Physiological verification of a geriatric population using the Simcyp R package

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Abstract

A geriatric Northern European Caucasian population was initially developed in Simcyp V13R1. The purpose of this work is to highlight the use of the Simcyp R package in generating a simulated geriatric population. The database can be interrogated via R to extract key physiological data related to the geriatric population for analysis. The accuracy of the simulated values in relation to observed data from multiple studies in terms of age, height, weight and abundance of serum proteins will then be determined. The work also aims to illustrate that data obtained via the Simcyp R package can be visualised effectively and reproducibly using the 'ggplot' package.

Simulating via R

```
Simcyp::Initialise("C:\\Program Files\\Simcyp Simulator V18\\Screens\\SystemFiles\\Human")
Simcyp::SetDatabaseExport(TRUE)
Simcyp::SetWorkspace("Sim_Geriatric NEC.wksz")
Simulate()
FindAndCopyDB("Geriatric.db")

Connj <- RSQLite::dbConnect(SQLite(),"Geriatric.db")

Geriatric<-data.frame(Index= seq(1:GetParameter("idNumberPopulation", CategoryID$SimulationData, 0)))
Geriatric$`Sex`<- GetAllIndividualValues_DB("idSex",Connj)
Geriatric$`Age`<- GetAllIndividualValues_DB("idAge",Connj)
Geriatric$`Serum Albumin (g/L)`<- GetAllIndividualValues_DB("idHSA",Connj)
```

Fig 1. Sample R code for initialising the Simcyp R engine to run a simulation and connecting to the database using the 'RSQLite' package.

Figure 1 shows an example of code used to establish a connection to the database allowing physiological parameter values for the geriatric population to be collected in a data frame using the GetAllIndividualValues_DB function included in the Simcyp R package.

Results

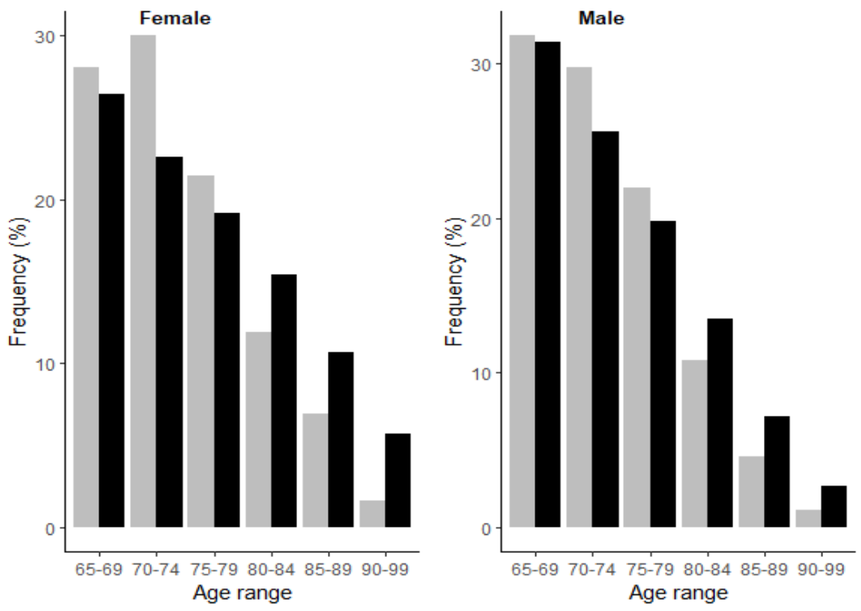

Fig 2. Simulated (grey; 10 trials x 100 geriatric patients, 65-98 yrs, 100% male , 100% female, and observed (black) age distribution of the Sim-Geriatric NEC population. Observed data from National Office of Statistics (2012).

The age distribution of the simulated population was based on a Weibull distribution model. The population distribution of 1000 individuals was similar to that of the observed data set (figure 2), with less than 5% discrepancy in frequency between the simulated and observed populations, in each individual age range.

The height and weight distribution of the simulated female geriatric population (figure 3) also showed a good degree of prediction of the parameters. In the male population, a slight under prediction of the population height was observed.

Albumin is the most abundant plasma protein and has a key role in the protein binding of many drugs. It has been observed that serum albumin concentrations decrease as age increases, with geriatric male and female serum albumin decreasing at a similar rate [1].

Conversely increasing alpha-1-acid glycoprotein (AAG) concentrations have been observed in healthy geriatric patients [2,3]. AAG is also a key binding protein for basic drugs and thus these two proteins were considered important to examine when determining the validity of the geriatric population.

Figure 4 shows that serum albumin and AAG concentrations are predicted with a good degree of accuracy within Simcyp, against 3 individual studies for albumin and two for AAG. For the male albumin simulation some degree of overprediction may be noted, however observations from one study showed consistently lower concentrations than those in other studies.

Results

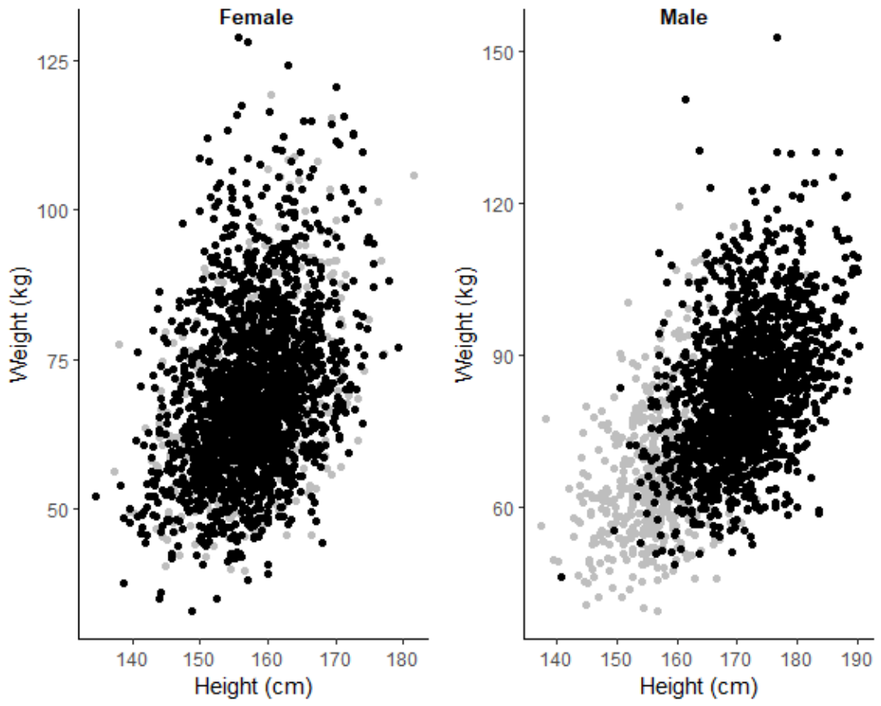

Fig 3. Simulated (grey; 10 trials x 100 geriatric patients, 65-98 yrs, 100% male , 100% female, and observed (black) height and weight distribution of the Sim-Geriatric NEC population. Observed data from National Office of Statistics (2012).

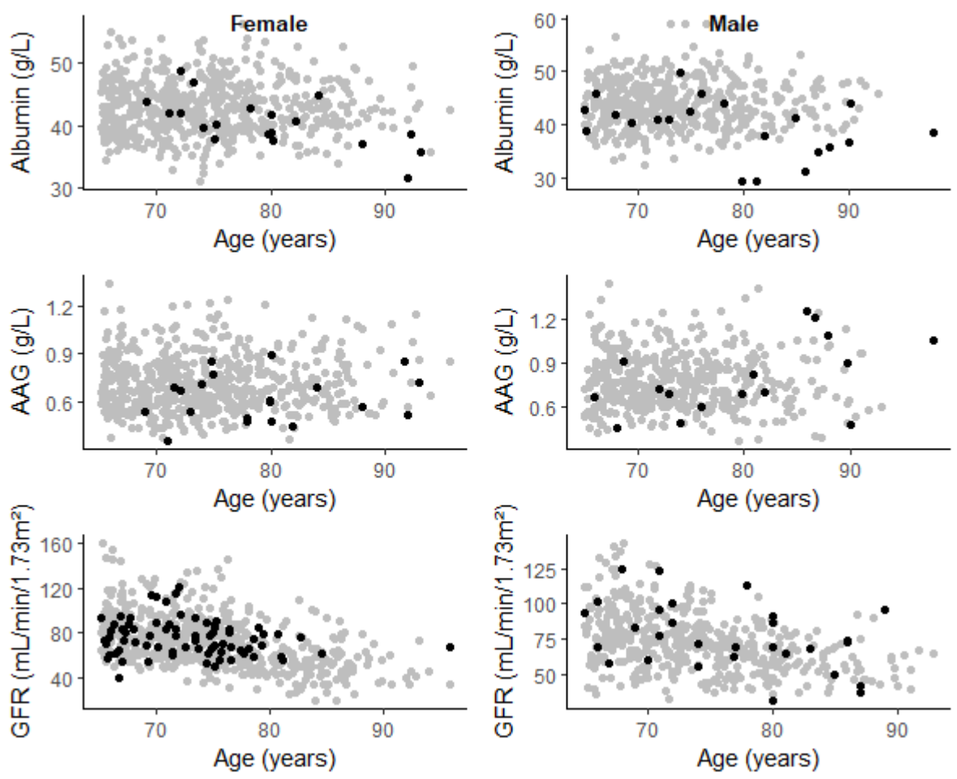

Fig 4. Simulated (grey; 10 trials x 100 geriatric patients, 65-98 yrs, 100% male , 100% female, and observed (black) serum albumin, alpha-1-acid glycoprotein concentrations and glomerular filtration rate (GFR) in relation to age.

Figure 4 also shows the relationship between glomerular filtration rate and age. The simulated values show a decrease in GFR in relation to increasing age which is supported by the observations from 3 studies, with observed GFR estimated via insulin clearance. The simulation also provided a good degree of prediction in relation to GFR in the geriatric population, with observed values within the range of the simulated data. The results support previous studies linking a decrease in kidney function with old age [4].

Conclusions

- The Sim-Geriatric NEC population in Simcyp V18 demonstrates simulated individuals are in line with observed geriatric age, weight and height. The simulation also gives a good level of accuracy in the prediction of key serum proteins albumin and AAG, mainly within 10 % of observed data, as well as glomerular filtration rate.
- The Simcyp R engine is a useful tool allowing users to carry out multiple simulations within the same script and effectively visualise the data. Due to the reproducible nature of the functions, similar verifications could be carried out using different populations or other physiological parameters.

References

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[3] D.R. Abernethy, L. Kerzner, Age effects on alpha-1-acid glycoprotein concentration and imipramine plasma protein binding, J Am Geriatr Soc, 32 (1984) 705-708.

[4] R. Abdulkader, E.A. Burdmann, M.L. Lebrao, Y.A.O. Duarte, D.M.T. Zanetta, Aging and decreased glomerular filtration rate: An elderly population-based study, PLoS One, 12 (2017) e0189935.