Separation of Concerns in Epidemiological Modelling

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Abstract

Modelling and simulation have been heavily used in epidemiology, for instance to study the transmission of infectious diseases, their pathogenicity and their propagation. A major hindrance to modelling in epidemiology is the mixing of concerns that ought to be separated. The most obvious one is the computer implementation that should not be mixed with domain aspects. But several domain concerns should also be separated from the core epidemiological ones. These include the distribution of the studied populations into spatial regions, age intervals, sexes, species, viral strains... We propose an approach that relies on a mathematical model of the dynamics of a compartment-based population. The separation of domain concerns is provided by expressing each one as a stochastic automaton and combining them with a tensor sum. A DSL, Kendrick, and a tool, support this approach that has been validated on several case studies.

Categories and Subject Descriptors D.2.10 [*Software Engineering*]: Design; I.6.5 [*Simulation and Modelling*]: Model Development

General Terms Design, Languages

Keywords Separation of concerns, domain specific languages, epidemiological modelling, compartmental models

1. Introduction

Modelling and simulation have been heavily used in epidemiology, for instance to investigate the mechanisms of disease propagation (Keeling and Rohani 2008; Xia et al. 2004), to explore evolutionary dynamics (Gandon et al. 2001; Read and Huijben 2009) and/or to inform control strategies (Bauch et al. 2009; Levin et al. 2011). Epidemiological models largely rely on the compartmental framework where the individuals of a population are grouped by their epidemiological status (Anderson and May 1991; Keeling and Rohani 2008). Those Susceptible to the pathogen (state S) can be infected, the Infectious ones (state I) can transmit the disease and the Recovered ones (state R) have become immune. More categories can be added to represent different transmission cycles *i.e SIR, SIS, SEIR, etc*.

Aside from these core epidemiological concerns, other concerns have to be taken into account in some models such as the age-structure, the social/sexual mixing and the spatial heterogeneity of the transmission that may be caused by geographical, urban, sociological or still other considerations. Each of these additional aspects may lead to further partitioning the population.

In deterministic approaches, a mathematical description (typically ordinary differential equations) is clearly separated from implementation choices (e.g. what solver to use, ...). This approach is often used first, when dealing with a new epidemic. It can also help estimate some parameters or help study the impact of control strategies in long time scales.

However, while deterministic models provide insights into the endemic equilibrium and its stability, shifting to stochastic models (typically continuous time Markov chains) is known to be more realistic to understand and predict the dynamics of infectious diseases. The modelling approach itself may then be seen as a concern as one may wish to switch from one approach to the other.

Moreover, domain experts are more and more tempted to take into account small-scale details that are very conveniently represented by agent-based implementations as arbitrary details can be

easily added to small groups or even single individuals. Simulations may then require a lot of computing resources (Roche et al. 2011) so that some optimisation skills may be required to run them efficiently. In addition, additional details jeopardise model validity as rigorous analyses becomes intractable. It is then crucial to be able to easily change some detail about a given concern without having to dig into code where it may be mixed with different concerns.

In this paper, we aim at separating concerns of epidemiological modelling so that models are easier to build and maintain. We are thus looking for a way to define epidemiological models with as little dependencies with each other as possible and for an operator to combine them as freely as possible.

Avoiding dependencies between concern definition implies to define them in terms of high-level abstractions. In order for the concerns to inter-operate a common meta-model is thus required. This meta-model must support the definition of concerns, their integration into models as well as model simulation.

2. Mathematical Meta-Model

In previous work (BUI et al. 2015) we defined a relatively superficial meta-model where the concept of compartment lacked clean semantics. It was then difficult to define a general concept of concern and a rigorous operator to combine them.

We then decided to prepare the definition of an object-oriented meta-model, well suited to implementation, by the definition of a clean mathematical one first. This meta-model has to answer two main questions: What is the cardinality of a given compartment at a given instant? What is the probability that some individual moves from a given compartment to another (given) one?

We chose a meta-model in which a set of individuals is partitioned by an equivalence relation. The Markov chain is described by a transition rate matrix. Concerns can be seen as combinable model transformations. The transformations may alter any part of a model provided that proper semantics is given but they typically refine the equivalence relation and/or alter the transition rate matrix.

We then realised that a model can be seen as a Stochastic Automata Network (Plateau and Stewart 2000) where each instance of a concern potentially introduces a new automaton which is integrated using a tensor sum. The state of an individual in some concern may be the region where the individual lives, their sex, their species etc.

The meta-model includes the following abstractions: *Population, Attribute, Equivalence Relation, Compartment, Parameter, Transition* and *Time Series*. A model is defined as follows:

Definition 1. $Model = \{P, \mathcal{A}, \mathcal{R}, Prms, Tr\}$

P is a set of individuals: the *population*. Each individual of the population is characterised by several *attributes* such as: species, sex, age,... An attribute is a mapping from P to some domain D_a. $\mathcal{A}$ is the set of attributes of the model. $\mathcal{R}$ is an equivalence relation on P. $\mathcal{C} = P/\mathcal{R}$, is the set of equivalence classes, i.e. the *compartments*, of the population. $Prms$ is a set of parameters (temporal functions).

$Tr \in \mathcal{C} \times \mathcal{C} \to \mathbb{R}^+$ is the transition rate matrix. Each element in Tr (except the main diagonal elements) represents the rate at which individuals move from one compartment to another one. The diagonal elements are defined as $q_{ii} = -\sum_{j \neq i} q_{ij}$. Therefore, the sum of each row in Tr is 0. For example, suppose that the population is decomposed into two regions R_1 and R_2. The transition rate matrix Tr is:

$$Tr = \begin{pmatrix} -\nu_1 & \nu_1 \\ \nu_2 & -\nu_2 \end{pmatrix}$$

The transition $Tr(C_{R1}, C_{R2}) = \nu_1$ represents the rate at which an individual from region R_1 immigrates to the region R_2 (C_{R_1}, C_{R_2} denote the compartments corresponding to R_1, R_2) and so on.

A model is fully instantiated when the initial states of the model (i.e. the initial cardinalities of each compartment) and the value of each parameter are provided.

3. Separation of Concerns

From a model-driven viewpoint, a concern can be seen as a model transformation. We however need a clean mathematical definition and an operator to combine them.

Definition 2. $C = \{\mathcal{A}_C, \mathcal{R}_C, Prms_C, F_C\}$

A concern may refine the equivalence relation of the model it is applied to, by providing an additional one $\mathcal{R}_C$ which typically uses new attributes that are introduced in $\mathcal{A}_C$. A concern may also introduce a set of parameters $Prms_C$ and a function F_C to change the transition rate matrix of the model.

3.1 Dependencies between Concerns

Concerns may or may not depend on each other. When concern definitions do not necessarily depend on of each other, some means should be provided to define them independently so that they can vary independently.

This however does not mean that instances of these concerns, i.e. their application to some model with some actual parameters, do not depend on each other! For instance, a general concept of spatial distribution may be defined independently of the concept of species. It may however happen that some species involved in the studied disease are not uniformly distributed on space. It is must be possible to define both concerns, spatial structure and species, independently of each other. It must also be possible, **in a second step**, to express that such and such species are more likely to be found in such or such kind of place.

The concept of structural dependency is akin to the concept of dependency that is commonly applied to source code, and applies to concern definitions but not to instances of concerns.

Definition 3. A concern C_2 structurally depends on another concern C_1 if the definition of C_2 mentions one or several entities defined by C_1.

If C_2 structurally depends on C_1, the former cannot be used without the latter and the simplest way to ensure this requires that C_1 is defined first. The same order is also required when applying concerns to a model.

To ease the definition of concerns, they should be as structurally independent as possible. A concern is called independent if it has no structural dependency on any other one. Each concern has to provide a function F_C to change the transition rate matrix of a model to which it is applied. The function F_C of a concern that depends structurally on another one is different to the one of an independent concern. In case of dependent concerns, the function F_C typically generates a sum of two matrices (the transition rate matrix of this concern and the one of the concern on which it depends). In this paper, we do not detail the application of dependent concerns to models. The main focus is to introduce an operator to integrate independent concerns, their function F_C and non-structural dependencies between them.

3.2 Applying a Concern to a Model

An independent concern C can be applied to a model M, yielding another model, through a binary operator, noted $\oplus$.

Definition 4. Given:
$M = \{P, \mathcal{A}, \mathcal{R}, Prms, Tr\}$

$C = \{\mathcal{A}_C, \mathcal{R}_C, Prms_C, F_C\}$
$M \oplus C \rightarrow M' = \{P, \mathcal{A}', \mathcal{R}', Prms', Tr'\}$ where
$\mathcal{A}' = \mathcal{A} \cup \mathcal{A}_C$
$\mathcal{R}' = \mathcal{R} \wedge \mathcal{R}_C$
$\mathcal{C}' = P/\mathcal{R}'$
$Prms' = Prms \cup Prms_C$
$Tr' = F_C(Tr)$

$\mathcal{A}' = \mathcal{A} \cup \mathcal{A}_C$ can be seen as a product of two automata provided that during a composite transition, only one automaton changes state. The function F_C typically generates the tensor sum (described by $\oplus$) of two transition rate matrices. Note that the tensor sum is defined in terms of the (usual) matrix sum of tensor products ($\otimes$) (Plateau and Stewart 2000), we can write:

$$F_C(Tr_M) = Tr_M \oplus Tr_C = Tr_M \otimes I_C + I_M \otimes Tr_C \quad (1)$$

where I_C and I_M are identity matrices corresponding to Tr_C and Tr_M respectively. The tensor product of two matrices $Q_1 \otimes Q_2$ is obtained by replacing each element q_{ij} in Q_1 by a block $q_{ij}Q_2$ (Plateau and Stewart 2000).

Theorem 1. *Let C_1, C_2 be two structurally independent concerns and M be a model. Assume that the function F of each concern produces the tensor sum of two transition rate matrices. The concerns can be applied in any order:*

$$\forall M : (M \oplus C_1) \oplus C_2 = (M \oplus C_2) \oplus C_1 \quad (2)$$

This theorem can be easily proved by taking into account the fact that the tensor sum operator satisfies the associativity and the pseudo-commutativity (Plateau and Stewart 2000).

3.3 Interaction between Structurally Independent Concerns

Although structurally independent concerns are defined separately and can be applied regardless in any order, they often interact with each other at the instantiation phase. This interaction can be seen as a non-structural dependency, i.e. a dependency between instances of concerns. These interactions may be *functional transition rates* or transitions in one automaton triggering transitions in other automata (Plateau and Stewart 2000). In epidemiological modelling, it is often the case that concerns are studied at different time-scales, *i.e* epidemiological time-scale (latent period - the period between the time of exposure and the time when infectiousness begins; infectious period - the time until recovering from infective class; etc.); demographic time-scale (birth/natural death rate); mobility time-scale etc. Therefore, transitions of different concerns do not happen simultaneously. We can make the assumption that during a transition, only one concern change the state, for instance the transmission of infection is ignored during the mobility of individuals between cities. Thus, only the former seems relevant to epidemiology. We define a functional transition rate as below.

Definition 5. Consider N concerns C_1, C_2,..., C_N with transition rate matrices Tr_1, Tr_2,..., Tr_N. Suppose that $\mathcal{S}_1$, $\mathcal{S}_2$,..., $\mathcal{S}_N$ are the set of states of N stochastic automata corresponding to those transition rate matrices ($\mathcal{S}_i = P/\mathcal{R}_i$). The rate of the transition from state $s_i^{(k)}$ to state $s_j^{(k)}$ in the k^{th} automaton depends on the state of other automata:

$$Tr_k(s_i^{(k)}, s_j^{(k)}) = f : \mathcal{S}_1 \times ... \times \mathcal{S}_{k-1} \times \mathcal{S}_{k+1} \times ... \times \mathcal{S}_N \mapsto \mathbb{R}^+$$

Functional transition rates are specified in the instantiation phase, after integrating concerns into the model. They are separated from the definition of concerns (Figure 1). So the interaction between instances of concerns has no impact on their definition. In the domain of epidemiology, due to the heterogeneities that arise from age, sex, species, space, etc. some individuals have a higher rate of contact than others. For example, the transmission of infection in one region may be higher or lower than in the others due to the environmental conditions, or the birth/natural death rate of an individual may be different because of the host species etc. Functional transition rates allow to easily capture such heterogeneities between individuals without any changes on the definition of concerns.

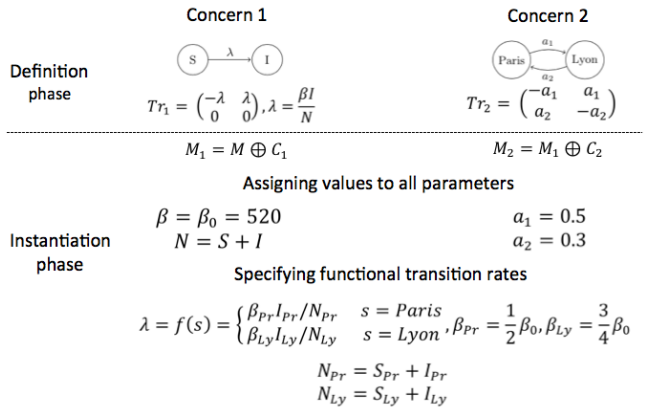

Figure 1. The definition of functional rates is separated from the definition and instantiation phases of concerns

4. Case Study and Validation

We have applied our approach to Kendrick - a simulation platform coupled with a domain-specific language for epidemiological modelling (BUI et al. 2015). The platform consists of three parts: the first part implements concepts of the general meta-model as well as the concrete syntax of the language; the second one allows to define concerns and to integrate them into models; the third one aims at establishing a set of semantic operations which either execute a simulation on the specified model or generate its C/C++ version. To demonstrate our approach, we build an avian influenza model (Arino et al. 2005). This model contains three concerns: SEIRS, multi-species and spatial. These concerns are defined separately and then applied to the model using the modelling language Kendrick.

4.1 Mathematical Model of Avian Influenza

The model considered here is an SEIR demographic model with loss of immunity in which the individuals are categorised in four classes: first, all newborn individuals are assumed in *Susceptible (S)* at birth rate μ, then enter in *Exposed (E)* class who are infected but not yet infectious with the force of infection $\lambda = \beta I/N$, become *Infectious (I)* after a latent period given by $1/\sigma$ and then, change to *Recovery (R)* after an infectious period $1/\gamma$. After a period given by $1/\nu$, the *Recovery* individuals move back to the *Susceptible* class. All individuals are assumed to die at rate μ. The SEIRS model can be expressed using the following system of Ordinary Differential Equations (ODEs):

$$\begin{cases} \frac{dS}{dt} &= \mu N + \nu R - \lambda S - \mu S \\ \frac{dE}{dt} &= \lambda S - \sigma E - \mu E \\ \frac{dI}{dt} &= \sigma E - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I - \mu R - \nu R \end{cases} \quad (3)$$

To this basic model, we add a spatial concern where individuals are organised in n geographical regions (also called *patches*)

(Keeling and Rohani 2008) (migration of individuals can take place between neighbouring patches). The mobility equation for the population in patch p with $p \in [1..n]$, N_p is the size of the population in patch p:

$$\frac{dN_p}{dt} = \sum_{q=1}^{n} \rho_{pq} N_q - \sum_{q=1}^{n} \rho_{qp} N_p \quad (4)$$

where ρ_{pq} represents the migration rate of individuals from patch q to patch p. Equation (4) shows two spatial effects: (1) the first term represents the increase of individuals because of the migration from other patches to patch p; (2) the second one describes that individuals leave patch p to move to other patches (Arino et al. 2005).

Suppose that the population consists of two species: *human* and *bird*. The transition rate matrix of the multi-species concern is zero because the species of an individual cannot be changed. The transition rate matrices of SEIRS and spatial concerns can be formed through the equations (3) and (4). Because of these concerns, the compartments of the model are: S_{ps}, I_{ps}, E_{ps} and R_{ps} where $p \in [1..n]$ and s is *human* or *bird*.

4.2 Interaction between Three Concerns

The three concerns are defined using Definition 2, then integrated into the model through the operator presented in Definition 4. Their instances interact with each other to represent the heterogeneities of contact between individuals of each species in each patch. First, the rate of some transitions of the SEIRS becomes functional depending on the state of two another ones. For instance, the birth/death rate μ is the function:

$$\mu = f(s,p) = \mu_{sp} \, with \, p \in [1..n] \, s \in [human, bird]$$

where μ_{sp} is a constant. The force of infection (λ) of a *Susceptible* individual also becomes a function depending on its species and its current patch:

$$\lambda(s,p) = \sum_{i}^{human,bird} \beta_{isp} I_{ip} / N_{ip}$$

The following system of ODEs represents the model integrated with three concerns:

$$\begin{cases} \frac{dS_{sp}}{dt} &= \mu_{sp} N_{sp} + \nu_{sp} R_{sp} - \lambda_{sp} S_{sp} - \mu_{sp} S_{sp} \\ &\quad + \sum_{q=1}^{n} \rho_{spq} S_{sq} - \sum_{q=1}^{n} \rho_{sqp} S_{sp} \\ \frac{dE_{sp}}{dt} &= \lambda_{sp} S_{sp} - \sigma_{sp} E_{sp} - \mu_{sp} E_{sp} \\ &\quad + \sum_{q=1}^{n} \rho_{spq} E_{sq} - \sum_{q=1}^{n} \rho_{sqp} E_{sp} \\ \frac{dI_{sp}}{dt} &= \sigma_{sp} E_{sp} - \gamma_{sp} I_{sp} - \mu_{sp} I_{sp} \\ &\quad + \sum_{q=1}^{n} \rho_{spq} I_{sq} - \sum_{q=1}^{n} \rho_{sqp} I_{sp} \\ \frac{dR_{sp}}{dt} &= \gamma_{sp} I_{sp} - \mu_{sp} R_{sp} - \nu_{sp} R_{sp} \\ &\quad + \sum_{q=1}^{n} \rho_{spq} R_{sq} - \sum_{q=1}^{n} \rho_{sqp} R_{sp} \end{cases} \quad (5)$$

4.3 Model Implementation

Each concern will be defined using the Kendrick modelling language. Kendrick is implemented as an embedded Domain Specific Language in Smalltalk, a dynamic object-oriented programming language. For example, the script of the multi-species concern:

```
multiHostConcern := KEConcern new.
multiHostConcern
     addAttribute: #species
     value: #(#human #bird).
```

Integrate this concern into the model as below:

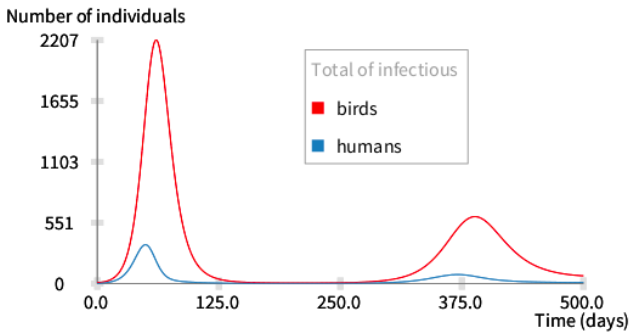

Figure 2. Total number of infectious birds and humans resulting from the RK4 simulation of Kendrick. $S_{b_1} = 4990, I_{b_1} = 10, S_{b_p} = 5000, I_{b_p} = 0, S_{h_p} = 500, I_{h_p} = 0, \beta_b = [00.42], \beta_h = [00.21], 1/\mu_b = 2\,years, 1/\mu_h = 75\,years, 1/\sigma_b = 1.5\,days, 1/\sigma_h = 2\,days, 1/\gamma_b = 4.3\,days, 1/\gamma_h = 4\,days, \rho_b = 0.1, \rho_h = 0.03, \forall p \in [1..5]$.

```
model := KEModel new population:
     (KEPopulation size: 27500).
model integrate: multiHostConcern.
```

We can specify the functional rate μ of the SEIRS concern, provided that this concern has been integrated into the model, as follow:

```
model atParameter: #mu
     assignValue: [ :aModel| |c val|
     c := aModel currentCompartment at: #species.
     c = #human ifTrue: [ val := 0.0000365 ].
     c = #bird ifTrue: [ val := 0.00137 ]. val ].
```

Here, the rate μ has one of two values (*constant function*) depending on the species of the studying individual. In the limited pages of this paper, we do not introduce the full script of the model. This script can be found at the development site of our modelling tool[1].

4.4 Verification and Validation

The model was interpreted using the simulation tools provided by the platform (BUI et al. 2015). Figure 2 shows the dynamics of total infectious human and bird during 500 days using a deterministic simulation. To resolve the system of ODEs (5), we used the fourth Runge-Kutta solver (Griffiths and Higham 2010). Other kind of simulations such as: Gillespie re-direct, tau-leap and agent-based are also supported.

We have validated the effectiveness of our approach by showing that the concerns are structurally independent and easily modifiable. First, we varied the integrating order of three concerns and compared the dynamics of the obtained deterministic models. The simulation results have shown that these dynamics are identical in all cases, suggesting that the order of integrating concerns has no impact on the model. Since they are structurally independent, the definition of each concern can be changed without impacting the others. For example, the number of patches or the connection between patches of the spatial concern or the considered species can be changed[2].

Moreover, the interactions between concerns can be changed to capture more issues of epidemiology such as controlling strategies. For instance, the effectiveness of the *quarantine* strategy (Keeling

[1] https://github.com/UMMISCO/kendrick/wiki

[2] More examples can be found on Kendrick's development site

and Rohani 2008) can be studied by restricting the travel of infectious individuals. This can be easily done by modifying the migration rates ρ ($\rho = 0$ for all infectious individuals). The result shows that the total number of infectious decreases compared with the one of no quarantine.

5. Related Work and Discussion

Epidemiological modellers have used a variety of tools for constructing models: general programming languages, mathematical modelling languages (Matlab, R, etc.), libraries targeted to epidemiology such as Epipy[3] - a Python tools for epidemiology, GillespieSSA[4] - an R package for generating stochastic simulation using Gillespie's algorithms (Gillespie 1977) or dedicated modelling software as GLEAMviz (Van den Broeck et al. 2011), STEM (Falenski et al. 2013), FRED (Grefenstette et al. 2013) etc. Such tools use different approaches to model the transmission of infectious diseases. However, either they are lower-level programming languages (so that do not focus on the domain of epidemiology) or they are usually closed platforms. They currently lack the ability to provide a level of abstraction to efficiently describe epidemiological models including a variability of domain concerns such as age-structure, social/sexual mixing, multi-species/strains, spatial heterogeneity, etc.

In this paper, we have introduced the separation of domain concerns from the core epidemiological ones by constructing a general mathematical model of the dynamics of a compartment-based population. We consider concerns as transformations done on a model. First, because of the separation of domain concerns from programming ones, the formers ones can be expressed with little or no skills in programming and are easily transformed towards different simulation engines such as deterministic, stochastic or agent-based. This is more flexible than what can be done with other tools that only focus on one kind of simulation (such as GLEAMviz, STEM formulating stochastic models or FRED using agent-based approach). Second, we have separated domain concerns from each other. In (Plateau and Stewart 2000), Plateau et al. have introduced the product form of stochastic automata networks to propose a numerical resolution of finite Markov chains. Inspired by this work, we have expressed each concern as a stochastic automaton and combined them with a tensor sum. Concerns are defined independently but can interact with each other through functional transition rates. The interaction between concerns allows to capture heterogeneities of contact between individuals that play an important role in epidemiological modelling.

In the current implementation, the general mathematical model is implemented as a classical object-oriented model. Compartments are simply assumed to be defined by equivalence relation on the population. In the current implementation, an equivalence relation is typically an expression of equality of attributes. Hence, the equivalent individuals are those with the same values for a given set of attributes. More complex kinds of equivalence relations can be introduced provided that a means is also provided to name each compartment unambiguously.

In the current version, a transition rate matrix is represented through a set of transitions. Different kinds of concrete syntaxes can be used to write transitions, for instance by discretising a deterministic model expressed by ODEs or directly specifying the rate at which an individual goes from one compartment to another one. A functional transition rate is specified using a low-level syntax (*block closure*). A more expressive concrete syntax will be considered to be developed in order to hide implementations details to end-users of this DSL.

[3] http://cmrivers.github.io/epipy

[4] http://cran.r-project.org/web/packages/GillespieSSA/index.html

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