Medicin Macro
A matemathical formulation of the algorithm, an efficient implementation and a new R interface

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... Tomy

- Exposure-outcome analysis
  - lalala
- Example: PPI

Input data: Drug database

Example data:

	pnr	atc	eksd	strnum	packsize	apk
1:	1	A07	1996-06-15	400	30	1
2:	1	A07	1997-04-14	500	60	1
3:	1	A07	1998-03-23	400	30	2
4:	1	A07	1998-11-05	200	300	1
5:	1	A07	1999-08-30	400	100	1
6:	1	A12B	1997-08-21	750	500	1
7:	2	A07	1995-05-03	400	60	2
8:	2	A07	1995-07-10	500	60	1
9:	2	A07	1995-09-02	400	60	2
10:	2	A07	1995-09-21	400	60	3
11:	2	A07	1995-11-19	500	100	1
12:	2	A07	1996-04-26	400	100	1
13:	2	A07	1996-09-21	200	60	1
14:	2	A07	1997-07-18	400	300	1
15:	2	A07	1999-05-19	400	100	2

Input data: Admission database

Example data:

```
     pnr     inddto      uddto
 1:    1  1999-02-27  1999-03-13
 2:    1  2008-01-14  2008-01-28
 3:    1  2010-12-29  2011-01-30
 4:    2  1996-10-14  1996-10-14
 5:    2  2003-08-25  2003-09-06
 6:    2  2004-02-21  2004-04-03
 7:    2  2007-11-22  2007-11-28
 8:    2  2010-05-20  2010-06-14
 9:    3  1999-06-23  1999-07-20
10:    3  2005-06-03  2005-06-22
11:    4  2008-04-07  2008-04-11
12:    4  2014-07-20  2014-08-17
13:    5  1999-03-01  1999-03-09
14:    5  2007-06-19  2007-07-06
15:    5  2011-05-07  2011-06-18
```

Current interface (medicin macro)

```
%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-hjlpe-macro eller andet program som ordner ALLE indlggelser pr PNR p
            EEN record med fortlbende inddto uddto */


        out, /* tabel over behandlingsperioder - navn p SAS datast valgt af brugeren*/
        1a, /* atc kode - den behandling som der skal beregnes p*/
        5, /* antal recepter der indgr i beregninger - testet med 5, alts op til 2 fr og 2 efter interesserecept */
        50, 75, 100, 125, /* Doser svarende til de flgende variable - det er pillestrrelser
            - her og de flgende variable skal ALLE have en vrdi. Hvis der findes frre skal der blot gentages*/
        10, 50, 25, 50,     /* Mindst accepterede dosis af lgemidler p 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 sktrrelse af "restdosis" som kan overfres til flgende receptperioder. Denne giver mulighed for
         at forhindre excessiv opbobning hvis sm antagelser om maxdosis medfrer til tiltagende stort depot
         Max_depot er piller*styrke - Hvis der hjst m gemmes 100 piller a 10 mg, s er max_depot 1000
         */
        '01sep12'd, /* frste og sidste dato som har interesse kan angives som en "SAS-dato" eller med konventionen
            'ddmmyy'd     */
        '02may20'd,
        1, /* Hvis vrdien er 1 s kommer der tracking udskrift i loggen - hvis nul, s ikke. Tilsvarende slettes en rkke
          temprre datast hvis vrdien er 0 */
        1, /* Hvis vrdien er 1 s kommer der grafer */
        test, /* prfix p generede variable som kan benyttes til at skelne fra lignende variable genereret i andre trin
    */
        1 /* danner tabeller "l_" hvor doser og sluttider KUN regnes bagud*/
        );
```

Output data

Continuing example: (FIXME: Except NOT the same)

```
   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
```

- Speed
  - `C++` can be used in `R`

- Lack of transparency
  - Mathematical formulas?

- Other issues:
  - Dependence on the future
  - Only possible to specify four different doses
  - Possible to run for parts of data? Only specific individuals?

Input data: Drug database (unchanged)

	pnr	atc	eksd	strnum	packsize	apk
1:	1	A07	1996-06-15	400	30	1
2:	1	A07	1997-04-14	500	60	1
3:	1	A07	1998-03-23	400	30	2
4:	1	A07	1998-11-05	200	300	1
5:	1	A07	1999-08-30	400	100	1
6:	1	A12B	1997-08-21	750	500	1
7:	2	A07	1995-05-03	400	60	2
8:	2	A07	1995-07-10	500	60	1
9:	2	A07	1995-09-02	400	60	2
10:	2	A07	1995-09-21	400	60	3
11:	2	A07	1995-11-19	500	100	1
12:	2	A07	1996-04-26	400	100	1
13:	2	A07	1996-09-21	200	60	1
14:	2	A07	1997-07-18	400	300	1
15:	2	A07	1999-05-19	400	100	2

Input data: Admission database (unchanged)

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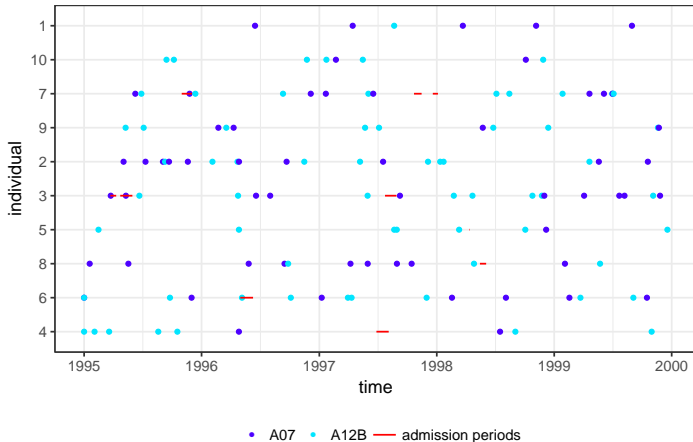
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```
       pnr      inddto       uddto
 1:      1  1999-02-27  1999-03-13
 2:      1  2008-01-14  2008-01-28
 3:      1  2010-12-29  2011-01-30
 4:      2  1996-10-14  1996-10-14
 5:      2  2003-08-25  2003-09-06
 6:      2  2004-02-21  2004-04-03
 7:      2  2007-11-22  2007-11-28
 8:      2  2010-05-20  2010-06-14
 9:      3  1999-06-23  1999-07-20
10:      3  2005-06-03  2005-06-22
11:      4  2008-04-07  2008-04-11
12:      4  2014-07-20  2014-08-17
13:      5  1999-03-01  1999-03-09
14:      5  2007-06-19  2007-07-06
15:      5  2011-05-07  2011-06-18
```

Tools for visualizing the data (input)

A `plot()`-function to show purchases and admission periods for the patients (i.e., visualizing input data):

How to use the interface

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 window of prescription dates to use in calculations:

```
pwindow(d) <- 3 ## use 3 prescriptions back in time
```

How to use the interface

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

```
process(d)
```

```
$treatment1
    id   X          B          E
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
```

How to use the interface

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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   X          B          E
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   X          B          E
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
```

How to use the interface

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

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

$treatment2
```
  id   X          B          E
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   X          B          E
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   X          B          E
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
```
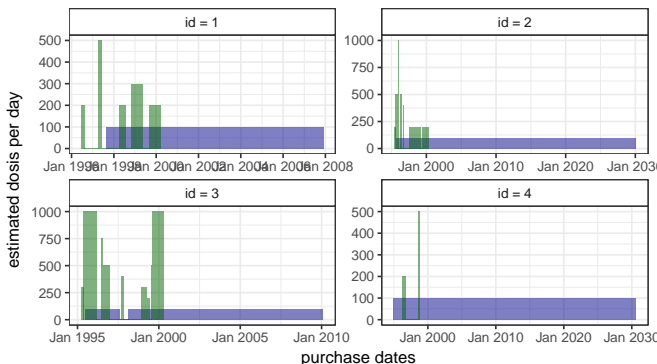
Built-in tools for output visulizations

A `plot()`-function to visualize the output is defined in the package:

```
out <- process(d)
plot(out, idmax = 4)
```

Technical details

... the mathematical part (formulas left out here) ...

- 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

More output visulizations

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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)
```
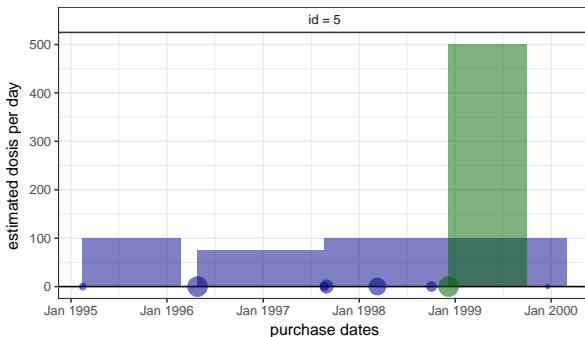

treatment (size of bubbles indicative of total amount purchased):   ● treatment1 ● trea

Example: Omeprazol

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:

	inddto	uddto
2004-01-20	12437	12437
2004-01-22	12439	12440
2006-06-20	13319	13319
2006-06-23	13322	13322
2010-01-21	14630	14629
2010-01-14	14623	14635
2010-01-26	14635	14650
2010-07-05	14795	14795
2010-10-21	14903	14911
2011-07-14	15169	15171
2011-12-01	15309	15322
2011-12-14	15322	15333
2011-12-25	15333	15337
2011-12-29	15337	15355

Plotting the data:

A02BC02 ——— admission periods

Example: Omeprazol

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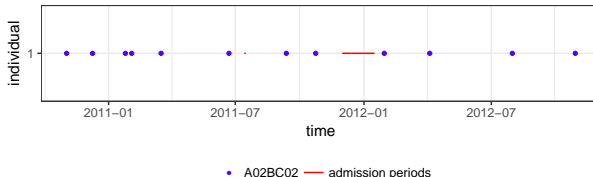
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Using medicin-macro:

```
%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-hjlpe-macro eller andet program som ordner ALLE indlggelser pr PNR p
             EEN record med fortlbende inddto uddto */

        omeprazol, /* tabel over behandlingsperioder - navn p SAS datast valgt af brugeren*/
        A02BC02, /* atc kode - den behandling som der skal beregnes p*/
        5, /* antal recepter der indgr i beregninger - testet med 5, alts op til 2 fr og 2 efter interesserecept */
        10, 20, 40, 40, /* Doser svarende til de flgende variable - det er pillestrrelser
            - her op de flgende variable skal ALLE have en vrdi. Hvis der findes frre skal der blot gentages*/
        10, 20, 40, 40,   /* Mindst accepterede dosis af lgemidler p 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 sktrrelse af "restdosis" som kan overfres til flgende receptperioder. Denne giver mulighed
    for
        at forhindre excessiv ophobning hvis sm antagelser om maxdosis medfrer til tiltagende stort depot
        Max_depot er piller*styrke - Hvis der hjst m gemmes 100 piller a 10 mg, s er max_depot 1000
        */
        '01jan1997'd, /* frste og sidste dato som har interesse kan angives som en "SAS-dato" eller med konventionen
            'ddmmyy'd     */
        '31dec2012'd,
        1, /* Hvis vrdien er 1 s kommer der tracking udskrift i loggen - hvis nul, s ikke. Tilsvarende slettes en rkke
            temporre datast hvis vrdien er 0 */
        1, /* Hvis vrdien er 1 s kommer der grafer */
        test, /* prfix p generede variable som kan benyttes til at skelne fra lignende variable genereret i andre trin
    */
        1 /* danner tabeller "l_" hvor doser og sluttider KUN regnes bagud*/
        );
```

Example: Omeprazol

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

process(d)
```

```
$omeprazol
  id  X      B          E
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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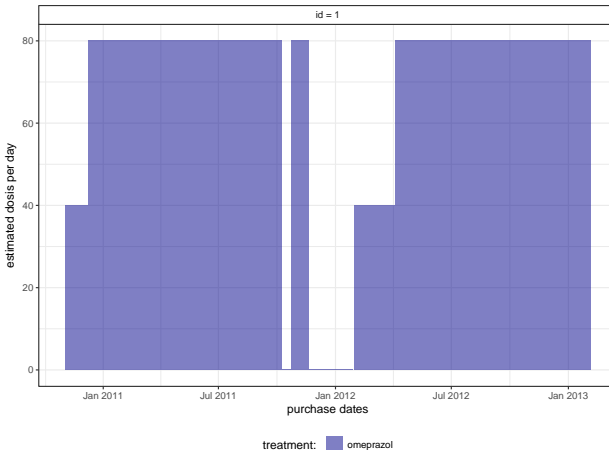Output data
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Plotting output:

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

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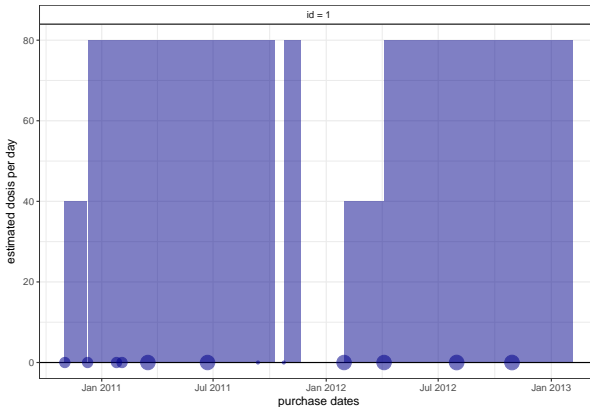limitations

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Plotting output with input:

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


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

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. . . Tomy
- cumulative exposure
  - andre macroer?
- tradition in other registry data research groups

Thank you