and $P_{\overline{AB}}$ are the haplotype frequencies of AB gametes in the presence and the absence of errors, respectively, and the change in genotype frequency of P_{AA} is: $dP_{AA} = P'_{AA} - P_{AA}$, where P'_{AA} and P_{AA} are the genotype frequencies of AA in the presence and the absence of errors, respectively. Table 1 provides the formulas for the change of haplotype frequencies, genotype frequencies, and gene frequencies for both the SEM and the DEM.

It can be seen that the change in frequency is a simple function of the genotyping-error rates at loci 1 and 2, and of the 'true' frequencies, in the absence of genotyping errors. Based on the formulas for the change in frequencies provided in table 1, we present the changes in composite LD measures in the presence of genotyping errors through differentiating the formulas (1) and (2) for the two composite LD measures:

$$dr_{AB} = r_{AB}\left[\frac{d\Delta_{AB}}{\Delta_{AB}} - \frac{1}{2}\left(\frac{d\tilde{P}_{Bb}}{\tilde{P}_{Bb}} + \frac{d\tilde{P}_{Aa}}{\tilde{P}_{Aa}}\right)\right], \qquad (3)$$

where $d\Delta_{AB} = dP_{\overline{AB}} - 2dP_A P_B - 2P_A dP_B$, $\tilde{P}_{Bb} = P_B P_b + D_B$, $\tilde{P}_{Aa} = P_A P_a + D_A$, $d\tilde{P}_{Bb} = P_B dP_b + dP_B P_b + dD_B$, $d\tilde{P}_{Aa} = P_A dP_a + dP_A P_a + dD_A$, $dD_A = dP_{AA} - 2P_A dP_A$, $dD_B = dP_{BB} - 2P_B dP_B$, $dP_a = -dP_A$, and $dP_b = -dP_B$.

and

$$d\Delta'_{AB} = \frac{d\Delta_{AB} \max \Delta_{AB} - \Delta_{AB} d\max \Delta_{AB}}{(\max \Delta_{AB})^2}, \qquad (4)$$

where $d\max \Delta_{AB} = \frac{dd-ds}{2} - dP_A(1-2P_B) - (1-2P_A)dP_B$ for $\Delta_{AB} < 0$ and $d\max \Delta_{AB} = \frac{dd-ds}{2} + dP_A(1-2P_B) + (1-2P_A)dP_B$ for $\Delta_{AB} > 0$.

Table 1. Change in frequencies in the presence of genotyping errors, for both SEM and DEM.

	SEM	DEM
Haplotype		
$dP_{\overline{AB}}$	$-2uP_{\overline{AB}} + uP_{\overline{aB}} + uP_{\overline{Ab}}$	$-2uP_{\overline{AB}}$
$dP_{\overline{Ab}}$	$-2uP_{\overline{Ab}} + uP_{\overline{ab}} + uP_{\overline{AB}}$	$-uP_{\overline{Ab}} + uP_{\overline{AB}}$
$dP_{\overline{aB}}$	$-2uP_{\overline{aB}} + uP_{\overline{AB}} + uP_{\overline{ab}}$	$-uP_{\overline{aB}} + uP_{\overline{AB}}$
$dP_{\overline{ab}}$	$-2uP_{\overline{ab}} + uP_{\overline{Ab}} + uP_{\overline{aB}}$	$uP_{\overline{Ab}} + uP_{\overline{aB}}$
Genotype		
dP_{AA}	$-2uP_{AA} + uP_{Aa}$	$-2uP_{AA}$
dP_{Aa}	$uP_{AA} - 2uP_{Aa} + uP_{aa}$	$uP_{AA} - uP_{Aa}$
dP_{aa}	$uP_{Aa} - 2uP_{aa}$	uP_{Aa}
dP_{BB}	$-2uP_{BB} + uP_{Bb}$	$-2uP_{BB}$
dP_{Bb}	$uP_{BB} - 2uP_{Bb} + uP_{bb}$	$uP_{BB} - uP_{Bb}$
dP_{bb}	$uP_{Bb} - 2uP_{bb}$	uP_{Bb}
Gene		
dP_A	$\left(dP_{\overline{AB}} + dP_{\overline{Ab}}\right)/2$	
dP_B	$\left(dP_{\overline{AB}} + dP_{\overline{aB}}\right)/2$	

Results

The effect that genotyping errors have on composite LD measures

We extensively explored how genotyping errors affect estimates of the composite LD using the formulas 1–4. Here, we first assume that both the HWD coefficients D_A and D_B are 0.08 for loci 1 and 2. Tables 2 and 3 present values of Δ'_{AB} and r_{AB} in the presence and the absence of genotyping errors over a broad range of allele frequencies for the SEM and the DEM, respectively. From tables 1 and 3, it can be seen that the composite LD measures have been affected profoundly by genotyping-error rates. For example, when $P_A = P_B = 0.9$ and $\Delta'_{AB} = 1$ in the absence of genotyping errors, a 3% error rate reduces Δ'_{AB} and r_{AB} to 0.68 and 0.75 for the SEM, respectively, and both to 0.84 for the DEM, respectively. Moreover, the robustness to genotyping errors increases with the minor-allele frequencies at SNP loci 1 and 2 increasing. It also can be seen that there are at least two differences between the two error models. The first is that the composite LD measure r_{AB} under the DEM is much more robust to genotyping errors compared to that under the SEM, except when the difference between the frequency of two SNP allele A and B is very large, for example, $P_A = 0.9$ and $P_B = 0.1$. The second is that, under the DEM, the values of Δ'_{AB} and r_{AB} are equal when $P_A = P_B$ and the values when $\Delta'_{AB} = 0.5$ is the half of those when $\Delta'_{AB} = 1$, whereas, under the SEM, the values of Δ'_{AB} and r_{AB} are equal only if $P_A = P_B = 0.5$ and the values when $\Delta'_{AB} = 0.5$ is half of those when $\Delta'_{AB} = 1$ and the minor-allele frequencies at SNP loci 1 and 2 are high.

Table 2. The effect that genotyping errors have on the composite LD measures under the SEM when the HWD coefficients are $D_A = D_B = 0.08$.

	LD when genotyping-error rate is							
	3%				5%			
P_B	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}
$P_A = 0.90$								
0.90	1.00	0.68	1.00	0.76	1.00	0.48	1.00	0.60
	0.50	0.22	0.50	0.25	0.50	0.14	0.50	0.10
0.50	1.00	0.64	0.42	0.36	1.00	0.41	0.42	0.33
	0.50	0.32	0.21	0.18	0.50	0.20	0.21	0.16
0.10	−1.00	−0.97	−1.00	−0.95	−1.00	−0.95	−1.00	−0.92
	−0.50	−0.50	−0.50	−0.46	−0.50	−0.49	−0.50	−0.43
$P_A = 0.70$								
0.90	1.00	0.58	0.63	0.47	1.00	0.31	0.63	0.36
	0.50	0.21	0.31	0.18	0.50	0.17	0.31	0.10
0.50	1.00	0.85	0.80	0.72	1.00	0.76	0.80	0.66
	0.50	0.40	0.40	0.34	0.50	0.34	0.40	0.30
0.10	−1.00	−0.75	−0.63	−0.57	−1.00	−0.60	−0.63	−0.54
	−0.50	−0.38	−0.31	−0.29	−0.50	−0.31	−0.31	−0.28
$P_A = 0.50$								
0.90	1.00	0.64	0.42	0.36	1.00	0.41	0.42	0.33
	0.50	0.32	0.21	0.18	0.50	0.20	0.21	0.16
0.50	1.00	0.91	1.00	0.91	1.00	0.85	1.00	0.85
	0.50	0.45	0.50	0.45	0.50	0.43	0.50	0.43
0.10	−1.00	−0.64	−0.42	−0.36	−1.00	−0.41	−0.42	−0.33
	−0.50	−0.32	−0.21	−0.18	−0.50	−0.20	−0.21	−0.16

Table 3. The effect that genotyping errors have on the composite LD measures under the DEM when the HWD coefficients are $D_A = D_B = 0.08$.

	LD when genotyping-error rate is							
	3%				5%			
P_B	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}
$P_A = 0.90$								
0.90	1.00	0.84	1.00	0.84	1.00	0.74	1.00	0.74
	0.50	0.42	0.50	0.42	0.50	0.38	0.50	0.38
0.50	1.00	0.71	0.42	0.38	1.00	0.53	0.42	0.35
	0.50	0.35	0.21	0.19	0.50	0.27	0.21	0.18
0.10	−1.00	−0.84	−1.00	−0.91	−1.00	−0.73	−1.00	−0.84
	−0.50	−0.42	−0.50	−0.45	−0.50	−0.36	−0.50	−0.42
$P_A = 0.70$								
0.90	1.00	0.71	0.63	0.56	1.00	0.58	0.63	0.52
	0.50	0.35	0.31	0.28	0.50	0.27	0.31	0.26
0.50	1.00	0.94	0.80	0.76	1.00	0.90	0.80	0.73
	0.50	0.47	0.40	0.38	0.50	0.45	0.40	0.37
0.10	−1.00	−1.00	−0.63	−0.60	−1.00	−1.00	−0.63	−0.58
	−0.50	−0.49	−0.31	−0.30	−0.50	−0.49	−0.31	−0.29
$P_A = 0.50$								
0.90	1.00	0.71	0.42	0.38	1.00	0.53	0.42	0.35
	0.50	0.35	0.21	0.19	0.50	0.27	0.21	0.18
0.50	1.00	0.96	1.00	0.96	1.00	0.93	1.00	0.93
	0.50	0.48	0.50	0.48	0.50	0.47	0.50	0.47
0.10	−1.00	−1.00	−0.42	−0.40	−1.00	−1.00	−0.42	−0.40
	−0.50	−0.49	−0.21	−0.20	−0.50	−0.49	−0.21	−0.20

Comparing the robustness of LD measures in the presence of genotyping errors

To compare which measure is more robust to genotyping errors, we consider the fractional true (FT) value λE/λT for the two composite LD measures similar to Akey *et al.* (2001), where λT denotes the true value of the LD measure in the absence of errors and λE denotes the value of the LD measure in the presence of genotyping errors. For example, the FT value of r_{AB} is r_{ABE}/r_{ABT}. Figure 1 plots the FT values for Δ'_{AB} and r_{AB} as a function of the genotyping-error rate for both the SEM and the DEM. Figure 1 shows that, as expected, the FT values decrease with the error rates increasing. Moreover, as mentioned above, genotyping errors that follow the DEM tend to be less severe compared to those follow the SEM for the measure r_{AB} except for $P_A = 0.9$ and $P_B = 0.1$. Whether a measure is more robust depends on the allele frequencies and the error model. The difference between Δ'_{AB} and r_{AB} becomes less severe as the difference between the frequency of two SNP allele A and B becomes small, and even equals 0 for the DEM.

We also explored how genotyping errors affect estimates of the composite LD if there is HWE. Table 4 present values

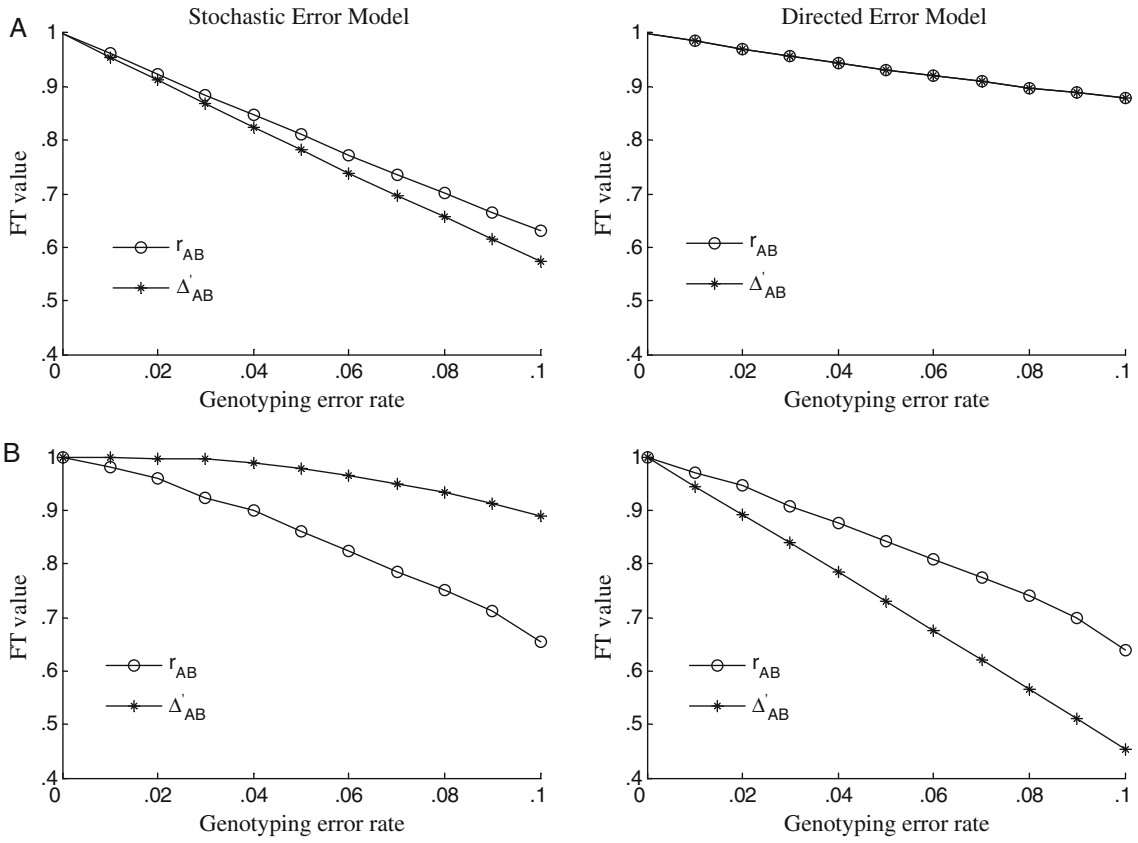

Figure 1. The effect that genotyping errors have on FT values. In panel A, $P_A = 0.6$, $P_a = 0.4$, $P_B = 0.4$, $P_b = 0.6$, $\Delta'_{AB} = 0.5$; in panel B, $P_A = 0.9$, $P_a = 0.1$, $P_B = 0.1$, $P_b = 0.9$, $\Delta'_{AB} = -0.5$.

Table 4. The effect that genotyping errors have on the composite LD measures when the HWD coefficients are $D_A = D_B = 0$.

	LD when genotyping-error rate is 3%							
	SEM				DEM			
P_B	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}	Δ'_{ABT}	Δ'_{ABE}	r_{ABT}	r_{ABE}
$P_A = 0.90$								
0.90	1.00	0.41	1.00	0.54	1.00	0.71	1.00	0.71
	0.50	0.14	0.50	0.15	0.50	0.36	0.50	0.36
0.50	1.00	0.64	0.66	0.51	1.00	0.71	0.66	0.55
	0.50	0.32	0.33	0.25	0.50	0.36	0.33	0.27
0.10	−1.00	−0.94	−1.00	−0.92	−1.00	−0.66	−1.00	0.83
	−0.50	−0.49	−0.50	−0.45	−0.50	−0.33	−0.50	0.42
$P_A = 0.70$								
0.90	1.00	0.60	0.65	0.38	1.00	0.77	0.65	0.53
	0.50	0.19	0.33	0.11	0.50	0.39	0.33	0.27
0.50	1.00	0.79	0.74	0.63	1.00	0.91	0.74	0.68
	0.50	0.36	0.37	0.29	0.50	0.46	0.37	0.34
0.10	−1.00	−0.87	−0.66	−0.55	−1.00	−0.93	−0.66	−0.61
	−0.50	−0.45	−0.33	−0.28	−0.50	−0.46	−0.33	−0.30
$P_A = 0.50$								
0.90	1.00	0.64	0.66	0.51	1.00	0.71	0.66	0.55
	0.50	0.32	0.33	0.25	0.50	0.36	0.33	0.27
0.50	1.00	0.88	1.00	0.88	1.00	0.94	1.00	0.94
	0.50	0.44	0.50	0.44	0.50	0.47	0.50	0.47
0.10	−1.00	−0.64	−0.66	−0.51	−1.00	−1.00	−0.66	−0.63
	−0.50	−0.32	−0.33	−0.25	−0.50	−0.50	−0.33	−0.31

of Δ'_{AB} and r_{AB} in the presence and the absence of genotyping errors under the two error models when the genotyping error rate is 3%. From table 4, we can see that the results are similar to those when there is HWD. For example, as the minor-allele frequencies at SNP loci 1 and 2 increase, the composite LD measures tend to become increasingly robust to genotyping errors, and the measure r_{AB} under the DEM is more robust to genotyping errors compared to that under the SEM, except when the difference between the frequency of two SNP alleles A and B is very large.

Discussion

In the present study, we evaluate the impact of genotyping error on the composite LD measures Δ'_{AB} and r_{AB}. The results showed that, whether there is HWD or not, Δ'_{AB} and r_{AB} are seriously affected by genotyping error and show varying degrees of robustness in the presence of errors for two error models of SEM and DEM. The measures tend to become increasingly robust to genotyping errors as the minor-allele frequencies at SNP loci 1 and 2 increase, and the measure r_{AB} under the DEM is much more robust to genotyping errors compared to that under the SEM, except when the difference between the frequency of two SNP alleles A and B is very large.

It should be noted that, if there is HWE, both the classical LD measure and the composite LD measure can be used in LD mapping or association-mapping studies (Weir and Cockerham 1979). Being compared with the results of Akey *et al.* (2001), we can see that, only when the frequency of two SNP allele A and B is very large (for example, $P_A = P_B = 0.9$, or $P_A = 0.7$ and $P_B = 0.9$), the classical LD measures Δ' and r are more robust to genotyping errors than the composite LD measures Δ'_{AB} and r_{AB}. With the minor-allele frequencies at SNP loci 1 and 2 increasing, the degrees of robustness in the presence of errors for both the composite LD measures and the classical LD measures are nearly equal. When the difference between the frequency of two SNP alleles A and B is very large (for example, $P_A = 0.9$ and $P_B = 0.1$), the composite LD measures Δ'_{AB} and r_{AB} are more robust to genotyping errors than the classical LD measures Δ' and r, respectively.

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