Applied Mathematics in the Time of Corona: A Survival Guide

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"I think that a mathematician is well suited to be in isolation"
Attributed to Sophus Lie, after his prison release
following a wrongful arrest in Paris (1870).

A looming storm

When and where did you first hear about COVID-19? This may not be a vivid memory like the time you heard about 9/11. Yet, we can all remember when the importance of this new disease first entered our consciousness for good. For me, it was early January. I was visiting my friend Yi Bin Fu in Tianjin and in the middle of my visit I was told not to worry. "Not to worry about what?" I asked, very worried. "There is a new disease, it is like SARS, people die, but it is confined to Wuhan, more than a 1,000km away. Nothing to worry about". Shortly after my return, the academic drums started to beat. First, a distant hum, the noise would soon be deafening. Robin Thompson, a bright young researcher in mathematical epidemiology in our department wrote one of the first papers [5] on the disease and gave, by the end of the month, an overcrowded talk about it. The picture was clear, with a reproduction number between 2 and 3, mortality rates hovering around 1%, and no natural immunity, the virus had all the potential to become a massive epidemic. But, if confined to China, there is really nothing to worry about, I reasoned naively. The following month would see the dominos falling one after the other. Travel bans were established, new individual cases popped up around the world, the first serious outbreaks appeared in Northern Italy, and panic took over populations and governments alike. The rest, as they say, is history. By mid February, we could clearly see the storm looming over the British shores. An extensive lockdown was inevitable. We would soon pack our books and papers and stay home for an indefinite period of time. Filled with a sense of dread, frustration, and impotence, my thoughts kept returning to the same questions: How can we, as a modeling community, help? How can I, as an individual, help?

The shortcomings of academia

There is no doubt that modeling has a clear and important role to play in such circumstances. Microscopes and telescopes allow us to probe the smallest and largest scales of the universe. Mathematical modeling is the only scientific crystal ball that we have to look at possible futures. It turns out that epidemiological models are the bread and butter of applied mathematics with a very large literature and striking successes to pandemic control, as I had already showcased in my little book [3]. Large specialized groups around the world worked on the problem and, at first, it was not clear that unsolicited help would actually improve the situation. I know many of them and admire their work. The problem was in good hands, I thought. Yet, soon enough, three main problems emerged that exposed clear shortcomings of our regular academic system in a time of crisis.

First, basic epidemiological models, such as the Suscetible-Infected-Recovered model, are deceptively simple to understand and code. Anyone who ever took an undergraduate course in differential equations can set up the system within minutes on a home computer and produce nice-looking curves showing the rise and fall of an infected population without realizing that the real problem is to get the correct parameters from the data and to properly extend such models for the current crisis. This apparent simplicity created a tsunami of low-quality preprints that soon clogged the system.

Second, there was no discussion, hence no clear consensus, across the multiple models developed by the leading groups. Typically, such consensus arises through the long multi-year academic cycle of publications, exchanges, testing, validation, and scientific meetings. The usual time frame for proper scientific debate, like the one for the development of a vaccine, was not suitable for the crisis.

Third, new reports were produced constantly, by university research groups, by companies, by government departments. At the government level, how could the proper advice be given when so many reports flooded the system? Which ones were good enough to inform policy decisions?

In the UK, a group of modelers attached to the venerable institution of the Royal Society decided to address this problem by creating a new national initiative for the Rapid Assistance in Modelling the Pandemic headed by Mike Cates in Cambridge. RAMP was born and the call for volunteers was soon answered by thousands of scientists around the country and around the world. In Oxford, Philip Mani and I were soon volunteered to lead the effort. Of particular interest to RAMP was an ongoing effort into a systematic literature review initiated by Robin Thomson and Eamonn Gaffney. Soon, Philip and I were tasked by RAMP to set up a new mechanism to quickly review models, softwares, and reports of possible interest to the various scientific committees and departments advising the government. The Rapid Review Group that we created is divided into 6 different subject panels and staffed by an all-star team of 120 dedicated expert volunteers. It stands ready to assess critical scientific work with a typical turnaround of 24 to 48 hours, bypassing the typical monthlong process offered by scientific journals. As the pandemic tides rose, every sector of the economy was in need of some form of modeling and the demand surged. Our group of volunteers, fueled by the collective ideal of scientific quality has been busy churning out new reviews to meet the demand and plans to continue its work through 2021. This new structure provides a shortcut to the academic cycle by both filtering out irrelevant work and giving further support to quality work. The way I see it, our small contribution is to maintain the highest level of academic standards in the midst of a crisis. Personally, the process was initially exhausting, but it gave me a small window of observation into the shifting interests of the government and allowed me to develop a better understanding of the entire field. It also made me realize that, now more than ever, there is a need for thorough review, critical assessment, and quality scientific advice. Whether or not scientific advice is heard and acted upon by governments is another story, one that still needs to be written.

My body for science

Living in Oxford provided me with another unexpected way to contribute. Oxford has always been a centre of excellence for the development of new vaccines and it was no surprise that the Jenner Institute was the first to come up with a new vaccine candidate, ChAdOx1 nCov-19, based on their earlier work on the MERS and SARS vaccines [6]. By April, they announced a phase 2 safety trial and asked for volunteers, soon followed by a phase 3 efficacy trial. Like everyone else, I was in lockdown at the time. There are only so many papers one can write and breads one can bake every day and I soon realized that apart from organizing rapid reviews my intellectual skills were not really needed for the crisis. But maybe, I thought, science could make some use of my body and I jumped on the opportunity. I enrolled in the trials and was eventually selected. Was my goal purely selfish or purely altruistic? Probably neither (or both). Clearly, the vaccine could offer some protection, but this assumes that you actually get the real stuff rather than the common meningitis vaccine in this randomized trial (about a fifty-fifty percent chance). It also assumes that the vaccine will actually work. Early indications are positive but the trial in the UK, with 12,330 participants, will run until August 2021. We will probably not know its outcome before January 2021, at the earliest. No, my main motivation was mostly intellectual. I found the process and the stakes fascinating and I wanted to be part of it so that I could experience it first hand, in the same way that I spent a day in neurosurgery when I first became interested in the brain. The abstract world that we build through modeling needs to be anchored in reality and the trial was a chance to ground myself. I also enjoy the poetic justice of self-metamorphising into a datum after having spent so many years abusing data.

The Phase 2 (safety) trial shows promising result [1]. Yes, the vaccine is safe and does trigger an immune response. In their paper, the authors list the standard side effects following the injection of ChAdOx1 compared to Meningitis. They report the fraction of people experimenting a given symptom for either vaccine. Now, here is an interesting Bayesian problem. If I have experienced a given symptom but not others, what is the probability that I have received the COVID vaccine? Many family members and friends are also part of the trial. Some have experienced some of these symptoms, some haven't. As you can imagine, this possibility of assigning probability leads to interesting (socially-distanced) conversations around the dinner table. Yet, I will refrain myself from actually assigning probability as it would partially unblind the experiment and risk skewing the results. A good datum knows its place and the exercise is left to the reader.

The Newfoundland story

Through the reviewing process and a nearly morbid fascination for data and graphs related to the evolution of the crisis, I became increasingly acquainted with many of the scientific challenges related to COVID. Yet, I was still reluctant to jump into the fray, assuming that better researchers are on it. Too many cooks spoil the broth. However, my long-time friend and collaborator, Ellen Kuhl from Stanford, did not share my restraints. As an extreme athlete, a marathoner, a triathlete and an iron-(wo)man, Ellen is fearless. Early on, she realized that the methods we had developed to model the propagation of toxic proteins on the brain connectome [2] could be readily adapted to the evolving crisis. Ellen combines a unique ability for modeling, amazing technical skills, and a great intuition for good problems. She quickly built elegant data-driven models for the spread of the diseases around the world. Eventually, she convinced me to collaborate on a couple of COVID projects, one of which would become the central evidence of a case in front of the Supreme Court of Newfoundland and Labrador [4].

The island of Newfoundland is part of the Canadian province of Newfoundland and Labrador. Following a travel ban on May 5, 2020, this Atlantic province enjoyed the rather exceptional and enviable position of having the coronavirus pandemic under control. By July 3, 2020, it had a cumulative number of 261 cases, with 258 recovered, 3 deaths, and no new cases for 36 days. The same day, the *Atlantic Bubble* opened to allow air travel between the four Atlantic Provinces, Newfoundland and Labrador, Nova Scotia, New Brunswick, and Prince Edward Island, with no quarantine requirements for travelers. With respect to COVID, the inhabitants of the province are in a dangerous position as they have the highest rates of obesity, metabolic disease, and cancer nationally, and an unhealthy lifestyle with the highest rate of cigarette smoking among all provinces. Despite its success in eliminating the virus, the government found itself in a precarious position. Its travel ban, Bill 38, was being challenged by a Halifax resident who was denied entry for her mother's funeral in the Spring and the lawsuit was further supported by the Canadian Civil Liberties Association. They are seeking a declaration from the provincial Supreme Court in St John's that the travel ban is unconstitutional, a decision that could apply to the entire country. Determined to keep control of its borders, the Office of the Attorney-General reached out to Ellen. Would her models be applicable to this situation? What would happen during gradual or full reopening under perfect or imperfect quarantine conditions?

Ellen and I had been talking about a hypothetical problem like this one. If the virus is eliminated from a region, can it come back, like a boomerang, when restrictions are eased? Newfoundland seemed to be the perfect case study for us, and with the help of her outstanding Post-doc, Kevin Linka and Dr Proton Rahman, a clinical epidemiologist and professor of medicine at Memorial University of Newfoundland, we jumped at the opportunity to test some of our ideas. Soon, we converged on a network model where each node represents a US state or a Canadian province. On each node, we run a local Suscetible-Exposed-Infected-Recovered epidemiological model and model air traffic by a graph Laplacian-type transport process as commonly done for network transport. Parameters are estimated by Bayesian inference with Markov-chain Monte Carlo sampling using a Student's t-distribution for the likelihood between the reported cumulative case numbers and the simulated cumulative case numbers.

Conceptually, the model is quite simple. I have a natural preference for parsimony when it comes to modeling complex phenomena as the assumptions are completely known and in full display. This is a personal choice and the outcomes of such models should be seen as estimates rather than hardcore forecast. What we found is quite interesting. Using air traffic information from the previous 15 months, we showed that opening Newfoundland to the Atlantic provinces or the rest of Canada would have negligible effects on the evolution of the disease as prevalence dropped considerably in Canada. Yet, opening the airports to the USA would lead to 2-5 infected passengers entering the island a week, with as many as 1-2 asymptomatic travelers. Without an air-tight quarantine system, the disease would reach 0.1% of the Newfoundland population within 1 to 2 months.

In the first week of August, evidence were presented to the court. The Chief Medical Officer of Health Dr. Janice Fitzgerald opened with the following quote: "*In 1775 the American revolutionary Patrick Henry declared, 'Give me liberty or give me death.' In this case, if the applicants' remedy is granted, it will result in both.*" The same week Proton testified in court about our model, its assumptions, and our findings. To my surprise, the scientists were heard and on 17 September, the judge rendered his verdict. In his ruling, Justice Burrage declared that '*'The upshot of the*

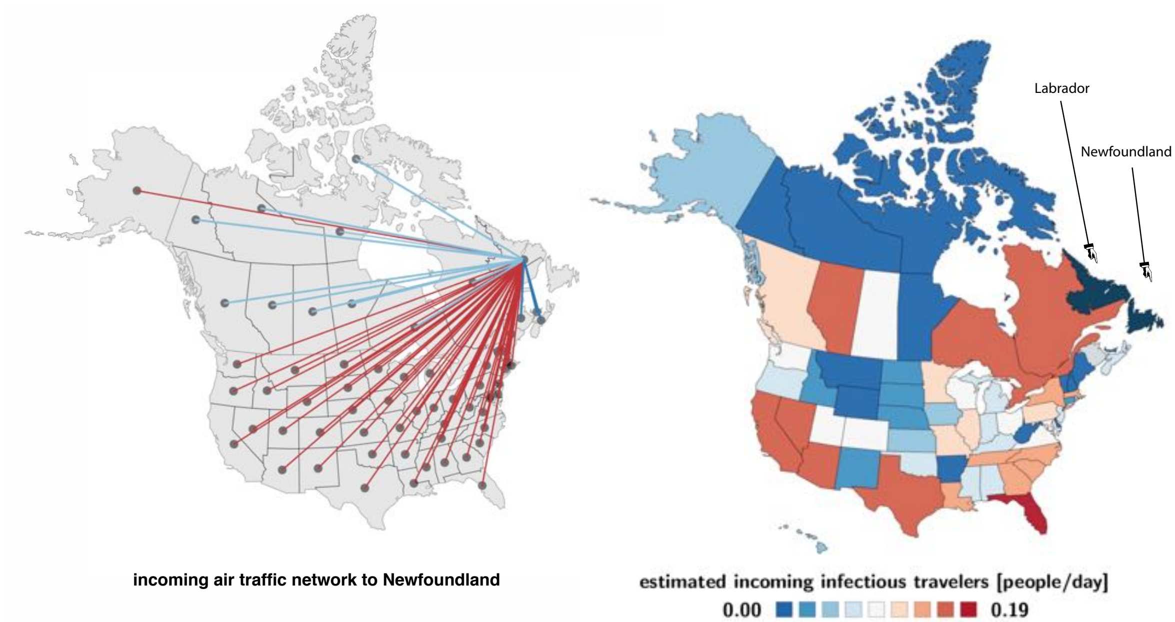

Figure 1: Left: Mobility modeling. Discrete graphs of the Atlantic Provinces, of Canada, and of North America with 4, 13, and 64 nodes that represent the main travel routes to Newfoundland and Labrador. Dark blue edges represent the connections from the Atlantic Provinces, light blue edges from the other Canadian provinces and territories, and red edges from the United States. Right: Estimated COVID-19 infectious travelers to Newfoundland and Labrador. Number of daily incoming air passengers from the Canadian provinces and territories and the United States that are infectious with COVID-19. Figures adapted from [4]

modelling ... is that the travel restriction is an effective measure at reducing the spread of COVID-19 in Newfoundland and Labrador." He concluded that yes, the ban was legal and justified. Having an impact on the lives of Newfoundlanders, however small, is a strange but rather pleasant feeling.

Final proof

The lockdown has been difficult for most people. Despite creating a feeling of helplessness, it has been also a time of personal reflection. Like many, I took the opportunity to build my bread-baking skills and ended producing a couple of loaves every other day for the last few months. The process is both soothing and fascinating. As days go by, it started to dawn on me that bread making is very much like mathematical modeling. It is a process that deeply relies on science yet is so complicated that craft, techniques, and tricks are necessary ingredients. Like modeling, baking cannot be taught but has to be practiced. You can only learn by putting your hands in the dough, literally and figuratively. The beauty of the living dough and the evolving model is that you'll never quite know what you'll end up with. At the end of the last proof, your creation can be a thing of beauty and pride or a miserable failure. Yet, the drive and curiosity that get me out of bed in the early morning are the same, and the pleasure of breaking the crust with my family or sharing mathematics with friends and colleagues, a source of constant pleasure.

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