

Medicin
Macro

Helene
Charlotte
Rytgaard

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A mathematical formulation of the algorithm, an efficient implementation and a new R interface

Helene Charlotte Rytgaard

University of Copenhagen, Section of Biostatistics

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Register data preprocessing steps

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Input:

pop, lmdb, lpr, indh, dod, sogne ...

Data preprocessing

code from hell, medicin macro, ...

Output:

Time 1	Time 2	Status	Age	Sex	Comorbidity in interval	Exposure in interval
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Existing SAS Interface

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Drug purchases:

	atc	eksd	pnr	strnum	apk	packsize
1	1a	2020-04-08	1000	75	3	20
2	1a	2011-10-30	1000	125	2	5
3	1a	2020-01-23	1000	125	1	5
4	1a	2015-09-17	1000	50	2	10
5	2a	2012-05-04	1000	50	3	5
6	2a	2011-10-11	1000	75	2	9
7	2a	2015-12-20	1000	125	1	9
8	2a	2015-10-27	1000	100	3	18

Admission dates:

	pnr	max_indl	inddto1	uddto1	inddto2	uddto2	inddto3	uddto3	inddto4	uddto4
1:	1000	3	2012-04-12	2012-04-25	2015-01-30	2015-02-14	2017-05-28	2017-05-31	2021-02-21	2021-03-08
2:	2000	2	2012-12-10	2012-12-15	2015-05-31	2015-06-05	NA	NA	NA	NA
3:	4000	1	2011-05-14	2011-05-23	NA	NA	NA	NA	NA	NA
4:	5000	4	2011-10-11	2011-10-13	2015-01-25	2015-02-01	2017-03-15	2017-03-23	2020-04-08	2020-04-21
5:	6000	1	2011-04-25	2011-04-30	NA	NA	NA	NA	NA	NA
6:	7000	1	2013-03-16	2013-03-21	NA	NA	NA	NA	NA	NA
7:	8000	4	2011-06-30	2011-07-02	2014-02-02	2014-02-07	2016-03-10	2016-03-23	2019-12-21	2019-12-28
8:	9000	4	2012-09-01	2012-09-14	2015-04-18	2015-05-03	2019-01-30	2019-02-12	2021-02-21	2021-02-27

Current interface (medicin macro)

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```
%x_recepter(recept_data, /* forventes at indeholde variable - skulle gerne passe med DST-standarder:
```

```
    pnr - cpr/patientidentifikation  
    atc - ATC kode  
    eksd - udleveringsdato som sas-dato  
    strnum - numerisk styrke  
    apk - antal udleverede pakker  
    packsize - antal piller i hver pakke*/
```

```
datoer, /* Et produkt af medicin-hjælpe-macro eller andet program som ordner ALLE indlæggelser pr PNR på  
      EEN record med fortløbende indtøddo */
```

```
out, /* tabel over behandlingsperioder - navn på SAS datasæt valgt af brugeren*/  
1a, /* atc kode - den behandling som der skal beregnes på*/  
5, /* antal recepter der indgår i beregninger - testet med 5, altså op til 2 før og 2 efter interesserecept */  
50, 75, 100, 125, /* Doser svarende til de følgende variable - det er pillestørrelser  
    - her og de følgende variable skal ALLE have en værdi. Hvis der findes færre skal der blot gentages*/  
10, 50, 25, 50, /* Mindst accepterede dosis af lægemidler på hver pillestyrke*/  
75, 200, 150, 150, /* Max accepterede dosis*/  
50, 100, 75, 100, /* Typiske doser - en slags "default" dosis - og startdosis altid ved left_only */  
10, /* Maximum sktørrelse af "restdosis" som kan overføres til følgende receptperioder. Denne giver mulighed for  
    at forhindre excessiv ophobning hvis små antagelser om maxdosis medfører til tiltagende stort depot  
    Max_depot er piller*styrke - Hvis der højst må gemmes 100 piller a 10 mg, så er max_depot 1000  
    */  
'01sep12'd, /* første og sidste dato som har interesse kan angives som en "SAS-dato" eller med konventionen  
    'ddmmyy'd /*  
'02may20'd,  
1, /* Hvis værdien er 1 så kommer der tracking udskrift i loggen - hvis nul, så ikke. Tilsvarende slettes en række  
    temporære datasæt hvis værdien er 0 */  
1, /* Hvis værdien er 1 så kommer der grafer */  
test, /* præfix på generede variable som kan benyttes til at skelne fra lignende variable genereret i andre tri  
1 /* danner tabeller "l_" hvor doser og sluttider KUN regnes bagud*/  
);
```

Output data

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Continuing example:

	pnr	dosis	startdag	slutdag
1	1000	50	17SEP15	06OCT15
2	1000	100	23JAN20	28JAN20
3	1000	100	08APR20	22MAY20
4	2000	20	15MAY13	05AUG13
5	2000	75	04NOV15	16NOV15
6	2000	100	15MAR17	21MAY17
7	3000	100	16MAR13	21MAR13
8	3000	100	26APR13	02MAY13
9	3000	50	10MAR16	08MAY16
10	3000	75	04JAN19	16JAN19
11	3000	100	14JUL19	04AUG19
12	3000	150	05AUG19	16AUG19
13	3000	75	17AUG19	22AUG19
14	3000	50	01NOV19	19NOV19
15	3000	75	20NOV19	16DEC19

Immediate limitations

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- Speed
 - Each drug must be processed separately, repeating the macro call
- Lack of transparency
 - Mathematical formulas?
- Other issues:
 - Dependence on the future
 - Only possible to specify four different doses
 - Graphical checks (working?)?

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New R Interface

Addressing the issues in SAS

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■ Speed

- We use the Rcpp to integrate C++-code directly in R

■ Lack of transparency

- We have written up all steps in the macro explicitly
- Everything is collected in a documentation article

■ New interface

- Object oriented coding for more efficiency
- Visualization tools to plot input data and output estimates
- Accessed via R-package heaven (github)

In R the package is installed via:

```
devtools::install_github("tagteam/heaven")
```

Intro to R-packages: <http://r-pkgs.had.co.nz/>

How to use Git in Rstudio: <http://r-pkgs.had.co.nz/git.html>

New R interface

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- Same input data sets as before (almost)
 - Admission dates data set long format

	pnr	inddto	uddto
1:	1	2003-12-20	2003-12-24
2:	1	2006-07-20	2006-09-01
3:	1	2007-04-30	2007-05-15
4:	1	2010-11-27	2011-01-02
5:	1	2013-05-11	2013-05-16

...

- Attach relevant data (more user details in a moment)

```
drugdb(d) <- drugdata  
admdb(d) <- admdata
```

- plot()-function to show purchases and admission periods

```
plot(d)
```

Input visualization tools

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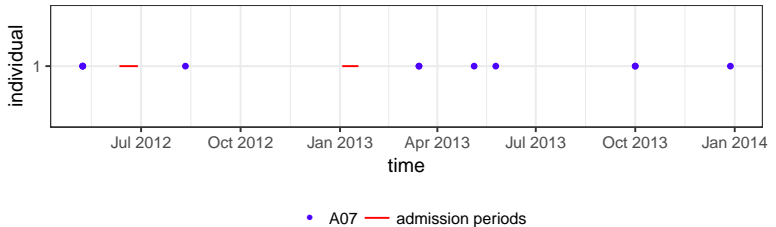
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Load package:

```
library(heaven)
```

Create empty object:

```
d <- dpp()
```

Attach relevant data:

```
drugdb(d) <- drugdata  
admdb(d) <- admissiondata
```

Add treatments:

```
drug(d, "treatment1") <- atc("A12B")  
drug(d, "treatment1") <- pack(c(750, 75),  
                               min = c(250, 25),  
                               max = c(1000, 100),  
                               def = c(750, 100))
```

Specify relevant period:

```
period(d) <- as.Date(c("2012-01-01", "2015-12-31"))
```

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When everything is specified, we perform the calculations by running:

```
process(d)
```

\$treatment1

	id	outdose	startdate	enddate
1	1	100	1997-08-21	2007-11-26
2	2	100	1995-09-09	2030-02-05
3	3	100	1995-06-21	1997-08-12
4	3	0	1997-08-13	1998-02-21
5	3	100	1998-02-22	2010-02-08
6	4	100	1995-01-01	2030-08-17
7	5	100	1995-02-14	1996-02-23
8	5	0	1996-02-24	1996-04-25
9	5	75	1996-04-26	1997-08-20
10	5	100	1997-08-21	2000-03-01
11	6	100	1995-01-01	1995-03-16
12	6	0	1995-03-17	1995-09-23
13	6	25	1995-09-24	1996-05-04
14	6	100	1996-05-05	2015-01-26
15	7	100	1995-06-27	1999-09-16
16	8	100	1996-09-26	2009-08-27
17	9	100	1995-05-09	1999-06-18
18	9	0	1999-06-19	1999-11-18
19	9	100	1999-11-19	2001-06-03
20	10	100	1995-09-13	2014-04-21

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We may add treaments:

```
drug(d, "treatment2") <- atc("A07")
drug(d, "treatment2") <- pack(c(200, 400, 500),
  min = c(100, 100, 250),
  max = c(400, 500, 1000),
  def = c(300, 200, 500))
```

And then perform calculations again:

```
process(d)
```

\$treatment1

	id	outdose	startdate	enddate
1	1	100	1997-08-21	2007-11-26
2	2	100	1995-09-09	2030-02-05
3	3	100	1995-06-21	1997-08-12
4	3	0	1997-08-13	1998-02-21
5	3	100	1998-02-22	2010-02-08
6	4	100	1995-01-01	2030-08-17

\$treatment2

	id	outdose	startdate	enddate
1	1	200	1996-06-15	1996-08-13
2	1	0	1996-08-14	1997-04-13
3	1	500	1997-04-14	1997-06-12
4	1	0	1997-06-13	1998-03-22
5	1	200	1998-03-23	1998-07-20
6	1	0	1998-07-21	1998-11-04

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The function can be used treatment and/or id specific:

```
process(d, treatment = "treatment2")
```

\$treatment2

	id	outdose	startdate	enddate
1	1	200	1996-06-15	1996-08-13
2	1	0	1996-08-14	1997-04-13
3	1	500	1997-04-14	1997-06-12
4	1	0	1997-06-13	1998-03-22
5	1	200	1998-03-23	1998-07-20
6	1	0	1998-07-21	1998-11-04

```
process(d, id = 9)
```

\$treatment1

	id	outdose	startdate	enddate
1	9	100	1995-05-09	1999-06-18
2	9	0	1999-06-19	1999-11-18
3	9	100	1999-11-19	2001-06-03

\$treatment2

	id	outdose	startdate	enddate
1	9	200	1996-02-22	1996-04-08
2	9	500	1996-04-09	1996-05-26
3	9	0	1996-05-27	1998-05-22
4	9	300	1998-05-23	1998-06-11
5	9	0	1998-06-12	1999-11-21
6	9	500	1999-11-22	2000-09-16

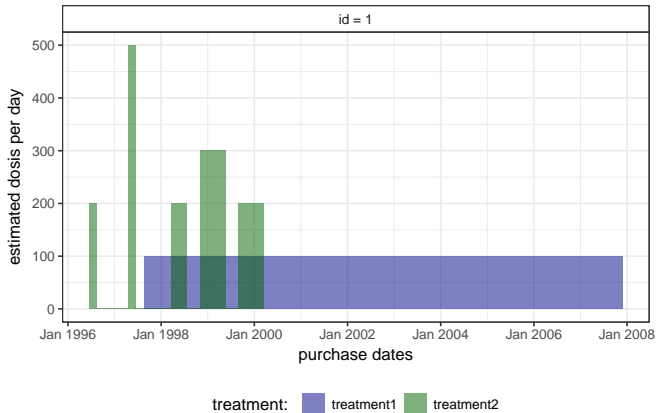
Built-in tools for output visualizations

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A `plot()`-function to visualize the output:

```
out <- process(d)
plot(out, id = 1)
```



Technical details

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... the mathematical part ...

- The R-interface and the following formulas are all based on the implementation of `medicin macro (left_only)`.
- The computations performed consists basically of an averaging over a set of prescriptions back in time (decided by the user)
- A number of things will for each prescription date help us determine how many dates back in time we should use for the calculations:
 - The number of days of supply of a certain drug is calculated based on the minimal possible doses for a drug
 - The actual number of dates between the prescription periods (where the number of days hospitalized is subtracted)
 - Whether or not the total amount of drug purchased at time k is approximately the same as purchased at earlier times
- Exposure periods are then calculated based on these average dose amounts

Final formula (a snippet of what we have worked on)

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

$$+ u_{k-1} \left[\quad (\text{Overlap}) \right.$$

$$1 \{ S_{b(k-1)} = S_{b(k)} \} \left(1 \{ W_k > s_{b(k)}^{\max} \} s_{b(k)}^{\max} \right. \\ \left. + 1 \{ W_k < s_{b(k)}^{\min} \} s_{b(k)}^{\min} \right. \quad (\text{I})$$

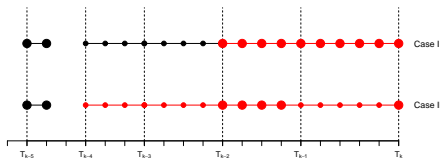
$$+ 1 \{ W_k \leq s_{b(k)}^{\max} \} 1 \{ W_k \geq s_{b(k)}^{\min} \} W_k \Bigg].$$

$$+ 1 \{ S_{b(k-1)} \neq S_{b(k)} \} \left(1 \{ M_k^{(2)} > s_{b(k)}^{\max} \} s_{b(k)}^{\max} \right. \\ \left. + 1 \{ M_k^{(2)} < s_{b(k)}^{\min} \} s_{b(k)}^{\min} \right. \quad (\text{II})$$

$$+ 1 \{ M_k^{(2)} \leq s_{b(k)}^{\max} \} 1 \{ M_k^{(2)} \geq s_{b(k)}^{\min} \} s_{b(k)}^* \Bigg].$$

$M_k^{(1)}, M_k^{(2)}$ are average doses **over the periods**

W_k is a rounding of $M_k^{(1)}$ to nearest multiple of relevant minimal dose



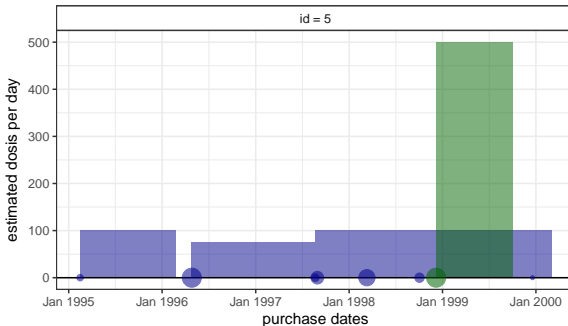
More output visualizations

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We may also take a closer view on the underlying purchases behind the final exposures estimated:

```
out1 <- process(d, keep_data = TRUE)
plot(out1, id = 5, trace = TRUE)
```



treatment (size of bubbles indicative of total amount purchased):



treatment1



treatment2

Example: Omeprazol

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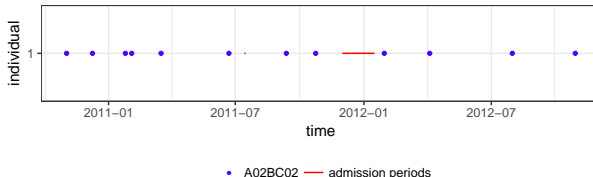
Drug purchases:

	pnr	eksd	packsize	strnum	apk	atc
1	1	25/01/2011	56	40	1	A02BC02
2	1	29/10/2012	100	40	1	A02BC02
3	1	31/07/2012	100	40	1	A02BC02
4	1	12/09/2011	28	40	1	A02BC02
5	1	24/10/2011	28	40	1	A02BC02
6	1	03/02/2011	56	40	1	A02BC02
7	1	09/12/2010	56	40	1	A02BC02
8	1	02/11/2010	56	40	1	A02BC02
9	1	04/04/2012	98	40	1	A02BC02
10	1	30/01/2012	98	40	1	A02BC02
11	1	22/06/2011	98	40	1	A02BC02
12	1	17/03/2011	98	40	1	A02BC02

Admission dates:

	id	inddto	uddto
1	1	2004-01-20	2004-01-20
2	1	2004-01-22	2004-01-23
3	1	2006-06-20	2006-06-20
4	1	2006-06-23	2006-06-23
5	1	2010-01-21	2010-01-20
6	1	2010-01-14	2010-01-26
7	1	2010-01-26	2010-02-10
8	1	2010-07-05	2010-07-05
9	1	2010-10-21	2010-10-29
10	1	2011-07-14	2011-07-16
11	1	2011-12-01	2011-12-14
12	1	2011-12-14	2011-12-25
13	1	2011-12-25	2011-12-29
14	1	2011-12-29	2012-01-16

Plotting the data:



Example: Omeprazol

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Using medicin-macro:

%x_recepter(PPI, /* forventes at indeholde variable - skulle gerne passe med DST-standarder:

pnr - cpr/patientidentifikation
atc - ATC kode
eksd - udleveringsdato som sas-dato
strnum - numerisk styrke
apk - antal udleverede pakker
packsize - antal piller i hver pakke*/

admData, /* Et produkt af medicin-hjælpe-macro eller andet program som ordner ALLE indlæggelser pr PNR på
EEN record med fortløbende indtø uddto */

omeprazol, /* tabel over behandlingsperioder - navn på SAS datasæt valgt af brugeren*/

A02BC02, /* atc kode - den behandling som der skal beregnes på*/

5, /* antal recepter der indgår i beregninger - testet med 5, altså op til 2 før og 2 efter interesserecept */
10, 20, 40, 40, /* Doser svarende til de følgende variable - det er pillestørrelser

- her og de følgende variable skal ALLE have en værdi. Hvis der findes færre skal der blot gentages*/

10, 20, 40, 40, /* Mindst accepterede dosis af lægemidler på hver pillestyrke*/

20, 40, 60, 80, /* Max accepterede dosis*/

10, 20, 40, 40, /* Typiske doser - en slags "default" dosis - og startdosis altid ved left_only */

4000, /* Maximum sktørrelse af "restdosis" som kan overføres til følgende receptperioder. Denne giver mulighed
at forhindre excessiv ophobning hvis små antagelser om maxdosis medfører til tiltagende stort depot

Max_depot er piller*styrke - Hvis der højst må gemmes 100 piller a 10 mg, så er max_depot 1000

*/

'01jan1997'd, /* første og sidste dato som har interesse kan angives som en "SAS-dato" eller med konventionen

'ddmmyy'd /*

'31dec2012'd,

1, /* Hvis værdien er 1 så kommer der tracking udskrift i loggen - hvis nul, så ikke. Tilsvarende slettes en række
temporære datasæt hvis værdien er 0 */

1, /* Hvis værdien er 1 så kommer der grafer */

test, /* præfix på generede variable som kan benyttes til at skelne fra lignende variable genereret i andre tri
1 /* danner tabeller "1_" hvor doser og sluttider KUN regnes bagud*/

);

Example: Omeprazol

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```
library(heaven)

d <- dpp()
drugdb(d) <- PPI
admdb(d) <- admData

drug(d, "omeprazol") <- atc("A02BC02")
drug(d, "omeprazol") <- pack(c(10, 20, 40, 40),
                             min = c(10, 20, 40, 40),
                             max = c(20, 40, 60, 80),
                             def = c(10, 20, 40, 40))

period(d) <- as.Date(c("1997-01-01", "2012-12-31"))
pwindow(d) <- 2
maxdepot(d) <- 4000

process(d)
```

\$omeprazol

	id	outdose	startdate	enddate
1	1	40	2010-11-02	2010-12-08
2	1	80	2010-12-09	2011-10-09
3	1	0	2011-10-10	2011-10-23
4	1	80	2011-10-24	2011-11-20
5	1	0	2011-11-21	2012-01-29
6	1	40	2012-01-30	2012-04-03
7	1	80	2012-04-04	2013-02-05

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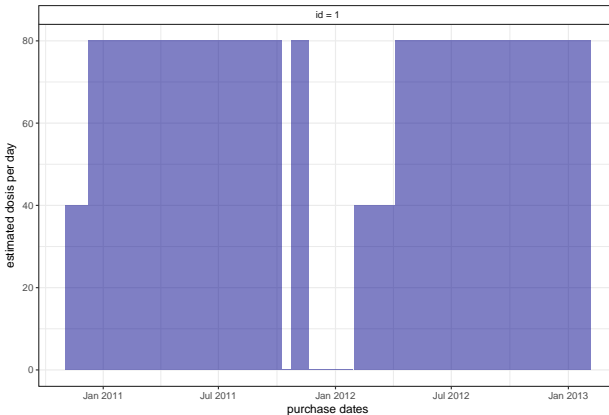
Input data
Output data
Immediate
limitations

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Visualization
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Technical
details

Real
Example

Plotting output:

```
out <- process(d)
plot(out)
```



Example: Omeprazol

Medicin
Macro

Helene
Charlotte
Rytgaard

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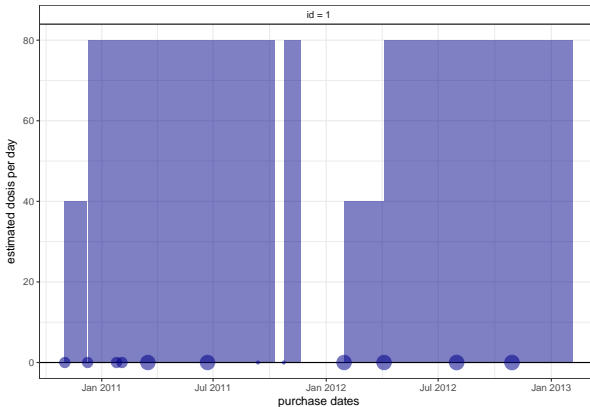
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Plotting output with input:

```
out1 <- process(d, keep_data = TRUE)
plot(out1, trace = TRUE)
```



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Thank you

