Raberg et al. investigate the relative abundance of branched GDGTs in a number of high-latitude lakes, and compare those distributions to previously published datasets from the tropics and mid-latitude sites. Through this work, they empirically derive global calibrations of the brGDGT distributions to temperature, salinity, and pH for use in paleoclimate reconstruction. The authors provide a comprehensive analysis of the existing and new data and develop a number of new indices to quantify the distributions of brGDGT abundances, some of which improve our understanding of how the lipid structures vary in response to environmental conditions. Overall, the authors have done a very good job and the new methods will be of wide interest to organic geochemists and the paleoclimate community. I recommend publication with minor but important revisions that I hope will improve the manuscript.

General notes:

1) The authors propose new ways to quantify brGDGT abundances through the use of ‘sets’ of brGDGTs with similar structures. This is a novel approach, although ultimately the authors seem to fall back on our existing understanding of how the different structures relate. Whatever the case, the authors should explain how and why they grouped the different sets. In addition, the authors examine a lot of different sets and report all of them, even though only some appear to be useful. The different ratios become a bit overwhelming by the end of the manuscript, and even though the authors should be commended for being comprehensive I’d suggest trying to limit the discussion to only the sets that ultimately proved useful.

2) The authors suggest that the ‘best’ temperature calibration is based on a set of methylated brGDGTs (the “meth” set, maybe not the ideal name) to the average temperature of the months above freezing. It would be worth some more thinking and
text about what “best” means. Ultimately, these calibrations will require extensive ‘field testing’ in different lacustrine environments to determine what works and what doesn’t (just because a calibration ‘works’ with surface sediment does not mean it will produce meaningful downcore reconstructions). And what makes one calibration ‘best’? Although the calculations of fractional abundances within brGDGT “sets” are a new approach and are discussed at length in the paper, ultimately the best temperature regression (as measured by RMSE) uses the traditional method with all 15 brGDGTs to calculate the abundances. Lastly, although the ‘months above freezing’ is meaningful in regions with strong temperature seasonality it is not a particularly meaningful concept in low-latitude areas where there is no monthly variation; thus, the calibration target might not be ‘best’ in these regions. It would be worth it to consider these issues more in the conclusions.

3) The Fit to MAF is interesting in that most sediment trap studies suggest brGDGT fluxes peak during events. Admittedly, “most” means only 2-3 studies, and it is not clear to me that those results can be reconciled with good fit to MAF. Does the improved fit to MAF imply that seasonal production and fluxes of brGDGTs are indeed biased toward summer, and if so, what are we missing from sediment trap studies? If calibrations are done to ‘shoulder season’ temperatures, are the calibrations worse? The authors briefly discuss these issues, but it would be interesting to dig a bit deeper.

4) I have some concerns about the section starting on line 580 that develops calibrations for dissolved oxygen. Although this is inconclusive, I question whether we the environmental data is good enough to meaningfully address this. Is DOmean the average of the entire water column? And over what seasons? Calculating this variable is a fraught exercise without access to each lakes' actual DO profiles, many of which do not appear to exist.

5) Several of the indices and calibrations utilize fractional abundances of the bicyclized penta- and/or hexamethylated compounds that are often not abundant in sufficient quantities to be accurately measured in many of the published datasets. It is not clear how (a) the authors treated those sites in their calibrations, (b) what their limits of detection are for the different compounds in their new sites and how those were determined, and (c) what they suggest to do at sites where these compounds (chiefly IIc, IIc', IIIb, IIIb', IIIc, IIIc') are below detection levels. This could create problems for some of the sets that isolate these structural groups.

6) Line 432. The text below highlights a challenge in working with these data – the environmental variables themselves are strongly correlated. This makes it difficult to conclusively support some of the statements in this paragraph – “temperature may therefore play a secondary role”... for instance. This assumes that temperature actually does play a role, rather than that temperature is correlated to pH and conductivity, and therefore is (spuriously) correlated to the brGDGTs. It might be worth considering application of multivariate statistical methods that take into account collinearity among the predictors, such as redundancy analysis, to address this issue.

Minor things:
Line 59. Why “however”? The shifts in community composition can track shifts in environmental conditions.

Line 74. As stated above, note that, at many sites, the highly cyclized brGDGTs are often below detection levels, such that equation 2 is reduced to the fractional abundances of only the most abundant compounds.

Line 138-139. How many sites had water chemistry data?

Line 220. Did the logarithmic scaling result in a normal distribution of these environmental variables?

Line 301. Here and elsewhere throughout the text, it would be best to provide p values for the correlations you report.

Line 398. There is some thinking that a substitution closer to the head group would be more influential on membrane fluidity (structural disruption closer to the surface of the compound). Your results suggest this is a minor effect.

Line 427. This does not suggest they have similar influences on brGDGTs. Rather, it suggests that conductivity and temperature covary in the environment.

Line 433. Could you cite a table or similar for this statement?

Line 471. Similarly, how did you assess that ring number is “primarily” correlated with pH rather than conductivity? Based on an r2 difference of 0.04?

Line 499. Regressions of the temperature variables onto what? Which brGDGT formulations?

Line 505. A challenge here is that MAT = MAF in the low latitudes. The main reason for the MAF formulation is to account for the additional complexity introduced by a global calibration that includes high latitude systems. It would be worthwhile to reemphasize this here.

Line 540. This would make some sense, since MAT = MAF in the sites included in the Russell et al. (2018) calibrations.
Line 541. “On a regional scale”... It would be worthwhile to mention the relatively unique (highly alkaline) nature of these lakes.

Figure 10. It is a bit difficult to figure out what is being plotted in these figures, in particular panel a. It would be most helpful if the equations are introduced alongside this figure. Related to this, it appears from the text that a very simple formulation, MBT'SMe, performs nearly as well as more mathematically complicated (e.g. equation 10) versions. Is this correct? Lastly, although a high r2 is great, the RMSE is in some ways more important to climate reconstruction. It might be good to include a plot showing the RMSE, similar to figure 10A.

Line 674. This is correct in a way, but the use of structural sets does not ultimately improve calibration performance. Correct?

Line 692, could add a clause of “particularly in high-latitude environments”.

The paper refers to papers by Sosa et al. (2020, 2020a) that are not in the references. Please provide the correct citations.