Population Modelling by Examples II

Population Modelling Working Group

ABSTRACT

Population modelling spans many domains and techniques, and new technologies offer cutting-edge opportunities to a growing field. The population modelling working group has been recently active in coordination amongst different population modellers ~~of~~ different fields. One activity is mapping the population modelling domain by examples of work. This is the second collaborative paper by group members. This paper includes new examples and authors in an attempt to define the field. Some analysis and discussion is provided in view of the existing examples.

Author Keywords

Population Modelling, Definition, Multi Disciplinary

1. INTRODUCTION

The Population Modelling Working group is active under the Interagency Modelling and Analysis Group (IMAG) umbrella [1]. The group conducts several activities such as webinars, collaborative papers and meetings. Members of this group meet annually at the MSM/IMAG meeting at the US National Institutes of Health alongside other groups. The working group maintains a web portal [2] and a mailing list [3, 4].

The group has recently grown and increased its activity volume. This was apparent last year when the groups published its first collaborative paper [5]. The paper showed activities of different group members by examples. One goal was an attempt to define the field boundaries and better define the term. The initial definition of the field was: "Modelling a collection of entities with different levels of heterogeneity". This definition was broad and required more details. The group addressed this by providing specific examples of work self-defined as population modelling. Those were initially posted to the mailing list and then gathered into the collaborative paper.

In the year after the publication of the first paper, new population modellers joined the group and introduced their work. This added to the examples to better define the field. This paper gathers these examples ~~in no particular order~~ and provides discussion regarding the field.

2. EXAMPLES

Robert Smith?

(Note that the question mark is part of this author's name.)

A few years ago, a group of researchers proposed a program for HIV called "Test and Treat" [6]. The idea was to test everyone in the world (or as many as they reasonably could) and, if someone was found to be HIV positive, then they would start treatment immediately. This sounds like a good idea in theory... but it doesn't account for the rise of drug resistance. Imperfect treatment can have a direct impact on the development of drug resistance, which wasn't included in the model. The mathematical model that was used was flawed [7], but the World Health Organisation adopted it anyway and began this widescale program. Our modelling took the original model but added in both drug resistance and also education (manifested through behaviour changes) [8]. We showed that, in the absence of education but with drug resistance included, then the "test and treat" program was highly likely to make matters worse, leading to widespread treatment failure down the line. However, if good-quality education was provided, either at the time of treatment or subsequently, then the effects of drug resistance could be overcome. This is true even if education is only partially effective.

Polio is a disease that's almost been eradicated from the world... but not quite. In 2013, the number of cases doubled from the previous year, prompting the World Health Organisation to declare a polio emergency. We have a good vaccine (although in some cases, the vaccine itself can give you polio), but a key question is when to take it. Many countries undertake mass vaccinations, on National Immunisation Days (NIDs). A single NID can result in millions of children being vaccinated at once. However, different countries vaccinate at different times. We wondered if these should be synchronised? Using impulsive differential equations to model pulse vaccinations, we see the benefits of synchronisation: they overcome the issue of migration, because migrants aren't lost between different NIDs [9]. We proved that, under some conditions, synchronising the pulses is a local minimum and hence the best strategy. However, seasonal effects can change the picture: it's important to vaccinate before the high-transmission season. If migration is low, then two countries with different seasonal patterns should de-link their NIDs. (Something that was not done recently when it should have been.) However, if migration is high, then this will swamp the effects of seasonality and neighbouring countries with high migration should re-synchronise their NIDs. It follows that understanding the effects of human behaviour is crucial if we are to eradicate this disease in the next few years.

Aristides Moustakas

Bovine Tuberculosis (TB) is a major problem for the agricultural industry in several countries. TB can be contracted and spread by species other than cattle, and this can cause a problem for disease control. In the UK and Ireland, badgers are a

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recognised reservoir of infection, and there has been substantial discussion about potential control strategies. Strategies in England consist largely of badger control, whereas Wales is focused on cattle testing; Scotland had a high-risk surveillance testing policy until 2009, when Scotland was declared TB free.

We developed a coupling of individual-based models of bovine TB in badgers and cattle, which captured key details of the natural history of the disease and of both species at approximately county scale [10]. Factors such as bigger herds and keeping cattle inside for winter could explain the rise in TB in recent decades. We showed that housing cattle in large sheds over winter could potentially double the number of infected animals, by creating conditions where TB can spread. This is likely to be significantly more effective than culling badgers.

We followed this with time-series statistical analysis of public data regarding TB incidence and prevalence in different regions in the UK [11]. By comparing different strategies used in different countries, we concluded that more frequent testing is leading to lower TB infections in cattle both in terms of TB prevalence as well as TB incidence.

Romualdo Santos

Knowledge of population growth of a particular region is of great importance for resource allocation and planning, with political, cultural and economic implications. We used Malthusian modelling to study population growth in Sergipe, Brazil's smallest state [12]. Until 1920, Sergipe exhibited sub-optimal growth, compared to the surrounding areas. However, growth subsequently increased, passing the surrounding areas after 1970. Using both differential equations and difference equations, we found that the estimation of population growth for Sergipe shows a decrease in the coming decades, until 2050; at this time, the Malthusian model can no longer be applied and the growth model changes from continuous to discrete.

Nieko Punt

Over the past decades, the relationship between the pharmacokinetic (PK) properties of antibiotics, minimum inhibitory concentrations and clinical effects has been increasingly well understood. Inter-patient variability in the PK profile, however, has only recently been recognised as a major factor in predicting the outcome in individual patients and establishing breakpoints for clinical susceptibility. Most predictions to date have used data from healthy volunteers [13]. One of the modelling tools we have developed is Edsim++ [14]. Edsim++ is an object-oriented visual pharmacokinetic pharmacodynamics (PKPD) modelling tool that is used in research and education. One of the unique feature of Edsim++ is its programmability (C# language) at multiple levels. These include programming at the low-level PKPD active pharmaceutical ingredient for building new (web) applications, programming new PKPD objects for visual use (or re-use) and programming plugins for adding new functionality.

Andreas Zeigler

Biomarkers are tools that enhance cardiovascular risk estimation. However, the value of biomarkers on risk estimation beyond standard risk scores remains unclear. Their comparative impact among different European regions and their role in personalised medicine also remains to be elucidated. As part of the the "Biomarker for Cardiovascular Risk Assessment in Europe" (BiomarCaRE) project, we assessed the value of established and emerging biomarkers for cardiovascular risk prediction using standard statistical approaches as well as machine-learning methods, such as random forests or support-vector machines [15]. The strength of BiomarCaRE lies in its well-defined primary and secondary prevention cohorts, including over 300,000 participants from 13 European countries.

William Jusko

Corticosteroids such as methylprednisolone affect almost all liver functions through multiple mechanisms of action, and long-term use results in dysregulation, causing diverse side effects. The complexity of involved molecular mechanisms necessitates a systems approach. Integration of information from the transcriptomic and proteomic responses has the potential to provide deeper insights into corticosteroids actions [16].

We also developed a pharmacodynamic model to quantify the pharmacological interactions between gemcitabine and trabectedin in two pancreatic cancer cell lines [17]. The model enabled quantification of the temporal profiles of drug combinations over a range of concentrations with drug-specific parameters.

Matthias Chung

Inferring information from observed population dynamics onto population interactions is inherently difficult. We consider parameter estimation methods to overcome such obstacles. Let us assume the dynamics of interacting species can mathematically be modelled by a generalised Lotka–Volterra system $\vec{y}' = \mathrm{diag}(\vec{y})(\vec{r} + A\vec{y})$. Here the vector function $\vec{y}$ describes the time-dependent dynamic, $\vec{r}$ captures the intrinsic growth, and A describes the interaction between species y_j. Notice that in higher dimensions (more than two species), the dynamics of $\vec{y}$ are highly sensitive to small changes in the interaction A. Hence inferring A from longitudinal observations $\vec{d}$ is notably difficult.

Single and multiple shooting methods are standard methods for point estimation of ordinary differential equations. However, these methods are known to fail for highly sensitive equations such as population dynamical systems. To overcome this issue, the underlying parameter estimation problem is reformulated as

$$\min \|m(\vec{s}) - \vec{d}\| + a\|\vec{s}' - \mathrm{diag}(\vec{s})(r + A\vec{s})\|,$$

where $\vec{s}$ is an adequate parameterised function approximation of $\vec{y}$ and m is a projection of that function onto the observation space. Further, $\|\cdot\|$ is the Euclidian norm and a is an appropriate regularisation parameter, while we optimise over A and $\vec{s}$. These continuous shooting methods have been shown

to generate robust estimates for the inferred parameters A [18, 19].

Sixten Borg

Heterogeneity in patient populations is an important issue in health-economic evaluations, as the cost-effectiveness of an intervention can vary between patient subgroups, while an intervention that is not cost-effective in the overall population may be cost-effective in particular subgroups. Identifying such subgroups is of interest in the allocation of healthcare resources. We modelled disease activity in a heterogeneous patient population, by dividing it into more homogeneous subgroups and using a finite-mixture-model framework to identify subgroups and fit a disease-activity model to each subgroup [20]. The fitted models can evaluate interventions using cost-effectiveness analysis and could indicate which intervention to use in a given subgroup.

Mélanie Prague

HIV treatment is often applied according to general rules that do not take into account the immune system of an individual patient; depending on general health, state of the disease or co-infections, one patient's immune system could be very different from another. We used predator–prey models consisting of immune cells and viruses in order to individualise the treatment and hence reduce side effects of lifelong treatment. Observations for a given patient can be used to dynamically tune the dose so that there is a high probability that the disease is controlled [21].

Bruce Lee

In order to address various public-health issues, it is critical to develop computational models and tools that decision-makers can utilise. One of those tools is an agent-based model (ABM), which uses individual characteristics, behaviours and interactions to describe a system as a collection of agents. These agents are autonomous, decision-making entities that can assess situations, make decisions and compete or cooperate based on pre-defined rules.

We developed RHEA (Regional Healthcare Ecosystem Analyst), a software platform that can generate an ABM of a health-care system with detailed representations of the healthcare facilities and the patients moving among these facilities and the surrounding community [22]. We applied this to all the acute and long-term care facilities in Orange County, California. We have used this model to better understand the spread and control of various healthcare-associated pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) [23], norovirus [24] and carbapenem-resistant Enterobacteriaceae (CRE) [25].

Large-scale ABMs can serve as virtual representations of entire towns, cities, counties and states to better understand the spread and control of both communicable and non-communicable diseases. These include ABMs of the Washington, DC, metropolitan area and Pennsylvania. During the 2009 influenza pandemic, our models were used by the US Health and Human Services to help with the national response [26].

Ayaz Hyder

Determinants of human health — environment, social, biology — operate at multiple levels (individual, neighbourhood, regional). We use systems-science methods to bring together theory, data and methods from multiple disciplines. This has applications in satellite-based air pollution exposure assessment and birth outcomes [27] and predictive validation of agent-based models for influenza [28, 29].

Carl Asche

The use of comparative effectiveness research and cost-effectiveness analysis can improve health-care decision-making. Economic models can help evaluate the long-term impact of diabetes treatment. New oral treatments for Type 2 diabetes mellitus have been developed, but it is critical to determine the cost-effectiveness of such techniques [30]. We have also used predictive modelling techniques to help reduce hospital no-shows and readmissions [31].

Robin Gras

Artificial-life-simulated ecosystems can be used to study the evolutionary process and the emergence of species. We developed an individual-based, evolving predator–prey ecosystem simulation called EcoSim [32, 33]. The agents evaluate their environment (e.g., distance to predator/prey, distance to potential breeding partner, distance to food, energy level), their internal states (e.g., fear, hunger, curiosity) and choose among several possible actions such as evasion, eating or breeding. The behavioural model of each individual is unique and is the outcome of the evolution process. One major and unique contribution of this simulation is that it combines a behavioural, an evolutionary and a speciation mechanism. This approach allows interesting studies on theoretical ecology and artificial life in collaboration with biologists. For example, it is used to study the species-abundance distribution, patterns and rates of speciation, the evolution of sexual and asexual populations, the interaction and diffusion of an invasive species or the effect of toxic chemicals in an existing ecosystem.

EcoSim is an individual-based model including three trophic levels (primary producers, prey and predators) in a large (1000×1000 cells) toroidal discrete world. Each individual possesses its proper behavioural model implemented by a Fuzzy Cognitive Map [34] composed of perception, internal and action concepts linked by excitatory and inhibitory edges allowing for positive and negative feedback loops to appear. The behavioural model and the physical characteristics (such as size, speed and vision range) of each individual are coded in its genome, allowing for the evolution of new behaviours and physical characteristics. Species are also represented as populations of individuals with high genomic similarities. Species can emerge or disappear at any time step due to the evolution, birth and death of their individuals [35]. Each individual is also associated with a reserve of energy that can be refilled through food consumption and a metabolism function determining its energy usage based on its physical characteristics, the complexity of its behavioural model and the type of action performed, sexual reproduction being a particularly costly one. An important property of our model is that

it does not rely on any pre-defined fitness function [36]. Instead, fitness emerges from the multiple interactions between the individuals and their changing environment.

With hundreds of thousands of unique individuals simultaneously living in a large and dynamic environment and being subject to evolution for thousands of generations, many biological and ecological theories can be investigate through EcoSim. EcoSim has been validated through several studies showing clear coherence of the features generated by the simulation with empirical data such as species abundance pattern, chaotic and multi-fractal patterns and species–area relationship.

Yifei Ma

Emergent technologies such as big data and high performance computing technologies offer the potential to improve simulation systems such as modelling and simulation of public-health policy for epidemic outbreaks. This allows us to improve both social behaviour modelling flexibility and simulation efficiency [37]. With this improvement, the latency of evaluating policies in the laboratory for real-time epidemic control is reduced. We can also evaluate the effectiveness of two strategies during an epidemic outbreak — self-motivated prevention behaviours and community-led interventions — by simulating the strategies in US cities during an influenza [38].

Valery Forbes

~~Population modelling can be used~~ to assess the risks of toxic chemicals and other stressors ~~such as extrapolating~~ from toxic effects at the individual level to consequences for population dynamics. Population modelling can add value to ecological risk assessment by reducing uncertainty when extrapolating from ecotoxicological observations to relevant ecological effects. ~~Population models have the potential for adding value to ecological risk assessment~~ by incorporating better understanding of the links between individual responses and population size and structure, and by incorporating greater levels of ecological complexity [39].

Tracy Comans

The delivery of health-care services presents difficult problems that simulation modelling can address. We used discrete-event simulation to model the most efficient way of providing hospital orthopaedic outpatient services [40]. This work was used to inform a service delivery change at a local hospital and has since been extended to a larger health district with four hospitals.

Bishal Paudel

Systems biology can be used to understand how cancer cells respond to therapies. Using BRAF-mutated melanoma as a model system and looking at their response dynamics in different targeted and chemo therapies, we have found the drug-response behaviour of these cells to be complex and non-linear [41]. We then developed a high-throughput assay to dissect the non-linearity in response dynamics and attribute it to non-genetic heterogeneity present within cell lines. Our recent data suggest cells might be rapidly switching between different epigenetic states to evade the apoptosis and eventually develop resistance. To understand the phenotypic state transitions, we developed a simple three-state model to describe the response dynamics we see in experimental data. We are in the process of identifying molecular signatures of such states, with a hope to calibrate the model in order to be able to predict the response dynamics of cancer cells before they eventually develop resistance.

Lucas Brotz

Fuzzy set theory and fuzzy logic, originally developed by Zadeh [42], allows the representation of variables according to a gradation or degree of membership, rather than the classic true/false membership of conventional Boolean sets. Fuzzy logic also allows a conclusion to be reached with an associated gradation or degree of belief. As such, fuzzy set theory and logic provide a useful system for combining information of variable cardinality and/or confidence. Fuzzy set theory is firmly established in engineering and science, and is increasingly being used for ecological applications [43]. Using fuzzy logic, we developed a framework for the dynamics of jellyfish populations around the globe. This allowed us to combine data of different "types" together in order to evaluate the underlying signals [44].

3. DISCUSSION

The various examples provided here demonstrate the wide range of applications that population modelling has: from infectious diseases to population growth, from health-care services to cancer treatment, from policy to pharmacodynamics. The modelling tools range from simulation-based (agent-based models, artificial-life-simulated ecosystem) to the theoretical (difference, differential and impulsive equations). Yet there is also unity, with a focus on the utilisation of computational and theoretical methods as useful tools for tackling the wide range of problems that can be elucidated by advanced techniques.

Nevertheless, many challenges still remain. As data become increasingly available, questions of privacy and security become more prominent. Big data are an excellent resource but can also result in big privacy violations, as seen with the recent Ashley Madison hack [45]. A growing challenge is the melding of the hard sciences with the social sciences. If human behaviour is to be truly understood, modelling must draw upon fields that have expertise in the qualitative understanding of social, cultural and behavioural norms in order to improve our quantitative models [46].

This paper, in conjunction with its predecessor, is a cumulative effort of all contributors who responded to the population-modeller call. Each contributor sent text to the mailing list. The editing process is documented in the list archives [4]. Readers are welcome to read the longer versions in the archives and join this discussion on the mailing list [3].

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