USING THE ONCOTREE PACKAGE

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Abstract. This paper shows a short example of building and exploring oncogenetic trees using the Oncotree package. A detailed description of the theory of oncogenetic trees can be found in

- Desper, R.; Jiang, F.; Kallioniemi, O.; Moch, H.; Papadimitriou, C. and Schäffer, A. A. "Inferring tree models for oncogenesis from comparative genome hybridization data." *Journal of Computational Biology*, 1999, 6, 37-51.
- Szabo, A. and Boucher, K. "Estimating an oncogenetic tree when false negatives and positives are present." *Mathematical Biosciences*, 2002, 176, 219-236.
- Szabo, A. and Boucher, K. "Oncogenetic trees" in *Handbook of cancer models with applications* Tan, Hanin (ed.) World Scientific, 2008.

A short introduction is given in doc/Oncotree.pdf.

We start by loading a dataset. The package contains an example dataset:

```
> library(Oncotree)
> data(ov.cgh)
> str(ov.cgh)
'data.frame':        87 obs. of  7 variables:
 $ 8q+: int  0 0 1 1 0 1 1 0 0 1 ...
 $ 3q+: int  0 0 1 0 0 1 1 1 1 0 ...
 $ 5q-: int  0 0 1 0 0 1 1 1 0 1 ...
 $ 4q-: int  0 1 1 0 0 1 1 0 0 1 ...
 $ 8p-: int  0 0 0 0 0 1 1 0 0 1 ...
 $ 1q+: int  1 1 0 0 0 0 0 0 0 1 ...
 $ Xp-: int  0 0 0 0 0 0 1 0 1 1 ...
```

Based on these data, we construct the oncogenetic tree using the default ℓ_2-distance error function to estimate the false-positive and false-negative error rates.

```
> ov.tree <- oncotree.fit(ov.cgh)
```

The fitted tree can be examined several ways: `print`ing it produces a quick summary, but the result of `plot`ting is easier to interpret (the plots are shown in Figure 1).

```
> ov.tree
Oncogenetic tree from 7 events
Parent function:
         8q+ <- Root
         3q+ <- 8q+
         5q- <- Root
         4q- <- 5q-
         8p- <- 5q-
         1q+ <- Root
         Xp- <- 8p-
Estimated error rates: epos= 0.2084556 , eneg= 0.02676960
> plot(ov.tree, edge.weights = "est")
> pstree.oncotree(ov.tree, edge.weights = "est", shape = "oval")
```

We can compare the observed and fitted marginal occurrence frequencies of the mutations (the distance between these two was minimized for the error-rate estimation). The plot is shown in Figure 2.

```
> print(obs <- colMeans(ov.tree$data))
     Root       8q+       3q+       5q-       4q-       8p-       1q+       Xp-
1.0000000 0.7011494 0.5517241 0.5287356 0.5057471 0.4712644 0.4367816 0.4252874
> print(est <- marginal.distr(ov.tree, with.errors = TRUE))
```

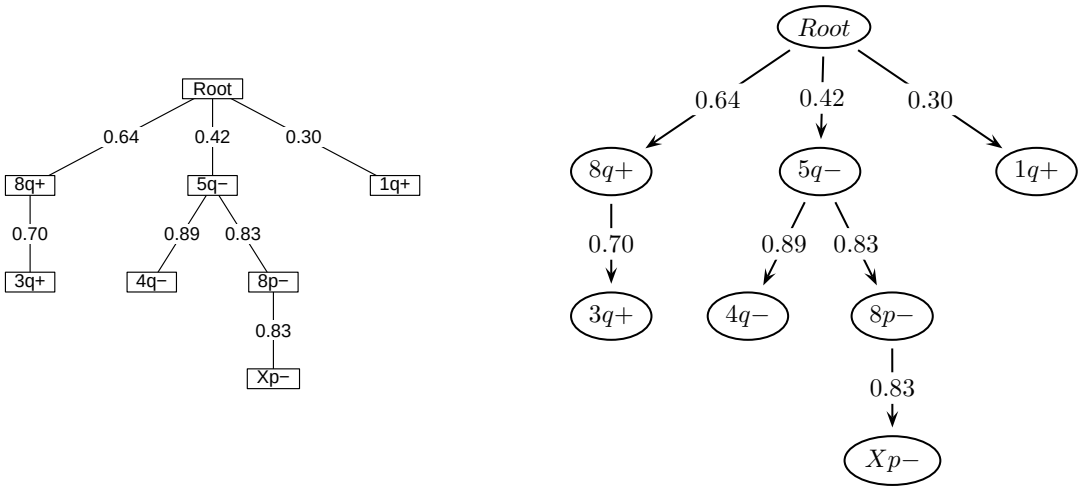


FIGURE 1. Fitted oncogenetic tree for the `ov.cgh` data set.

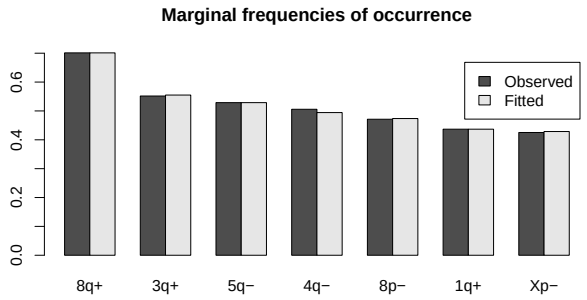


FIGURE 2. Observed and fitted frequencies of occurrence of each event.

```
     Root       8q+       3q+       5q-       4q-       8p-       1q+       Xp-
1.0000000 0.7011494 0.5550202 0.5287356 0.4943105 0.4736503 0.4367816 0.4286807
```

```
> barplot(rbind(obs[-1], est[-1]), beside = T, legend.text = c("Observed", "Fitted"),
+     main = "Marginal frequencies of occurrence")
```

In addition to the marginal frequencies, it is possible to estimate the entire joint distribution generated by the tree:

```
> dd <- distribution.oncotree(ov.tree, with.errors = TRUE)
> head(dd)
```

```
  Root 8q+ 3q+ 5q- 4q- 8p- 1q+ Xp-        Prob
1    1   0   0   0   0   0   0   0 0.029222901
2    1   1   0   0   0   0   0   0 0.027992097
3    1   0   1   0   0   0   0   0 0.009202964
4    1   1   1   0   0   0   0   0 0.062160896
5    1   0   0   1   0   0   0   0 0.008323722
6    1   1   0   1   0   0   0   0 0.007973145
```

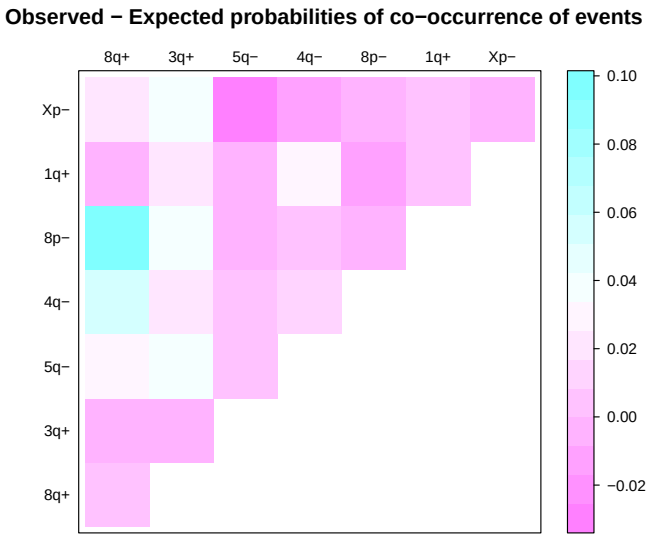


FIGURE 3. Goodness-of-fit plot: difference between observed and expected probabilities of two events being observed.

Using the overall joint distribution, it is straightforward to obtain marginal joint distributions (2- or higher way) if needed (the plot is shown in Figure 3).

```
> print(est2way <- t(data.matrix(dd[2:8])) %*% diag(dd$Prob) %*% data.matrix(dd[2:8]))

          8q+       3q+       5q-       4q-       8p-       1q+       Xp-
8q+ 0.7011494 0.4834457 0.3707227 0.3465855 0.3320996 0.3062492 0.3005693
3q+ 0.4834457 0.5550202 0.2934589 0.2743523 0.2628855 0.2424226 0.2379265
5q- 0.3707227 0.2934589 0.5287356 0.3884206 0.3683135 0.2309420 0.3245477
4q- 0.3465855 0.2743523 0.3884206 0.4943105 0.3393380 0.2159057 0.2992688
8p- 0.3320996 0.2628855 0.3683135 0.3393380 0.4736503 0.2068817 0.3130649
1q+ 0.3062492 0.2424226 0.2309420 0.2159057 0.2068817 0.4367816 0.1872399
Xp- 0.3005693 0.2379265 0.3245477 0.2992688 0.3130649 0.1872399 0.4286807

> print(obs2way <- t(ov.tree$data[, -1]) %*% ov.tree$data[, -1]/nrow(ov.tree$data))

          8q+       3q+       5q-       4q-       8p-       1q+       Xp-
8q+ 0.7011494 0.4827586 0.4022989 0.4022989 0.4252874 0.2988506 0.3218391
3q+ 0.4827586 0.5517241 0.3333333 0.2988506 0.2988506 0.2643678 0.2758621
5q- 0.4022989 0.3333333 0.5287356 0.3908046 0.3678161 0.2298851 0.2988506
4q- 0.4022989 0.2988506 0.3908046 0.5057471 0.3448276 0.2413793 0.2873563
8p- 0.4252874 0.2988506 0.3678161 0.3448276 0.4712644 0.1954023 0.3103448
1q+ 0.2988506 0.2643678 0.2298851 0.2413793 0.1954023 0.4367816 0.1954023
Xp- 0.3218391 0.2758621 0.2988506 0.2873563 0.3103448 0.1954023 0.4252874

> oe.diff <- obs2way - est2way
> oe.diff[lower.tri(oe.diff)] <- NA
> require(lattice)
> levelplot(oe.diff, xlab = "", ylab = "", scales = list(x = list(alternating = 2),
+     tck = 0), main = "Observed - Expected probabilities of co-occurrence of events")
```

Another way to evaluate goodness-of-fit is through bootstrap resampling of the data. Two approaches are implemented: a paramteric bootstrap that assumes that the model is correct and a non-parametric bootstrap. The plot is shown in Figure 4.

```
> set.seed(43636)
> ov.boot <- bootstrap.oncotree(ov.tree, type = "nonparam", R = 1000)
> ov.boot
Out of the 1000 replicates there are 309 unique trees with frequencies from 83 down to 1
The bootstrap process found the original tree 83 times
> opar <- par(mfrow = c(3, 2))
> plot(ov.boot, minfreq = 45)
> par(opar)
```

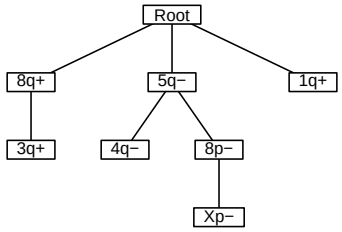
The non-parametric bootstrap gives an estimate of the reconstruction confidence: the original tree was obtained 83 times out of 1000 resamples, so the estimated confidence is 8.3%.

We can look at the frequency of edge occurrences in the bootstrapped trees:

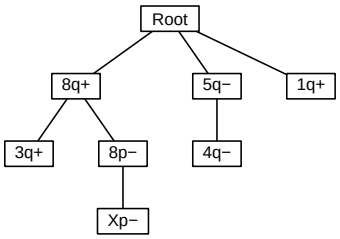
```
> ov.boot$parent.freq
```

Parent \ Child	Root	8q+	3q+	5q-	4q-	8p-	1q+	Xp-
	1000	0	0	0	0	0	0	0
Root	0	997	69	519	225	4	807	67
8q+	0	0	929	89	162	409	24	7
3q+	0	2	0	44	0	0	94	42
5q-	0	1	2	0	522	399	9	169
4q-	0	0	0	275	0	143	50	116
8p-	0	0	0	70	84	0	4	599
1q+	0	0	0	0	4	0	0	0
Xp-	0	0	0	3	3	45	12	0

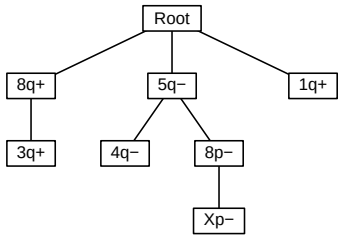
It is clear that some edges are really stable: Root $\rightarrow$ 8q+, 8q+ $\rightarrow$ 3q+, root $\rightarrow$ 1q+, all with confidence $> 80\%$, while other edges are less stable (for example, 8p- is the child of 8q+ about as often as of 5q-).



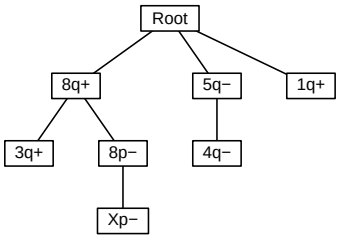
Original Tree



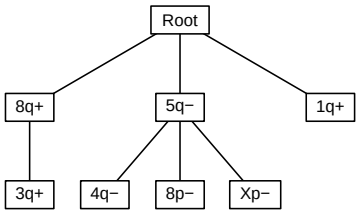
Tree based on most frequent parent



Observed Frequency = 83



Observed Frequency = 63



Observed Frequency = 49

FIGURE 4. The most frequently occurring bootstrap trees.