

Demography of Diabetes in Denmark

or: How to put real probabilities in your transition matrix and use them

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Demography of diabetes in DK

- ▶ How does diabetes spread in the population?
- ▶ Life time risk of DM
- ▶ ... and complications

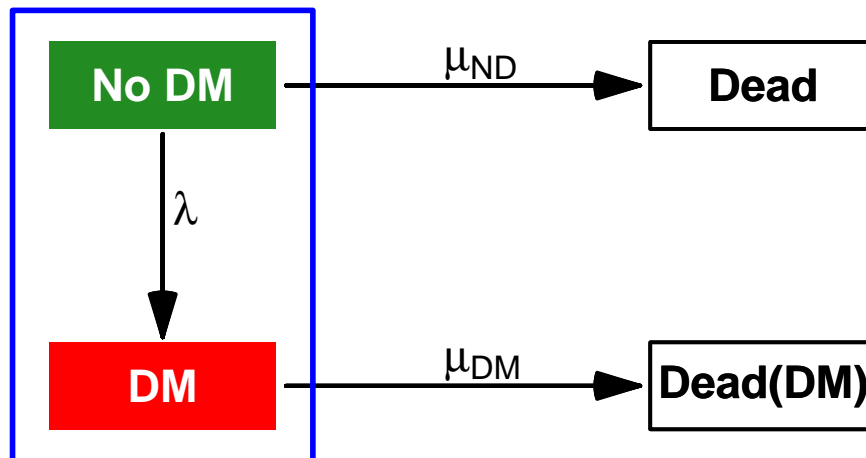
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Prevalence of diabetes

- ▶ Prevalence of diabetes has been increasing, while
- ▶ Incidence rates have been **increasing** (4% / year)
- ▶ Mortality rates have been **decreasing** (2% / year)
- ▶ What is the relative contribution of each?

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Demographic scenario



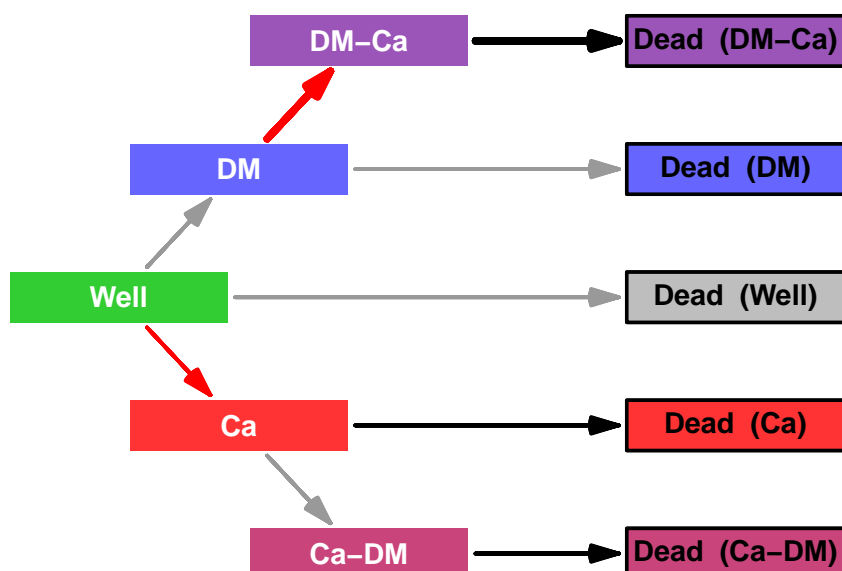
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Cancer among diabetes patients

- ▶ Cancer is about 15% higher in DM ptt
- ▶ Life-time risk of cancer and DM both in the range 30–40%
- ▶ Assess:
 - ▶ Lifetime risk of DM and Cancer (and both) in DK
 - ▶ Changes in these 1995–2012
 - ▶ Impact of the DM vs noDM cancer incidence RR

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Demographic scenario



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Multistate models

- ▶ Distribution across boxes (states) is completely determined by:
 - ▶ 1) Initial state distribution
 - ▶ 2) Transition intensities
 - ▶ Time scale?
 - ▶ ... or rather, what shall we call it?
 - ▶ **Age-specific transition rates**
 - ▶ ... as continuous functions of age
 - ▶ ... and possibly other time scales

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Prevalence of DM — updating

Transition rates between states as function of a and p :

$$\lambda(a, p), \quad \mu_{\text{ND}}(a, p), \quad \mu_{\text{DM}}(a, p)$$

Transition probabilities for an interval of length ℓ :

$$P_{\text{ND,DM}}(\ell) = P \{ \text{DM at } (a + \ell, p + \ell) \mid \text{No DM at } (a, p) \}$$

$$P_{\text{ND,ND}}(\ell) = \exp(-(\lambda + \mu_{\text{ND}})\ell)$$

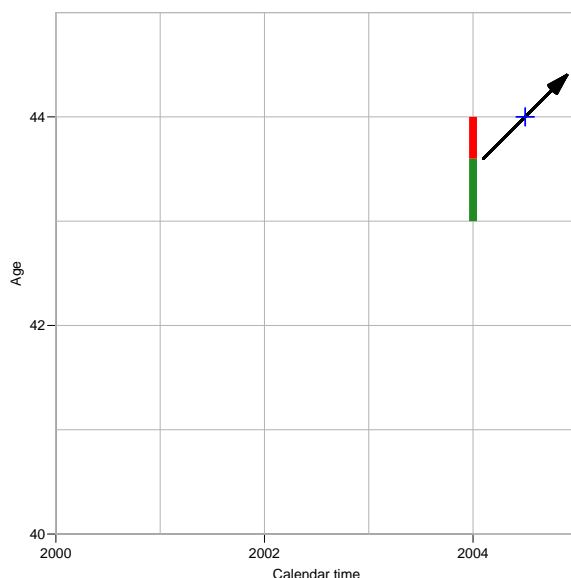
$$P_{\text{ND,Dead}}(\ell) = \frac{\mu_{\text{ND}}}{\lambda + \mu_{\text{ND}}} \left(1 - \exp(-(\lambda + \mu_{\text{ND}})\ell) \right)$$

$$P_{\text{ND,DM}}(\ell) = \frac{\lambda}{\lambda + \mu_{\text{ND}}} \left(1 - \exp(-(\lambda + \mu_{\text{ND}})\ell) \right)$$

$$P_{\text{DM,Dead}}(\ell) = 1 - \exp(-\mu_{\text{DM}}\ell)$$

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Prevalence of DM — updating



Where do we get the rates from?
— and —
Why are the formulae wrong?
and how do we rectify that?

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Transition intensities revisited — assumptions

$$P_{ND,ND}(\ell) = \exp(-(\lambda + \mu_{ND})\ell)$$

$$P_{ND,Dead}(\ell) = \frac{\mu_{ND}}{\lambda + \mu_{ND}} \left(1 - \exp(-(\lambda + \mu_{ND})\ell)\right) \approx \mu_{ND}\ell$$

$$P_{ND,DM}(\ell) = \frac{\lambda}{\lambda + \mu_{ND}} \left(1 - \exp(-(\lambda + \mu_{ND})\ell)\right) \approx \lambda\ell$$

$$P_{DM,Dead}(\ell) = 1 - \exp(-\mu_{DM}\ell)$$

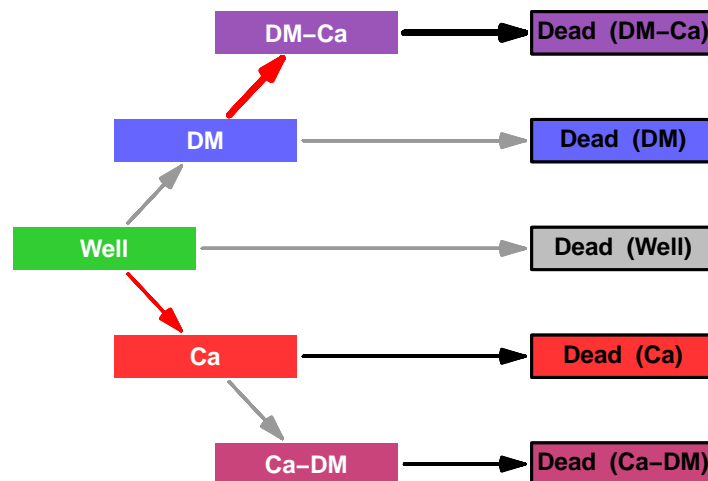
Assumes that ℓ is so small so that:

- ▶ the **approximations** are valid
- ▶ the probability of **2 or more** transitions during ℓ is negligible.
- ▶ \Rightarrow 1-year intervals usually too long
- ▶ \Rightarrow rates only assumed constant in intervals of length ℓ

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Accuracy of multistate calculations

Transition probabilities in DM-Ca study, from age 70 \rightarrow 75, based on 1, 3 and 6-month intervals respectively



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Accuracy of multistate calculations

Transition probabilities in DM-Ca study, from age 70 \rightarrow 75: based on 1, 3 and 6-month intervals respectively:

1:	to	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well	7306	600	33	813	42	722	67	388	20	10	10001
	DM	.	6867	653	.	.	.	1783	.	697	.	10000
	DM-Ca	.	.	2146	7854	.	10000
	Ca	.	.	.	4182	463	.	.	5174	.	181	10000
	Ca-DM	5242	4758	10000

3:	to	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well	7306	604	33	825	41	722	65	378	18	9	10001
	DM	.	6867	670	.	.	.	1783	.	680	.	10000
	DM-Ca	.	.	2146	7854	.	10000
	Ca	.	.	.	4182	468	.	.	5174	.	176	10000
	Ca-DM	5242	4758	10000

6:	to	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well	7313	610	33	841	40	718	62	360	16	8	10001
	DM	.	6874	695	.	.	.	1777	.	653	.	9999
	DM-Ca	.	.	2149	7851	.	10000
	Ca	.	.	.	4187	477	.	.	5167	.	169	10000
	Ca-DM	5248	4752	10000

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Accuracy of multistate calculations

Differences in transition probabilities, from age 70 → 75:
based on 3, 6 and 12-month vs. 1 month intervals:

3 vs. 1: to		DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well										
	Well	. 4	. 12 -2	. -11	. -2	. -1	. .	
	DM	. .	. 17 -17	
	DM-Ca	
	Ca 5 -5	. .	
	Ca-DM	

6 vs. 1: to		DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well										
	Well	. 7	. 10	. 29	. -1	. -4	. -6	. -28	. -4	. -2	. 1
	DM	. .	. 7	. 42 -6	. .	. -44	. .	. -1
	DM-Ca 3 -3
	Ca 5	. 14 -6	. .	. -13	. .
	Ca-DM 6 -6	. .

12 vs. 1: to		DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
from	Well										
	Well	. 21	. .	. 68	. -3	. -1	. -12	. -60	. -9	. -4	. .
	DM	. .	. 1	. 98 -1	. .	. -97	. .	. 1
	DM-Ca 1 -1
	Ca 29 -1	. .	. -29	. -1
	Ca-DM 1 -1	. .

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Rule of thumb for multistate calculations

- ▶ Transition probabilities over each interval should be less than **2%**,
- ▶ if they exceed that, use **shorter** intervals for calculations,
- ▶ consider whether you should use a model with rates varying **continuously** (smoothly) with age, date, ...
- ▶ it **will** actually make life easier

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Data base (both studies)

- ▶ National Diabetes Register, 1995–2011
- ▶ Danish Cancer Register, 1943–2011
- ▶ Mortality, Statistics Denmark
- ▶ Population, Statistics Denmark

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Incidence and mortality rates: Data

Example: state **No DM**

- ▶ Time at risk:
 - ▶ **from** date of birth or start of study
 - ▶ **to** date of **DM** or **Dead** or **Ca** (or end of study)
- ▶ Events (transitions)
 - ▶ **DM**
 - ▶ **Dead**
 - ▶ **Ca**
- ▶ Classification of follow-up (time and events) by age (0–100), calendar time (1995–2011) and date of birth (1-year classes) (Lexis triangles)
- ▶ Similar for the study with cancer states

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Incidence and mortality rates: Models

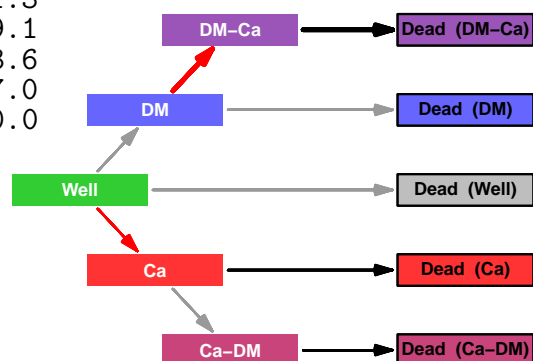
- ▶ Incident cases / deaths from each state
- ▶ Person-years in each state
- ▶ Classified by age / date / birth in 1-year classes
- ▶ Age-Period-Cohort Poisson-model with smooth effects of A, P & C
- ▶ Note: Only use the predictions from the models

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Events and risk time

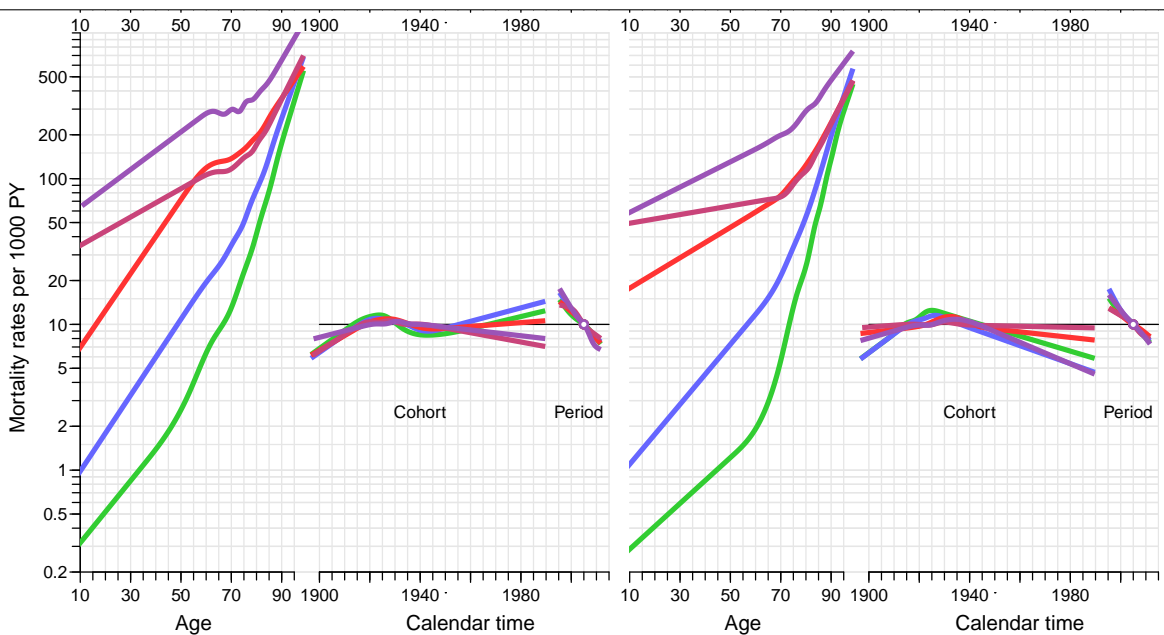
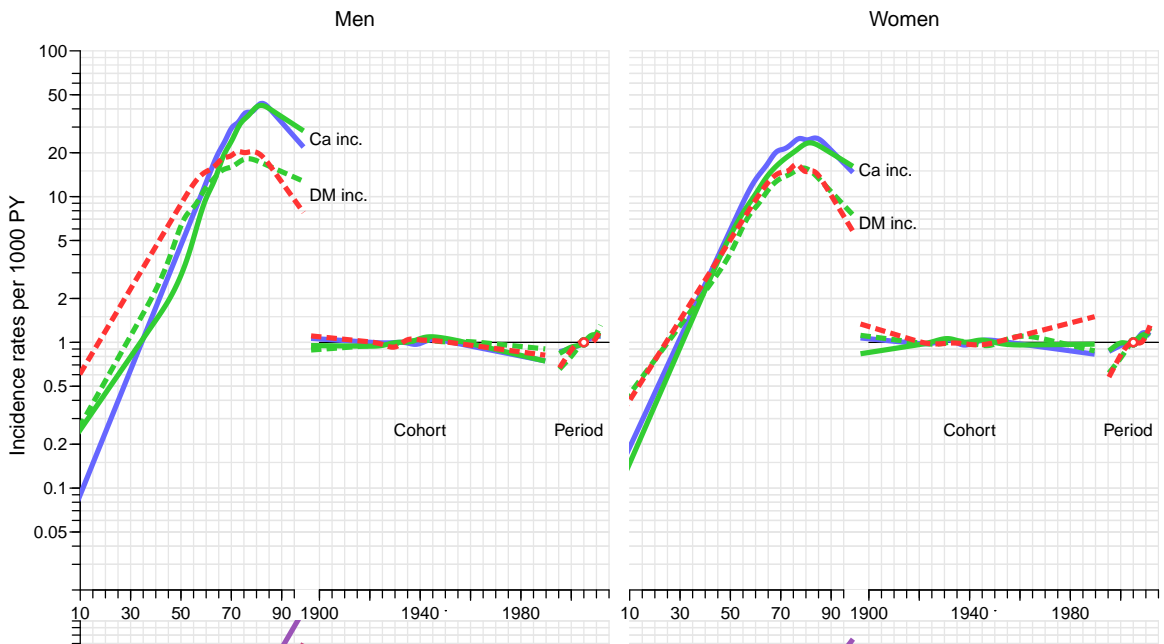
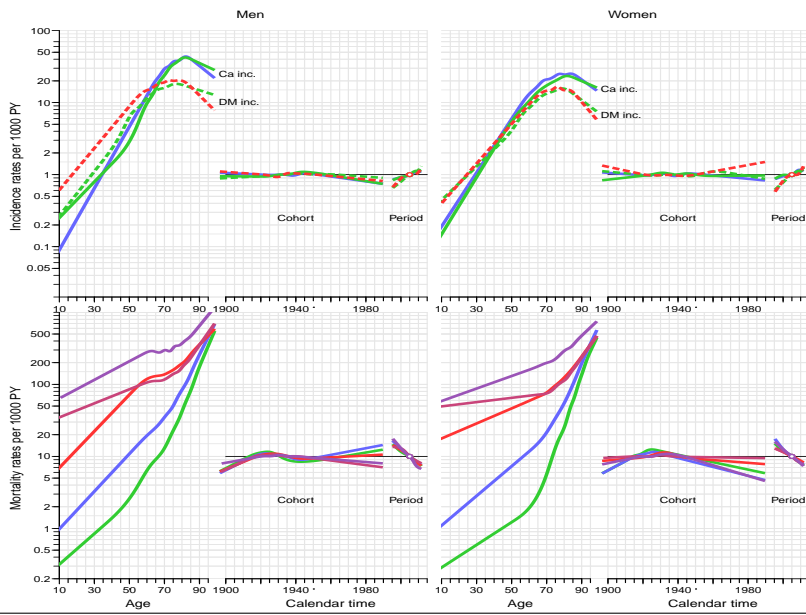
```
> cbind(
+ xtabs( cbind( D.ca, D.dm, D.dd ) ~ state, data=dcd ), round(
+ xtabs( Y/1000 ~ state, data=dcd ), 1 ) )
```

	D.ca	D.dm	D.dd	Y
Well	447419	345400	628705	87502.9
DM	35145	0	73480	2031.3
DM-Ca	0	0	24153	89.1
Ca	0	23508	222966	1973.6
Ca-DM	0	0	14703	117.0
Dead	0	0	0	0.0



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Incidence and mortality rates



Transition rates

```
> int <- 1/12
> a.pt <- seq(int,102,int) - int/2

> system.time(
+ for( yy in dimnames(PR)[[4]] )
+ {
+ nd <- data.frame( A=a.pt, P=as.numeric(yy), Y=int )
+
+ PR["Well" , "DM" , , yy, "M"] <- ci.pred( M.w2dm$model , newdata=nd )[,1]
+ PR["Well" , "Ca" , , yy, "M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" , "D-W" , , yy, "M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM" , "DM-Ca" , , yy, "M"] <- ci.pred( M.dm2ca$model , newdata=nd )[,1]
+ PR["DM" , "D-DM" , , yy, "M"] <- ci.pred( M.dm2dd$model , newdata=nd )[,1]
+ PR["Ca" , "Ca-DM" , , yy, "M"] <- ci.pred( M.ca2dm$model , newdata=nd )[,1]
+ PR["Ca" , "D-Ca" , , yy, "M"] <- ci.pred( M.ca2dd$model , newdata=nd )[,1]
+ PR["DM-Ca" , "D-DC" , , yy, "M"] <- ci.pred( M.dc2dd$model , newdata=nd )[,1]
+ PR["Ca-DM" , "D-CD" , , yy, "M"] <- ci.pred( M.cd2dd$model , newdata=nd )[,1]
}
```

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Transition matrices

Use the rates to generate the **1 month transition probabilities**:

```
> print.table( round( addmargins( ci2pr( PR[, , 800, 1, 1] ) * 10^4,
+                               margin=2 ) ),
+             zero.print="." )
```

from	to	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well		9963	8	.	12	.	17	10000
DM		.	9943	16	.	.	.	40	.	.	.	10000
DM-Ca		.	.	9578	422	.	10000
Ca		.	.	.	9815	9	.	.	175	.	.	10000
Ca-DM		9865	135	10000
D-W		10000	10000
D-DM		10000	.	.	.	10000
D-Ca		10000	.	.	10000
D-DC		10000	.	10000
D-CD		10000	10000

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State occupancy probabilities

```
> PV <- PR[1, , , ] * 0

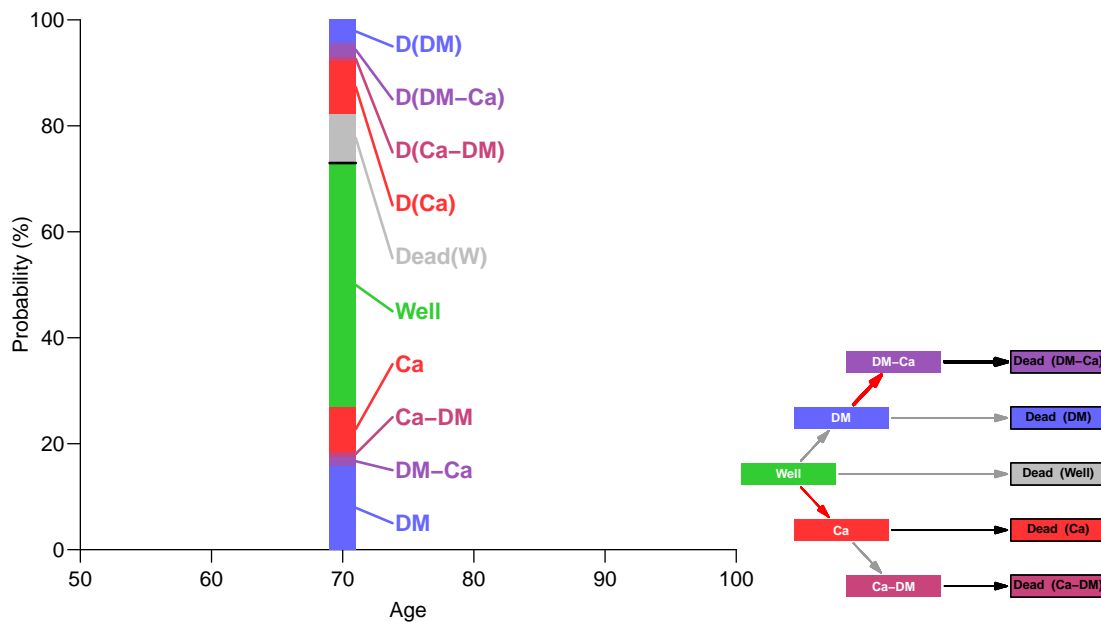
> for( sc in dimnames(PRp)[["per"]] )
+ for( sx in dimnames(PRp)[["sex"]] )
+ {
+ # Initialize to all well at age 0:
+ PV[1, sc, sx] <- c(1, rep(0, 9))
+ # Compute distribution at endpoint of each age-interval
+ for( ag in 1:dim(PRp)[3] ) PV[ag, sc, sx] <- PV[ , max(ag-1, 1), sc, sx] %%%
+                               PRp[ , , ag , sc, sx]
+ }
```

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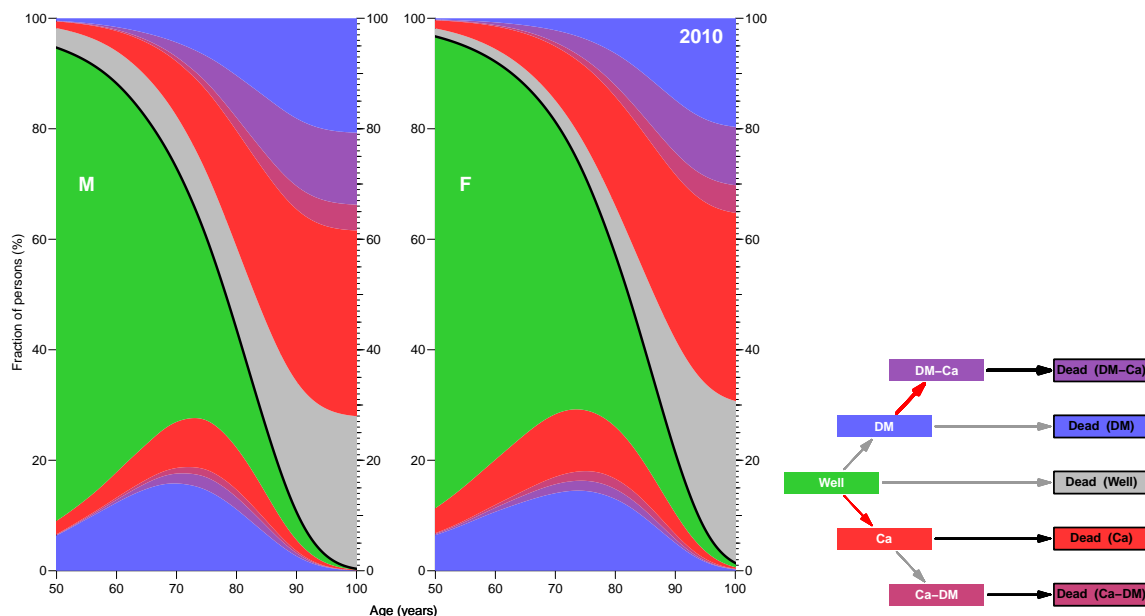
Prediction methods

- ▶ Start all in age 0 in state “Well”
- ▶ Use rates to predict how many transfer to “DM”, “Ca”, “Dead” during a small interval
- ▶ Transfer to next possible states in next interval
- ▶ Interval length: 1 month
- ▶ Compute fraction in each state at each age
- ▶ Different scenarios using estimated (cross-sectional) rates at 1 January 1995, 1996, . . . , 2012

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Cancer rates among DM-ppt inflated 20% 50%

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Transition rates

```

> int <- 1/12
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> system.time(
+ for( yy in dimnames(PR)[[4]] )
+ {
+ nd <- data.frame( A=a.pt, P=as.numeric(yy), Y=int )
+
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+ PR["Well" , "Ca" , ,yy, "M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" , "D-W" , ,yy, "M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM" , "DM-Ca" , ,yy, "M"] <- ci.pred( M.dm2ca$model , newdata=nd )[,1]
+ PR["DM" , "D-DM" , ,yy, "M"] <- ci.pred( M.dm2dd$model , newdata=nd )[,1]
+ PR["Ca" , "Ca-DM" , ,yy, "M"] <- ci.pred( M.ca2dm$model , newdata=nd )[,1]
+ PR["Ca" , "D-Ca" , ,yy, "M"] <- ci.pred( M.ca2dd$model , newdata=nd )[,1]
+ PR["DM-Ca" , "D-DC" , ,yy, "M"] <- ci.pred( M.dc2dd$model , newdata=nd )[,1]
+ PR["Ca-DM" , "D-CD" , ,yy, "M"] <- ci.pred( M.cd2dd$model , newdata=nd )[,1]

```

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Transition rates

```

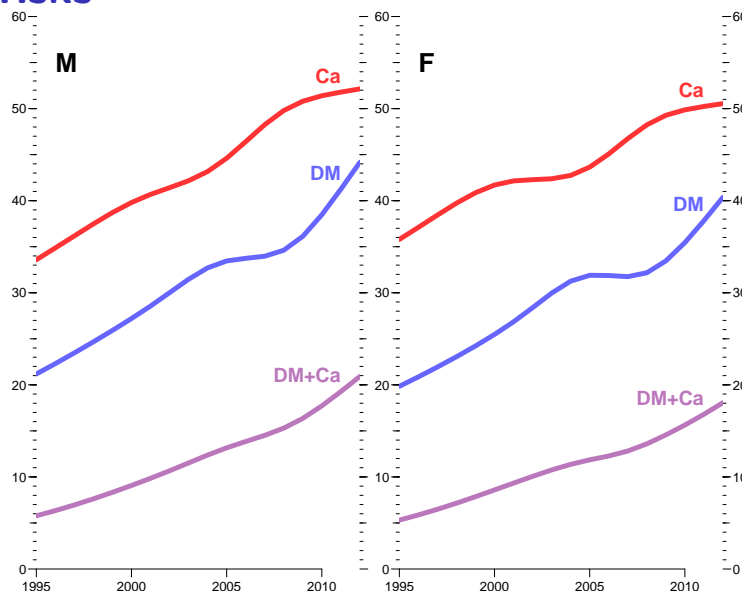
> int <- 1/12
> a.pt <- seq(int,102,int) - int/2

> system.time(
+ for( yy in dimnames(PR)[[4]] )
+ {
+ nd <- data.frame( A=a.pt, P=as.numeric(yy), Y=int )
+
+ PR["Well" , "DM" , ,yy, "M"] <- ci.pred( M.w2dm$model , newdata=nd )[,1]
+ PR["Well" , "Ca" , ,yy, "M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" , "D-W" , ,yy, "M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM" , "DM-Ca" , ,yy, "M"] <- ci.pred( M.dm2ca$model , newdata=nd )[,1] * 1.5
+ PR["DM" , "D-DM" , ,yy, "M"] <- ci.pred( M.dm2dd$model , newdata=nd )[,1]
+ PR["Ca" , "Ca-DM" , ,yy, "M"] <- ci.pred( M.ca2dm$model , newdata=nd )[,1]
+ PR["Ca" , "D-Ca" , ,yy, "M"] <- ci.pred( M.ca2dd$model , newdata=nd )[,1]
+ PR["DM-Ca" , "D-DC" , ,yy, "M"] <- ci.pred( M.dc2dd$model , newdata=nd )[,1]
+ PR["Ca-DM" , "D-CD" , ,yy, "M"] <- ci.pred( M.cd2dd$model , newdata=nd )[,1]

```

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Lifetime risks



Date of rate evaluation

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Lifetime risks - RR inflated 20%

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Lifetime risks - RR inflated 50%

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Demographic changes in DM & Cancer 1995–2012

- ▶ Changing **rates** in period 1995–2012:

Diabetes incidence	4%/year
Cancer incidence	2%/year
Mortality	-4%/year

- ▶ Changing **life-time risk** 1995–2012:

		+20% Ca DM	+50% Ca DM
Diabetes	20% to 42%	20% to 42%	20% to 42%
Cancer	35% to 51%	36% to 52%	36% to 55%
DM + Ca	6% to 20%	6% to 21%	7% to 23%

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Conclusion — DM & Cancer

- ▶ Increasing incidence rates of DM and Cancer is what matters for (changes in) lifetime risk. . .
- ▶ **not** the (slightly) elevated risk of Cancer among DM patients.

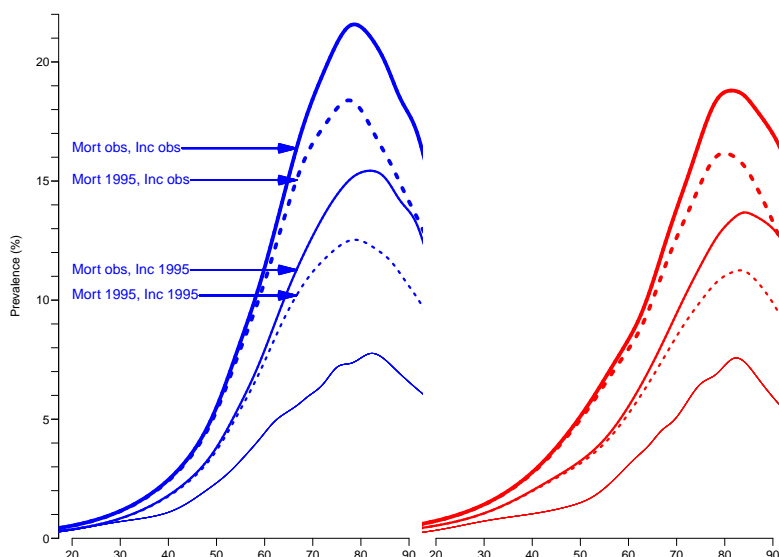
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Prevalence of DM — updating

- ▶ Start with age-specific prevalences 1995
- ▶ Use fitted models for incidence and mortality - as function of age and calendar time — to predict prevalences 2012
- ▶ 1-month intervals for updating
- ▶ Assume:
 - ▶ Incidence rates had remained at 1995 level
 - ▶ Mortality rates had remained at 1995 level
 - ▶ Both had remained at 1995 level
- ▶ Differences between predicted prevalences gives the contribution from incidence rate changes, mortality rate changes and 1995 disequilibrium.

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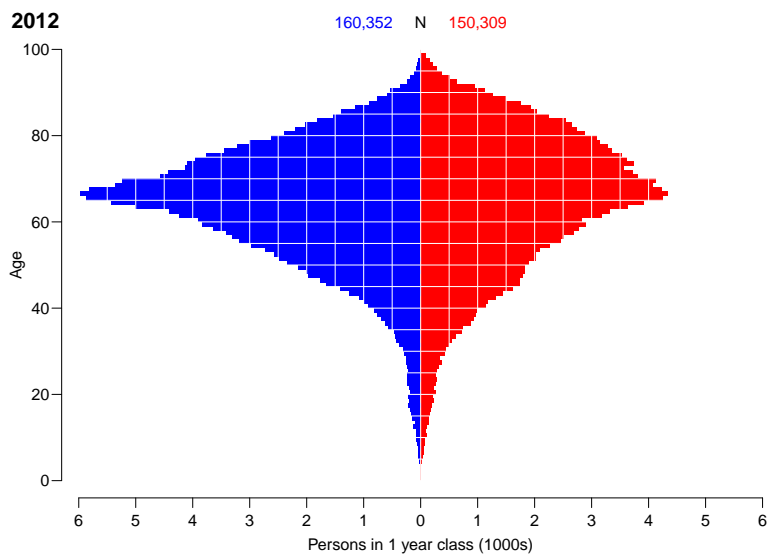
Prevalence of DM — updating



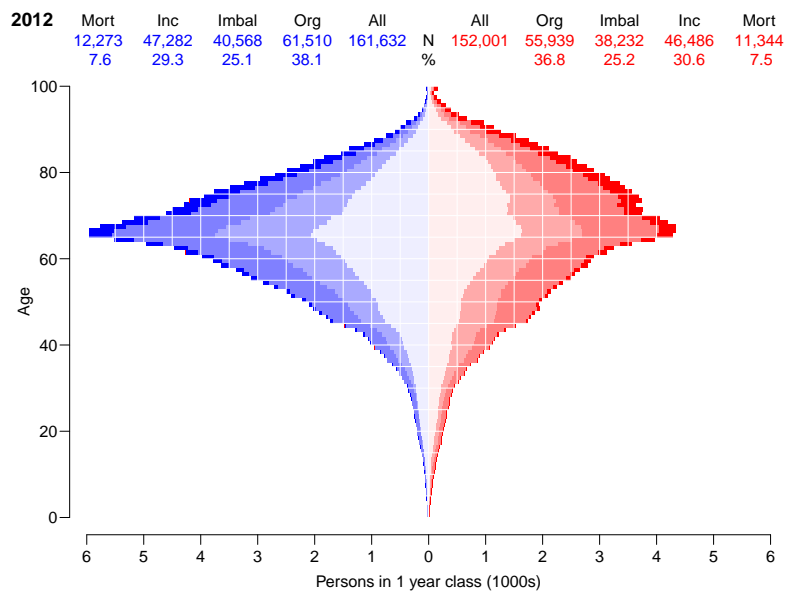
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Components of prevalent cases

Prevalent cases



Components of prevalent cases



Thanks for your
attention

