RItools and Optmatch:
Tools for the Analysis of Observational Studies (à la Rosenbaum 2002)

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Optmatch is a unified suite of tools for matching in observational studies. **RItools** provides the basic tools for diagnostic checks and effect estimation in matching and randomization based analysis.

Case Study: The Effect of Deadlines on Drug Safety

The Prescription Drug User Fee Act (PDUFA) of 1992 required the US Food and Drug Administration to act on 90% of "standard" drugs within 12 months. This was the first time that time pressure became a part of the assessment of drug safety in the USA. Our question is: **Does Haste make Waste?** Olson (2002,2004) says yes. Grabowski and Wang (2006) say no.

Seven drugs submitted and approved under the new regime were withdrawn for safety reasons (ex: the Cholesterol treatment Baycol caused potentially fatal muscle disorders; the Parkinson's treatment, Tasmar, caused liver failure, others withdrawn include Duract, Famvir, Posicor, Prelay, and Rezulin).

Analytic Strategy

Strengthen Our Argument for Ignorability using Choice and Adjustment:

Choose drugs submitted in a small window of time around the discontinuity that occurred on Sep 1, 1992 (± 4 years): 98 drugs pre-PDUFA, 121 drugs post-PDUFA.

Gently **adjust** using full matching (Hansen 2004) and a wide caliper on a propensity score (3 sd), which excludes 2 out of the 98 controls.

Test for balance using only assumptions about Z|X; Re-match if necessary.

Estimate Effects using Randomization Inference:

Specify a variety of hypotheses about the attributable effect (Rosenbaum, 2001).

Test these hypotheses.

The set of hypotheses accepted at some α is a 100(1-α) CI.

A Randomization Based Test for Balance using RItools.

Well known randomization tests like those proposed by Fisher or Mantel and Haenszel represent null hypotheses with test statistics that are all members of the class of sum statistics $t(\mathbf{Z},\mathbf{r})$;

$$t(\mathbf{Z},\mathbf{r}) = \mathbf{Z}^T\mathbf{q},$$

where **Z** records treatment assignment, **r** represents response or outcome, and **q** is some function of **r** (see Rosenbaum 2002, Chapter 2).

Sum statistics have well known normal approximations, allowing us to test hypotheses and produce confidence intervals quickly. Since the exact tests are available either via analytic development (e.g. mantelhaen.test) or simulation or sampling, we can always check the veracity of these approximations. The function xBalance() implements randomization based hypothesis tests based on the normal approximations for sum statistics.

```
xBalance                package:RItools                R Documentation

STANDARDIZED DIFFERENCES FOR STRATIFIED COMPARISONS

Description:

     Given covariates, a treatment variable, and a stratifying factor
     calculates standardized differences (biases) along each covariat
     with and without the stratification.  Also, tests for conditiona
     independence of the treatment variable and the covariates within
     strata.

Usage:

     xBalance(fmla, groups, data, chisquare.test=FALSE)

Arguments:

    fmla: A formula containing an indicator of treatment assignment o
          the left hand side and covariates at right.

  groups: A formula with no left hand side and a single term, a
          stratifying factor, on the right hand side.

    data: A data frame in which the preceding formulas are to be
          evaluated.

chisquare.test: Logical flag as to whether to perform  optional
          chisquare tests for global departure from randomization
          distribution
```

Initial Balance

We stratify on two kinds of drugs: "priority" (post-1992 deadline of 6 months) and "standard" (post-1992 deadline of 12 months).

```
bal1<-xBalance(z~x1+...+xk,~priority, data=fdapdufa,chisquare.test=TRUE)
print(bal1)
```

	pre.difference	pre.sig	post.difference	post.sig
media	0.08745		0.09759	
I(prevgenxA/1000)	0.16445		0.15179	
prevgenxANA	0.05222		0.03739	
dthrtgenA	-0.21066		-0.19159	
dthrtgenANA	0.27672	*	0.25807	.
I(hhospdisc/1e+05)	-0.09987		-0.10916	
orderent	-0.02537		-0.06041	
fsubmitsA	0.02939		0.05432	
fsubmitsANA	-0.30854	*	-0.33747	*
I(medline1total/1000)	-0.17449		-0.16235	
I(medline3total/1000)	-0.26091	.	-0.24556	.
I(medline1safetytotal/10000)	-0.27009	*	-0.24983	.
I(medline3safetytotal/1000)	-0.22926	.	-0.20845	
factor(discodeA)1600	0.21353		0.20423	
factor(discodeA)2300	-0.09396		-0.10720	
factor(discodeA)2500	-0.02884		-0.03216	
factor(discodeA)3100	0.07719		0.07689	
factor(discodeA)3230	-0.10414		-0.11445	
factor(discodeA)3300	-0.02030		-0.00510	
factor(discodeA)3500	-0.34503	*	-0.32153	*
factor(discodeA)3700	-0.16670		-0.15383	
factor(discodeA)3800	0.17361		0.17778	
factor(discodeA)4050	0.17361		0.16605	
factor(discodeA)4100	-0.21478		-0.21190	
factor(discodeA)4140	-0.02030		-0.01679	
factor(discodeA)4400	-0.14851		-0.15640	
factor(discodeA)5200	-0.02030		-0.01679	
factor(discodeA)5260	-0.21478		-0.22366	.
factor(discodeA)5400	-0.02884		-0.03216	
factor(discodeA)5500	0.04173		0.02151	
factor(discodeA)5610	0.10861		0.10575	
factor(discodeA)6100	-0.02030		-0.01679	
factor(discodeA)6140	0.09525		0.12291	
factor(discodeA)6200	0.17361		0.17778	
factor(discodeA)6400	-0.33995	*	-0.34575	*
factor(discodeA)6500	-0.21478		-0.22366	.
factor(discodeA)6640	-0.02030		-0.02848	
factor(discodeA)7500	-0.21478		-0.21190	
factor(discodeA)10100	-0.02030		-0.01679	
factor(discodeA)10400	-0.02884		-0.03216	
factor(discodeA)10800	-0.21478		-0.20015	
factor(discodeA)10820	-0.21478		-0.22366	.
factor(discodeA)10900	0.05418		0.04440	
factor(discodeA)11600	-0.10414		-0.10488	
factor(discodeA)11700	-0.21478		-0.22366	.
factor(discodeA)12300	0.17361		0.17778	
factor(discodeA)13000	-0.21478		-0.21190	
factor(discodeA)13100	0.17361		0.16605	
factor(discodeA)13120	-0.02030		-0.02848	
factor(discodeA)80200	0.21353		0.21385	
factor(discodeA)80300	-0.02030		-0.00510	
factor(discodeA)80700	0.21353		0.20423	
factor(discodeA)82200	0.27803	*	0.28846	*
factor(discodeA)85300	-0.03549		-0.04298	
factor(discodeA)88888	-0.05938		-0.07903	

```
Pre:  X-squared = 83.018, df = 55, p-value = 0.00867
Post: X-squared = 83.486, df = 55, p-value = 0.00791
```

The hypothesis of balance is rejected, with or without stratification on "priority."

Full Matching Using Optmatch

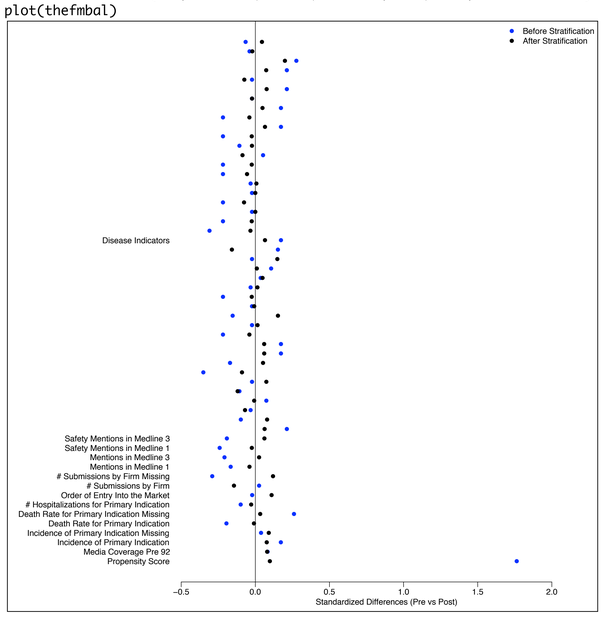
First, make a list of distance matrices (one matrix for priority and one for standard drugs), including a caliper.

```
absDist <- function(trtvar,data,scalarname,cal=Inf){
     sclr <- data[names(trtvar), scalarname]
     names(sclr) <- names(trtvar)
     dist<-abs(outer(sclr[trtvar],sclr[!trtvar], '-'))
     dist/(dist<=cal)}

psdistlist<-makedist(pdufaT~priorityF,data=fdapdufa,
                     fn=absDist,scalarname="ps4yr",cal=3)

thefm<-fullmatch(psdistlist)
```

	Matched Sets				
	Standard Drugs			Priority Drugs	
Set	PrePDUFA	PostPDUFA	Set	PrePDUFA	PostPDUFA
St.01	1	0	Pr.1	1	13
St.02	1	0	Pr.10	2	1
St.1	1	21	Pr.13	1	5
St.10	1	1	Pr.2	5	1
St.14	1	4	Pr.21	1	3
St.2	1	15	Pr.3	1	2
St.21	1	1	Pr.30	2	1
St.24	1	1	Pr.31	6	1
St.27	1	1	Pr.33	15	1
St.28	1	2	Pr.4	1	9
St.37	1	1	Pr.5	1	1
St.39	1	1	Pr.6	1	1
St.40	1	1			
St.46	36	1			
St.5	1	14			
St.53	1	1			
St.59	3	1			
St.6	1	4			
St.7	1	2			
St.71	1	1			
St.75	1	1			
St.77	1	1			
St.8	1	1			
St.9	1	6			

Discontinuity +Matching=Balance

```
thefmbal<-xBalance(balpsformula,~thefm,data=fdapdufa,chisquare.test=TRUE)
plot(thefmbal)
```



Attributing Effects to the Change in Regulatory Regime.

We define a treatment effect at the unit level:

$$\tau_i = r_{ti} - r_{ci}$$

The estimand is the effect attributable to the PDUFA regime:

$$t(\mathbf{Z},\mathbf{r}) = \sum_{s=1}^{S}\sum_{i=1}^{n_s} Z_{si} r_{si}$$

We can test for A=0...7 by adjusting the outcomes in 96 ways:

$A=$	0	1	2	3	4	5	6	7
# Attributions Possible=	1	6	16	25	25	16	6	1

```
##the Matrix deltas (96x6) contains all of the allowable attributions.
tc <- table(pdufa=fdapdufa[good,"pdufaF"],
            withdraw=fdapdufa[good,"anywithdraw"],
            match=thefm[good,drop=TRUE],exclude=NULL)

myattrib.arr<-array(0,dim=c(2,2,34,nrow(deltas)),
                    dimnames=list(0:1,0:1,
                                  dimnames(tc)[[3]],1:nrow(deltas)))
myattrib.arr[1,1,,]<-tc["PostDiscont",'0',]
myattrib.arr[2,1,,]<-tc["PostDiscont",'1',]

myattrib.arr[2,1,clevs,]<-myattrib.arr[2,1,clevs,]-t(deltas)
myattrib.arr[2,2,clevs,]<-t(deltas)

thezs<-rdz(tc,myattrib.arr)
aes1<-data.frame(A=theAs,Z=thezs,p=pnorm(abs(thezs),lower=FALSE)*2)
tapply(aes1$p,aes1$A,range)
```

Tests of $t(\mathbf{Z},\mathbf{r})$ for each possible attribution using the same kind of normal approximation this time with the rdz() function, yielded a CI containing all of the possible attributions, including 0.

$A=$	0	1	2	3	4	5	6	7
lo p	0.3	0.3	0.3	0.3	0.3	0.5	0.7	.6
hi p		0.5	0.7	0.9	1.0	0.9	0.9	

How many safety based withdrawals can be attributed to the change in the FDA rules? Zero is probable, but 6 is more probable than 0.

References

Bowers, Jake and Ben B. Hansen. 2005. "Attributing Effects to A Cluster Randomized Get-Out-The-Vote Campaign: An Application of Randomization Inference Using Full Matching." Unpublished manuscript..

Grabowski, Henry and Y. Richard Wang. 2006. "Determinants of New Drug Safety in the United States, 1993-2003." Unpublished manuscript.

Hansen, Ben B. 2006. "Appraising Covariate Balance after Assignment to Treatment by Groups." Technical Report 436 Statistics Department: University of Michigan .

Hansen, Ben B. 2004. "Full Matching in an Observational Study of Coaching for the SAT." *Journal of the American Statistical Association* 99:609.

Hansen, Ben B. and Stephanie Olsen Klopfer. 2005. "Optimal full matching and related designs via network flows." Technical Report 416 Statistics Department, University of Michigan.

Olson, Mary K. 2002. "Pharmaceutical Policy Change and the Safety of New Drugs." *Journal of Law and Economics* XLV:615–642.

Olson, Mary K. 2004. "Are novel drugs more risky for patients than less novel drugs? " *Journal of Health Economics* 23:1135–1158.

Rosenbaum, Paul R. 1989. "Optimal Matching for Observational Studies." *Journal of the American Statistical Association* 84:1024–1032.

Rosenbaum, Paul R. 2001. "Effects Attributable to Treatment: Inference in experiments and observational studies with a discrete pivot." *Biometrika* 88:219–231.

Rosenbaum, Paul R. 2002. *Observational Studies*. Springer.

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