The authors evaluate the best method of estimating the effect of HARRT on CD4 count by comparing Dynamic models with Marginal structural Models (MSM) and Generalized Estimating Equations (GEE). In all models, treatment was considered as a binary variable (i.e., treated Vs untreated). Of interest was CD4 recovery within first year of therapy, and after first year. These models were applied on the Swiss HIV cohort and Aquitatine cohort and compared them to simulated data.

For the GEE model—model 1, they used number of times the patient was on treatment till most recent visit and cumulated most recent time while on treatment as predictors. They used GEE here because they assumed the outcome—CD4 response—was positively correlated, and they were also interested in the population average.

In the MSM, they constructed two models with the outcome remaining the same in both and they used inverse-probability-of-treatment weighting:

1. In model 2, they used the same predictors as model 1 but added time of follow-up and baseline of CD4 count.
2. In model 3, they added to model 2 a potential predictor of viral load. Based on the nature of confounding by indication in cohort studies.

In the Discrete-time dynamical models, 3 models were generated:

1. In model 4—analyzed as a linear mixed-effects model—the outcome was defined as a change in CD4 count between current and most recent. This was based on the assumption that current state of a patient is based on the previous state. Potential predictors were ART treatment, and random effects (assumed to be normally distributed with mean of zero). For data with non-equally spaced time points, every change in CD4 count was divided by the duration between measurements. This model was classified as a two slope model because it had two covariates of most recent CD4 counts (i.e., in the first year as well as in the after the first year).
2. In model 5, they incorporate the concept of equilibrium points in dynamical models. In this vain, the first model whose outcome is change in the CD4 count from most recent visit and current visit, corresponds to an autoregressive model of order 1. This assumption translates into including as predictors most recent CD4 count, treatment status, and random effects.
3. Model 6 was based on a system of two difference equations (i.e., same model as model 5, and added viral load). The model for viral load had similar potential predictors as model 5, above.

Model 7 was a continuous dynamical model (mechanistic model). This model combines target cell model, inter-individual variability model for parameters, and an observation model. Justification for using this model was that in reality biological process follow a continuous rather than discrete process.

Conclusions: Model 1—under estimated treatment effect; Model 2&3 (MSM) corrected for the treatment effect so better than model 1; Model 4 gives good estimates for the mean causal effect but just like in previous models, increase in CD4 count is infinite; Models 5-7 consist of equilibrium points which help correct the infinite increases in CD4 count—a problem with previous models. Model 5 however doesn’t capture the initial (first year) increase in CD4; Models 6 & 7 capture the increase in the first year of therapy therefore giving a correct estimate of CD4 count increase. They both provide a qualitative explanation of treatment effect on CD4 count mediated by decreasing viral load. However model 7 provides a mechanistic interpretation of infection and provides estimates for biological parameters.

The authors provide great insight in CD4 count modeling and suggest some of the things I need to consider for objective 3 in the PhD protocol. However, I have not done any discrete-time dynamical modelling before, not to mention continuous dynamical model (mechanistic models).