CANSSI - Reviewer Comments

Project Title: *Statistical Methods for Daily Mortality and Multiple Environmental Risk Factors*

General Comments

The Scientific Advisory Committee requests that the full proposal specfically address the following issues

1. Provide details about the mentoring of the HQP, linking HQP directly to specific mentors. Include details on the mentoring of the student at Laval and how the student will be a full participant in the team.
2. Clarify how the team will function and how team members will interact and collaborate. Describe the roles of the lead investigators in the project and research.
3. Provide more details on how the aims associated with the application are related to the statistical methodology.
4. Briefly describe the available data sets and the confounders present therein.
5. Discuss why you model mortality from asthma, rather than occurrence.
6. Detail the technical challenges to be addressed, provide references to what is already known and clearly state what is to be developed. In your discussion, include the following.
   A. Provide explicit information on the kinds of constraints you will place on the prior distributions. Provide more extensive references to the literature on shape constrained models.
   B. Describe the challenges of introducing Bayesian approaches.
   C. You propose to initiate the models in STAN. Does this mean the research is very straightforward? If not, what are the challenges?

You may wish to consider that the SAC determined that strengths of the proposed project include:

1. The applied aspect is particularly strong, with a real investment by the partner, Health Canada.
2. The proposed research addresses problems of importance to society.
3. The SAC was particularly enthusiastic about the proposed development of a Bayesian methodology for inference with constrained group-wise additive index models.

Reviewer One

The methodological extensions are not compelling, but the application to air pollution epidemiology is novel.

The inclusion of Health Canada is a major advantage. The interdisciplinary and collaborative nature of the project makes it an excellent training opportunity for early career researchers. The LOI is very clear.

Remarks: This reviewer has positive comments for the LOI, except their first one regarding methodology.

Reviewer Two

A lot of details are left out about the research involved in achieving the three main objectives.

1. What research would be needed to construct the new bcAQHI once the new bcGAIM is built and implemented?
2. Does each health outcome needs its own index? Asthma is very different than other conditions, for instance.
3. Future forecasting − if the AQHI were deemed to be of value, a mother deciding on whether to send her asthmatic child to school would be guided at least in part by that day's AQHI.

The cGAIM is by no means a new idea. See Hardle (1993) for $K = 1$ and Wang et al (2015) for $K > 1$. Special cases were published between 1993 and 2015. The benefits of the bcGAIM are:

1. It will quantify uncertainty about α that may show it is not identifiable. If α is identifiable, it may show the relative contributions of one pollutant against another.
2. The resulting bcGAIM will be able to accommodate higher dimensional α's.

The three main research objectives are given short shrift so it is difficult to judge their value. Consider the three research objectives:

1. The new AQHI would be novel by taking into account of the joint effect of the multiplicity of pollutants, but not knowing how the AQHI will be constructed from the bcGAIM makes it hard to judge the novelty of the work.
2. An epidemiology study: there are countless studies of the associations between air pollutants and human health, but with less data so the research will be novel.
3. The most novel: how the bcAQHI might be used to assess COVID-19 mortality. Why not build a new bcAQHI designed specifically for that purpose? Why use all-causes mortality to estimate α and transform into an index? Ozone is more relevant as a risk index for asthma and $PM_{2.5}$ is or COPD. Why not just publish the pollutant concentrations themselves?

A major challenge will be the *big data* issue, since daily mortality counts will be modelled using a semi-parametric model. This would be simplified by designing a different model for each Canadian city. The applicants do not intend to incorporate city-level random city effects to enable strength to be borrowed deficiency. This compromise may be needed for feasibility.

This work could have a significant impact because the proposed collaborative team has a direct pipeline to Health Canada. The LOI could have done better clarifying the links of the Investigators and Collaborators in the proposed project. What is clear is that the LOI/project is designed to provide a pipeline from data to the AQHI. What is not clear is how the collaboration is to be managed. I would like to see is an active group interaction plan, beyond meeting at the SSC. For example,

1. An effective manager
2. Subgroups for each component research program would meet regularly − weekly
3. Monthly meeting for the full research group. Students and postdocs might be selected to make presentations.

What is Chebana's role in the project? Masselot was a PDF at INRS for three years but is not eligible to be an investigator, but has a long list of publications and developed the cGIAM.

From the information provided, it's not clear the work is suitable for a postdoctoral fellow, where greater depth and sophistication is expected. The discussion of the bcGAIM is well done, but the three main objectives (and how they relate to each other) should have been better described before diving into methodological details.

Remarks: This reviewer's comments are constructive and in-depth. They center around the relationship of the three research objectives, how the collaboration will be managed, and how the bcGAIM will be transformed into an AQHI.

Reviewer Three (*)

Three research objectives (developing an improved air quality index, undertaking epidemiological studies, and investigating how air pollution affects daily COVID-19 mortality) are listed, there is little discussion on the 2$^{\text{nd}}$ and 3$^{\text{rd}}$ objectives. It is not clear how they can be achieved. For instance, naïve case/mortality rate (Objective 3) is subject to undercounting in the numerator and denominator.

Since the cGAIM is newly proposed and not yet published, it is hard to assess the novelty of the bcGAIM and cGAIM compared to existing methods like the BKMR. Although four methodological advancements of the bcGAIM are listed, those seem like incremental changes of the cGAIM. The potential impact seems marginal since these are incremental changes.

The LOI was not written with clarity. The proposal does not explain how the bcGAIM will help develop an AQHI, so it is not clear how the bcGAIM contributes to achieving the research objectives Also, no specific research plans are presented to achieve Objectives 2 and 3. Also, how the bcGAIM helps with developing an AQHI is not clearly explained.

Remarks: This reviewer had a short review that was the anomalous negative review in the .

Reviewer Four

A well-written proposal that aims to solve important real-world problems. Their semiparametric and dimension reduction (via index) nature make them useful when one is analyzing data of an unknown/unsure nature. Having high methodology novelty is not the selling point for this proposal. There are no issues in feasibility, except when the dimension of α is high.

The involvement of Health Canada strengthens the potential impact and merit of this proposal. The links among other collaborators and how will those benefit the project could be better explained. The team has the potential to provide an excellent environment for interdisciplinary training of students. It would be helpful to add the names of the faculty supervisors/collaborators to the mentoring plan. The part for the roles of personnel could be further clarified.

Remarks: This reviewer asks for clarification on the mentoring plan and the role of personnel.

Reviewer Five

While the project is motivated by multi-pollutant modeling, it could be strengthed by identifying other applications for this model. Regardless, the three research goals are:

1. Develop a multi-pollutant air quality index
2. Develop multi-pollutant exposure models for health effects
3. Investigate how mixtures of pollutants affects daily COVID-19 mortality.

Bayesian methods provide uncertainty quantification for both α and s, which optimization methods do not. The posterior distribution of weights can indicate which directions are well identified, giving the advantage of interpretability. This is an emerging area and has advantages over linear models as positive correlations among exposures complicates interpretation.

Development of a health-outcome model and air-quality index is an additional novelty. However, the proposal should provide more details about how these are related. The following additional areas also need clarification:

1. What is the relationship between the linear combination of α's goes into s and the AQHI? How will the AQHI indicate not/safety based on $s or α? More details on data sources would be helpful (hospital admissions – asthma, mortality, other conditions)?
2. The proposal lacks details about the desired shape constraints. There is a significant literature on Bayesian shape constrained modeling (monotonicity). Is this a straightforward to model in Stan, or are there methodological advancements to be made?
3. The researchers propose developing this model using non-MCMC methods such as INLA. How will this carry over to the Bayesian shape constrained model where s, α, and f must be estimated? This may provide computational efficiencies in point estimation, but how does it address uncertainty quantification compared to the cGAIM? 4.The proposal rejects placing a prior on the expansion of s, instead placing it directly on s. What priors on function spaces will be used - Gaussian process priors or others? How are the constraints incorporated?
4. Will this be a joint model for COVID versus non-COVID deaths with a common/different s? Will there be common/different linear combinations of exposures? Will this utilize the proposed AQHI? What data is available? Does it provide the necessary information about potential confounders or other covariates? Is individual or aggregated data available? Missing data is an issue with COVID-19 deaths but this is not addressed. Other covariates/confounders could potentially include: SES, comorbidities, access to health insurance, housing (nursing homes, dorms, single family, number of inhabitants)
5. What data is available for each research aims? How will these data sources be integrated?
6. The proposal mentions developing random effects in s. What do these capture and what is the motivation – spatial random effects, treating the weights as random effects?

Some aims use Stan, while others propose to develop INLA-like methods. The methodology draws upon existing methods so there is a is a high probability for success. Even if no novel methodology is developed, there is a high probability of advancement in air pollution research. There is potential for advancement in Bayesian shape constrained modeling (particularly priors and representation) and efficient inference through INLA. Development of multi-pollutant models that are robust to the correlation of mixtures of exposures and interpretable, and an associated AQHI would have broad impact for research and the public.

Potential weaknesses in the current proposal are that methodological details are sparse – is this a relatively routine model to fit in Stan or are there methodological advancements there? What are the challenges of extending single pollutant models to the multi-pollutant models using INLA like approximations beyond scaling in dimension to say 3 or higher with lags?

Highlighting previous collaborations among the team members would strengthen the proposal. Is there is a single senior lead investigator? Who will be mentors for the PDF and PhD students (beyond the PDF)?. There are no faculty listed as investigators at the University of Laval – the proposal could be strengthened by (briefly) discussing who is leading the team, the frequency of team meetings, and the roles of the lead investigators. The objectives and aims are well laid out. More details about advancements, challenges, and data sources for each aim would strengthen the proposal.

Remarks: This is a very thorough review. It raises a number of issues, beginning with the role of the lead investigators and the supervisory structure of the project. It also asks for a number of methodological clarifications, some of which were also raised by other reviewers. These include:

- How is the bcGAIM related to the AQHI (and safe/not safe indicator)? Are the shape constraints easy to implement in Stan? Does the INLA-like implementation also provide uncertainty quantification? What priors will be used on s? What data is available for each research aim; how will they be integrated? What is the motivation for developing random effects on s? More details are needed on the COVID aim.

Finally, the reviewer asks for more details on the challenges of extending from single to multi-pollutant models using INLA-like approximations (beyond scaling in dimension to 3 or higher with lags).

Details on Shape Constraints

Setting priors to enforce shape constraints is a challenging problem. We seek simple and interpretable priors, so that non-statistical experts can use it. This is especially important for this project, as it is interdisciplinary and the resulting models will likely being used and interpreted by non-statistical with a variety of different backgrounds. Achieving such an interpretable prior is a very challenging goal. For example, suppose we wished to constrain s to be monotonic. Ideally, to achieve our desired level of interpretability, a prior parameter θ would control the deviation of s from monotonicity. Moreover, the relationship between θ and the degree of monotonicity of s should be easy to communicate visually, to enable eliciting prior information from the non-statistical experts that will be using this model. We would like to develop interpretable priors for Gaussian processes, such as random walks. Monotonic, convexity, and concavity constraints (that is, first and second derivative constraints) are most applicable for our multi-pollutant model.

The multi-pollutant model is being initially implemented in Stan because it facilitates iterative model development, which we will be doing while developing suitable priors. Using a Bayesian approach to conduct constrained inference is challenging for two reasons. The first is related to the interpretability of the prior: s may not have any parameters related to the desired shape constraint. For example, a 1^{st}-order random walk has no parameters related to monotonicity. We could address this by re-parameterizing the random walk, or exploiting the structure of the 1^{st}-order random walk by (for example) modifying the prior on the first differences. The second is that priors can affect the posterior distribution in subtle but undesirable ways. For example, a truncated multivariate normal (tMVN) prior can induce monotonicity if placed on the coefficients β of a basis expansion of s (Maatouk and Bay 2017). However, the tMVN prior places neglible mass in near-flat regions of s. The effect of air pollution is often quite flat, so this would be very undesirable behavior for our motivating application. Zhou et al. (2020) remedy this by introducing a scale parameter on the coordinates of the tMVN distribution. However, the modified tMVN prior is placed on β, which can be more difficult to interpret than the prior on s.

There is a vast frequentist literature on shape-constrained inference, which we briefly review. Ramsay (1988) proposed monotone regression splines for splines of most quadratic order. Meyer (2008) extends these results for additional shape constraints, and Mammen and Thomas-Agnan (1999) describes a correspondence between fitting a constrained function and fitting then projecting an unconstrained function onto a constrained space. Sysoev and Burdakov (2019) uses a penalized likelihood to enforce monotonicity to maintain desirable smoothness properties. Leitenstorfer and Tutz (2007) applies constraints to the coefficients of the basis expansion to enforce montonicity. Compared to these approaches, we are using a Bayesian approach and have found that random walks better estimate the effect of air pollution than splines (**CITE**). Finally, there is an emerging branch of machine learning literature focusing on shape constrained inference, which aims to provide more interpretable predictions (S. 1998; Gupta et al. 2016; Wehenkel and Louppe 2019).

We now turn to Bayesian shape-constrained inference for Gaussian processes. The distribution of a constrained Gaussian process is no longer a Gaussian process, so placing shape constraints on Gaussian processes is difficult. However, the derivative of a Gaussian process is a Gaussian process. Riihimäki and Vehtari (2010) enforce monotonicity by using a data augmentation scheme where the derivatives of the Gaussian process are required to be positive at the virtual locations. Unfortunately, this requires introducing enough virtual observations to ensure the shape constraint holds globally with high probability. Agrell (2019) and Wang and Berger (2016) found that a relatively small number of virtual observations need to be introduced. However, we have found that the effect of air pollution can deviate quite substantially from monotonicity (Rai et al. 2020). Moreover, the air pollution data sets in this project have over 6000 daily observations, such that adding more virtual observations is not computationally feasible. Therefore, the data augmentation approach is not the best one for this project.

Another common approach is to approximate the Gaussian process with a basis expansion and constrain the coefficients of that expansion (López-Lopera et al. 2018; Maatouk and Bay 2017). However, it can be difficult to relate the priors of these coefficients to the shape of s, making it hard to solicit prior information from non-statistical experts (**CITE**). Another approach is seen in, where Lin and Dunson (2014) project unconstrained Gaussian processes onto a shape-constrained space. However, this approach has two limitations. The first is that it cannot conduct inference on covariance parameters, as those posterior distributions are affected by the projection. The second is that the projection often produces non-smooth sample paths, which reduces interpretability (Golchi et al. 2015). Both limitaions make it undesirable for this project. In yet another approach, Lenk and Choi (2017) assume the q^{th} derivative of s are squares of Gaussian processes, where $q = 1$ for monotonicity and $q = 2$ for convexity. They place priors on the coefficients of a Karhunen-Loeve expansion, which are not particularly interpretable.

Next, we consider two papers with approaches that have more directly the one taken in this project. In Shively, Sager, and Walker (2009), .

In Bürkner and Charpentier (2020), proposes a Bayesian model to estimate ordinal predictors with monotonic effects. They employ a simplex parameter ζ to model normalized differences between categories, and a scale parameter b. Importantly, these parameters are very interpretable. Using a Bayesian methodology allows for more complex models and the use of prior distributions. These prior distributions allow for the incorporation of subject matter knowledge, and regularize model predictions. The prior on b express prior knowledge on the average differences between adjacent categories, while the prior on the simplex ζ expresses prior knowledge on individual differences between adjacent categories. The authors suggest using an $N(0, \sigma)$ prior on b, and a $Dirichlet(\alpha)$ prior on ζ. Larger values of σ implies larger average differences between categories, and α expresses the individual differences between adjacent categories. Therefore, σ and α penalize the average and individual differences between adjacent categories. The authors provide visuals in the paper, such that values for σ and α may be elicited from non-statistical experts. These are the exact advantages of the Bayesian approach that make it so attractive for this project.

Details on cGAIM

The cGAIM uses an iterative two-step optimization scheme. In the first step, α is updated using a quadratic program. In the second step, the s_i are updated using the shape-constrained additive model methodology from Pya and Wood (2015). α can be constrained to have non-negative components that sum to one, so that it is a vector of weights on the entries of Z. Once estimated, these weights give the relative contribution of each component to the mortality outcome. The cGAIM can also constrain s by, for example, requiring it to be monotonic or convex. The bcGAIM will initially be implemented in Stan, a statistical modeling language that performs optimization using Hamiltonian Monte Carlo (Carpenter et al. 2017). With Stan performing the optimization, the initial task is to develop priors that enforce the constraints seen in the cGAIM. As a simple example, setting a Dirichlet prior on α constrains it to be a vector of weights (Betancourt 2012).

Details on bcGAIM

Compared to the cGAIM, the bcGAIM provides two main statistical benefits. The first is that it provides credible intervals for α, while the cGAIM does not provide confidence intervals for α. Quantifying the uncertainty of the estimates for α is important for a very important scientific question – can the bcGAIM determine how much specific pollutants contribute to polluted air? Narrow credible intervals indicate that it can attribute the health effects to specific pollutants. Wide credible intervals indicate that it can identify the health effects but not attribute them to specific pollutants. Either result would be a significant contribution to the development of multiple pollutant models, as it would provide evidence if the health effects of air pollution can be associated to particular pollutants through α or only to a mixture through s. The second advantage is that the bcGAIM can identify and address multi-modality in the posterior of α. If α is multimodal under an uniformative prior, one can use relevant scientific knowledge to place stronger priors on α. In comparison, the cGAIM only provides a point estimate for α and cannot detect multi-modality.

Following its implementation in Stan, the bcGAIM will be implemented to be estimated non-MCMC inference methods, similar to Iterated Nested Laplace Approximation (INLA) (Rue, Martino, and Chopin 2009). These methods provide computational and ease-of-use and benefits, and will expand the types of problems and number of users who can make use of the bcGAIM methodology.

We will also explore using different response distributions. The standard single pollutant model is the log-linear Poisson model (Dominici et al. 2002; Liu et al. 2019), while the case crossover has seen increased attention in the air pollution literature (Wei et al. 2019; Stringer, Brown, and Stafford 2020). It can be viewed as a conditional Poisson model, obtained by stratifying by subject and conditioning on the number of events occurring in an observation period.

The Available Data Sets

Air pollution and mortality/morbidity data sets for 25 cities across Canada from Health Canada. Air pollution and mortality/morbidity data sets for ... cities in Quebec from ... COVID-19 case and mortality data for regions across Canada.

Environmental data that may confound the effect of air pollution, such as temperature and humidity, is publicly available. For COVID-19, the potential confounders and other relevant variables are still being actively investigated. Potential confounders include socio-economic status, race, population density, and occupation.

How Are The Aims Associated With The Statistical Methodology?

This project has three research aims:

1. Develop a multi-pollutant air quality health index (AQHI).
2. Develop multi-pollutant exposure models for health effects.
3. Investigate how mixtures of pollutants affects daily COVID-19 mortality.

We address how the proposed statistical methodology will be used in each research aim.

The first research aim is to develop a multi-pollutant air quality index. We will do so by developing the bcGAIM, the multi-pollutant model discussed above. With a Poisson response distribution and the response variable being the appropriate health outcome, the bcGAIM will output a relative risk for every combination of (measured or forecasted) pollutant values input into the model. The AQHI will take the relative risks as inputs and output warnings, based on cutpoints for the relative risk. Forecasted pollutant values will be provided by Environment Canada.

The motivating research question in developing the bcGAIM is the air quality index. The inquiry into shape-constrained priors is motivated by the air pollution application. A priori, we may believe that increasing levels of an multi-pollutant mixture is associated with worse health outcomes. There are also extreme air pollution events, such as forests fires, such that we may believe that rapidly increasing pollutant levels leads to even worse health outcomes. Thus, we may wish to constrain s to be negative (**CITE**) To express this in a Bayesian framework, we see to develop priors that

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The second research aim is to develop multi-pollutant exposure models for health effects. I don't know what this means.

The third research aim is to investigate how mixtures of air pollutants affect daily COVID-19 mortality. This is an application of the bcGAIM, where the response variable is COVID-19 mortality and the argument of s is a linear combination of pollutants. The air pollution model also includes linear terms such as day-of-the-week effects and seasonal terms, and smooth functions of confounders such as time and temperature. The research into relevant regression variables and confounders is ongoing. **ADD**. There has also been confounders in COVID-19 model will be different, and will reflect

Extending This to an "INLA-like" Methodology

The major benefit of the bcGAIM model is that is provides uncertainty bounds on the weights of the multi-pollutant mixture. In addition to the Stan implementation, we also wish to develop a non-MCMC inference implementation, similar to those used in INLA. For the INLA approximation to work, the conditional posterior of s and α must be log-concave such that they can be reasonably approximated by a Gaussian distribution. However, many different values of α are likely to evaluate to the same value of s. That is, the posterior distributions of α is multi-modal, and hence not log-concave. The multi-modality renders the posterior not log-concave, such that significant methodological innovations are required.

The multi-modal posterior of α is a property of the model, While Stan will return a posterior distribution for α, discerning between the possible modes of α will be a challenging problem even when conducting inference in Stan. In the motivating application of multi-pollutant models, it may be possible to use

Comment: Ask Patrick (and Alex?) about the best way to present the INLA extension.

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