

# From %x\_receptor to Rcpp: a mathematical formulation of the algorithm, a new R-user interface and an efficient implementation

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## 1 Introduction

The Danish National Prescription Registry (NCBI) provides patient-level data on all prescription drugs sold in Danish community pharmacies since 1994 (?). Effects and side effects of drugs can be assessed in a Danish nation wide registry study. For this the prescription data are linked to the cause of death register and other Danish registries (?).

This document describes the *medicin macro* by Christian Torp-Pedersen, a complex algorithm for the computation of drug exposure strength and length relative to a prespecified study period  $[a, b]$  in calendar time. Note that the start of the study period has to be after the start of the registry in 1994.

## 2 Drug prescription data

We describe the data of a single person who has purchased the drug of interest at  $K$  different dates in the study period  $[a, b]$ . The setup can easily be generalized to multiple patients. The set of ordered drug purchase dates for one patient is denoted as

$$T_1 < \dots < T_K.$$

Here  $K$  is the number of times the patient has purchased one or more packages of the same drug product in the period  $[a, b]$ . One package of each drug product is defined by the drug strength of the smallest unit (e.g., one pill or half a pill) and the amount of such units that it contains. For each drug product we distinguish  $J \geq 1$  different package types according to the different strengths:

$$S_1 < \dots < S_J.$$

Note that the original SAS macro allowed at most 4 different package types but that the new implementation does not have this limitation. For each drug

strength  $S_j$ , the values  $s_j^{\min}$ ,  $s_j^{\max}$ ,  $s_j^*$  define the minimal, maximal and typical dose per day, respectively.

We now describe the total amount of drug purchased on date  $T_k$  and the corresponding maximal number of days of supply. First, note that since  $s_j^{\min}$  is the minimal dosis, one unit of strength  $S_j$  can supply a maximal number of  $(S_j/s_j^{\min})$  days. Next, consider that on date  $T_k$  the patient purchases  $G_{jk}$  many packages of strength  $S_j$ . If the patients purchases no package of strength  $j$  on date  $T_k$  then  $G_{jk} = 0$ . Since each package may include a different number of units, the total amount of units of strength  $S_j$  purchased on date  $T_k$  is given by

$$m_{jk} = \sum_{g=1}^{G_{jk}} (\text{number of units in package } g)$$

We convert this number to the scale defined by smallest units and define the total amount of smallest units of strength  $S_j$  purchased on date  $T_k$  as

$$n_{jk} = m_{jk} \frac{S_j}{s_j^{\min}}.$$

The total amount  $D_k$  of the drug purchased on date  $T_k$  is given by the formula

$$D_k = \sum_{j=1}^J m_{jk} S_j = \sum_{j=1}^J n_{jk} s_j^{\min}.$$

The maximal number of days of supply based on  $D_k$  is

$$n_k = \sum_{j=1}^J n_{jk}.$$

## 2.1 Example

Consider a patient for who we have recorded four purchase dates,  $T_1, T_2, T_3, T_4$ , on which the patient purchased a drug in two different strengths,  $S_1 = 50$  and  $S_2 = 80$ . On the first date, the patient buys two packages with drug strength  $S_1 = 50$ , the first one contains 15 pills and the other one contains 10 pills, and also one package with 15 pills of drug strength  $S_2 = 80$ . This means that

$$m_{1,1} = 15 + 10 = 25, \quad m_{2,1} = 15.$$

We let the minimal doses corresponding to  $S_1, S_2$  be  $s_1^{\min} = 25$  and  $s_2^{\min} = 20$ . This gives

$$n_{1,1} = 25 \cdot \frac{50}{25} = 50, \quad n_{2,1} = 15 \cdot \frac{80}{20} = 60.$$

Thus, the total amount of drug purchased on date  $T_1$  is,

$$D_1 = 50 \cdot 25 + 60 \cdot 20 = 2450,$$

and the maximal number of days of supply is  $n_1 = 50 + 60 = 110$ .

We put the date on a form appropriate for the implemented software.

```
org(d$drugdb)
```

	id	atc	pdate	strength	npack	ppp
1	1	A07	2012-05-08	50	10	1
2	1	A07	2012-05-08	50	15	1
3	1	A07	2012-05-08	80	10	1
4	1	A07	2012-08-11	50	15	1
5	1	A07	2013-03-15	50	10	1
6	1	A07	2013-03-15	50	10	2
7	1	A07	2013-05-05	80	10	1
8	1	A07	2013-05-25	80	15	3
9	1	A07	2013-10-01	50	10	2
10	1	A07	2013-10-01	80	10	1
11	1	A07	2013-12-28	80	10	1

We illustrate how the data is preprocessed according to Section 2. In the table below, we have the unique list of dates, B, the total doses, D, and the days of supply, nk.

```
org(ex$exdrug[, names(ex$exdrug) %in% c("B", "D", "nk")])
```

	B	D	nk
1	2012-05-08	2050	90
2	2012-08-11	750	30
3	2013-03-15	1500	60
4	2013-05-05	800	40
5	2013-05-25	3600	180
6	2013-10-01	1800	80
7	2013-12-28	800	40

### 3 Hospital admission data

Hospitals usually deliver drugs for their patients. It therefore seems reasonable to take into account periods of hospitalization in the calculation of exposure lengths. For a single patient we define up to  $Q$  periods of hospitalization by the admission dates  $L_1, \dots, L_Q$  and the corresponding discharge dates  $R_1, \dots, R_Q$ .

We compute the number of days a patient is not hospitalized in the period  $[T_k, T_{k+1})$  as:

$$H_k = (T_{k+1} - T_k) - \sum_{q=1}^Q \max(0, \min(T_{k+1}, R_q) - \max(T_k, L_q))$$

### 3.1 Example (continued)

We consider again the patient of the example in section 2.1 and now also assume that the patient was hospitalized two times (Figure 1).

```
org(d$admdb)
```

	id	inddto	uddto
1	1	2012-06-11	2012-06-28
2	1	2013-01-03	2013-01-18

We compute the number of days hospitalized, DH, and the number of days non-hospitalized, H.

```
org(ex$exdrug[, names(ex$exdrug) %in% c("B", "DH", "H")])
```

	B	H	DH
1	2012-05-08	78	17
2	2012-08-11	201	15
3	2013-03-15	51	0
4	2013-05-05	20	0
5	2013-05-25	129	0
6	2013-10-01	88	0
7	2013-12-28	1	0

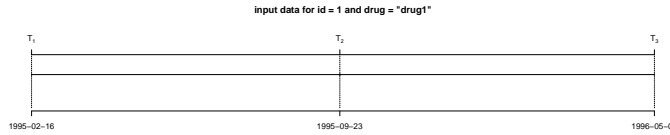


Figure 1: Illustration of the four prescription dates and the two periods of hospitalization of our example patient.

## 4 Exposure strength and exposure lengths

The aim is to estimate the ends of the exposure periods  $E_k$  and for each exposure period to estimate the exposure strength per day  $X_k$ . It is important to note

that the estimates are only based on the data of the current patient and on specific assumptions which may or may not be valid for a given patient and a given drug. The estimates are based on the drug prescription data (Section 2) and the hospitalization dates (Section 3) and depend further on an integer  $N$  that defines the number of prescription dates back in time to use in the calculations of exposure in a given period  $[T_k, T_{k+1})$ .

#### 4.1 Remark

The original SAS macro also uses prescription dates in the future to estimate the current exposure strength. However, since usually the aim is to use the exposure in Poisson and Cox regression where this would violate the mathematical framework the authors of this report hesitate to implement this feature. To motivate the feature we would very much like to see an example which demonstrates that the results of the Cox or Poisson regression can be improved when estimates of the current exposure depend on future purchases of the drug.

#### 4.2 Definition of periods included in the estimates

To express the exposure in period  $[T_k, T_{k+1})$  recall from section 2 that based on the total drug purchase on date  $T_k$  the patient can be exposed at most  $n_k = \sum_{j=1}^J n_{jk}$  days. We use the following notation to define potential overlap, i.e., to indicate if the maximal number of exposure days exceeds the number of non-hospitalized days in period  $[T_k, T_{k+1})$ :

$$u_k = \begin{cases} 0, & n_k \leq H_k, \text{ in words: the supply at } T_k \text{ is empty before } T_{k+1} \\ 1, & n_k > H_k, \text{ in words: the supply at } T_k \text{ can be sufficient to reach } T_{k+1}. \end{cases}$$

##### 4.2.1 Example (continued)

Figure 2 shows again the data of section 2.1, together with an illustration of the number of days of supply. The black lines show the actual days of medicine supply, and the red lines are the days hospitalized.

A first preliminary version of the average dosis per day in period  $[T_k, T_{k+1})$  is calculated as

$$A_k = \frac{1}{c_k} \sum_{j=1}^J G_{jk} S_j$$

where  $c_k = \sum_{j=1}^J G_{jk}$  is the total number of purchases on date  $T_k$ .

Since the preliminary average  $A_k$  may lie between two of the available drug strengths we define a second, still preliminary, version of the average dosis per day as the nearest drug strengths which does not exceed the average strength. That is, the index

$$b(k) = \max \{j \in \{1, \dots, J\} : S_j \leq A_k\} \quad (1)$$

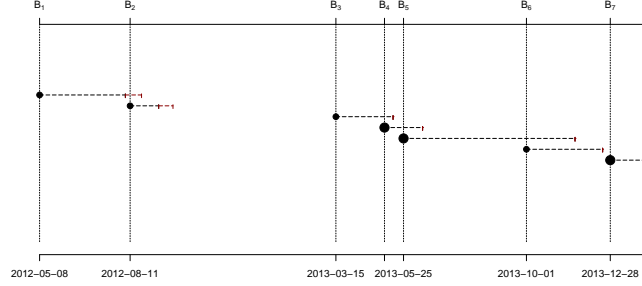


Figure 2: For our example patient the figures shows the maximal number of days of supply calculated at each time point based on the formula in Section 2.

identifies the nearest drug strength which does not exceed the first preliminary average strength, and  $S_{b(k)}$  is nearest drug strength.

#### 4.2.2 Example (continued)

For the patient of our example we have

$$A_1 = \frac{1}{2+1} (2 \cdot 50 + 80) = 60.$$

We see that  $b(1) = 1$ , as  $S_1 = 50$  is the nearest drug strength not exceeding the average of  $A_1 = 60$  computed above. Note that in this notation,  $S_{b(k-1)}$  refers to the nearest drug strength of the previous prescription date. For instance, at date  $T_2$  of our patient we have  $b(k-1) = b(1) = 1$  and  $S_{b(k-1)} = 50$ .

On the following still quite long remaining part of the pilgrim trail towards the final estimate of the average daily dosis in period  $[T_k, T_{k+1})$ , the next thing to do is to decide how many purchase dates back in time should be used. We distinguish between two cases which are also illustrated in Figure 3. Which case to be used will be made clear later.

**Case 1:**  $T_{I_k^{(1)}}$  is the closest purchase date back in time, such that there is both continuous potential overlap and average dosis match. The index is defined as

$$I_k^{(1)} = \max \left( \min \{ \ell \in \{ \max(1, k-N), \dots, k-1 \} : u_\ell = \dots = u_{k-1} = 1 \}, \right. \\ \left. \min \{ \ell \in \{ \max(1, k-N), \dots, k \} : B_\ell = \dots = B_k \} \right),$$

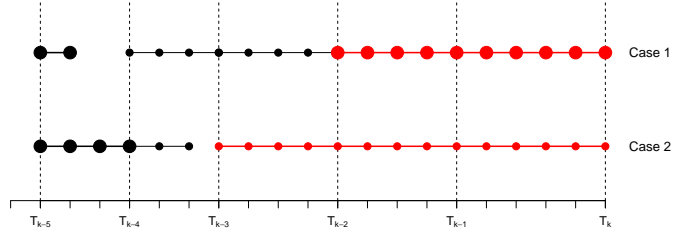


Figure 3: Illustration of the periods back in time to include into the final estimate of the average daily dose at  $T_k$ . Shown are two independent examples illustrating case 1 and case 2, respectively. The size of the dots indicates the preliminary average strength. The red periods are included in the final estimate of the average daily dose in period  $[T_k, T_{k+1})$ . See also Figure 5.

The average daily dose in the period  $[T_{I_k^{(1)}}, T_{k+1})$  is defined as

$$M_k^{(1)} = \frac{\sum_{\ell=I_k^{(1)}}^{k-1} D_\ell}{\sum_{\ell=I_k^{(1)}}^{k-1} H_\ell}.$$

**Case 2:**  $T_{I_k^{(2)}}$  is the closest purchase date back in time, such that there is continuous potential overlap. The index is defined as

$$I_k^{(2)} = \min\{\ell \in \{\max(1, k-N), \dots, k-1\} : u_\ell = \dots = u_{k-1} = 1\}.$$

The average daily dose in the period  $[T_{I_k^{(2)}}, T_{k+1})$  is defined as

$$M_k^{(2)} = \frac{\sum_{\ell=I_k^{(2)}}^{k-1} D_\ell}{\sum_{\ell=I_k^{(2)}}^{k-1} H_\ell}.$$

At last, we define the rounding of the average daily dose  $M_k^{(1)}$  to the nearest multiple of the minimal dose  $s_{b(k)}^{\min}$  (the index  $b(k)$  defined in equation (1)) smaller than the average dose, that is

$$W_k = \left\lfloor \frac{M_k^{(1)}}{s_{b(k)}^{\min}} \right\rfloor s_{b(k)}^{\min}.$$

#### 4.2.3 Example (continued)

Figure 4 shows the periods to be used in the calculations for our example patient, and the following output shows the computed average daily doses.

```
org(ex$exdrug[, names(ex$exdrug) %in% c("B", "S", "Sjk", "M")])
```

	B	M	S	Sjk
1	2012-05-08	50.00000	60	50
2	2012-08-11	26.28205	50	50
3	2013-03-15	50.00000	50	50
4	2013-05-05	29.41176	80	80
5	2013-05-25	40.00000	80	80
6	2013-10-01	29.50000	65	50
7	2013-12-28	60.00000	80	80

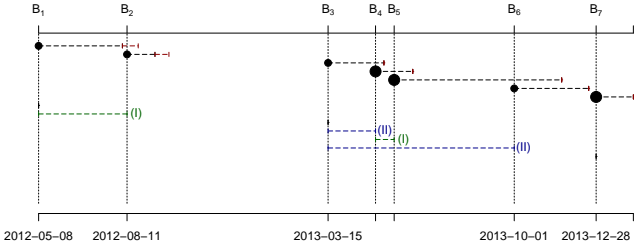


Figure 4: The cases for our patient.

#### 4.2.4 Final estimate of the daily dosis

The final estimate of the average daily dosis  $X_k$  per day in period  $[T_k, T_{k+1})$  is computed as follows, the computations are illustrated in Figure 5.

$$X_k = (1 - u_{k-1}) s_{b(k)}^* \quad (\text{No overlap})$$

$$+ u_{k-1} \left[ \begin{array}{l} \text{(Overlap)} \\ 1\{S_{b(k-1)} = S_{b(k)}\}W_k \end{array} \right. \quad \text{(I)}$$

$$\begin{aligned}
& + 1\{S_{b(k-1)} \neq S_{b(k)}\} \left( 1\{M_k^{(2)} > s_{b(k)}^{\max}\} s_{b(k)}^{\max} \right. \\
& + 1\{M_k^{(2)} > s_{b(k)}^{\min}\} s_{b(k)}^{\min} \\
& \left. + 1\{M_k^{(2)} \leq s_{b(k)}^{\max}\} 1\{M_k^{(2)} \geq s_{b(k)}^{\min}\} s_{b(k)}^* \right) \Bigg]. \tag{II}
\end{aligned}$$



#### 4.2.5 Example (continued)

```
org(ex$exdrug[, names(ex$exdrug) %in% c("B", "S", "Sjk", "M", "X")])
```

	X	B	M	S	Sjk
1	50	2012-05-08	50.00000	60	50
2	25	2012-08-11	26.28205	50	50
3	50	2013-03-15	50.00000	50	50
4	60	2013-05-05	29.41176	80	80
5	40	2013-05-25	40.00000	80	80
6	50	2013-10-01	29.50000	65	50
7	60	2013-12-28	60.00000	80	80

FIXME: læs her!!!! We now suppose that our example patient made only one drug purchase on the second date  $T_2$ , where he bought a package with 10 pills of drug strength  $S_1$ . We have already shown that  $S_{b(1)} = 50$ , and also get  $S_{b(2)} = 50$ . This means that  $S_{b(2)} = S_{b(1)}$ . Figure 2 shows that  $u_1 = 1$ , i.e., the maximal number of days of supply exceed the period from  $T_1$  to  $T_2$ . Hence, we are in case (I) of 5 and calculate  $X_2$  as

$$M_2^{(1)} = \frac{D_1}{H_1} = \frac{1700}{98} \approx 17.35.$$

This value is rounded to the nearest multiple of the minimal corresponding dosis  $s_{b(2)}^{\min} = 25$  and hence  $X_2 = W_2 = 1 \cdot s_{b(2)}^{\min} = 25$ .

**Remark:** Note that the original SAS macro (even under the left-only option) also conditioned on the dosis at time  $T_{k+1}$  but that we do not want to condition on the future until we are convinced by means of real examples that the potential damage (the mathematics of the Cox and Poisson regression are violated) can be counterbalanced by potential benefit.

#### 4.2.6 Calculating the leftover doses, $R_1, \dots, R_k$

The leftover doses are computed as,

$$R_k = u_{k-1} \cdot \min \left[ \text{maxdepot}, \max \left\{ 0, D_{k-1} + R_{k-1} - X_{k-1} \left( E_{k-1} - T_{k-1} - \sum_{q=1}^Q \max(0, \min(T_{k+1}, R_q) - \max(T_k, L_q)) \right) \right\} \right],$$

where maxdepot is some user-specified maximum amount of dosis to be “stored” from one prescription date to the next, and

$$\sum_{q=1}^Q \max(0, \min(T_{k+1}, R_q) - \max(T_k, L_q))$$

is again the number of hospitalized days in the period.

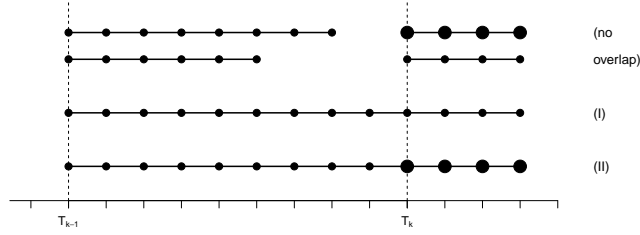


Figure 5: Illustration of the formula for the final estimate of the daily dosis (section 4.2.4). The size of the dots indicates the preliminary average strength  $S_{b(k)}$ . The upper most two lines illustrate the cases without overlap and the other two lines the cases with overlap.

#### 4.2.7 Calculating the dates of end of exposure, $E_1, \dots, E_k$

Note that since  $D_k + R_k$  is the total prescription dose at  $T_k$  and  $X_k$  is the estimated dose per day the result of  $\frac{D_k + R_k}{X_k}$  has days as unit. However, the result is not necessarily an integer. Therefore, in the following,  $\lfloor x \rfloor$  denotes the largest integer value not exceeding  $x$ , i.e., the downward rounded value. The estimated end of the exposure period in which the daily dose is estimated as  $X_k$  is,

$$E_k = \min \left( T_{k+1} - 1, T_k - 1 + \left\lfloor \frac{D_k + R_k}{X_k} \right\rfloor \right).$$

## 5 User interface

work in progress

```
library(Publish)
library(heaven)
set.seed(18)
org(simPrescriptionData(1))
```

pnr	atc	eksd	strnum	packsize	apk
1	A07	1995-01-01	400	30	1
1	A07	1995-03-17	200	300	3
1	A07	1995-06-18	400	30	3
1	A07	1995-08-06	500	30	1
1	A07	1996-07-15	200	60	2
1	A07	1997-08-17	200	300	1
1	A07	1998-03-20	400	30	1
1	A07	1999-09-11	400	100	3
1	A07	1999-12-17	200	60	1
1	A12B	1995-02-16	750	500	2
1	A12B	1995-09-23	75	250	1
1	A12B	1996-05-04	750	250	1

```
set.seed(18)
org(simAdmissionData(1))
```

pnr	inddto	uddto
1	1996-01-27	1996-02-06
1	1996-07-28	1996-08-13
1	2006-07-02	2006-07-31
1	2009-03-16	2009-04-02
1	2014-04-26	2014-05-19

```
d <- dpp()
set.seed(18)
recept_data <- simPrescriptionData(1)
datoer <- simAdmissionData(1)
drug(d, "drug1") <- atc("A12B")
## drug(d, "drug2", add=TRUE) <- atc("ATC7")
drug(d, A12B) <- pack(c(50, 75, 100, 125),
  min = c(10, 50, 25, 50),
  max = c(75, 200, 150, 150),
  def = c(50, 100, 100, 125))
drugdb(d, add=FALSE, id=pnr) <- recept_data
admdb(d) <- datoer
period(d) <- as.Date(c("1995-01-01", "2015-05-01"))
N(d) <- 2
d
```