A General Microsimulation Toolkit for Patient Specific Predictions, Treatment Efficiency and Life Expectancy

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Abstract

Microsimulation can be used to predict the prognosis of an individual patient based on a virtual patient population of copies of that patient.

In this study we compare the outcomes of an existing validated microsimulation program that is designed to study valvular heart disease and a newly developed microsimulation program that is designed to study heart diseases in general.

We studied in depth the results of both systems to model the prognosis of a 40 year old male patient undergoing allograft surgery. Furthermore we studied the model results in relation to age and sex to provide a general overview of the most important outcome variables including operative mortality, average survival time, average event free time and average time to reoperation.

Our results show a good agreement between the two systems regarding all simulations of allograft surgery. We intend to use the newly developed software to explore other disease/event related prognostic models.

1. Introduction

One of the simplest forms of microsimulation is the simulation of a coin flip. By using computer software we may throw a coin a large number of times. For an honest coin (i.e. probability of "head" is 0.5; note that parameters can be freely chosen) we should expect to observe approximately the same number of either heads or tails. A more advanced version of this technique can be used in medicine to predict disease prognosis as described below.[1]

1.1. Microsimulation in AVR

The use of microsimulation is a widely accepted and useful strategy to support clinicians in choosing an appropriate treatment for patients with an indication for aortic valve replacement (AVR).[2,3] Microsimulation simulates the probability of operative mortality and AVR related adverse events for an individual patient based on his clinical characteristics and the type of AVR that is being considered. Specifically, it creates a virtual population of patients with identical baseline characteristics, and calculates the event-free period after surgery, reoperations and life expectancy, for each type of AVR.

For each virtual patient, a lifetime of events and reoperations is simulated, using functions and random distributions, based on parameters derived from epidemiological studies.

Consecutive events during the patients' lifecourse are simulated as follows. After the initial operation, the time to each individual valve-related incident is calculated. The event that occurs after the shortest time period is chosen as the one that actually took place in the virtual patient. After this event, a reoperation may be needed or another event may occur. This second event is simulated by repeating the procedure. The simulation for a virtual patient ends when the patient dies, either due to background mortality, event-related mortality or operative mortality.

1.2. AVRSim

In the past, our centre has developed software (AVRSim) for simulating the lifecourse of AVR patients to support physicians in choosing the most appropriate type of AVR. This software was validated internally and externally.[4-6]

AVRSim is specifically tailored to handle AVR patients. The software compares the following types of AVR: allograft, bioprothesis, mechanical, and autograft. Unfortunately, the current version of AVRSim could not be easily transformed to other disease/event/treatment related models. AVRSim is available, after registration, for download.[7]

Event	Risk function	Age dep.	Mortality Risk	Reoperation risk	Reoperation
Valve thrombosis	Zero-risk	0	0	1	Allograft
Thromboembolism	Exponential(0,006)	0	0.1	0	
Hemorrhage	Exponential(0,001)	0	0.07	0	
Non-structural dysfunction	Exponential(0,005)	0	0	1	Mechanical
Endocarditis	Exponential(0,005)	0	0.25	1	Allograft
Structural dysfunction	Weibull(2,234,;3,669)	0,0112	0	1	Mechanical

Table 1 Parameters of the allograft microsimulation model used in both systems

1.3. General microsimulation toolkit

We hypothesize that the microsimulation technique can also be applied to other clinical patient populations. For this purpose, we have developed a new software package, General Microsimulation Toolkit (GMT). With this package we aim to provide a microsimulation toolkit that is applicable to any given type of disease (or disease related event) and treatment strategy.

The key features of a disease in the system are the time function to develop the disease (or disease related event), the mortality function for the disease, the adjustment for baseline parameters and the function to determine the most likely treatment. Each treatment has a mortality function (for example the risk of dying during an operative procedure), a time function to determine the most likely time to treatment-related event and the adjustment for baseline parameters.

The GMT is a web based system developed in C# and uses the JEP.NET library [8] for the mathematical functions. The system can handle a variety of statistical methods such as: (logistic) regression models, (log) normal, 2-period, Weibull, Pareto, and Gompertz.

The system has a user-friendly interface to incorporate these statistical methods into a patient-event-treatment microsimulation model. It calculates the time-to-event, event-free period, life expectancy, treatment efficiency and treatment related events. Moreover, it facilitates the comparison of the outcomes of each simulation (statistically and graphically in a survival curve) for different treatment choices.

2. Methods

The aim of this study is to compare the results of AVRSim and GMT. In this paper, we consider one case in depth; the case of a 40 year old male undergoing allograft surgery. We also consider different populations with different ages and genders.

2.1. Case of a 40 year old male

In this study, we compare the results of a hypothetical case study of a 40 year old male undergoing allograft surgery. We have generated a virtual patient population of 10000 identical individuals in both systems.

In Table 1 we show the parameters of the allograft model. The risk function, together with the age dependency, calculates the time to an AVR related event, of the event occurrence after an allograft procedure.

The mortality risk describes the mortality risk when the event occurs. The reoperation risk is the risk of undergoing a reoperation after the event. The reoperation type describes the reoperation which is performed after the event.

The operative mortality odds for an allograft at age 40 is 0.0260; the odds ratio (OR) for age (per year) is 0.0218; the OR per reoperation is 0.5306. We used a background mortality based on the Dutch life tables and a hazard ratio of 3.65.

2.2. Different patient populations

In a second analysis we constructed different virtual patient populations consisting of men and women with ages defined by 10-year age-intervals (n=10000, age-range 10 to 70). We simulated an allograft replacement operation in each population. We analyzed operative mortality, the average survival, the average freedom of event time and the average freedom of reoperation time.

We used similar parameters for an allograft as described in table 1 and subheading 2.1. However the operative mortality is different because it is age dependent. The hazard ratio used to calculate the background mortality is age and gender dependent. Again, we use the Dutch life tables for the background mortality.

3. Results

3.1. Results case of a 40 year old male

	AVRSim	GMT
Survival (years)	21.17	21.30
Event free (years)	10.70	10.76
Reoperation free (years)	11.11	11.41
Number of event free	1670	1683
Number of reoperation free	1937	2073
Mortality first operation	242	234
Mortality non-related	8218	8235
Valve thrombosis		
1	46	44
Thromboembolism		
1	1600	1556
2	177	144
3	13	13
4	0	1
Hemorrhage		
1	1337	1378
2	203	144
3	23	12
4	3	1
Non structural dysfunction		
1	878	878
2	63	54
3	1	2
Endocarditis		
1	575	631
2	29	23
3	2	0
Structural dysfunction		
1	7326	7144

Table 2 Results of a case study of 40 year old male after allograft surgery in AVRSim and GMT.

In table 2, the output of both systems is displayed for 10000 simulations after allograft operation.

Negligible differences were present in the average survival in years after the allograft procedure, average event free period, average number of persons free of reoperation, number of event free persons, number of individuals that didn't receive a reoperation, the mortality of the initial allograft procedure and the number of individuals that died due to non-valve related events/operations ('mortality non related').

Table 2 also shows also the number of events for each event. In AVRsim, 1600 individuals developed a thromboembolism, 177 individuals developed 2 thromboembolisms and 13 individuals developed 3 thromboembolisms.

3.2. Results different patient populations

Table 3 shows the results for the populations of patients undergoing allograft operation that we generated. For each population, we simulated age from 10 to 70 for both genders. The table shows the most relevant outcome parameters; percentage of operative mortality of the allograft operation ('Op. mortality'), average survival time in years, average time to first event ('Event free') and average time to first reoperation ('Reoperation free'). The last row displays the range of the maximum difference between each of the columns.

Due to the fact that AVRSim uses a non-seeded random function, the results are always the same. This is clearly shown by the identical operative mortality for both genders.

4. Discussion and conclusions

We have demonstrated good agreement between AVRSim and GMT. We conclude that the underlying mathematical functions are correctly implemented. The AVRSim models have been internally and externally validated. With the current study, the GMT model for AVR has been validated against the AVRSim AVR model.

The next step is the application of this software to other prognostic models, including cardiovascular diseases and treatments. Obviously, these new models need to be evaluated internally and externally before they can be used in daily practice.

	Gender	Op. mortality (%)		Survival (years)		Event free (years)		Reoperation free (years)	
		AVRSim	GMT	AVRSim	GMT	AVRSim	GMT	AVRSim	GMT
10	M	1.38	1.15	41.34	41.60	8.49	8.48	8.74	8.94
	F	1.38	1.45	44.35	44.30	8.51	8.47	8.76	8.96
20	M	1.55	1.50	33.58	33.60	9.27	9.25	9.57	9.81
	F	1.55	1.42	36.51	36.55	9.35	9.37	9.66	9.97
30	M	1.94	2.09	26.77	26.98	10.12	10.01	10.48	10.72
	F	1.94	2.06	28.62	28.62	10.14	10.09	10.50	10.76
40	M	2.42	2.34	21.17	21.30	10.70	10.76	11,11	11.41
	F	2.42	2.30	22.67	22.84	10.73	10.75	11,14	11.42
50	M	2.97	3.07	16.77	16.82	10.76	10.77	11.20	11.37
	F	2.97	3.12	18.78	18.90	11.15	11.04	11.61	11.76
60	M	3.58	3.88	13.08	12.92	10.05	9.93	10.45	10.43
	F	3.58	3.77	14.41	14.41	10.76	10.72	11.2	11.36
70	M	4.46	4.72	9.87	9.77	8.52	8.41	8.82	8.75
	F	4.46	4.60	10.29	10.37	8.93	8.91	9.25	9.32
Range diff		-0.3 ; 0.23		-0.26 ; 0.16		-0.06 ; 0.12		-0.31 ; 0.07	

Table 3 The results of AVRSim vs. GMT for different virtual populations with different initial age in years and gender (M for male and F for female). Op. mortality is the percentage of the population that died during the initial allograft procedure.

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