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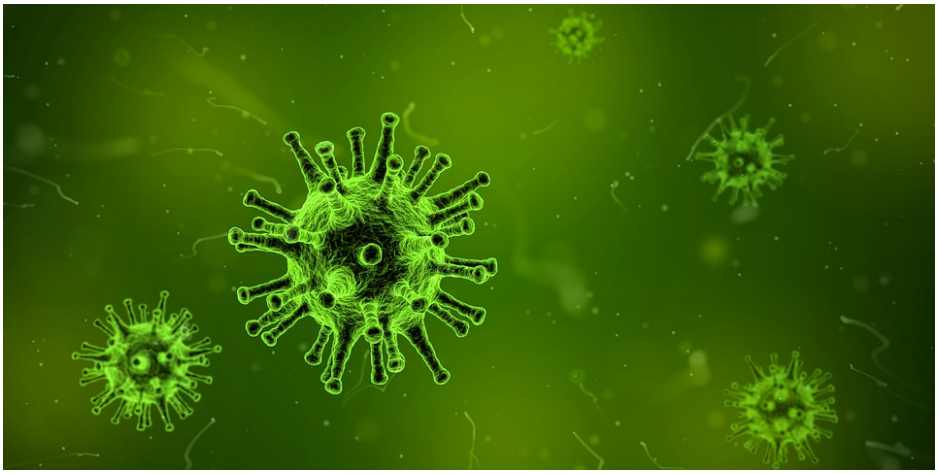

Modelling for Multi-Morbidity

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BIOSENSORS BEYOND BORDERS

Contents

1. Introduction

Diseases can only be treated, and eliminated, if they can be accurately identified; if there are additional diseases present in an individual, a different treatment may be needed than if a single disease is present. When multiple diseases occur together, known as a multi-morbidity, they often lead to increased disease severity, fuelling economic hardship within communities.

Multiple diseases interacting with one another often leads to increased disease severity.

Many of the world's most deadly diseases affect those living in low and middle-income countries. Biosensors Beyond Borders Ltd (BBB) develops innovative new diagnostic services with the goal of increasing access to diagnostics in these parts of the world. BBB wants to determine the performance characteristics of its screening methods. A series of mathematical techniques and concrete experiments is needed to determine the performance and reliability of BBB's system, including the scenario where only partial data or data at a single time interval are available.

Our aim is to develop a population-scale mathematical model describing the evolution of multiple diseases and multi-morbidities.

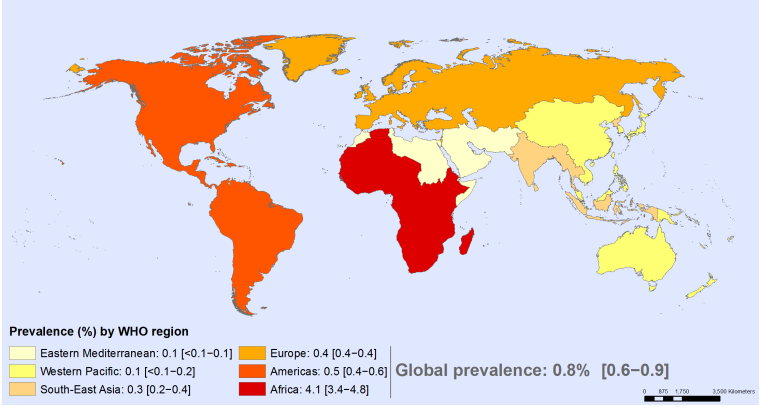

Figure 1 – Prevalence of HIV among adults aged 15 to 49, 2017 [1].

Glossary

- **Markov Model:** This is a probabilistic model describing a sequence of possible events in which the probability of each event depends only on the state of the previous event.
- **Hidden Markov Model:** This is a Markov model in which the system being modelled is assumed to be a Markov process with unobserved (i.e. hidden) states.
- **Digraph:** This is a directed graph consisting of set of nodes (e.g. the number of individuals in a state) connected by edges (e.g. the movement between states).
- **Disease State:** This is an abstract categorisation of an individual's overall health. For example, one state may be "having cancer", and another state "having cancer and HIV".
- **Multi-Morbidity:** This is the presence of additional diseases in an individual.
- **Coupling:** This is a system in which the evolution of one variable influences the evolution of another.

2. Individual Multi-Morbidity Model

We follow [2] and formulate a mathematical model to describe the disease state and multi-morbidities of a patient, given clinical features at discrete time intervals. An individual's health

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is abstractly categorised into one of M disease states S_1 to S_M, while the multi-morbidities X_k, which are either 'on' or 'off', represent specific health problems.

Disease state transitions evolve independently of the multi-morbidities, but each multi-morbidity is disease dependent, hence there is one way coupling between them. A schematic of the individual disease state and multi-morbidity progression of the Markov model proposed in [2] for the case of three disease states and two multi-morbidities is shown in Figure 2.

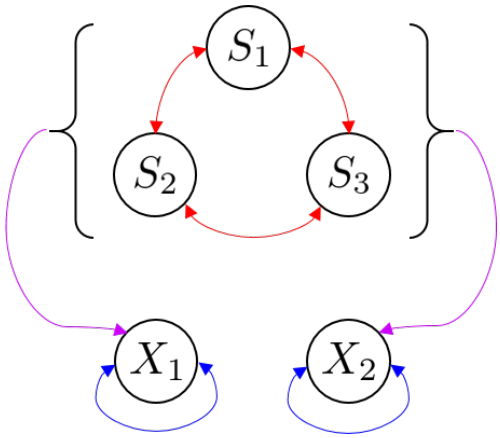


Figure 2 – Schematic of individual disease transition model with 3 disease states and 2 multi-morbidities.

Multi-morbidities can either be 'on' or 'off'.

In Figure 3, we present the resuts from a simulation of the disease state Markov model, showing a single individual transitioning between the three different states, starting in disease state S_1. Note that an individual can transition from each disease state to any other disease state. Similarly, in Figure 4 we show a simulation of the multi-morbidity Markov model, where the lines represent the times where the multi-morbidities are 'on' in the individual. Initially the multi-morbidity X_1 is 'on' whilst X_2 is 'off', so that the individual only has the health problem X_1.

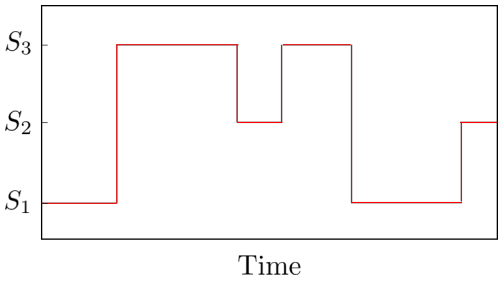


Figure 3 – Simulation of disease state transition within an individual using a model with 3 disease states.

3. Population Multi-Morbidity Model

Markov Model

Starting from the individual disease transition model (see Section 2), by considering the transition between disease states of individuals, we derive a population-level model describing the likely number of individuals in each disease state. We define the number of individuals in

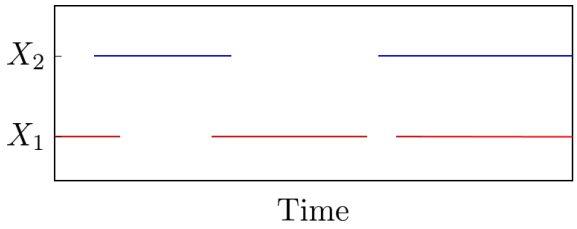


Figure 4 – Simulation of multi-morbidity transitions within an individual using a model with 2 multi-morbidities.

disease state S_m by $\mathcal{S}_m$, so for instance if 2 individuals in the population are in disease state S_1 then $\mathcal{S}_1 = 2$.

In each small time interval a disease state transition by one individual can occur.

In figure 5 we display a digraph of the disease state model for $\mathcal{S}_1$, showing that, in any small time interval, $\mathcal{S}_1$ can stay the same or increase or decrease by 1, but has to remain bounded above by N and below by 0. Similarly, in figure 6 we display a digraph of the disease state model for $\mathcal{S}_1$ and $\mathcal{S}_2$ which, in this case, is a two dimensional lattice, showing the possibilities in which $(\mathcal{S}_1, \mathcal{S}_2)$ can change.

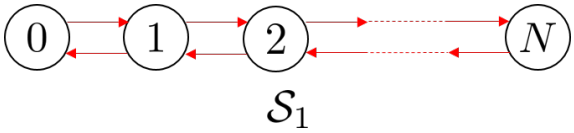


Figure 5 – Digraph of the population disease state model with 2 disease states for $\mathcal{S}_1$.

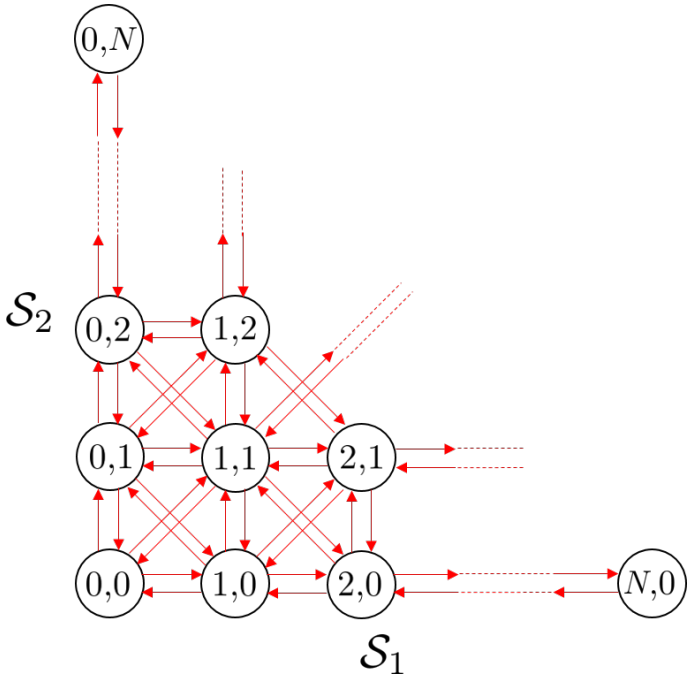
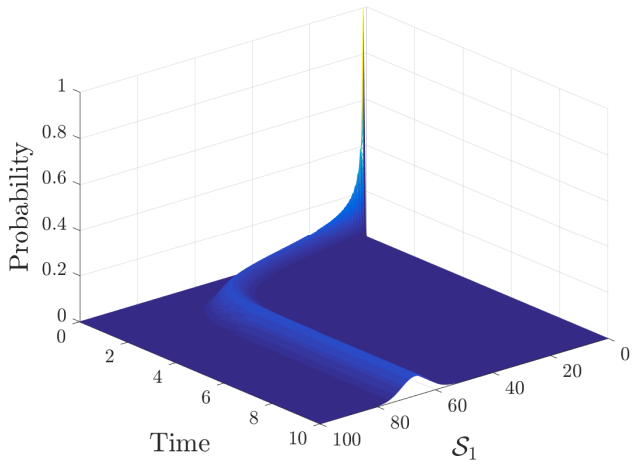


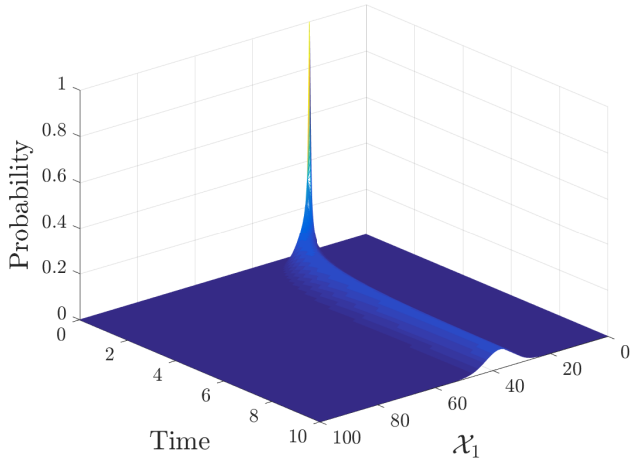
Figure 6 – Digraph of the population disease state model with 3 disease states for $\mathcal{S}_1$ and $\mathcal{S}_2$.

The number of individuals in a disease state and with a certain multi-morbidity reaches an equilibrium after a long time.

In Figure 7, we show numerical simulations of the population disease state and multi-morbidity models for a population of 100 individuals. In figure 7 (a), we show the probability distribution of $\mathcal{S}_1$ as time evolves, with there initially being 2 individuals in state S_1. Similarly, in figure 7 (b) we show the distribution of $\mathcal{X}_1$, the number of individuals who have multi-morbidity X_1. We see that, in both simulations, the system reaches an equilibrium in which it remains unchanged after a long time period.



(a) $\mathcal{S}_1$



(b) $\mathcal{X}_1$

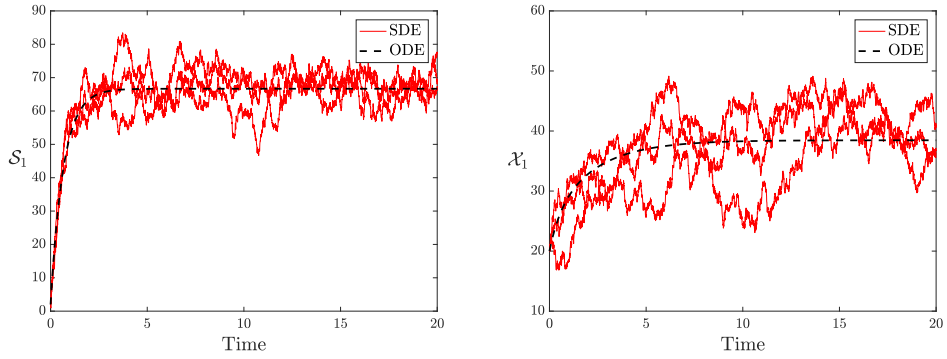
Figure 7 – Markov model probability distributions of disease state $\mathcal{S}_1$ and multi-morbidity $\mathcal{X}_1$.

Ordinary and Stochastic Differential Equation Models

As well as formulating a population-level Markov model, we also formulate two differential equation models. An ordinary differential equation (ODE) model, which describes the mean of the population distribution, and a stochastic differential equation (SDE) model which also incorporates fluctuations in the population.

Stochastic differential equations incorporate fluctuations in the population.

In Figure 8, we show simulations of the SDE and ODE models for $\mathcal{S}_1$ and $\mathcal{X}_1$. In both cases, the mean remains unchanged after a long time, while the SDE model fluctuate around the ODE equilibrium.



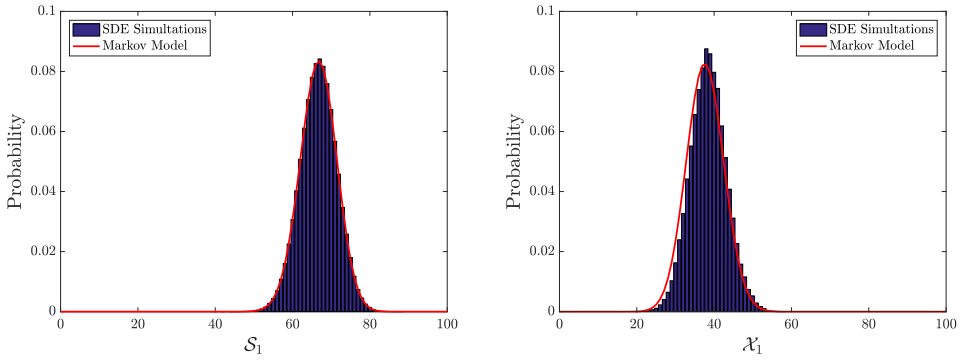
(a) $\mathcal{S}_1$ **(b)** $\mathcal{X}_1$

Figure 8 – Three simulations of the SDE models and the corresponding ODE models governing the disease state $\mathcal{S}_1$ and multi-morbidity $\mathcal{X}_1$.

Long-Term Distribution

Simulations of the SDE and Markov models match in the limit of a large population.

We are interested in the long-term behaviour of the population and we find that the long-term probability distributions of $\mathcal{S}_1$ and $\mathcal{X}_1$ follow the binomial distribution. In Figure 9, we plot the long-term distribution of the population disease state and multi-morbidity Markov models and a historgram of results from 100,000 SDE simulations. In Figure 9 (a), we show that the SDE simulations for $\mathcal{S}_1$and the Markov model match exactly. However, in 9 (b), we show that, although the two models for $\mathcal{X}_1$ match closely, there is a discrepancy due to the fact that the transition of the multi-morbidities is dependent on the disease state. The SDE simulations are an accurate approximation of the Markov model for $\mathcal{X}_1$ in the limit of a large population.



(a) $\mathcal{S}_1$ **(b)** $\mathcal{X}_1$

Figure 9 – Long-term distributions of $\mathcal{S}_1$ and $\mathcal{X}_1$. The solution of the Markov models in red, and a histogram of 100,000 simulations of the stochastic differential equations.

4. Discussion, Conclusions & Recommendations

We have built upon the work of [2], deriving aggregate models for the transition of disease states and multi-morbidities within a population. Starting from the hidden Markov model for the progression of a disease of an individual, we have derived various population models.

We formulated equations governing the likelihood of a certain number of individuals being in each disease state and having a multi-morbidity. From these we derived an ordinary differential equation model which we used to estimate the mean of the evolution of a disease within a population. Finally, we derived stochastic differential equation models in order to incorporate the effects of noise on the population.

In the limit of large time, the system was shown to reach a steady state where, although the disease transitions within each individual may still be ongoing, the population as a whole remains unchanged. Through computational and mathematical means, we showed that our different models are equivalent. Moreover, we showed that, for the case of two disease states, the equilibrium is given by a binomial distribution.

Existing knowledge from compartmental population based models can be used to inform the disease states of individuals.

Following on from our research, BBB will continue to develop their work on mathematical models. A possible caveat is the lack of sufficient real world data, since capturing a full disease trajectory may require a longitudinal study, hence giving rise to the necessity to utilise existing knowledge from compartmental population-based models. Future work would investigate how we can employ knowledge from existing compartmental models and use this knowledge and supplementary material for further development.

The mathematical models formulated in this project have been disease agnostic and have just considered abstract disease states and multi-morbidities. Our work serves as an introductory part of the theoretical grounding for modelling specific disease-states within a population. Our long term aim is to use mathematical models and data to enable forecasting of dangerous disease combinations.

5. Potential Impact

This project is an entry point into the development of forecasting techniques which, if successful, could help to set priorities and aid in planning to address dangerous disease combinations in populations. A changing situation on the ground coupled with a number of challenges in clinical presentation, the variable genetic factors involved, and considerable individual variation, present significant challenges.

Leonidas Eleftheriou, Head of Artificial Intelligence at Biosensors Beyond Borders, commented:

"By helping us to assess the performance and reliability of our system in this project, we move one-step closer to achieving our mission of increasing access to sensitive diagnostics for in-need populations globally. "

References

[1] World Health Organization HIV World Map 2017. `http://www.who.int/gho/hiv/en/`.

[2] Xiang Wang, David Sontag, and Fei Wang. *Unsupervised Learning of Disease Progression Models*. Proceedings of the 20th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, KDD '14, pages 85-94, New York, NY, USA, 2014. ACM.