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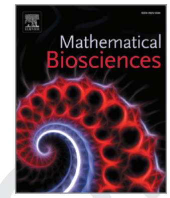

Evaluating targeted interventions via meta-population models with multi-level mixing

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ABSTRACT

Among the several means by which heterogeneity can be modeled, Levins' (1969) meta-population approach preserves the most analytical tractability, a virtue to the extent that generality is desirable. When model populations are stratified, contacts among their respective sub-populations must be described. Using a simple meta-population model, Feng et al. (2015) showed that mixing among sub-populations, as well as heterogeneity in characteristics affecting sub-population reproduction numbers, must be considered when evaluating public health interventions to prevent or control infectious disease outbreaks. They employed the convex combination of preferential within- and proportional among-group contacts first described by Nold (1980) and subsequently generalized by Jacquez et al. (1988). As the utility of meta-population modeling depends on more realistic mixing functions, the authors added preferential contacts between parents and children and among co-workers (Glasser et al., 2012). Here they further generalize this function by including preferential contacts between grandparents and grandchildren, but omit workplace contacts. They also describe a general multi-level mixing scheme, provide three two-level examples, and apply two of them. In their first application, the authors describe age- and gender-specific patterns in face-to-face conversations (Mossong et al., 2008), proxies for contacts by which respiratory pathogens might be transmitted, that are consistent with everyday experience. This suggests that meta-population models with inter-generational mixing could be employed to evaluate prolonged school-closures, a proposed pandemic mitigation measure that could expose grandparents, and other elderly surrogate caregivers for working parents, to infectious children. In their second application, the authors use a meta-population SEIR model stratified by 7 age groups and 50 states plus the District of Columbia, to compare actual with optimal vaccination during the 2009–2010 influenza pandemic in the United States. They also show that vaccination efforts could have been adjusted month-to-month during the fall of 2009 to ensure maximum impact. Such applications inspire confidence in the reliability of meta-population modeling in support of public health policymaking.

1. Introduction

Agent-based, network and population models each have features that, for particular applications, make one the obvious choice. For others, identifying the best approach involves weighing their respective strengths and weaknesses. While each can incorporate structural heterogeneity, agent-based and meta-population modeling sacrifice and preserve, respectively, the most analytical tractability. As analyses invariably increase understanding, we seek to augment the usefulness of systems of weakly coupled large sub-populations, or meta-populations [11], in modeling the spread of pathogens, arguably the most important of several challenges that Ball et al. [1] describe.

In consolidating and extending earlier contributions to our understanding of the impact of heterogeneity (in characteristics affecting sub-population reproduction numbers) and non-random mixing, Feng et al. [5] used a convex combination of preferential within- and proportional among-group contacts [10]. In that mixing function, the fraction of within-group contacts and their complements correspond to Ball et al.'s [1] coupling strength, which determines location on a continuum whose limiting meta-populations behave as one or as multiple independent sub-populations. The simplicity of this function facilitates theoretical studies, but it is too simple for most applications.

Accordingly, we generalized the function of Jacquez et al. [10] by including preferential contacts between parents and

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children and among co-workers as well as contemporaries [7]. Here we include grandparents and grandchildren, but omit co-workers. Together with observations from a study of face-to-face conversations, a proxy for contacts by which the pathogens causing respiratory diseases might be transmitted [13], this new function permits us to describe mixing patterns within and between genders by age. Motivated by the consistency of results with everyday human experience, we develop a formal multi-level mixing scheme.

We present several two-level examples and show that modeling influenza by age and gender or location could inform pandemic mitigation efforts. Our first application aims to facilitate reevaluating the impact of prolonged school closures, which could increase mortality among grandparents and other elderly surrogates for working parents, and second to assist in optimally allocating available vaccine among groups [5], a recurring theme with respect to influenza. As public health resources invariably are limited, other potential applications of our approach abound.

2. Methods

Mixing is inconsequential only in homogeneous populations. Feng et al. [5] show that heterogeneity in factors affecting sub-population reproduction numbers increases the meta-population reproduction number even if mixing is random, and that non-random mixing increases it further, especially if heterogeneous. Accordingly, meta-population models must specify the manner in which sub-population members mix (i.e., proportionally or preferentially, and if the latter, how).

2.1. Theory

Busenberg and Castillo-Chavez [2] define c_{ij} as proportions of contacts members of group i have with group j, given that i has contacts. Their criteria that mixing functions should meet are:

1) $c_{ij} \geq 0$,
2) $\sum_{j=1}^{k} c_{ij} = 1,\ j = 1, \ldots, k,$ and
3) $a_i N_i c_{ij} = a_j N_j c_{ji}$,

where the N_i are group sizes and a_i are average *per capita* contact rates of groups $i=1, \ldots, k$, called activities. Formulae derivable from these conditions follow.

2.1.1. A simple function

If a proportion ε_i of i-group contacts is reserved for others in group i, called preference, and the complement $(1-\varepsilon_i)$ is distributed among all groups, including i, via the proportional mixing formula,

$a_i N_i / \sum_j a_j N_j$, then the fractions of their contacts that members of group i have with members of groups j are

$$c_{ij} = \varepsilon_i \delta_{ij} + (1-\varepsilon_i)\frac{(1-\varepsilon_j)a_j N_j}{\sum_k (1-\varepsilon_k)a_k N_k},$$

where δ_{ij} is the Kronecker delta (i.e., $\delta_{ij}=1$ if $i=j$ and $\delta_{ij}=0$ if $i \neq j$). Jacquez and colleagues [10] obtained this expression by allowing the fraction of within-group contacts, ε, to vary among groups in Nold's [14] preferred mixing function.

2.1.2. One-Level Mixing

When groups are age classes, Glasser et al. [7] generalized this function to contacts between parents and children and among co-workers as well as contemporaries. Here we add a second generation (i.e., grandchildren and grandparents, another set of sub- and super-diagonals). For simplicity, we omit contacts among co-workers and assume that generation time, G (average age of women at the birth of their daughters) and longevity, L (average expectation of life at birth or age at death) are constant. Then the fractions of their contacts that members of group i have with members of group j may be defined as

$$c_{ij} := \phi_{ij} + \left(1 - \sum_{s=1}^{5}\varepsilon_{si}\right) f_j,\ f_j := \frac{(1-\sum_{s=1}^{5}\varepsilon_{sj})a_j N_j}{\sum_{k=1}^{n}(1-\sum_{s=1}^{5}\varepsilon_{sk})a_k N_k},$$

where the ε_{si} are fractions of contacts reserved for the sth sub-population, $s=1, \ldots, 5$ (contemporaries, parents, children, grandparents, and grandchildren), and a_i and N_i are the *per capita* contact rates and sizes of the ith age group, $i=1, \ldots, n$. Because people whose ages equal or exceed G but are less than $2G$ may have children, but not grandchildren; people whose ages equal or exceed $2G$ can have both children and grandchildren; people whose ages are less than or equal to L–$2G$ may have parents and grandparents; people whose ages are less than or equal to L–G may have parents, but not grandparents; and those whose ages are between $2G$ and L–$2G$ may have children, grandchildren, parents and grandparents; we define ϕ_{ij} as

$$\phi_{ij} := \begin{cases} \delta_{ij}\varepsilon_{1i} + \delta_{i(j+G)}\varepsilon_{2i}, & G \leq i < 2G, \\ \delta_{ij}\varepsilon_{1i} + \delta_{i(j+G)}\varepsilon_{2i} + \delta_{i(j+2G)}\varepsilon_{4i}, & i \geq 2G, \\ \delta_{i(j-2G)}\varepsilon_{5i} + \delta_{i(j-G)}\varepsilon_{3i} + \delta_{ij}\varepsilon_{1i}, & i \leq L-2G, \\ \delta_{i(j-G)}\varepsilon_{3i} + \delta_{ij}\varepsilon_{1i}, & L-2G < i \leq L-G \end{cases}.$$

If age groups are 0–4, 5–9, … and the generation time is 25 years, by $i > G$ we mean age greater than class 5. Thus,

$$\delta_{ij} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{otherwise} \end{cases},\ \delta_{i(j\pm G)} = \begin{cases} 1 & \text{if } i = j \pm G \\ 0 & \text{otherwise} \end{cases}$$

and $\delta_{i(j\pm 2G)} = \begin{cases} 1 & \text{if } i = j \pm 2G \\ 0 & \text{otherwise} \end{cases}$.

To satisfy Busenberg's and Castillo–Chavez' [2] third condition (that contacts must balance), the non-zero elements of $\vec{\varepsilon}_2$ and $\vec{\varepsilon}_3$ and of $\vec{\varepsilon}_4$ and $\vec{\varepsilon}_5$ must be related. Again, if age groups are 0–4, 5–9, … and the generation time is 25 years, $a_i \times N_i \times \varepsilon_{4i} = a_j \times N_j \times \varepsilon_{5j}$, for $i=11, 12, \ldots, n$ and $j=i-2G$. This ensures that $a_i \times N_i \times c_{ij} = a_j \times N_j \times c_{ji}$ for $j=i-2G$. Note also that $0 \leq \sum_{s=1}^{5}\varepsilon_{si} \leq 1$.

2.1.3. Multiple-level mixing

Some applications require multiple strata. Beginning with two, consider m sub-populations (e.g., locations or genders) and n classes (e.g., age or activity groups). Let l_i denote the ith location (l for location) and a_j denote the jth age group (a for age), $1 \leq i \leq m$ and $1 \leq j \leq n$. We use this compound notation whenever indices might otherwise be confused.

Let $A_{l_i a_j}$ denote the activity, or average *per capita* contact rate, of individuals at location l_i and age a_j and $N_{l_i a_j}$ denote the number of people at location l_i of age a_j. Then the probability of contact between persons in location l_i, age a_j and location l_p, age a_q may be described by a matrix with entries

$$c_{l_i a_j l_p a_q} := \varepsilon_{l_i a_j}\delta_{l_i l_p}\delta_{a_j a_q} + (1-\varepsilon_{l_i a_j}) f_{l_p a_q}, \quad 1 \leq i, p \leq m, \quad 1 \leq j, q \leq n,$$

where

$$f_{l_p a_q} := \frac{(1-\varepsilon_{l_p a_q})A_{l_p a_q}N_{l_p a_q}}{\sum_{j=1}^{n}\sum_{i=1}^{m}(1-\varepsilon_{l_i a_j})A_{l_i a_j}N_{l_i a_j}}.$$

In these expressions, $\varepsilon_{l_i a_j}$ represents preference for one's own age/location group, δ_{rs} is the Kronecker delta function, taking values of 1 (if $r=s$) or 0 (if $r \neq s$), and $f_{l_p a_q}$ is random mixing (i.e., proportional to contacts, $A_{l_p a_q}N_{l_p a_q}$). For some applications, however, mixing among ages and locations (or other strata) are independent (e.g., members of an age class may contact others of the

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