Maths Vs. Covid-19
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Introductions

Let me start by introducing myself and my research. I'm broadly interested in using mathematics to understand infectious disease dynamics. Before COVID-19 ("BC"), the main topics within my research were (i) models for evolving viruses, particularly multiple co-circulating strains; (ii) the spatial patterns of disease transmission, for example in exploring the observed patterns of spread of pandemic influenza in the US in 2009; (iii) virus bioinformatics, and methods for signal detection of genetic constraint, and (iv) in recent years we have been working on the "BBC pandemic" – a large citizen science project to understand better how people are mixing and moving in the UK, to prepare for modelling future pandemics (when the corresponding BBC programme was broadcast in 2018, of course we were hoping this work would not be needed any time soon). Running through all of this, influenza has been my longstanding interest.

Since February 2020, I have been very much involved in the UK scientific response to the COVID-19 pandemic. I remain an independent university academic, and I'm one of the many scientists offering our time and expertise in scientific advice to the UK government through SPI-M and SAGE. I should emphasise that today I'm talking in my own capacity as an independent scientist.

A lot has happened in the science, in the policy advice, and I also want to talk a bit about the human side: the experience of being a mathematician working on COVID-19 during this crisis. Things for us have often been deeply challenging and some days seem just beyond what is humanly possible. Working on a pandemic *during the pandemic*, has been horrifying. But among all this, there have been bright moments: I've got to work with some amazing people who seem to achieve the impossible on a regular basis, I've had a privileged front row seat on the evolving science and science advice. I've seen my own research field change at a mind-blowing pace. And I feel lucky to have had the honour of working at a time when it's our opportunity to step up to the mark and do our thing.

As I speak, this is not something over in the past, but is all very much live - we are still very much in the thick of an ongoing global pandemic. The conundrum for me for this lecture has been what to include. I left options open somewhat with the title "Maths vs COVID-19". What I've decided to do is include the elements which I hope will be most interesting, which means rather than one long topic with a start and end, we will hop around between ideas, themes and also along the timeline of the pandemic.

Maths of Epidemics… Applied to COVID-19

Mathematical modelling plays a variety of different roles in fighting COVID-19. Some of those roles are more obvious and visible, but others maybe more hidden. Some of these roles:

- Providing specific predictions – forecasting – and perhaps this is what people first think of when we are thinking of pandemic modelling.

- A more exploratory role of models is in testing different possible scenarios. In other words, questions like “what if we do this intervention, what would happen next?”.
- Mathematical modelling can be used to explore observed patterns and understand what are the drivers that can and can’t explain observations.
- The models themselves provide a useful language and help us to build our own understanding and intuition in a robust way (so it can be applied to new situations).

The last two are perhaps less obvious and generally more hidden within the scientific advice, so I will focus on these now. I give an example in Figure 1 of the third role above: using models to understand what is behind observed patterns. This is in the context of early March 2020 and explores how spatial patterns would differ depending on whether COVID-19 were established in the UK from a single successful introduction or from many introductions. For multiple introductions around the same time period, different regions in the UK would be quite well synchronised in epidemic upswing. With a single introduction, there may be rapidly rising cases in one region, but the epidemic has yet to take hold in another region.

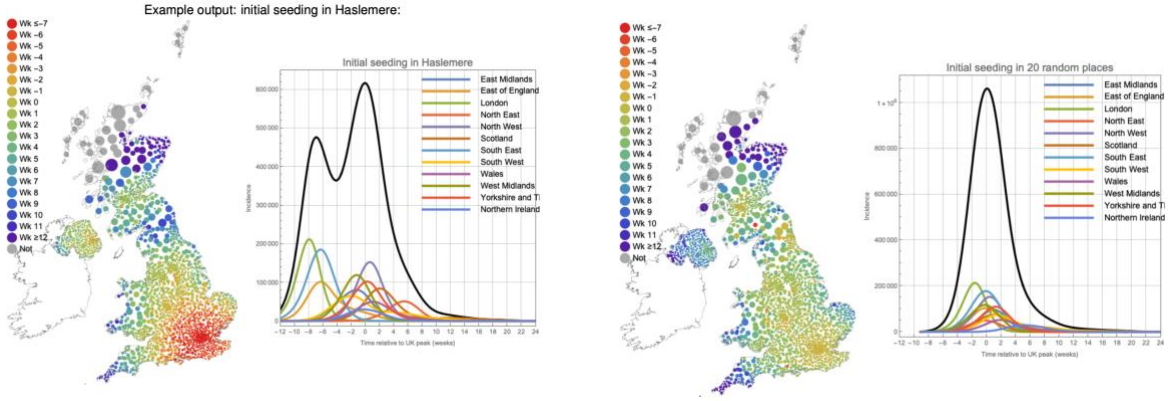

Figure 1: Simulations from the BBC pandemic model, modified for COVID-19 to illustrate the difference between typical patterns if the UK epidemic were sparked by a single introduction (in Haslemere on the left panel) or by multiple introductions (seeding in 20 randomly chosen places on the right panel). The black line on the plots shows the total cases in the UK, while the coloured lines break this down into separate regions (the horizontal axis is time in weeks, set so week 0 is the national peak). The coloured dots on the map show the week that cases peak in each location.

Extracted from a report from Julia Gog to SPI-M, 2nd March 2020 (see Klepac *et al*. 2018 for a description of the BBC pandemic model[1]).

The classic SIR model itself yields valuable insights. This is described in some detail in a recently published paper[2] (so I will not recap it fully in this transcript). A summary of some key insights was seen by SAGE in February 2020[3], noting:

[1] *Contagion! The BBC Four Pandemic – The model behind the documentary*. Klepac, Kissler and Gog 2018. Epidemics. https://doi.org/10.1016/j.epidem.2018.03.003

[2] *Epidemic interventions: insights from classic results*. Gog & Hollingsworth, 2021. Phil. Trans. R. Soc. B https://doi.org/10.1098/rstb.2020.0263

[3] *Transmission-reducing interventions: prediction of reduction in overall attack rate and peak incidence from simple models* (Julia Gog, SAGE repository 24th February 2020). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/891872/S0021_SAGE10_Transmission-reducing_Interventions_SIMPLE_MODELS.pdf

"This simple approach should not replace models including more details, but if predictions from more complex models deviate substantially from those shown here, the factors behind that difference should be identified."

We can even go further in the direction of simplicity, and yet still use the maths to help to build our intuition on epidemics. Consider simple geometric growth:

$$y(n) = aR^n$$

where *y(n)* is the number of cases in infection generation *n*, *a* is multiplicative constant, and *R* is the most famous parameter of 2020: the basic reproduction ratio. A typical plot is given in Figure 2 (left) for a=1000 and R=1.2 (so a gently growing epidemic, starting from 1000 cases in the zeroth generation).

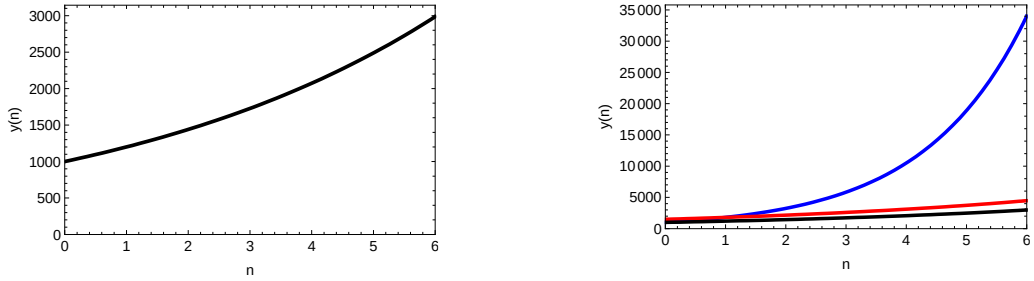

Figure 2: Left: y(n) vs n for a=1000, R=1.2.
Right: same again in black, *a* increased by 50% in red and *R* increased by 50% in blue.

Exploring what happens when we change the parameters *a* or *R*, we see an example in Figure 2 (right). Increasing the coefficient *a* will just scale the whole curve up and down (red curve is just black curve scaled up), but changing *R* leads to a much more dramatic change after a few disease generations (blue curve rapidly diverges from the black curve).

Translating from the numbers back to what this could represent (and this translation and interpretation really is the modelling happening), suppose that y(t) now represents hospitalisations, say. Then the coefficient *a* will be taking into account both initial number of cases but also what proportion of those cases will end up hospitalised. What do the changing parameter estimates correspond to now with this interpretation? A higher disease severity (more likely to end up hospitalised) would translate to increasing *a*, whereas higher transmissibility would mean increasing R.

And this is where gut feeling and maths can clash: it somehow feels more dangerous to increase severity, yet we can see here that increasing transmission is much more important after a few generations of infection. Higher severity is concerning of course for someone who is infected, but the key is that far fewer people are infected than if transmission were higher. In summary: this simple model of geometric growth underlines that really it is the transmission that matters above all when we're thinking about consequences for a population.

The Scientific Response to Modelling COVID-19

This is part of the talk will be more narrative on what has been happening with the modelling, and how we have worked together to assist with government scientific advice. This is necessarily from my own point of view of events and organisations.

SPI-M[4] existed before 2020, but of course it has spun up: both in terms of many more meetings, and also many researchers, pulling in wider epidemic modelling expertise in light of the needs of this pandemic. SPI-M works by combining insights from different models and different modellers. We're routinely worked under intense time pressure, and often on questions which are not always even answerable. The cycle of how intensely busy we are has unfolded with the epidemic, but somehow we have really never had a quiet period since the start of 2020, to date, and we're still working at full pace.

In March 2020, I wrote an opinion piece[5] for Nat Rev Phys: this has a bit a story to it... I actually wrote it one evening before the lockdown but when the looming pandemic was very much on everyone's minds. My inbox was full of emails from researchers from fields just outside my own (wider maths and quantitative sciences, not disease modelling), and really this was my reaction to that. I have to be honest, that first draft I sent was a bit of a frustrated rant about things that *would not* help with COVID-19 modelling, but a marvellous editor developed it into a positive article. There's still some of the original snark that survives in the second paragraph. (Please see the original article for further details.)

JUNIPER is short for Joint UNIversities Pandemic and Epidemiological Research, and is a consortium which spans several UK universities, bringing together disease modellers from many research groups. This has allowed us to combine expertise and scale up to address larger problems as structured research programmes, and also respond rapidly to emerging questions. Please see our website[6] or social media for more information on our latest activities. We are closely interlinked with Isaac Newton Institute, which means we can interconnect with the wider research community.

Science communication is woven into what we do in JUNIPER, particularly through working with Plus Magazine[7] and its editors, Marianne Freiberger and Rachel Thomas. I think this is unusual for a research group or consortium but with the Plus editors involved live while the research is happening, they are producing articles for general audience while they are highly topical. You can find recent articles in collaboration with JUNIPER online[8]. Among these are "explainers", for example one on growth rates[9], which has been cited with the government's weekly updates on "The R value and growth rates".[10]

And there's many topics and areas where we have been bringing disease modelling to bear as part of our contributions to scientific advice. These include schools and the role of children in transmission, higher education, new variants, and many more.

Some Very Live Research Themes

For this last part of this lecture, we will turn to a very live topic: vaccination. First, let us think through what the effects of vaccination are. Someone who is vaccinated is:

- Less likely to get infected at all (i.e., become a case, whether mild or severe)
- *Even if they are infected*, less likely to infect other people (less infectious, less likely to transmit)

[4] https://www.gov.uk/government/groups/scientific-pandemic-influenza-subgroup-on-modelling
[5] *How you can help with COVID-19 modelling*, Gog 2020, Nature Reviews Physics https://doi.org/10.1038/s42254-020-0175-7
[6] https://maths.org/juniper and https://twitter.com/JuniperConsort1
[7] http://plus.maths.org/
[8] https://plus.maths.org/content/juniper
[9] https://plus.maths.org/content/epidemic-growth-rate
[10] https://www.gov.uk/guidance/the-r-value-and-growth-rate

- *Even if they are infected*, less likely to have a severe infection and serious outcome such as requiring hospitalisation or death.

These three effects can be combined into two main overall effects: *disease blocking* (getting infected AND having severe disease) and *transmission blocking* (getting infected AND infecting others). We can also translate these effects back to insights above from simple geometric growth. If vaccination blocks disease, it is like reducing the coefficient *a*, and if vaccination blocks transmission, it is like reducing *R*. As illustrated in Figure 3, again something that impacts transmission has the bigger effect than something which only changes the coefficient out the front, at least after a few disease generations.

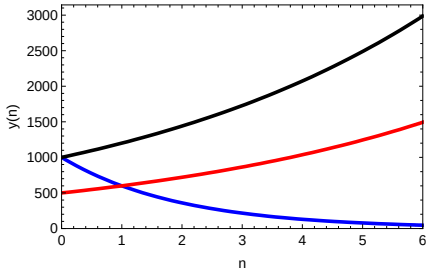

Figure 3: Black: y(n) for a=1000, R=1.2. Reduce *a* by 50% in shown in red and reduce *R* by 50% in blue.

Finally, I now turn to a more open-ended question: who should we target with vaccination? While we are now at a time after this has been decided and implemented for COVID-19 vaccination in the UK, which started rollout in December 2020, I think it is important the science and modelling thinks about this. We are allowed to explore the “what would have happened if”, and there may be lessons for other situations in future.

There are many subtle and difficult decisions to be made in choosing who to target in what order in vaccine rollouts. We could ask who should be first? Those who highest chance of severe disease? Those who are put most at risk by their work? Those who are most needed at work? Those who are most connected with other people? There really isn't a simple answer here, and it is all about what we are trying to achieve. There are some highly complex ethical issues here for society. Mathematical modelling cannot decide this for us, but what it can do is show us what the population-level consequences might be from the different options.

We can explore this by considering the population described by just two groups: *vulnerable* and *mixers*. For simplicity initially, suppose these groups are equal numbers. The vulnerable have a higher chance of severe disease if they are infected, and the mixers are more connected with others. This is clearly a gross simplification of the fine structures of our society in reality, but still, we can see that the vulnerable could loosely correspond to the older population, and the mixers to the younger (though of course there are exceptions both ways, and more complexities such as health care settings intersecting with both roles of mixing and vulnerability).

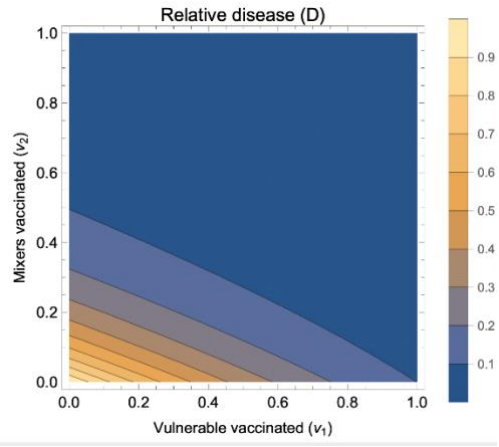

Figure 4: For a population consisting of "vulnerables" and "mixers", the proportion of each group vaccinated is shown on the axes (vulnerable on horizontal, mixers on vertical). So, no vaccination is bottom left, everyone in both groups vaccinated is top right, and everywhere else corresponds to some partially vaccinated population. The colour corresponds to the total number of severe cases we would expect over some period of time. Blue is low and yellow is high. Full details and parameter values are in the preprint listed above. These parameters are assuming there are other interventions in place, so a modest vaccination coverage is enough to bring total cases to near zero. If we increase vaccination in either group, the number severe cases decreases. However, vaccinating mixers has a stronger effect on decreasing disease than vaccinating vulnerable.

This work is described in more detail in a preprint[11] (so I will omit many of the details in this transcript). A key result can be interpreted from Figure 4. In short, if our key objective is to reduce severe disease, then for this model and for these parameters, it is optimal to prioritise vaccination to the mixers. You will recognise that this follows from the insights from earlier: something that shapes transmission has a much more substantial effect in the long run.

There are many caveats to this work (see our preprint for many of them), and in particularly I would highlight that on a short timescale the reverse result holds: as the cumulative effects of transmission require a few disease generations, if our concerns are over mitigating disease over the short term, then the vulnerable should be targeted (though bearing in mind the time it takes for vaccination to take full effect). And of course, it will matter the exact distribution of vulnerability and the more intricate mixing structures of our society.

Combining these caveats with the insights that we have. It could be that optimal strategy under realistic conditions will likely always be to vaccinate the most extremely vulnerable at first, but there may be a point in a vaccination rollout when it would make sense to pivot to focus on the mixers, those who have the most contact with others. But, when this point is, or even whether it would ever be reached not only depend on the population but of course also depend on the vaccine efficacy,

[11] Vaccine escape in a heterogeneous population: insights for SARS-CoV-2 from a simple model. 2021, Gog, Hill, Danon and Thompson.
https://www.medrxiv.org/content/10.1101/2021.03.14.21253544v2
This preprint includes the two-population model described in this lecture, and the consquences for vaccine distribution choices, but also goes on to explore vaccine escape (the pressure on the virus to evolve in a way that evades some of the effects of vaccination). Extensions to the model are included, and very many caveats.

both in terms of disease blocking and transmission blocking. Quantitative estimates for the strengths of these effects, particularly transmission blocking, are often hard to make accurately.

And this is where we get to for this lecture. I hope it has been of interest to see some of these topics and some of the unfolding story of the scientific advice, and how maths is being used in the fight against COVID-19.