Multipanel multicountry comparison

Introduction

The panels compared in this R markdown script include the GTseq panel (`GTseq`); the GTseq panel with CSP, TRAP, SERA2 and AMA1 removed (`GTseq_notCTSA`); a panel using only CSP, TRAP, SERA2 and AMA1 (`onlyCTSA`); and a panel based on the Sanger barcode (`sanger_barcode`). The marker and frequency data for `GTseq` and thus the data for panels derived from it (`GTseq_notCTSA` and `onlyCTSA`) are attached as example data along with the **paneljudge** package. The Sanger barcode data used to generate the results plotted in this R markdown script were processed by `Process_Sanger_Barcode.R`. The relatedness results based on all four panels mentioned above were generated by `Generate_results_multipanel_comparison.R`.

The frequencies of the GTseq panel and its derivations are based on *Plasmodium falciparum* sample data collected in Colombia, French Guiana, Senegal and Mali. At present, the frequencies of the Sanger panel are based on identical *P. falciparum* sample data collected in Colombia, French Guiana and Senegal, but not Mali (omitted). *Plasmodium falciparum* sample data are not included in this example analysis nor in the distribution of the **paneljudge** package.

There is substantial overlap (code and text) between this Rmd file and the paneljudge vignette, which is more pedagogical. To see all the source code used to generate `multipanel_multicountry.pdf`, please consult `multipanel_multicountry.Rmd`. To run `multipanel_multicountry.Rmd` please set the working directory to source file location.

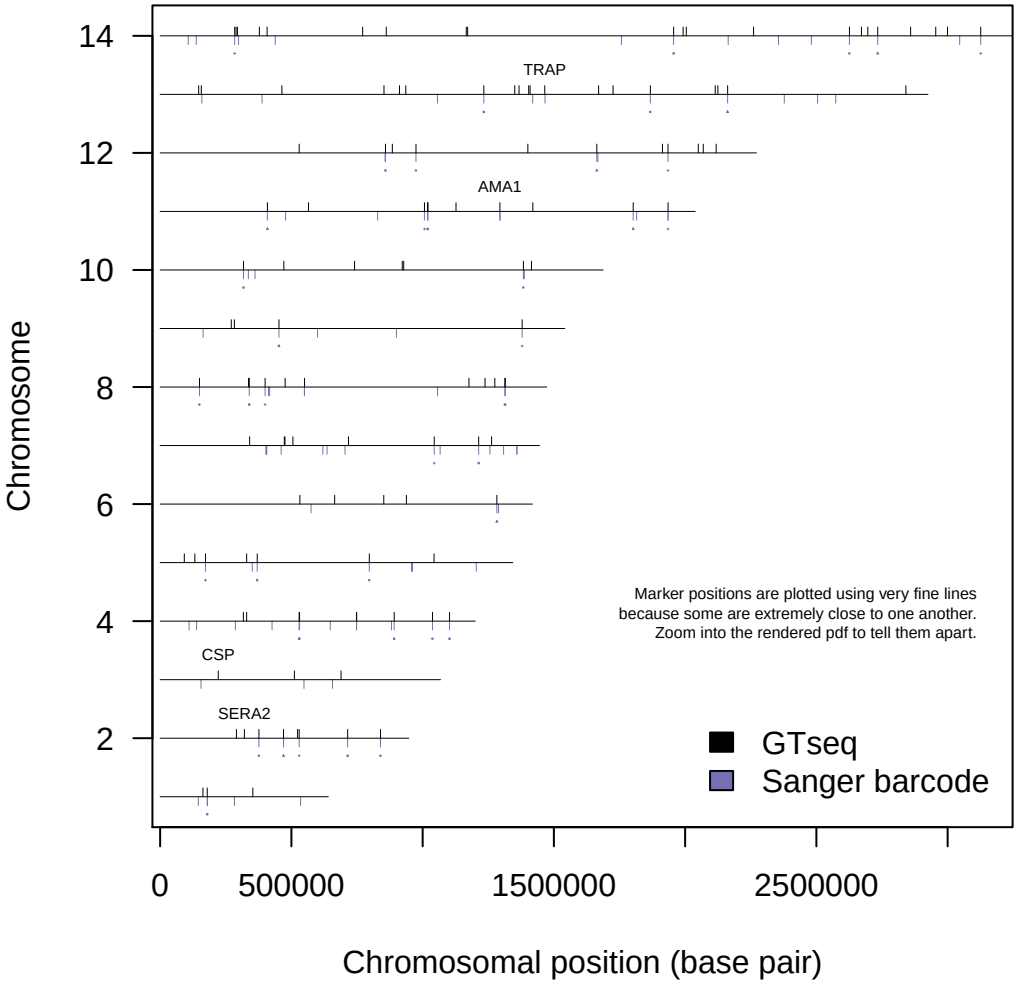
To see the paneljudge vignette and all of its code, type `vignette("paneljudge_example")` and `edit(vignette("paneljudge_example"))`.

```
#> Loading required package: RColorBrewer
#> Loading required package: kableExtra
#> Warning: package 'kableExtra' was built under R version 3.5.2
```

Comparative summaries and results

Marker counts and positions

For relatedness inference, panels with many, evenly spaced and highly diverse markers are informative (1). The GTseq panel has 126 markers distributed across 14 of 14 chromosomes; the Sanger panel has 118 markers distributed across 14 of 14 chromosomes:



Data on the GTseq panel are generated by sequencing amplicons spanning regions of the genome that encompass two or more single nucleotide polymorphisms (SNPs). We refer to these regions as microhaplotype markers. Their lengths are too small to perceive on the above plot of the microhaplotype marker positions, and some are very close together; see the paneljudge vignette for a summary of the distributions of microhaplotype marker lengths and inter mid-point distances (the minimum inter mid-point distance in the GTseq panel is 295.5 base pairs).

Data on the Sanger panel are generated by sequencing amplicons spanning regions containing individual SNPs [is that true?]. Some of the Sanger barcode SNPs are so close to one another (the minimum inter-marker distance is 179 base pairs) that they could be considered together as microhaplotypes versus individual SNPs. We do not have length information for the Sanger barcode. However, GTseq regions contain 0 to 1 Sanger panel markers, totaling 44 across all 126 regions (they are marked below by a point whose symbol varies to facilitate distinction between markers that are extremely close to one another). Otherwise stated, there appears to be substantial overlap between `GTseq` and `sanger_barcode`. Despite very close proximity to TRAP and AMA1, there are 0 Sanger panel markers within the CTSA regions of the GTseq panel.

Marker diversities and effective cardinalities

Please see the vignette of the R package **paneljudge** for a summary of how to interpret diversities and effective cardinalities and the function documentation (accessed via e.g. `?compute_eff_cardinalities()`) for details on how they are computed.

Table 1: Diversities GTseq

	Colombia	French Guiana	Mali	Senegal
Min.	0.00	0.00	0.00	0.00
1st Qu.	0.04	0.03	0.42	0.40
Median	0.41	0.22	0.52	0.53
Mean	0.33	0.25	0.52	0.51
3rd Qu.	0.50	0.44	0.70	0.70
Max.	0.74	0.70	0.93	0.95

Table 2: Diversities GTseq without CTSA

	Colombia	French Guiana	Mali	Senegal
Min.	0.00	0.00	0.00	0.00
1st Qu.	0.04	0.03	0.41	0.36
Median	0.40	0.20	0.52	0.52
Mean	0.33	0.24	0.51	0.49
3rd Qu.	0.50	0.44	0.69	0.67
Max.	0.74	0.70	0.93	0.93

Table 3: Diversities CTSA only

	Colombia	French Guiana	Mali	Senegal
Min.	0.04	0.19	0.76	0.82
1st Qu.	0.35	0.38	0.87	0.86
Median	0.48	0.49	0.91	0.91
Mean	0.41	0.45	0.88	0.89
3rd Qu.	0.53	0.56	0.91	0.94
Max.	0.64	0.63	0.93	0.95

Table 4: Diversities Sanger Barcode

	Colombia	French Guiana	Senegal
Min.	0.00	0.00	0.00
1st Qu.	0.01	0.03	0.28
Median	0.36	0.20	0.45
Mean	0.27	0.23	0.41
3rd Qu.	0.45	0.44	0.50
Max.	0.69	0.71	0.91

Table 5: Effective cardinalities GTseq

	Colombia	French Guiana	Mali	Senegal
Min.	1.00	1.00	1.00	1.00
1st Qu.	1.04	1.03	1.72	1.67
Median	1.69	1.29	2.08	2.11
Mean	1.70	1.47	2.82	2.84
3rd Qu.	2.00	1.80	3.31	3.30
Max.	3.92	3.28	13.95	20.33

Table 6: Effective cardinalities GTseq without CTSA

	Colombia	French Guiana	Mali	Senegal
Min.	1.00	1.00	1.00	1.00
1st Qu.	1.04	1.03	1.71	1.55
Median	1.66	1.26	2.07	2.09
Mean	1.69	1.46	2.59	2.53
3rd Qu.	2.00	1.77	3.19	3.08
Max.	3.92	3.28	13.70	14.34

Table 7: Effective cardinalities CTSA only

	Colombia	French Guiana	Mali	Senegal
Min.	1.04	1.23	4.21	5.42
1st Qu.	1.65	1.65	8.68	7.24
Median	1.92	1.96	10.64	11.91
Mean	1.92	1.97	9.86	12.39
3rd Qu.	2.19	2.28	11.82	17.06
Max.	2.80	2.74	13.95	20.33

Table 8: Effective cardinalities Sanger Barcode

	Colombia	French Guiana	Senegal
Min.	1.00	1.00	1.00
1st Qu.	1.02	1.03	1.38
Median	1.57	1.24	1.81
Mean	1.50	1.41	2.03
3rd Qu.	1.83	1.78	1.99
Max.	3.22	3.50	10.83

Table 9: Top 3 per country GTseq

	eff_cardinality	Diversity
Colombia.PF3D7_0827100	3.92	0.74
Colombia.P38	3.50	0.71
Colombia.PF3D7_1473700	3.31	0.70
French Guiana.PF3D7_1035700	3.28	0.70
French Guiana.PF3D7_1302900	3.17	0.68
French Guiana.PF3D7_0501800	3.12	0.68
Mali.zAMA1	13.95	0.93
Mali.PF3D7_1352900	13.70	0.93
Mali.zTRAP	11.10	0.91
Senegal.zCSP	20.33	0.95
Senegal.zAMA1	15.97	0.94
Senegal.PF3D7_1352900	14.34	0.93

Table 10: Top 3 per country GTseq not CTSA

	eff_cardinality	Diversity
Colombia.PF3D7_0827100	3.92	0.74
Colombia.P38	3.50	0.71
Colombia.PF3D7_1473700	3.31	0.70
French Guiana.PF3D7_1035700	3.28	0.70
French Guiana.PF3D7_1302900	3.17	0.68
French Guiana.PF3D7_0501800	3.12	0.68
Mali.PF3D7_1352900	13.70	0.93
Mali.P38	6.82	0.85
Mali.PF3D7_0615900	6.16	0.84
Senegal.PF3D7_1352900	14.34	0.93
Senegal.P38	6.06	0.84
Senegal.PF3D7_1475900	5.62	0.82

Table 11: Top 3 per country sanger barcode

	eff_cardinality	Diversity
Colombia.Pf3D7_14_v3_3126219	3.22	0.69
Colombia.Pf3D7_11_v3_408668	2.86	0.65
Colombia.CRT_371	2.83	0.65
French Guiana.Pf3D7_05_v3_350933	3.50	0.71
French Guiana.Pf3D7_04_v3_1102392_E808D_A	2.48	0.60
French Guiana.Pf3D7_06_v3_1282691_803K_A	2.27	0.56
Senegal.Pf3D7_13_v3_1466422	10.83	0.91
Senegal.Pf3D7_11_v3_1295068_E405K	9.22	0.89
Senegal.Pf3D7_13_v3_1419519	7.34	0.86

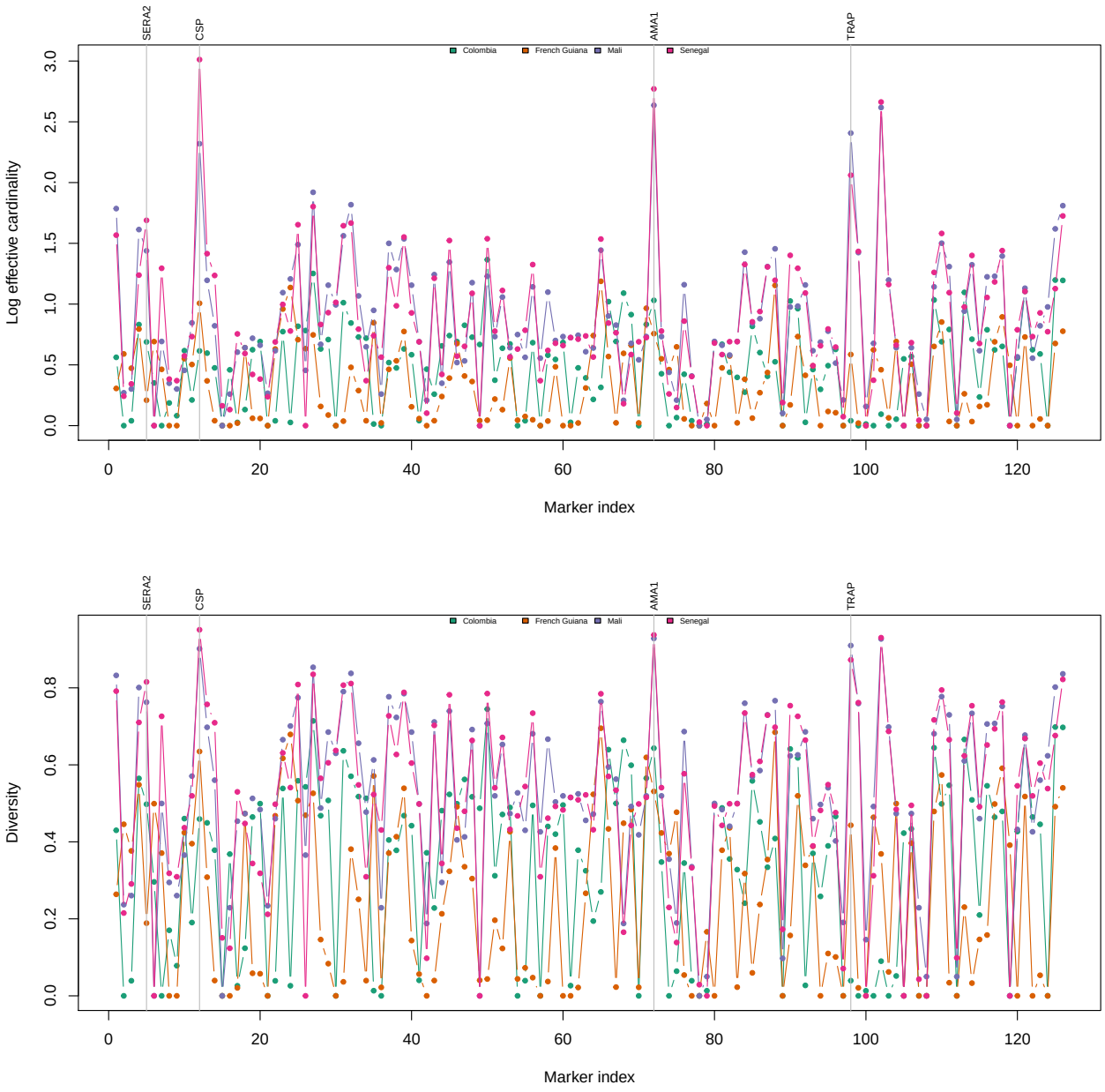


Figure 1: Marker summaries (diversities and effective cardinalities) for the GTseq panel

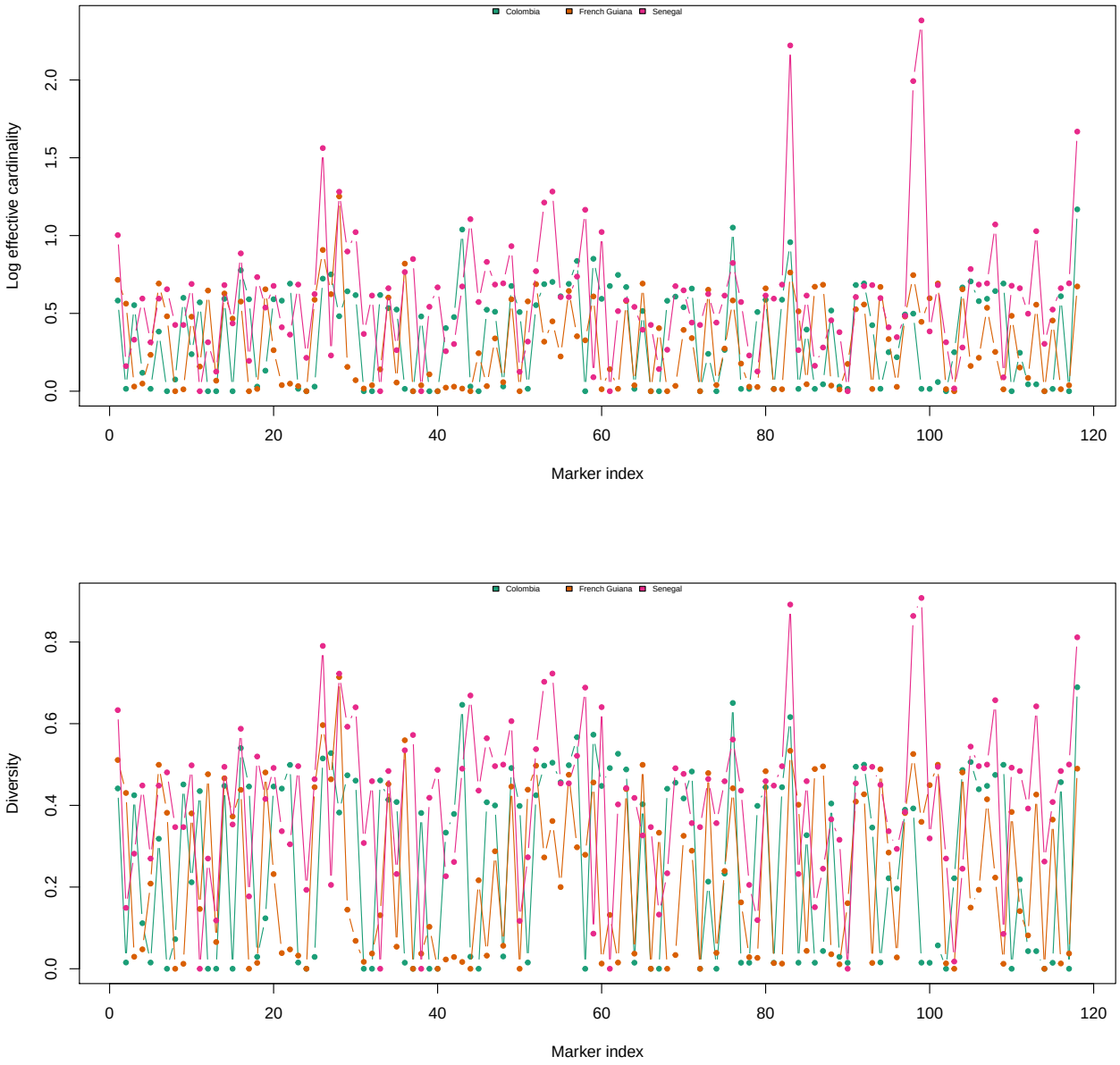


Figure 2: Marker summaries (diversities and effective cardinalities) for the Sanger panel.

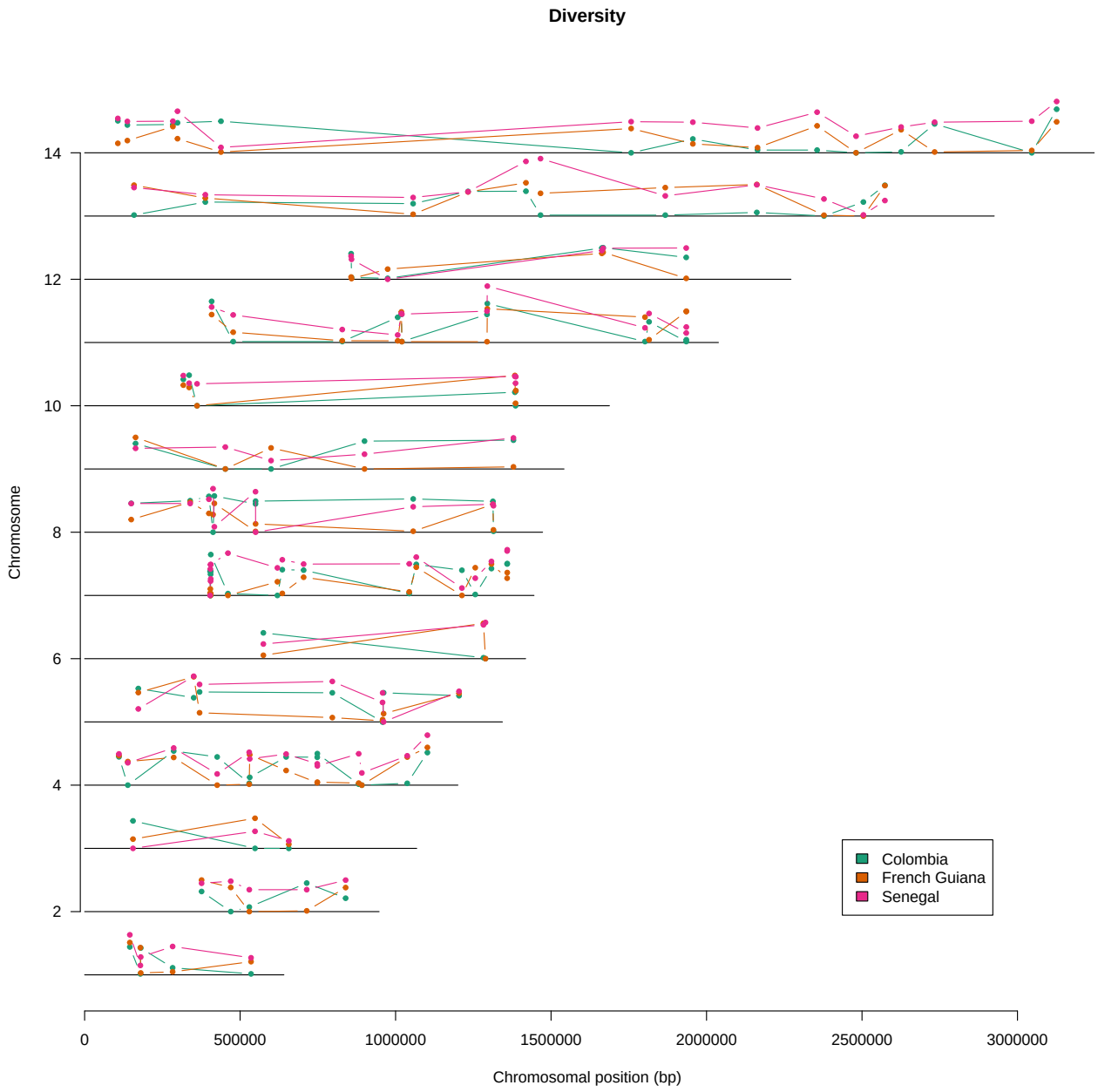


Figure 3: Marker diversities and positions for the Sanger panel: e.g. an alternative vizualisation of diversity.

Relatedness estimates and their CIs based on simulated data

Based on the marker count multiplied by the mean effective cardinality (i.e. the effective cardinality summed over all markers), we can get a rough idea of how confidence intervals around relatedness estimates might scale, e.g. from large (least informative) to smaller (more informative), the panels considered here are ordered as follows: onlyCTSA, sanger_barcode, GTseq_notCTSA, GTseq.

References

1. Taylor AR, Jacob PE, Neafsey DE, Buckee CO. Estimating relatedness between malaria parasites. Genetics. 2019;212(4):1337–51.

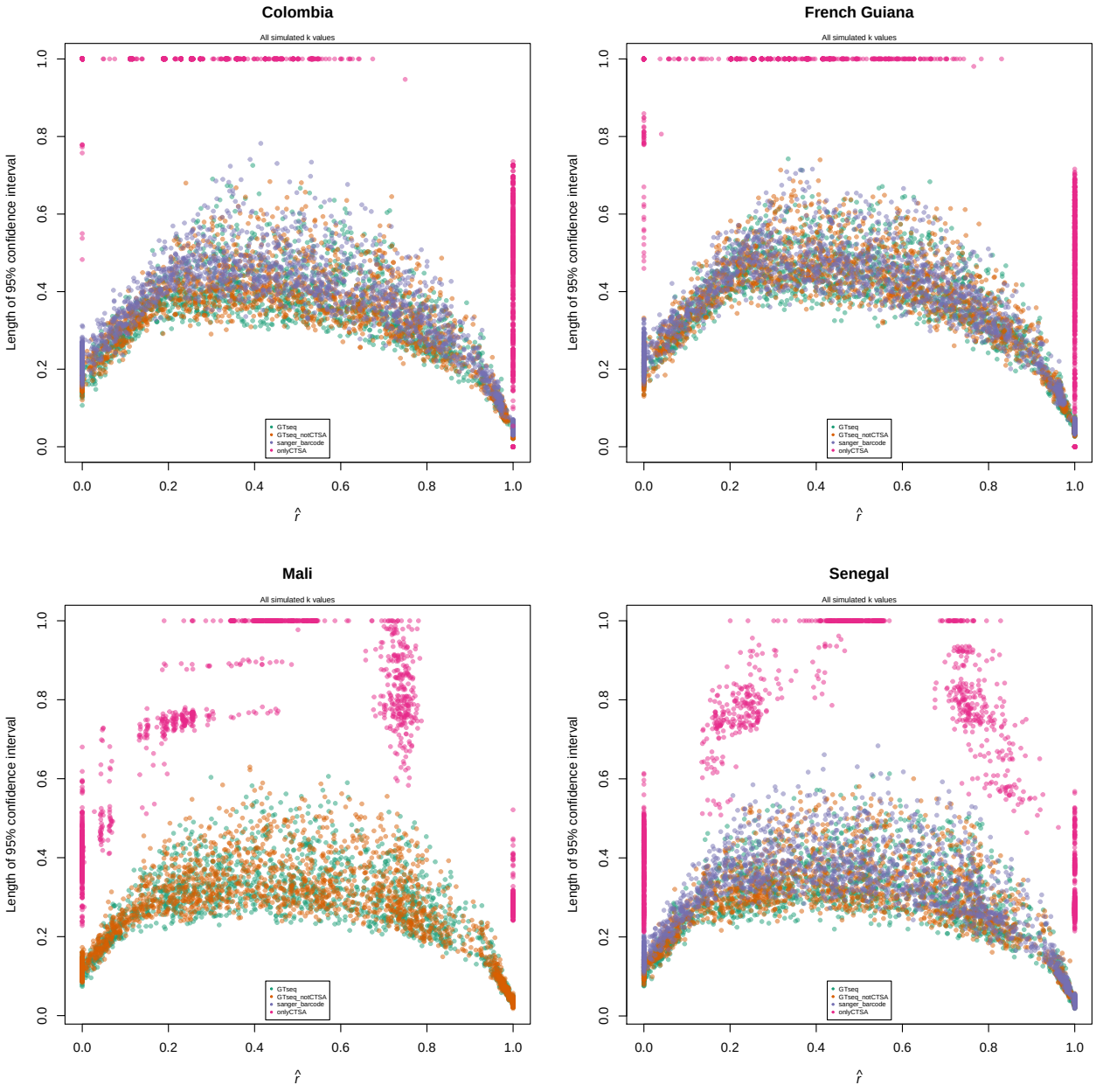


Figure 4: Lengths of 95% confidence intervals around relatedness estimates based on data simulated using various data-generating relatedness and switch rate parameters, r and k, respectively: panel comparison per country.

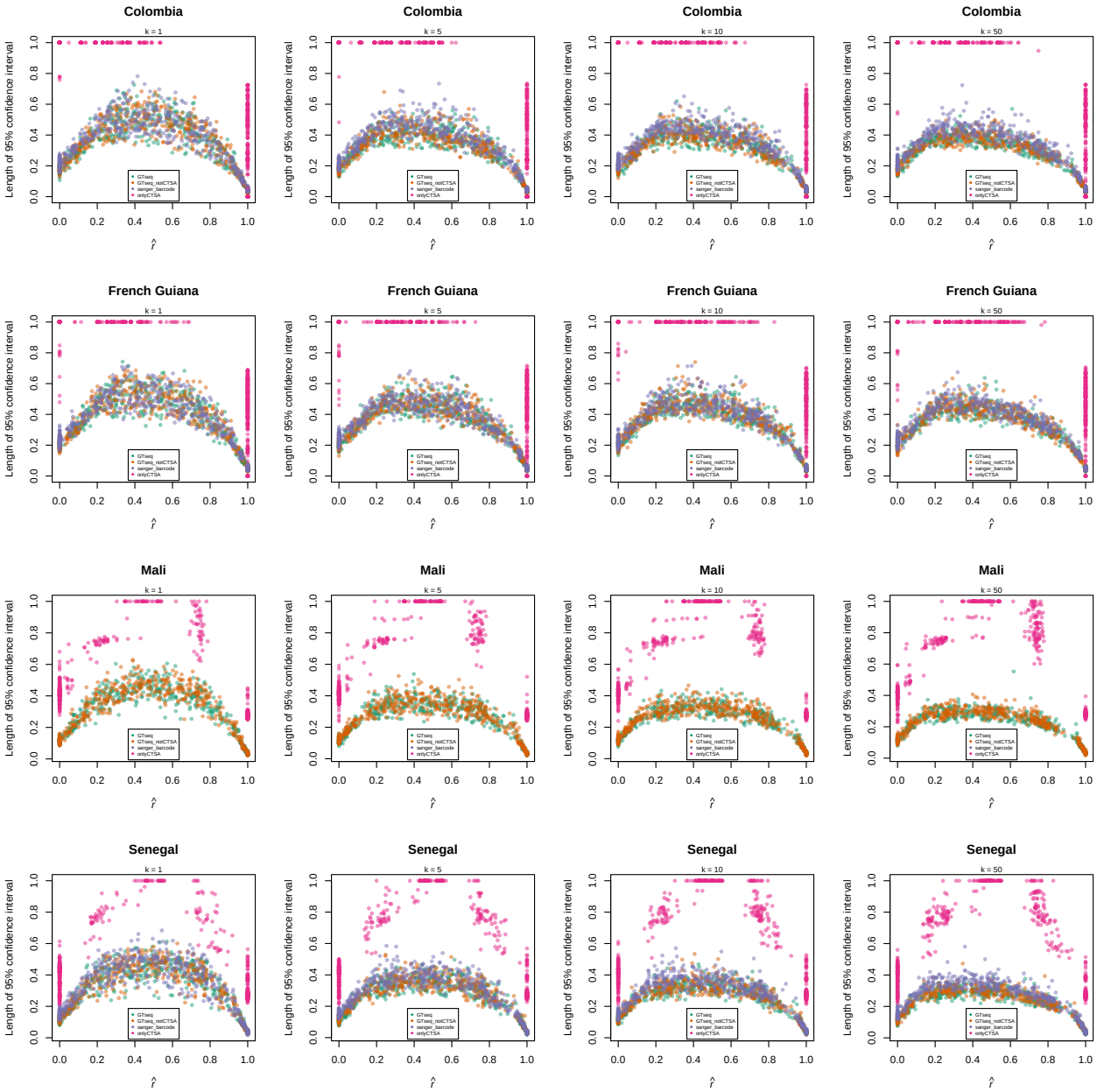


Figure 5: Lengths of 95% confidence intervals around relatedness estimates based on data simulated using various data-generating relatedness and switch rate parameters, r and k, respectively, with separate plots for each k: panel comparison per country.

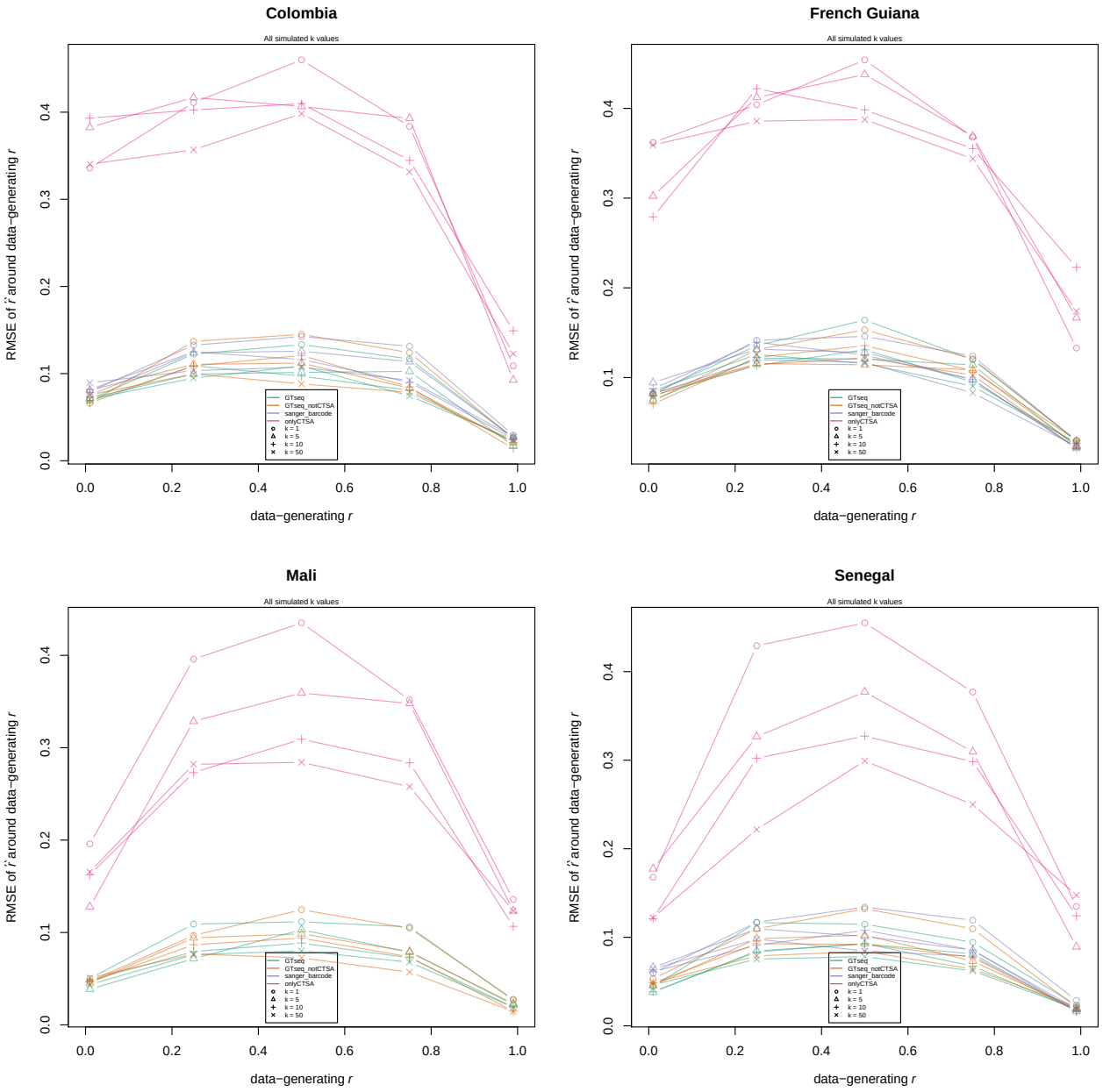


Figure 6: Root mean square error (RMSE) of relatedness estimates based on data simulated using various data-generating relatedness and switch rate parameters, r and k, respectively: panel comparison per country.

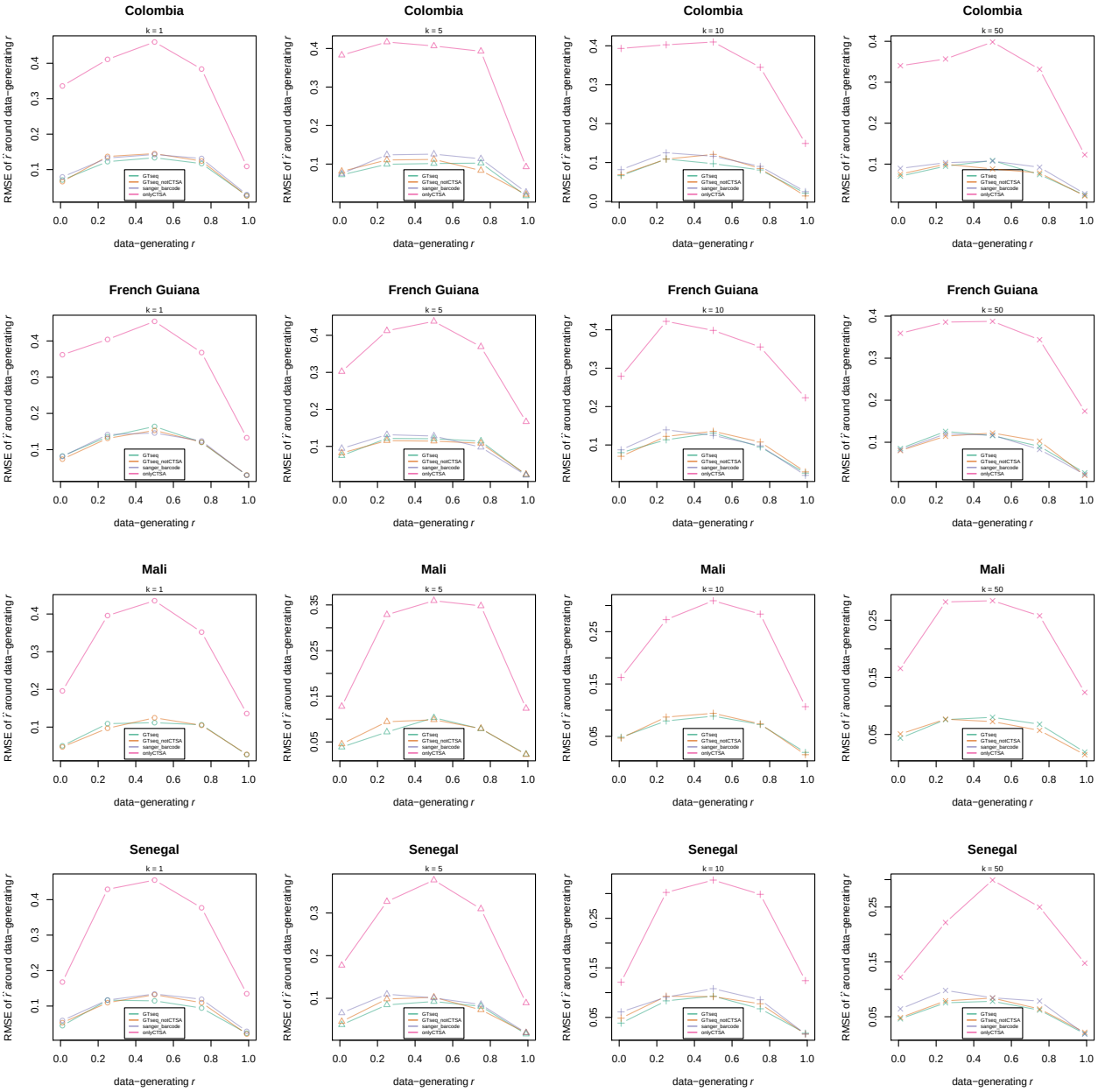


Figure 7: Root mean square error (RMSE) of relatedness estimates based on data simulated using various data-generating relatedness and switch rate parameters, r and k, respectively, with separate plots for each k: panel comparison per country.

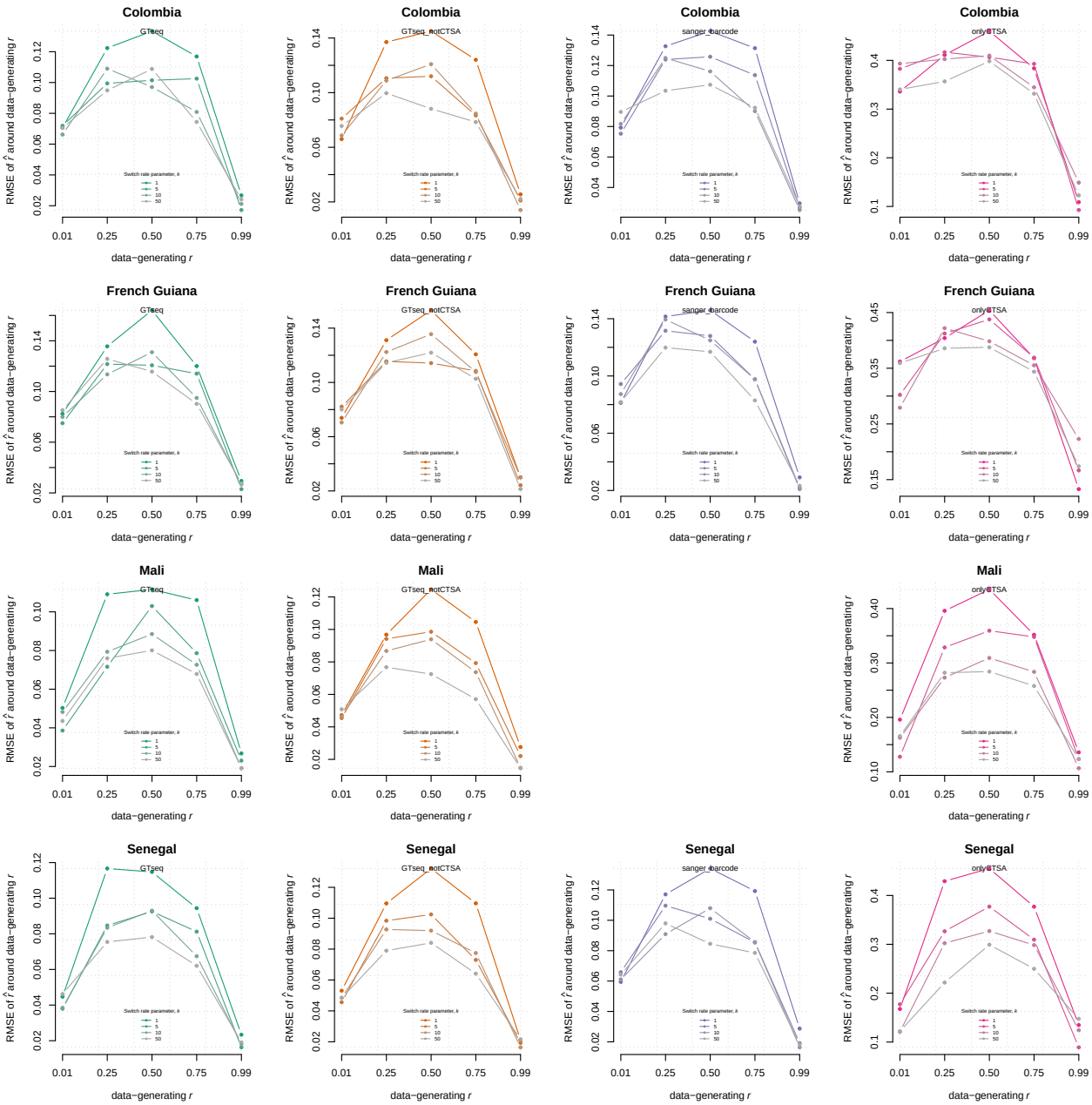


Figure 8: Root mean square error (RMSE) of relatedness estimates based on data simulated using various data-generating relatedness and switch rate parameters, r and k, respectively, with separate plots for each country and panel: comparison across k.

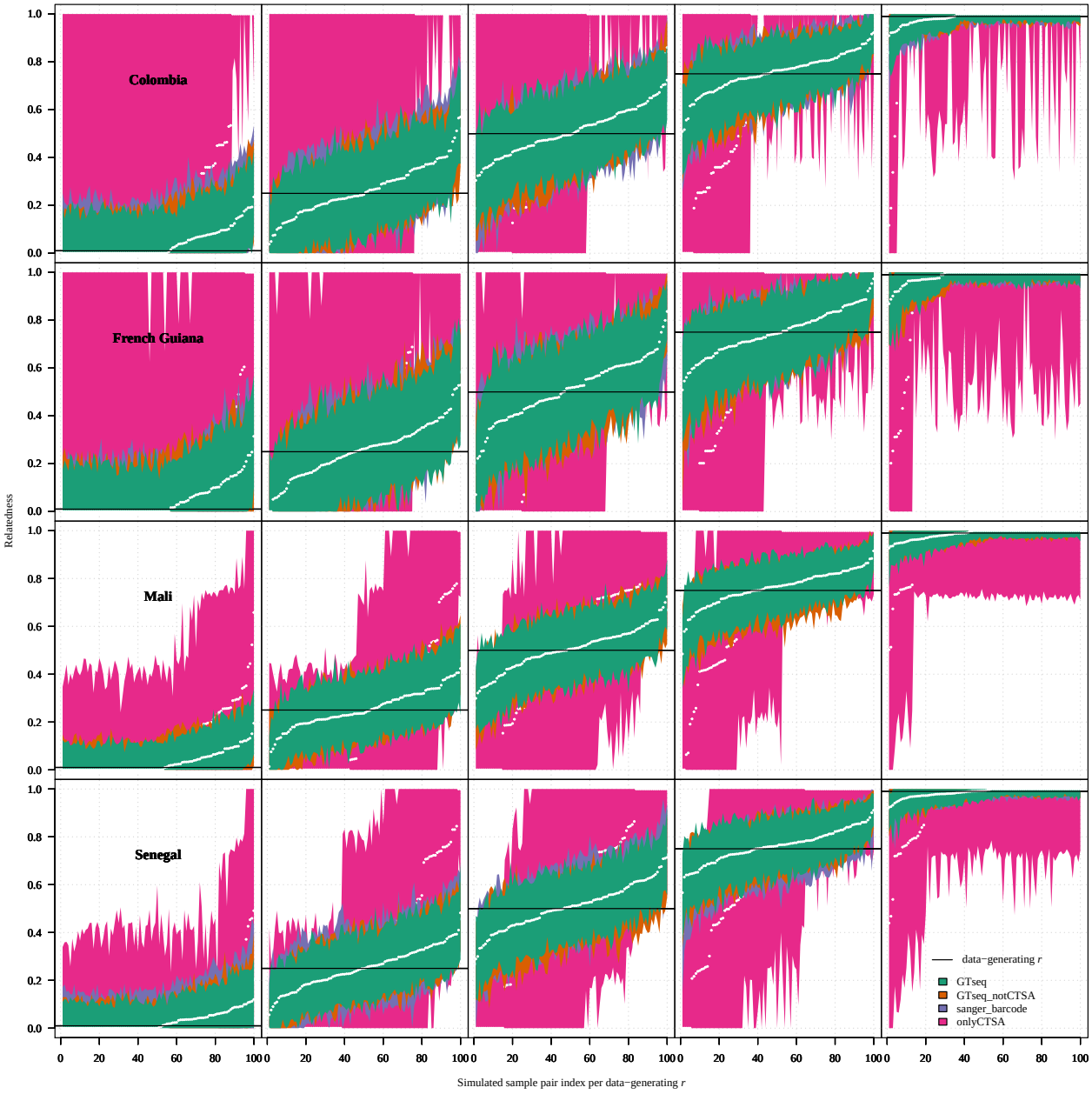


Figure 9: Confidence intervals around relatedness estimates based on data simulated using various data-generating relatedness parameters, r, and switch rate parameter k=10.