SIMULATIVE MODELS

Sara Silvestrelli
Dipartimento di Economia, Metodi Quantitativi e Strategie di Impresa
Università degli studi di Milano-Bicocca

ABSTRACT

Given the limited availability of longitudinal observational data describing clinical trials due to privacy constraints and contractual regulations, a common way to obtain this data is to resort to simulation.

In particular, this work recall Kyle Humphrey's simulation study [1] which in turn was largely inspired by Yufan Zhao, Kosorok, and Zeng et al. [2] and Yufan Zhao, Zeng et al. [3]. They describe a generic cancer clinical trial for a predefined number of stages with the aim of finding the optimal treatment regime (dose of a drug) for each patient maximizing survival time.

***K*eywords** DTR · Simulative Models · Data Simulation · DTR

1 Introduction

This trial compares a different number of stages of treatment that are one month long. Each patient was assigned a random dose of the drug and the initial clinical conditions of the disease were measured.

Patient model The clinical picture of a patient is described through four main features: Toxicity W, Tumor Mass M, Renal Function RF and Stress STR.

Toxicity represents the negative of wellness for a patient and it is measured at the beginning every month t:

$$W_t^* = 0.1\ M_{t-1} + 1.2\ (D_{t-1} - 0.5) + W_{t-1} \tag{1}$$

$$W_t = \begin{cases} W_t^* & \text{if } W_t^* > 0 \\ 0 & \text{if } W_t^* \leq 0 \end{cases} \tag{2}$$

Tumor mass indicates the size of the cancer and is defined as follows:

$$M_t^* = [0.15\ W_{t-1} - 1.2\ (D_{t-1} - 0.5) + M_{t-1}]\ I(M_{t-1} > 0) \tag{3}$$

$$M_t = \begin{cases} M_t^* & \text{if } M_t^* > 0 \\ 0 & \text{if } M_t^* \leq 0 \end{cases} \tag{4}$$

Renal Function is usually monitored in cancer trials due to its influence in in the pharmacokinetics and the pharmacodynamics of many drugs [4] [5] and this indicator is defined as:

$$RF_t{}^* = 1.2\ (D_{t-1} - 0.5)\ - 0.1\ (M_t - M_{t-1}) - 0.1\ W_{t-1} + RF_{t-1} \tag{5}$$

$$RF_t = \begin{cases} RF_t{}^* & \text{if } RF_t{}^* > 0 \\ 0 & \text{if } RF_t{}^* \leq 0 \end{cases} \tag{6}$$

It is assumed that an increase in tumor mass and lower overall health (higher W_{t-1}) decrease RF since they are assumed to lead to worst clinical conditions. On the contrary, higher dosage of the drug (above 0.5) improve the renal function.

Cancer involves different aspects of an individual's life and studies prove that combined medical and psychological interventions reduce general stress and significant changes were also seen in quality of life and its domain [6]. It is here assumed that a patient's stress increases with the passage of time and the accumulation of drugs. This variable is modeled as:

$$\begin{aligned} STR_t^* = \; & STR_{t-1} \; + \; 0.1 \, (M_t - M_{t-1}) \; + \; 0.2 \, (W_t - W_{t-1}) + \\ & + \; 0.8 \, D_{t-1} \; + \; 0.5 \, D_{t-2} \; + \; 0.3 \, D_{t-3} \end{aligned} \tag{7}$$

$$STR_t = \begin{cases} STR_t^* & \text{if } STR_t^* > 0 \\ 0 & \text{if } STR_t \leq 0 \end{cases} \tag{8}$$

Initial values at stage zero (the first month) for patient's tumor mass, M_0, toxicity, W_0, renal function, RF_0, and stress STR_0, were generated independently as follows:

$$\begin{aligned} W_0 &\overset{iid}{\sim} \text{Unif}(0,2) \qquad & M_0 &\overset{iid}{\sim} \text{Unif}(0,2) \\ RF_0 &\overset{iid}{\sim} \text{N}(0,1) \qquad & STR_0 &\overset{iid}{\sim} \text{Unif}(0,2) \end{aligned} \tag{9}$$

More specifically the resulting values of RF_0 were bounded by 0 taking them as their absolute form so as to avoid negative outcomes.

Survival model Survival times were generated every month t from an exponential distribution considering tumor mass more important than toxicity. The rate parameter λ was modeled as:

$$\lambda_t(M_{t+1}, W_{t+1}) = \exp(-5.5 + W_{t+1} + 1.2 \, M_{t+1} + 0.75 \, W_{t+1} \, M_{t+1}). \tag{10}$$

2 Scenarios

Three different scenarios and data settings were considered for this clinical study: basic, interaction and predictive noise scenario.

Basic scenario This is the simplest scenario with the main variables: toxicity, tumor mass, stress. Two parameters are arbitrarily chosen:

- Number of T months (or stages) s.t. $t = 0, ..., T-1$;
- Number of K treatment options or possible dosages s.t. $k = 1, ..., K$.

Doses D_t may assume values in the range $[0, 1]$ where $D_t = 0$ is a placebo and $D_t = 1$ represents the maximum tolerable dose. Dosages depend on the number of treatment options selected K as follows:

$$\frac{0}{K-1}, \frac{1}{K-1}, ..., \frac{K-1}{K-1}. \tag{11}$$

For example with a value of $K = 5$ treatment options will include:

$$(0, \; 0.25, \; 0.5, \; 0.75, \; 1) \, .$$

Every month toxicity, tumor mass, stress and rate parameter for the next stage were updated using equations 1, 3, 7 and 10 and survival times, S_t, were randomly sampled from the exponential distribution as follows:

$$S_t \sim \; \text{Exp}(\lambda_t(M_{t+1}, W_{t+1})) \tag{12}$$

$$= \; \text{Exp}(\exp(-5.5 + W_{t+1} + 1.2 \, M_{t+1} + 0.75 \, W_{t+1} \, M_{t+1})) \tag{13}$$

If $S_{it} \leq 1$ the reward is calculated as the sum of the log of the survival time plus the number of months elapsed in addition to another quantity influenced by the stress. Reward function was modeled as a continuous outcome (14).

$$R_{t+1} = \begin{cases} R_{t+1} = \; \log(S_t + \sum_{j=0}^{t} j) \; + \; \frac{1}{\sum_{j=0}^{t} j \; + \; STR_t \; + \; 1} & \text{if } S_t \leq 1 \text{ or } t = T-1 \\ 0 & \text{otherwise} \end{cases} \tag{14}$$

Interaction scenario This scenario adds two covariates, X_1 and X_2, that are simulated from uniform distributions in the range of $[0, 1]$:

$$X_1, X_2 \overset{iid}{\sim} \text{Unif}(0, 1). \tag{15}$$

Based on the values that have been generated, four different patient groups are classified in order to increase individualization:

1. $[X_1 < 0.5 \;\&\; X_2 < 0.5]$: patients are identical to those in the basic scenario.
2. $[X_1 > 0.5 \;\&\; X_2 < 0.5]$: patients are 50% more sensitive to the effects of the drug:
$$W_t^* = W_t' = 0.1\, M_{t-1} + 1.2\, (1.5\, D_{t-1} - 0.5) + W_{t-1} \tag{16}$$
3. $[X_1 < 0.5 \;\&\; X_2 > 0.5]$: patients are 50% more effected by the treatment:
$$M_t^* = M_t' = [0.15\, W_{t-1} - 1.2\, (1.5\, D_{t-1} - 0.5) + M_{t-1}]\, I(M_{t-1} > 0) \tag{17}$$
4. $[X_1 > 0.5 \;\&\; X_2 > 0.5]$: patients are 50% more effected by the drug and the 50% more sensitive to its effects:
$$W_t^* = W_t' = 0.1\, M_{t-1} + 1.2\, (1.5\, D_{t-1} - 0.5) + W_{t-1} \tag{18}$$
$$M_t^* = M_t' = [0.15\, W_{t-1} - 1.2\, (1.5\, D_{t-1} - 0.5) + M_{t-1}]\, I(M_{t-1} > 0) \tag{19}$$

Predictive noise scenario In this scenario may arbitrarily be included new predetermined additional variables $p+q+v$ simulated from a Normal distribution as follows:

$$Z_1, \ldots, Z_p \overset{iid}{\sim} N(1, 1) \tag{20}$$

$$Z_{p+1}, \ldots, Z_{p+q} \overset{iid}{\sim} N(-1, 1) \tag{21}$$

$$V_1, \ldots, V_v \overset{iid}{\sim} N(0, 1) \tag{22}$$

Z variables influence the λ parameter through a weight w:

$$\begin{aligned} \lambda_t'(M_{t+1}, W_{t+1}) = \exp(&-5.5 + W_{t+1} + 1.2\, M_{t+1} + \\ &+ 0.75\, W_{t+1}\, M_{t+1} + w\, (\sum_{i=1}^{q} Z_i)\,) \end{aligned} \tag{23}$$

where this modification only shifts the expected survival up or down. In this thesis weight w is equal to 0.05.

RF is available only in the high complexity model (**??**) but when present it also influences the λ together with the Z variables:

$$\begin{aligned} \lambda_t'(M_{t+1}, W_{t+1}, RF_{t+1}) = \exp(&-5.5 + W_{t+1} + 1.2\, M_{t+1} + \\ &+ 0.75\, W_{t+1}\, M_{t+1} + w\, (\sum_{i=1}^{q} Z_i + RF_{t+1})\,) \end{aligned} \tag{24}$$

3 Models

Starting from the basic scenario the number of variable goes to increase with the complexity of the model. Each model was trained on a predefined number of patients, N, considering different stages, T, and treatment options K for a total of 81 different trainings, 27 for each model. Possible combinations are obtained from the following values for each previously mentioned category:

- $N = (200,\ 600,\ 1.000)$
- $T = (3,\ 8,\ 16)$
- $K = (3,\ 6,\ 15)$

These settings are shown in more detail in the Tables 1, 2, 3.

3.1 Low complexity model

The here called "low complexity model" works solely with the three main variables that define the patient's clinical status, which are tumor mass, toxicity, and stress. This is the simplest model but also the one that is not subject to inputs that can create noise.

N	T	K	N(1, 1)	N(-1, 1)	N(0, 1)
200	3	3	0	0	0
200	3	6	0	0	0
200	3	15	0	0	0
200	8	3	0	0	0
200	8	6	0	0	0
200	8	15	0	0	0
200	16	3	0	0	0
200	16	6	0	0	0
200	16	15	0	0	0
600	3	3	0	0	0
600	3	6	0	0	0
600	3	15	0	0	0
600	8	3	0	0	0
600	8	6	0	0	0
600	8	15	0	0	0
600	16	3	0	0	0
600	16	6	0	0	0
600	16	15	0	0	0
1000	3	3	0	0	0
1000	3	6	0	0	0
1000	3	15	0	0	0
1000	8	3	0	0	0
1000	8	6	0	0	0
1000	8	15	0	0	0
1000	16	3	0	0	0
1000	16	6	0	0	0
1000	16	15	0	0	0

Table 1: Training parameters of low complexity model with 3 covariates.

3.2 Medium complexity model

The "medium complexity model" considers, in addition to the three low model, pure noise variables belonging to the predictive noise scenario together with the variables $X1$ and $X2$ of the interaction scenario for a total of 35 covariates. The Predictive noise scenario includes p variables generated from $N(1, 1)$, q variables generated from $N(-1, 1)$ and v variables from $N(0, 1)$ available in the medium model as follows:

- $p = 0$
- $q = 0$
- $v = 30$

The noises variables are generated without influencing the survival rate.

3.3 High complexity model

The "high complexity model" is the one that includes all the scenarios and variables seen above for a total of 106 covariates including the renal function indicator. The settings for the Predictive noise scenario are:

- $p = 5$
- $q = 5$
- $v = 90$

N	T	K	N(1, 1)	N(-1, 1)	N(0, 1)
200	3	3	0	0	30
200	3	6	0	0	30
200	3	15	0	0	30
200	8	3	0	0	30
200	8	6	0	0	30
200	8	15	0	0	30
200	16	3	0	0	30
200	16	6	0	0	30
200	16	15	0	0	30
600	3	3	0	0	30
600	3	6	0	0	30
600	3	15	0	0	30
600	8	3	0	0	30
600	8	6	0	0	30
600	8	15	0	0	30
600	16	3	0	0	30
600	16	6	0	0	30
600	16	15	0	0	30
1000	3	3	0	0	30
1000	3	6	0	0	30
1000	3	15	0	0	30
1000	8	3	0	0	30
1000	8	6	0	0	30
1000	8	15	0	0	30
1000	16	3	0	0	30
1000	16	6	0	0	30
1000	16	15	0	0	30

Table 2: Training parameters of medium complexity model with 35 covariates.

N	T	K	N(1, 1)	N(-1, 1)	N(0, 1)
200	3	3	5	5	90
200	3	6	5	5	90
200	3	15	5	5	90
200	8	3	5	5	90
200	8	6	5	5	90
200	8	15	5	5	90
200	16	3	5	5	90
200	16	6	5	5	90
200	16	15	5	5	90
600	3	3	5	5	90
600	3	6	5	5	90
600	3	15	5	5	90
600	8	3	5	5	90
600	8	6	5	5	90
600	8	15	5	5	90
600	16	3	5	5	90
600	16	6	5	5	90
600	16	15	5	5	90
1000	3	3	5	5	90
1000	3	6	5	5	90
1000	3	15	5	5	90
1000	8	3	5	5	90
1000	8	6	5	5	90
1000	8	15	5	5	90
1000	16	3	5	5	90
1000	16	6	5	5	90
1000	16	15	5	5	90

Table 3: Training parameters of high complexity model with 106 covariates.

4 Additions to Bibliographical References

The following additions have been made to the reference papers:

- The simulation models were extended with two more factors to be monitored that are part of the patient's clinical picture: stress and renal function (5, 7);
- The chosen approaches were evaluated on numerous combinations of different parameters and strategies in order to assess the best set for each approach considered (3).

References

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