Using statistical methods and reproducible tools to gain new insights from biomedical and public health data

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MfPH Next Generation Seminar Series

3/15/23

MATHEMATICS FOR PUBLIC HEALTH

Introduction

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- This is specially true in the case of health research: public health, or biomedical data can be complex, and decisions along the analysis can result in different interpretations.
- In this talk I will focus on two examples that showcase how we can get more insight from looking at data from a different perspective.

The Case of Public Health Data: COVID-19 Vaccination

COVID-19: Why?

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[2] Gerretsen et al. 2021.

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- Individuals with lower income, and those belonging to a racial/ethnic minority have had lower vaccination uptake[1,2].
- This is important because these differences in vaccination uptake have implications on virus transmission.

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    - The survey ran between late 2021 and early 2022 and collected socio-demographic information along with self-reported vaccination status ("Have you received the first dose of the Covid vaccine?")

COVID-19: The Case of Ontario

Table 1: Selected socio-economic factors from the survey

Variable	Levels
Age group	16-34,35-54,55 and over
Income bracket (CAD)	under 25,000, 25,000-59,999, 60,000 and above
Race/ethnicity	Arab/Middle Eastern, Black, East Asian/Pacific Islander, Indigenous, Latin American, Mixed, South Asian, White Caucasian, Other

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- We could do the same, but what else can we get from this data?
    - There have been some interesting changes in Ontario with regard to healthcare.

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- There were 14 LHINs, with additional subdivisions.

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- Problems with the LHINs:
- In multiple cases, the boundary of a LHIN did not match a municipal boundary.
  - One part of a city would be in a LHIN whereas another part of it would be in another LHIN.
  - Weakness in this approach due to complexity, lack of funding and bureaucracy were identified[3].

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- In late 2019, Ontario adopted the Health Regions approach for healthcare and phased out the Local Health Integration Network (LHIN) approach.
- The change is relatively new. Multiple challenges:
    - Data for the Health Regions is not available from the Census.
    - **Have the Health Regions helped in reducing disparities in healthcare in the province?**

COVID-19: The Case of Ontario

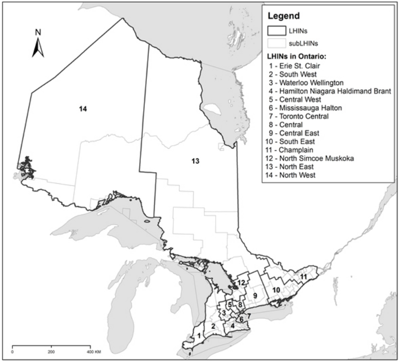

Figure 1: Ontario LHINs (Crighton et al. 2015)

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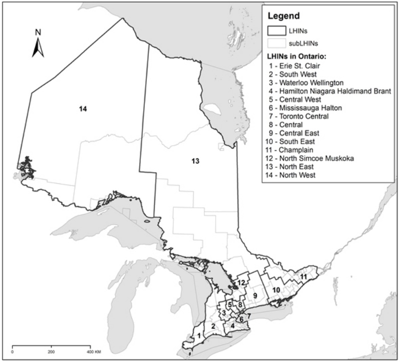

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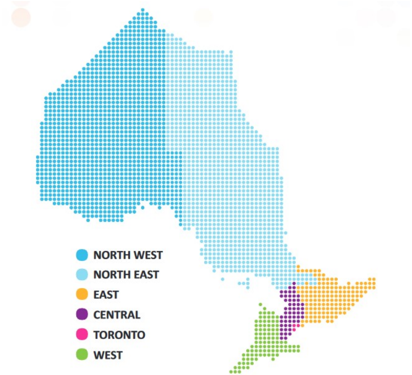

Figure 2: Ontario Health Regions (Ontario Business Health Plan 2022-2023)

COVID-19: The Case of Ontario

- Where in Ontario did responses come from?

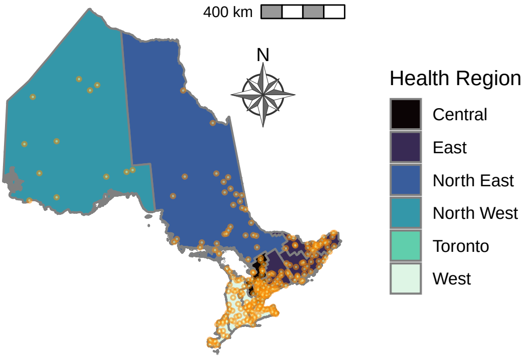

Figure 3: Geographic representation of the survey data collected by the Fields Institute

COVID-19: The Case of Ontario

- Therefore, we decided to integrate the different Health Regions in our analysis to determine the odds of vaccination.

$$\log\left(\frac{p(\text{vac})}{1-p(\text{vac})}\right) = \beta_0 + \beta_1(\text{Age group}) + \beta_2 \text{ Race} + \beta_3 \text{ Health Region} + \beta_4 \text{ Income} + \tag{1}$$

$$\beta_5(\text{Health Region} \times \text{Race}) + \beta_6 \ (\text{Income} \times \text{Race})$$

Results

Table 2: **Selected** Multivariable Regression Results

Characteristic	OR	95% CI	p-value
Income (CAD)			
60000 and above	—	—	
25000-59999	0.59	0.39, 0.89	0.011
under 25000	0.37	0.25, 0.56	<0.001
Race			
White/Caucasian	—	—	
Arab/Middle Eastern	0.31	0.14, 0.69	0.004
Black	0.32	0.17, 0.60	<0.001
East Asian/Pacific Islander	1.15	0.50, 2.66	0.7
Indigenous	0.44	0.19, 1.02	0.056
Latin Aamerican	0.28	0.11, 0.67	0.004
Mixed	0.64	0.25, 1.65	0.4
Other	0.22	0.12, 0.41	<0.001
South Asian	0.91	0.49, 1.69	0.8
Health Region			
Toronto	—	—	
Central	1.47	0.92, 2.35	0.11
East	1.42	0.90, 2.23	0.13
West	1.55	1.05, 2.30	0.029
Income and Race			
25000-59999 * Arab/Middle Eastern	1.79	0.67, 4.83	0.2
under 25000 * Arab/Middle Eastern	3.05	1.26, 7.39	0.013
25000-59999 * Black	1.34	0.59, 3.05	0.5
under 25000 * Black	3.19	1.45, 6.99	0.004
25000-59999 * East Asian/Pacific Islander	0.42	0.17, 1.05	0.062
under 25000 * East Asian/Pacific Islander	1.16	0.47, 2.86	0.8
25000-59999 * Indigenous	1.36	0.48, 3.89	0.6
under 25000 * Indigenous	1.45	0.55, 3.80	0.5
25000-59999 * Latin American	1.24	0.45, 3.43	0.7

Results

Characteristic	**OR**	**95% CI**	**p-value**
under 25000 * Latin American	2.80	1.04, 7.51	0.041
25000-59999 * Mixed	0.85	0.32, 2.26	0.7
under 25000 * Mixed	1.10	0.37, 3.27	0.9
25000-59999 * Other	6.93	2.65, 18.1	<0.001
under 25000 * Other	4.59	2.33, 9.05	<0.001
25000-59999 * South Asian	1.20	0.51, 2.85	0.7
under 25000 * South Asian	2.00	0.93, 4.30	0.077
Race and Health Region			
Arab/Middle Eastern * Central	0.66	0.26, 1.70	0.4
Black * Central	0.44	0.19, 0.98	0.046
East Asian/Pacific Islander * Central	0.98	0.38, 2.53	>0.9
Mixed * East	0.91	0.28, 3.03	0.9
other * East	1.05	0.39, 2.83	>0.9
South Asian * East	0.52	0.19, 1.45	0.2
Arab/Middle Eastern * West	1.00	0.37, 2.73	>0.9
Black * West	0.76	0.32, 1.80	0.5
East Asian/Pacific Islander * West	0.52	0.20, 1.34	0.2
Indigenous * West	0.39	0.14, 1.09	0.073
Latin American * West	0.94	0.32, 2.72	>0.9
Mixed * West	0.37	0.12, 1.16	0.089
Other * West	0.41	0.18, 0.93	0.032
South Asian * West	0.41	0.18, 0.95	0.037

[1] OR = Odds Ratio, CI = Confidence Interval

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- People in certain racial minority groups had lower odds of vaccination than White/Caucasian individuals.
- However, individuals that identified with a racial/ethnic minority and that were in a low household income bracket (<60k CAD) had higher odds of vaccination than individuals with a high household income.

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- Our results show that there were disparities in vaccination uptake in Ontario.
- People in certain racial minority groups had lower odds of vaccination than White/Caucasian individuals.
- However, individuals that identified with a racial/ethnic minority and that were in a low household income bracket ($<$60k CAD) had higher odds of vaccination than individuals with a high household income.
- This is likely caused by the type of occupation: people in racial minorities, and those with a low household income work in essential occupations (gas station workers, grocery store workers, agricultural workers)[4], and thus potentially got the vaccine to be able to work.

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- But there are also intra-provincial differences in vaccine uptake within the Health Regions:
  - For example, South Asian individuals in the West Health Region had lower odds of vaccination that in other Health Regions.
  - These results provide a more comprehensive assessment of COVID-19 vaccination rates within Ontario, as they showed that certain minority groups within specific income brackets and certain Health Regions had differences in vaccination.

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- A more granular view of data (in this case, examining differences within Health Region, Income and Race) can provide insight for public policy development.

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- Data cleaning is **important**}
  - Unifying geographical data can be challenging
  - Specially because most data relies on legacy information from the LHINs
- A more granular view of data (in this case, examining differences within Health Region, Income and Race) can provide insight for public policy development.
- There is a need for future studies that examine more in detail these differences and can provide a rationale.

The Case of Biomedical Data

Longitudinal Data

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- Biomedical studies often collect longitudinal data to see the effect of an intervention over time:
  - How a chemotherapy treatment changes the metabolism of a tumor
  - How the concentration of a drug changes over time in the blood
- How is this data typically analyzed?

Linear Models

$$
\begin{aligned}
y_{ijt} = \beta_0 + \beta_1 \times treatment_j + \beta_2 \times time_t + \\
\beta_3 \times time_t \times treatment_j + \varepsilon_{ijt}
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A LMEM follows the same exact structure, only incorporates a random effect α_{ij}, which allows for different intercepts.

Trends Over Time

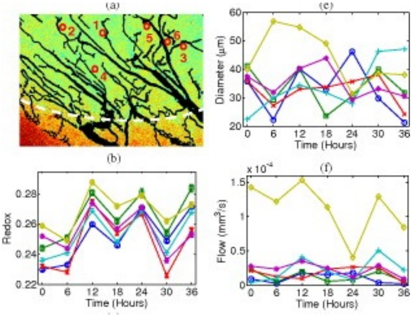

Figure 4: Tumor imaging data (Skala et al. 2010)

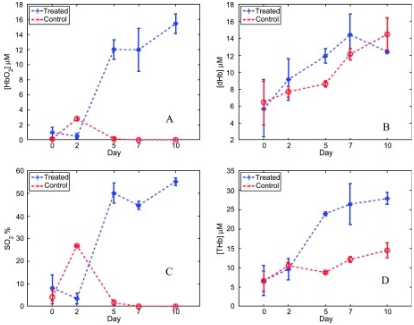

Figure 5: Tumor oxygenation data (Vishwanath et al. 2009)

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[5] Beck and Jackman 1998.

Trends Over Time

- The issue in those data is that the trends are not linear, and therefore, a linear model will miss changes in the signal where some metabolic or physiological relevant change is taking place.
- Polynomial effects can be used, but they create biases at the boundaries of the covariates[5].

[5] Beck and Jackman 1998.

Generalized Additive Models (GAMs)

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- We can use a *basis function* to estimate the smooth function.
- Splines are helpful as basis functions: Thin plate regression splines (TPRS) are computationally efficient, and the underlying principle is that of polynomial pieces "joined" together

How GAMs work

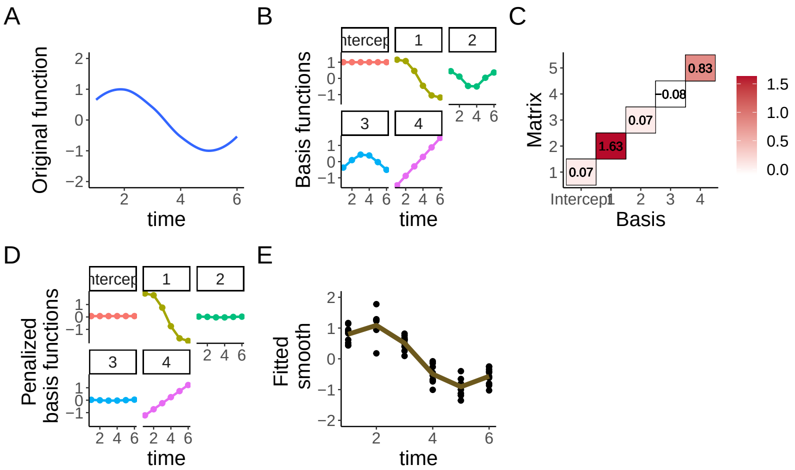

Figure 6: Fitting process of a GAM.

An Example

- Simulated data from a study on radiotherapy in a mouse model of melanoma[6].

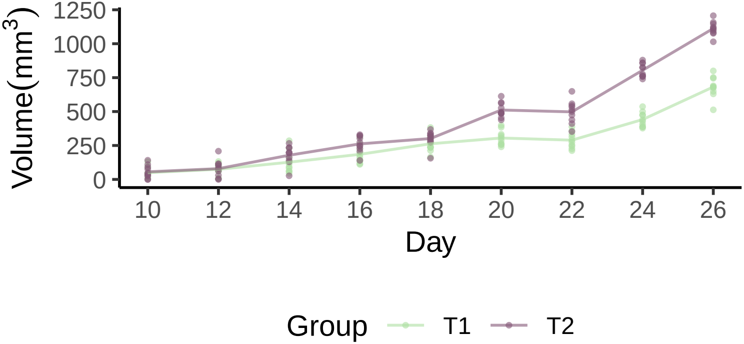

Figure 7: Tumor volume in two groups of tumors under radiotherapy

[6]Sen et al. 2011.

Fitting a GAM

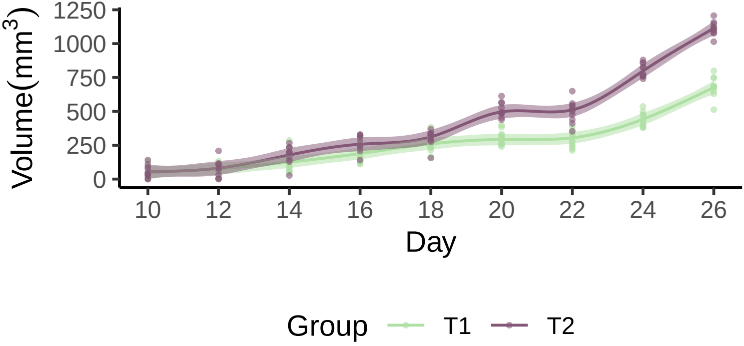

Figure 8: GAM fitted to simulated data

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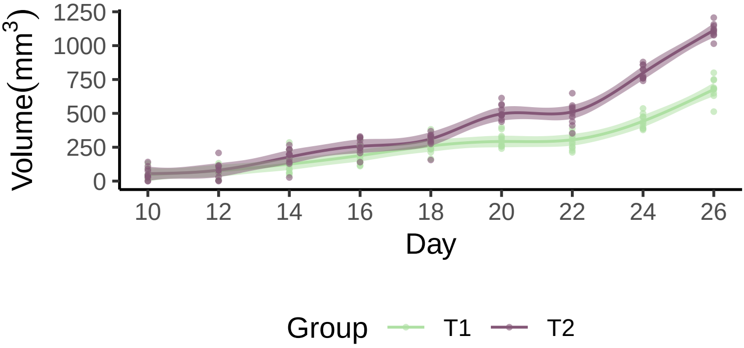
Fitting a GAM



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- The model captures the trend of the data
- We can furthermore compare the trends.

Differences

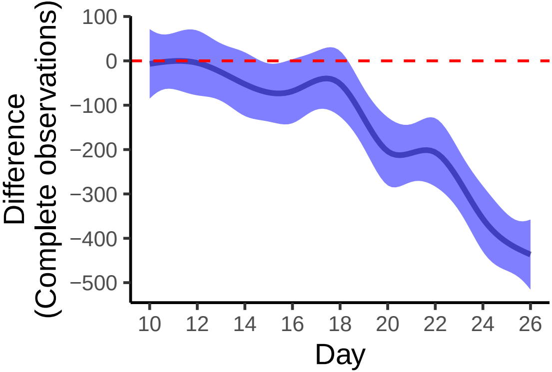

Figure 9: Pairwise comparisons between smooths

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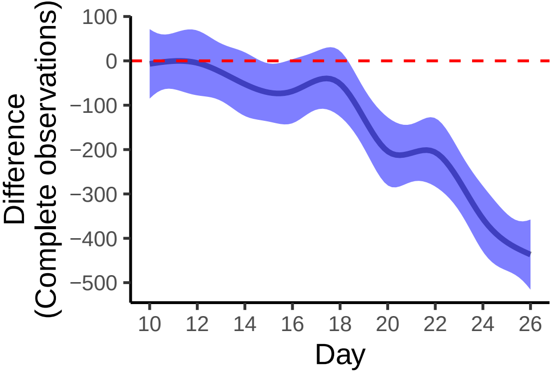

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- This can give an idea of further explorations of biological

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  - A model that captures non-linear trends in the data
  - This allows to examine specific time points that might be of interest, where metabolic, or physiological relevant changes might be occuring
  - Lets the data speak for itself

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- In synthesis, sharing all the information used to create a paper such that anyone can re-create the analysis, results, and the paper itself from the files provided.

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  https://github.com/aimundo/GAMs-biomedical-research

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  https://github.com/aimundo/GAMs-biomedical-research
- COVID-19: Work is ongoing, but repository will be ready when paper is submitted

Conclusion

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- There is an ongoing need of analyzing public health data to address important disparities in areas such as vaccination.
- Semi-parametric statistical to analyze biomedical/public health longitudinal data, such as GAMs can provide better insight on periods where important biological changes might occur.

Acknowledgements

- The Nasri Lab (Université de Montréal)
  - Bouchra Nasri, PhD (PI)
  - Idriss Sekkak, PhD
  - Rado Ramasy
  - Fatima El-Mousawi
  - Rawda Berkat
- The Muldoon Lab (University of Arkansas)
  - Timothy J. Muldoon (PI)
- John R. Tipton (Los Alamos National Laboratory)

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Beck, Nathaniel and Simon Jackman (Apr. 1998). “Beyond Linearity by Default: Generalized Additive Models”. In: *American Journal of Political Science* 42.2, p. 596. DOI: 10.2307/2991772. URL: https://doi.org/10.2307/2991772.

Gerretsen, Philip et al. (Nov. 2021). “Individual determinants of COVID-19 vaccine hesitancy”. In: *PLOS ONE* 16.11. Ed. by Leeberk Raja Inbaraj, e0258462. DOI: 10.1371/journal.pone.0258462. URL: https://doi.org/10.1371/journal.pone.0258462.

Hawkins, Devan (June 2020). “Differential occupational risk for COVID-19 and other infection exposure according to race and ethnicity”. In: *American Journal of Industrial Medicine* 63.9, pp. 817–820. DOI: 10.1002/ajim.23145. URL: https://doi.org/10.1002/ajim.23145.

Nafilyan, Vahe et al. (July 2021). "Sociodemographic inequality in COVID-19 vaccination coverage among elderly adults in England: a national linked data study". In: *BMJ Open* 11.7, e053402. DOI: 10.1136/bmjopen-2021-053402. URL: https://doi.org/10.1136/bmjopen-2021-053402.

Sen, Arindam et al. (May 2011). "Mild Elevation of Body Temperature Reduces Tumor Interstitial Fluid Pressure and Hypoxia and Enhances Efficacy of Radiotherapy in Murine Tumor Models". In: *Cancer Research* 71.11, pp. 3872–3880. DOI: 10.1158/0008-5472.can-10-4482. URL: https://doi.org/10.1158/0008-5472.can-10-4482.

Tsasis, Peter, Jenna M. Evans, and Susan Owen (Sept. 2012). "Reframing the challenges to integrated care: a complex-adaptive systems perspective". In: *International Journal of Integrated Care* 12.5. DOI: 10.5334/ijic.843. URL: https://doi.org/10.5334/ijic.843.