

cn.FARMS: a latent variable model to detect copy number variations in microarray data with a low false discovery rate

— Manual for the *cn.farms* package —

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1 Introduction

The `cn.farms` package provides a novel copy number variation (CNV) detection method, called “cn.FARMS”, which is based on our FARMS (“factor analysis for robust microarray summarization” (Hochreiter *et al.*, 2006)) algorithm. FARMS is since 2006 the leading summarization method of the international “affycomp” competition if sensitivity and specificity are considered simultaneously. We extended FARMS to cn.FARMS (Clevert *et al.*, 2011) for detecting CNVs by moving from mRNA copy numbers to DNA copy numbers.

In the following section we will briefly describe the algorithm and provide a quick start guide. For further information regarding the algorithm and its assessment see the `cn.farms` homepage at <http://www.bioinf.jku.at/software/cnfarms/cnfarms.html>.

2 cn.FARMS: FARMS for CNV Detection

cn.FARMS is described “in a nutshell” by the preprocessing pipeline depicted in Figure 1: **(1) Normalization** is performed at two levels. It has as *input* the raw probe intensity values and as *output* intensity values at chromosome locations which are leveled between arrays and are allele independent. At the *first level* normalization methods remove technical variations between arrays arising from differences in sample preparation or labeling, array production (e.g. batch effects), or scanning differences. The goal of the first level is to correct for array-wide effects. At the *second level* alleles are combined to one intensity value at a chromosome location and a correction for cross-hybridization between allele A and allele B probes is performed. Cross-hybridization arises due to close sequence similarity between the probes of different alleles, therefore a probe of one allele picks up a signal of the other allele. The optional corrections for differences in PCR yield can be performed at this step or after “single-locus modeling”. We propose sparse overcomplete representation in the two-dimensional space of allele A and B intensity to correct for cross-hybridization

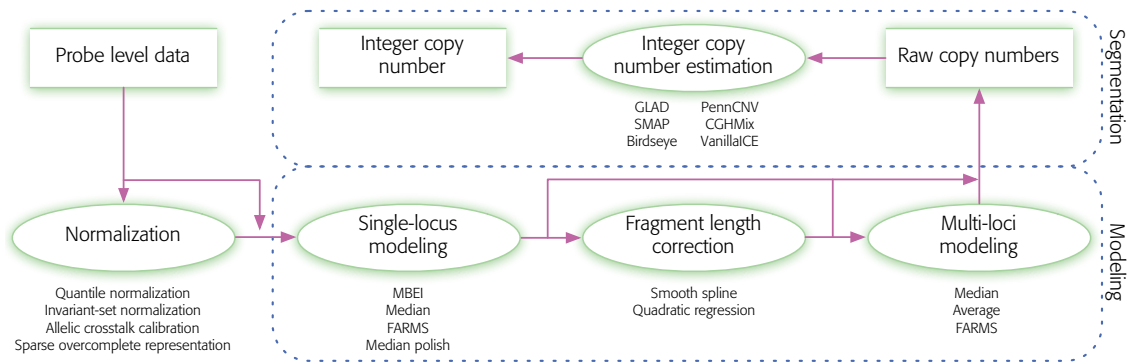


Figure 1: Copy number analysis for (Affymetrix) DNA genotyping arrays as a three-step pipeline: (1) Normalization, (2) Modeling, and (3) Segmentation. Modeling is divided into “single-locus modeling” and “multi-loci modeling” with “fragment length correction” as an optional intermediate step. The cn.FARMS pipeline is: normalization by sparse overcomplete representation, single-locus modeling by FARMS, fragment length correction, and multi-loci modeling by FARMS.

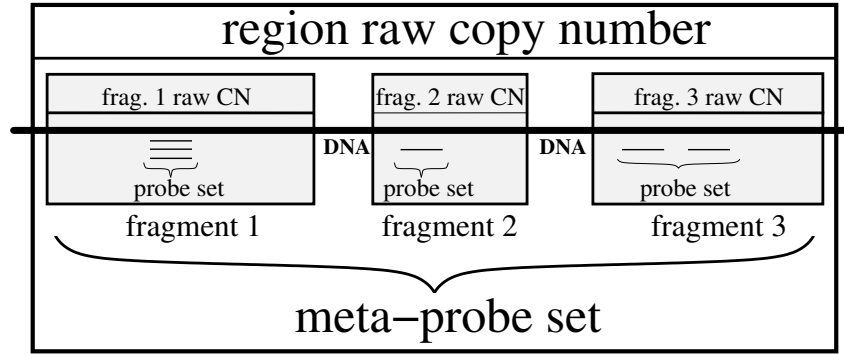


Figure 2: The copy number hierarchy probes-fragment-region. Fragment copy numbers serve as meta-probes used for “multi-loci modeling” which yields region copy numbers. Inner boxes: The probes which target a fragment (often at a SNP position) are single-locus summarized to a raw copy number of this fragment. Note, that instead of fragments a DNA probe loci can be summarized. Outer box: The raw fragment copy numbers are the meta-probes for a DNA region and are multi-loci summarized to a raw region copy number.

between allele A and allele B probes. Therefore we do not only estimate the AA and the BB cross-hybridization like CRMA (Bengtsson *et al.*, 2008) but also the AB cross-hybridization. The latter takes into account that hybridization and cross-hybridization may be different for the AB genotype, where for both allele probes target fragments are available and compete for hybridization. After allele correction, we follow CRMA and normalize by scaling the probes to a pre-specified mean intensity value. CNV probes which have only one allele are scaled in the same way. **(2) Modeling** is also performed at two levels. The *input* is the probe intensity values which independently measure the copy number of a specific target fragment or DNA probe locus. The *output* is an estimate for the region copy number. At the *first level*, “single-locus modeling” the probes which measure the same fragment are combined to a raw fragment copy number (“raw” means that the copy number is still a continuous values) — see Figure 2. These raw fragment copy numbers are estimated by FARMS. The original FARMS was designed to summarize probes which target the same mRNA. This can readily transferred to CNV analysis where FARMS now summarizes probes which target the same DNA fragment. Either both strands can be summarized together or separately where our default is the former. Nannya *et al.* (2005) suggested considering fragment characteristics like sequence patterns and the length because they affect PCR amplification. For example, PCR is usually less efficient for longer fragments, which lead to fewer copies to hybridize and result in weaker probe intensities. Following these suggestions cn.FARMS performs an optional intermediate level to correct for the fragment length and sequence features to make raw fragment copy numbers comparable along the chromosome. At the *second level*, “multi-loci modeling”, the raw copy numbers of neighboring fragments or neighboring DNA probe loci are combined to a “meta-probe set” which targets a DNA region. The raw fragment copy numbers from single-locus modeling are now themselves probes for a DNA region as depicted in Figure 2. Again we use FARMS to summarize meta-probes and to estimate a raw copy number for the region. This modeling across samples is novel as previous methods only model along the chromosome. Multi-loci modeling considerably reduces the false discovery rates, because raw copy numbers of neighboring fragments or neighboring DNA probe loci must agree to each other on

the copy number, which reduces the likelihood of a discovery by chance. However, low FDR is traded against high resolution by the window size for multi-loci modeling, i.e. by how many raw copy numbers of neighboring fragments or neighboring DNA probe loci are combined. The more loci are combined, the more the FDR is reduced, because more meta-probes must mutually agree on the region's copy number. The window size for multi-loci modeling is a hyperparameter which trades off low FDR against high resolution. We recommend a window size of 5 as default, 3 for high resolution, and 10 for low FDR. Alternatively to a fixed number of CNV or SNP sites, the cn.FARMS software allows defining a window in terms of base pairs. In this case, multi-loci modeling may use a different number of meta-probes at different DNA locations, in particular for less than two meta-probes multi-loci modeling is skipped. Note, however that controlling the FDR is more difficult because a minimal number of meta-probes cannot be assured for each window and modeling with few meta-probes is prone to false discoveries. FARMS supplies an informative/non-informative (I/Ni) call (Talloon *et al.*, 2007, 2010) which is used to detect CNVs. Additionally, the I/Ni value gives the signal-to-noise-ratio of the estimated raw copy number. **(3) Segmentation** can afterwards be performed by DNACopy.

3 Getting Started: cn.FARMS

As usual, it is necessary to load the `cn.farms` package:

```
library(cn.farms)
```

3.1 Quick start : Process SNP 6.0 array

The `hapmapsnp6` package is loaded for testing purpose.

```
> library("hapmapsnp6")
> celDir <- system.file("celFiles", package="hapmapsnp6")
> filenames <- dir(path=celDir, full.names=TRUE)
```

Next, the user specifies a working directory on the harddisk whereto save the results.

```
> workDir <- "~/tmp"
> dir.create(workDir, showWarnings=F, recursive=T)
> setwd(workDir)
```

For reasons of computational time and memory consumption `cn.farms` supports high-performance computation. The parameter `cores` specifies number amount of CPUs requested for the cluster and the parameter `runtype` indicates how the data matrix should be stored. `runtype = "ff"` creates a transient flat-file which will not be saved automatically. Whereas `runtype = "bm"` creates a persistent flat-file which can be save permanently.

```
> cores <- 2
> runtype <- "bm"
```

Next, the user specifies a subdirectory whereto save the flat-files.

```
> dir.create("ffObjects/ff", showWarnings=F, recursive=T)
> oligoClasses::ldPath(file.path(getwd(), "ffObjects"))
> options(fftempdir = file.path(oligoClasses::ldPath(), "ff"))
```

The directory (celDir = "where/are/my/cel-files") which contain the cel-files has to be specified.

```
> celDir <- system.file("celFiles", package="hapmapsnp6")
> filenames <- dir(path=celDir, full.names=TRUE)
```

The following step will create the annotation file.

```
> if(exists("annotDir")) {
>     createAnnotation(filenames=filenames, annotDir=annotDir)
> } else {
>     createAnnotation(filenames=filenames)
> }
```

Afterwards, the data will be corrected for cross-hybridization and normalized.

```
> normMethod <- "SOR"

> ## normalization of SNP data
> if(exists("annotDir")) {
>     normData <- normalizeCels(filenames, method=normMethod, cores, alleles=T,
>                             annotDir=annotDir, runtype=runtype)
> } else {
>     normData <- normalizeCels(filenames, method=normMethod, cores, alleles=T,
>                             runtype=runtype)
> }
```

Now, the normalized data will be summarized at DNA probe loci. `summaryMethod <- "Variational"` indicates which FARMS approach should be used and `summaryParam$cyc <- c(10, 10)` specifies the number of iterations of the EM-algorithm. The parameter `summaryWindow` indicates whether DNA probe loci on the same DNA fragments are summarized together (`summaryWindow="fragment"`) or if the DNA probe loci are summarized separately (`summaryWindow="std"` is the default setting).

```
> summaryMethod <- "Variational"
> summaryParam <- list()
> summaryParam$cyc <- c(10)
> callParam <- list(cores = cores, runtype = runtype)
> slData <- slSummarization(normData, summaryMethod = summaryMethod,
+   summaryParam = summaryParam, callParam = callParam, summaryWindow = "std")
```

```

2011-04-05 10:05:08 | Starting summarization
2011-04-05 10:05:08 | Computations will take some time, please be patient
R Version: R version 2.13.0 Under development (unstable) (2010-12-21 r53879)

```

```

2011-04-05 10:05:13 | Summarizing batch 1 ...
2011-04-05 10:05:15 | Summarization done
Time difference of 7.390061 secs

```

```
> show(slData)
```

```

ExpressionSet (storageMode: list)
assayData: 319 features, 3 samples
  element names: intensity, L_z, INICall, IC, lapla
protocolData: none
phenoData
  rowNames: NAO6985_GW6_C NAO6991_GW6_C NAO6993_GW6_C
  varLabels: filenames batch gender
  varMetadata: labelDescription
featureData
  featureNames: 906474 745070 ... 888581 (319 total)
  fvarLabels: chrom start ... fragment_length2 (10 total)
  fvarMetadata: labelDescription
experimentData: use 'experimentData(object)'
Annotation: pd.genomewidesnp.6

```

```
> assayData(slData)$intensity[1:10, ]
```

```

      [,1]      [,2]      [,3]
[1,] 12.20755 12.17502 12.32406
[2,] 10.11318 10.37334 10.28581
[3,] 10.63524 10.67435 10.67910
[4,] 11.97147 11.86901 12.19888
[5,] 11.35531 11.64151 11.57714
[6,] 11.80594 11.69453 11.88172
[7,] 10.83750 11.30031 11.52272
[8,] 11.15025 11.61968 11.34616
[9,] 11.79847 11.79846 11.79846
[10,] 11.65713 12.14412 12.42084

```

```
> assayData(slData)$L_z[1:10, ]
```

```

      [,1]      [,2]      [,3]
[1,] -7.517762e-03 -0.040046276 1.089872e-01
[2,] -1.705384e-01 0.089626390 2.094587e-03
[3,] -3.764501e-02 0.001457699 6.213158e-03

```

```
[4,] -4.024762e-04 -0.102867004 2.270022e-01
[5,] -2.218426e-01 0.064355342 -1.436268e-05
[6,] 3.354704e-05 -0.111374832 7.581430e-02
[7,] -4.616970e-01 0.001114454 2.235242e-01
[8,] -1.983893e-01 0.271041282 -2.482165e-03
[9,] 7.178394e-06 0.000000000 -3.878486e-06
[10,] -4.869916e-01 0.000000000 2.767239e-01
```

Now, the intensity values of the non-polymorphic probes (CN-probes) were normalized.

```
> if (exists("annotDir")) {
  npData <- normalizeNpData(filenames, cores, annotDir=annotDir)
} else {
  npData <- normalizeNpData(filenames, cores, runtype=runtype)
}
```

This step combines non-polymorphic probes and single-locus summarized SNP-probes.

```
> combData <- combineData(slData, npData, runtype = runtype)
> show(combData)
```

```
ExpressionSet (storageMode: list)
assayData: 638 features, 3 samples
  element names: intensity
protocolData: none
phenoData
  rowNames: NAO6985_GW6_C NAO6991_GW6_C NAO6993_GW6_C
  varLabels: filenames batch gender
  varMetadata: labelDescription
featureData
  featureNames: 906474 9064741 ... 8885811 (638 total)
  fvarLabels: chrom start end man_fsetid
  fvarMetadata: labelDescription
experimentData: use 'experimentData(object)'
Annotation: pd.genomewidesnp.6
```

In this final step intensity values of non-polymorphic probes and single-locus summarized SNP-probes are multi-locus summarized with a windows size of 5 probes (`windowParam$windowSize <- 5`). The window size for multi-loci modeling is a hyperparameter which trades off low FDR against high resolution. We recommend a window size of 5 as default, 3 for high resolution, and 7 for low FDR. Setting `windowParam$overlap <- TRUE` indicates that the multi-locus summarization is done by step-wise moving the window over the genome. Alternatively to a fixed number of CNV or SNP sites, the cn.FARMS software allows defining a window in terms of base pairs. To make use of this option set `windowMethod <- "bps"`. In this case, multi-loci modeling may use a different number of meta-probes at different DNA locations, in particular for less than two meta-probes multi-loci modeling is skipped. Note, however that controlling the FDR is more difficult

because a minimal number of meta-probes cannot be assured for each window and modeling with few meta-probes is prone to false discoveries.

```
> windowMethod <- "std"
> windowParam <- list()
> windowParam$windowSize <- 5
> windowParam$overlap <- TRUE
> summaryMethod <- "Variational"
> summaryParam <- list()
> summaryParam$cyc <- c(20)
> callParam <- list(cores = cores, runtype = runtype)
> mlData <- mlSummarization(slData, windowMethod = windowMethod,
+   windowParam = windowParam, summaryMethod = summaryMethod,
+   summaryParam = summaryParam, callParam = callParam)

2011-04-05 10:05:16 | Starting summarization
2011-04-05 10:05:16 | Computations will take some time, please be patient
2011-04-05 10:05:22 | Summarizing batch 1 ...
2011-04-05 10:05:23 | Summarization done

> assayData(mlData)

$intensity
ff (open) double length=945 (945) dim=c(315,3) dimorder=c(1,2)
      [,1]      [,2]      [,3]
[1,]  11.25614  11.36881  11.34344
[2,]  11.17581  11.28848  11.26311
[3,]  11.31831  11.46689  11.48400
[4,]  11.43798  11.64570  11.60267
[5,]  11.56560  11.56560  11.56560
[6,]  11.67900  11.67900  11.67900
[7,]  11.75993  11.75994  11.75994
[8,]  11.98562  11.98562  11.98562
:      :      :      :
[308,] 12.45345 12.36589 12.57690
[309,] 12.63058 12.54857 12.73486
[310,] 12.37031 12.31327 12.43549
[311,] 12.50302 12.36214 12.54567
[312,] 12.37075 12.21500 12.37619
[313,] 12.38909 12.23160 12.43595
[314,] 12.17181 12.17181 12.17181
[315,] 12.46419 12.46419 12.46419

$L_z
ff (open) double length=945 (945) dim=c(315,3) dimorder=c(1,2)
      [,1]      [,2]      [,3]
```

```

[1,] -8.712036e-02 2.554806e-02 1.771981e-04
[2,] -8.713133e-02 2.554272e-02 1.720637e-04
[3,] -1.475322e-01 1.048626e-03 1.815850e-02
[4,] -1.622197e-01 4.549467e-02 2.469572e-03
[5,] -4.772754e-07 2.053982e-07 8.198186e-08
[6,] -2.405087e-07 6.353837e-08 1.026209e-07
[7,] -2.532603e-06 3.560109e-07 1.486818e-06
[8,] -4.093355e-11 -9.282559e-11 1.374473e-10
:
:
:
[308,] -1.365211e-05 -8.758209e-02 1.234337e-01
[309,] -3.249869e-06 -8.201717e-02 1.042746e-01
[310,] -1.612020e-04 -5.719566e-02 6.501597e-02
[311,] -3.235122e-05 -1.409128e-01 4.261905e-02
[312,] -3.011554e-07 -1.557494e-01 5.439266e-03
[313,] -6.016888e-05 -1.575518e-01 4.680149e-02
[314,] -4.343949e-14 -6.959897e-13 1.294788e-13
[315,] 0.000000e+00 -2.302694e-09 1.053619e-09

```

\$INICall

```

ff (open) double length=315 (315) dim=c(315,1) dimorder=c(1,2)
      [,1]

```

```

[1,] 1.523963e-01
[2,] 1.524092e-01
[3,] 1.796878e-01
[4,] 1.900381e-01
[5,] 2.239515e-12
[6,] 4.782716e-13
[7,] 6.163425e-11
[8,] 0.000000e+00
:
:
[308,] 1.241166e-01
[309,] 1.243723e-01
[310,] 1.119241e-01
[311,] 1.127761e-01
[312,] 1.095954e-01
[313,] 1.087332e-01
[314,] 0.000000e+00
[315,] 0.000000e+00

```

\$IC

```

ff (open) double length=945 (945) dim=c(315,3) dimorder=c(1,2)
      [,1]      [,2]      [,3]
[1,] 5.6682722 5.6593622 -1.4422158
[2,] 5.7116205 5.7029681 -1.4407859
[3,] 5.0689252 0.9523697 4.9911356
[4,] 3.1157307 3.0460854 -1.0574463

```

```
[5,] -2.7825724 -3.6766874 -5.6732631
[6,] -2.2851859 -4.1516919 -3.2054672
[7,] -2.3131709 -5.8497754 -2.8056725
[8,] -16.7660839 -15.2916332 -14.9079047
:      :      :      :
[308,] -10.8474429 5.3582017 5.3595555
[309,] -11.0885036 7.1354541 7.1357227
[310,] -6.3387786 3.1714310 3.1734243
[311,] -9.4629885 4.5953200 4.5820613
[312,] -16.0794333 7.9579910 7.8831565
[313,] -9.7776991 3.6691009 3.6439874
[314,] -30.1954206 -24.9145587 -27.2740543
[315,] -Inf -3.4968829 -4.2837363
```

```
$lapla
```

```
ff (open) double length=945 (945) dim=c(315,3) dimorder=c(1,2)
      [,1] [,2] [,3]
[1,] 1.527427e-01 1.518023e-01 1.105326e-03
[2,] 1.527454e-01 1.518321e-01 1.073691e-03
[3,] 1.804455e-01 1.040254e-02 1.709736e-01
[4,] 1.932613e-01 1.841533e-01 1.071256e-02
[5,] 1.453323e-01 7.820001e-02 1.959646e-02
[6,] 2.051590e-01 5.626213e-02 1.084072e-01
[7,] 2.012177e-01 1.733972e-02 1.430238e-01
[8,] 8.972343e-06 2.493215e-05 3.252921e-05
:      :      :      :
[308,] 1.643938e-06 1.242426e-01 1.243593e-01
[309,] 4.063703e-07 1.244171e-01 1.244402e-01
[310,] 1.544024e-04 1.125933e-01 1.127490e-01
[311,] 6.634377e-06 1.131808e-01 1.121454e-01
[312,] 6.367406e-09 1.096348e-01 1.040928e-01
[313,] 9.802667e-06 1.094547e-01 1.075659e-01
[314,] 8.133410e-10 3.162063e-08 6.161572e-09
[315,] 0.000000e+00 8.857952e-02 5.134130e-02
```

Next, the summarized data will be segmented in order to identify break points. Therefore we provide a parallelized version of DNACopy.

```
> colnames(assayData(mlData)$L_z) <- sampleNames(mlData)
> segments <- dnaCopySf(x = assayData(mlData)$L_z, chrom = featureData(mlData)@data$chrom,
+   maploc = featureData(mlData)@data$start, cores = cores,
+   smoothing = FALSE)
```

```
Library ff loaded.
```

```
Library DNACopy loaded.
```

```
Time difference of 7.25407 secs
```

```
> featureData(segments)@data
```

	chrom	start	end	num.mark	seg.mean	individual
1	1	564621	752566	4	-0.1210	NA06985_GW6_C
2	1	761732	2456203	153	-0.0054	NA06985_GW6_C
3	1	2473258	2553624	9	0.2969	NA06985_GW6_C
4	1	2553758	2766971	12	-0.0149	NA06985_GW6_C
5	1	2783040	2787707	3	0.1621	NA06985_GW6_C
6	1	2789108	2859724	17	-0.0071	NA06985_GW6_C
7	1	2865778	2867961	4	-0.1951	NA06985_GW6_C
8	1	2878366	2925522	13	0.0006	NA06985_GW6_C
9	1	2926555	2936480	5	-0.0632	NA06985_GW6_C
10	1	2936870	2974212	16	-0.0008	NA06985_GW6_C
11	1	2981841	2996602	5	-0.1455	NA06985_GW6_C
12	1	3000924	3025712	6	0.0005	NA06985_GW6_C
13	1	3026100	3044181	3	0.2138	NA06985_GW6_C
14	1	3044977	3080940	10	-0.0037	NA06985_GW6_C
15	1	3089849	3101863	6	-0.2318	NA06985_GW6_C
16	1	3103312	3112417	4	-0.0923	NA06985_GW6_C
17	1	3112979	3225940	45	0.0001	NA06985_GW6_C
18	1	564621	1871337	75	-0.0164	NA06991_GW6_C
19	1	1888193	1948400	5	-0.4476	NA06991_GW6_C
20	1	1972462	2996602	161	-0.0239	NA06991_GW6_C
21	1	3000924	3047252	11	-0.1100	NA06991_GW6_C
22	1	3049713	3220101	54	-0.0043	NA06991_GW6_C
23	1	3220160	3225940	9	-0.0852	NA06991_GW6_C
24	1	564621	792480	9	0.0112	NA06993_GW6_C
25	1	798959	1003629	11	0.1959	NA06993_GW6_C
26	1	1017216	1218086	20	0.0661	NA06993_GW6_C
27	1	1242215	1365570	8	0.1774	NA06993_GW6_C
28	1	1411876	1500941	7	0.0000	NA06993_GW6_C
29	1	1506035	1663831	4	0.1057	NA06993_GW6_C
30	1	1688192	2285414	66	0.0151	NA06993_GW6_C
31	1	2286408	2302911	4	0.1805	NA06993_GW6_C
32	1	2303512	2329564	11	0.0000	NA06993_GW6_C
33	1	2329661	2455633	15	0.0660	NA06993_GW6_C
34	1	2455863	2553758	12	0.0048	NA06993_GW6_C
35	1	2701816	2723345	3	0.1696	NA06993_GW6_C
36	1	2723552	2833332	20	0.0043	NA06993_GW6_C
37	1	2833743	2846274	5	0.1422	NA06993_GW6_C
38	1	2851238	2932446	23	0.0204	NA06993_GW6_C
39	1	2934312	2950334	9	0.1407	NA06993_GW6_C
40	1	2950370	3050594	27	0.0336	NA06993_GW6_C
41	1	3054106	3089849	7	0.1476	NA06993_GW6_C
42	1	3094831	3114952	11	0.0645	NA06993_GW6_C
43	1	3119489	3127925	7	0.1607	NA06993_GW6_C

```

44      1 3135175 3152968      11 0.0071 NA06993_GW6_C
45      1 3165267 3197480       6 0.1902 NA06993_GW6_C
46      1 3197747 3225940      19 0.0436 NA06993_GW6_C

```

To get further information, e.g. how to process Affymetrix 500K arrays, please check the followings demos.

```
> demo(package = "cn.farms")
```

Demos in package 'cn.farms':

```

demo01Snp6           Demo for an Affymetrix SNP6 data set
demo02Snp5           Demo for an Affymetrix SNP5 data set
demo03Snp500k        Demo for an Affymetrix 500K data set
demo04Snp250k        Demo for an Affymetrix 250K NSP data set
demo05Testing         Run the examples

```

4 Setup

This vignette was built on:

```
> sessionInfo()
```

```

R version 2.13.0 Under development (unstable) (2010-12-21 r53879)
Platform: x86_64-unknown-linux-gnu (64-bit)

```

locale:

```

[1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C
[3] LC_TIME=en_US.UTF-8       LC_COLLATE=en_US.UTF-8
[5] LC_MONETARY=C             LC_MESSAGES=en_US.UTF-8
[7] LC_PAPER=en_US.UTF-8      LC_NAME=C
[9] LC_ADDRESS=C              LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

```

attached base packages:

```

[1] tools      stats      graphics  grDevices  utils      datasets  methods
[8] base

```

other attached packages:

```

[1] DNACopy_1.25.0  snow_0.3-3      cn.farms_0.99.5 ff_2.2-1
[5] bit_1.1-6       Biobase_2.11.8

```

loaded via a namespace (and not attached):

```

[1] affxparser_1.23.1  affyio_1.19.3      Biostrings_2.19.8
[4] DBI_0.2-5          grid_2.13.0         IRanges_1.9.21

```

[7] lattice_0.19-17 oligo_1.15.2 oligoClasses_1.13.9
[10] preprocessCore_1.13.5 snowfall_1.84 splines_2.13.0

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