# A naive TCR:pMHC interaction model

```
library(data.table)
```

```
## Warning: package 'data.table' was built under R version 3.2.5
```

```
library(ggplot2)
library(reshape2)
```

```
## Warning: package 'reshape2' was built under R version 3.2.5
```

```
##
## Attaching package: 'reshape2'
```

```
## The following objects are masked from 'package:data.table':
##
##     dcast, melt
```

```
library(dplyr)
```

```
## Warning: package 'dplyr' was built under R version 3.2.5
```

```
## ------------------------------------------------------------------------------
```

```
## data.table + dplyr code now lives in dtplyr.
## Please library(dtplyr)!
```

```
## ------------------------------------------------------------------------------
```

```
##
## Attaching package: 'dplyr'
```

```
## The following objects are masked from 'package:data.table':
##
##     between, first, last
```

```
## The following objects are masked from 'package:stats':
##
##     filter, lag
```

```
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
```

```
library(ggbeeswarm)
library(RColorBrewer)
library(pROC)
```

```
## Type 'citation("pROC")' for a citation.
```

```
##
## Attaching package: 'pROC'
```

```
## The following objects are masked from 'package:stats':
##
##     cov, smooth, var
```

```
library(stringr)
```

```
## Warning: package 'stringr' was built under R version 3.2.5
```

```
library(gplots)
```

```
## Warning: package 'gplots' was built under R version 3.2.4
```

```
##
## Attaching package: 'gplots'
```

```
## The following object is masked from 'package:stats':
##
##     lowess
```

```
df = fread("../result/structure.txt", header=T, sep="\t")[tcr_region %in% c("CDR1", "CDR2", "CDR3")]

df$tcr_chain = as.factor(substr(as.character(df$tcr_v_allele), 1, 3))
df$contact = df$distance <= 4.5
df$aa_pair = with(df,
  as.factor(ifelse(as.character(aa_tcr) < as.character(aa_antigen), paste(aa_tcr, aa_antigen, sep = "_"

summary(df)
```

```
##     pdb_id             species            mhc_type
##  Length:62077       Length:62077       Length:62077
##  Class :character   Class :character   Class :character
##  Mode  :character   Mode  :character   Mode  :character
##
##
##
##
##  mhc_a_allele       mhc_b_allele       antigen_seq
##  Length:62077       Length:62077       Length:62077
##  Class :character   Class :character   Class :character
##  Mode  :character   Mode  :character   Mode  :character
##
##
##
##
##  tcr_v_allele        tcr_region        tcr_region_seq
##  Length:62077       Length:62077       Length:62077
##  Class :character   Class :character   Class :character
##  Mode  :character   Mode  :character   Mode  :character
##
##
##
##
##     aa_tcr            aa_antigen           len_tcr       len_antigen
##  Length:62077       Length:62077       Min.   : 3.00   Min.   : 8.00
##  Class :character   Class :character   1st Qu.: 6.00   1st Qu.: 9.00
##  Mode  :character   Mode  :character   Median :12.00   Median :10.00
##                                        Mean   :10.33   Mean   :10.94
##                                        3rd Qu.:14.00   3rd Qu.:13.00
##                                        Max.   :18.00   Max.   :20.00
##
##     pos_tcr         pos_antigen        distance        distance_CA
##  Min.   : 0.000   Min.   : 0.000   Min.   :  2.231   Min.   :  3.696
##  1st Qu.: 1.000   1st Qu.: 2.000   1st Qu.: 10.622   1st Qu.: 13.907
```

```
##  Median : 4.000   Median : 5.000   Median : 15.135   Median : 18.415
##  Mean   : 4.663   Mean   : 4.971   Mean   : 17.691   Mean   : 20.927
##  3rd Qu.: 7.000   3rd Qu.: 7.000   3rd Qu.: 20.351   3rd Qu.: 23.483
##  Max.   :17.000   Max.   :19.000   Max.   :126.207   Max.   :129.029
##
##   distance_CB          energy         tcr_chain    contact
##  Min.   :  2.164   Min.   :-76.1000   TRA:30674   Mode :logical
##  1st Qu.: 13.952   1st Qu.:  0.0000   TRB:31403   FALSE:59961
##  Median : 18.757   Median :  0.0000               TRUE :2116
##  Mean   : 21.205   Mean   : -0.2774               NA's :0
##  3rd Qu.: 24.256   3rd Qu.:  0.0000
##  Max.   :132.255   Max.   :774.0000
##                    NA's   :160
##     aa_pair
##  L_S    : 1232
##  G_S    : 1200
##  G_L    : 1146
##  A_G    : 1047
##  A_S    :  902
##  G_Y    :  869
##  (Other):55681
```

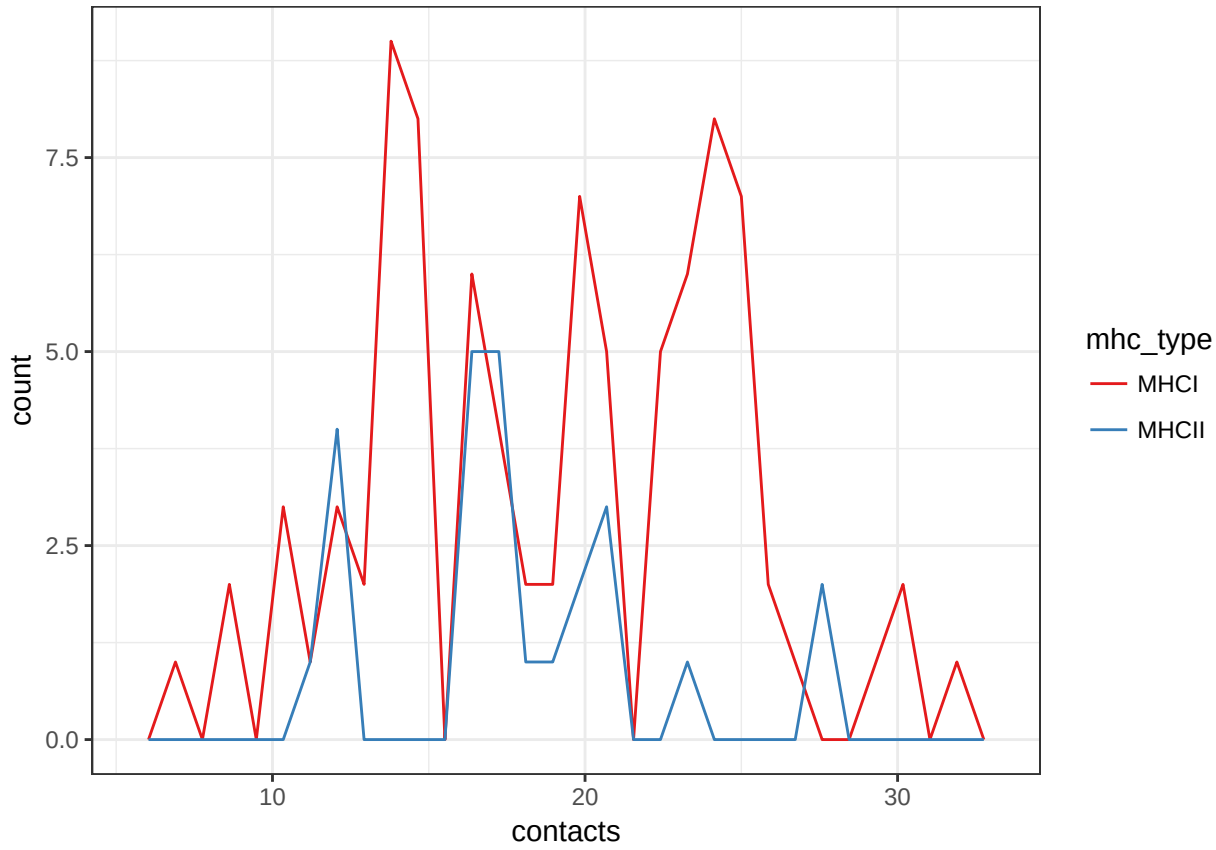
# Some EDA

## Contact distribution

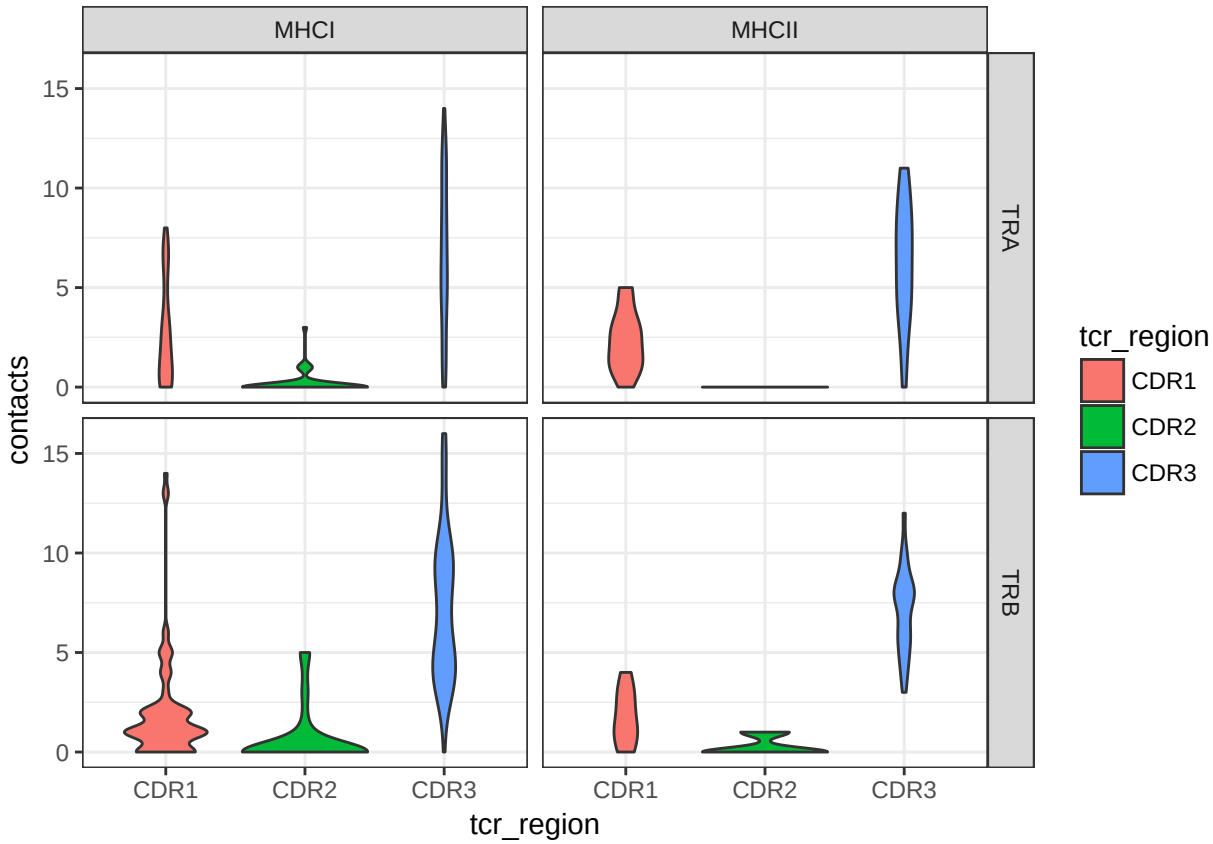
Contacts by MHC, chain and CDR

```
df.contact.sum = df[,.(contacts = sum(contact)),by=.(pdb_id, tcr_chain, tcr_region, mhc_type)]

df.contact.sum.pdb = df.contact.sum[,.(contacts = sum(contacts)), by=.(pdb_id, mhc_type)][contacts>5]

ggplot(df.contact.sum.pdb, aes(contacts, color = mhc_type)) +
  geom_freqpoly() +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```




```
df.contact.sum = df.contact.sum[pdb_id %in% df.contact.sum.pdb$pdb_id]

ggplot(df.contact.sum, aes(x=tcr_region, group = tcr_region, y = contacts, fill = tcr_region)) +
  geom_violin() +
  facet_grid(tcr_chain~mhc_type) +
  theme_bw()
```




```
a = aov(contacts~tcr_chain*tcr_region*mhc_type, df.contact.sum)
anova(a)
```

```
## Analysis of Variance Table
##
## Response: contacts
##                                Df Sum Sq Mean Sq  F value    Pr(>F)
## tcr_chain                       1    2.3    2.35   0.3763  0.539802
## tcr_region                      2 4994.2 2497.09 400.0655 < 2.2e-16 ***
## mhc_type                        1    5.3    5.34   0.8561  0.355160
## tcr_chain:tcr_region            2   61.7   30.85   4.9432  0.007396 **
## tcr_chain:mhc_type              1    0.3    0.26   0.0419  0.837848
## tcr_region:mhc_type             2    0.2    0.10   0.0160  0.984121
## tcr_chain:tcr_region:mhc_type   2    0.8    0.40   0.0642  0.937830
## Residuals                     665 4150.7    6.24
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(a, "tcr_region")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = contacts ~ tcr_chain * tcr_region * mhc_type, data = df.contact.sum)
##
## $tcr_region
##                 diff       lwr       upr p adj
## CDR2-CDR1 -1.901461 -2.454139 -1.348784     0
```

```
## CDR3-CDR1  4.570796  4.018732  5.122861     0
## CDR3-CDR2  6.472258  5.919580  7.024935     0
```

```
TukeyHSD(a, "tcr_chain:tcr_region")
```

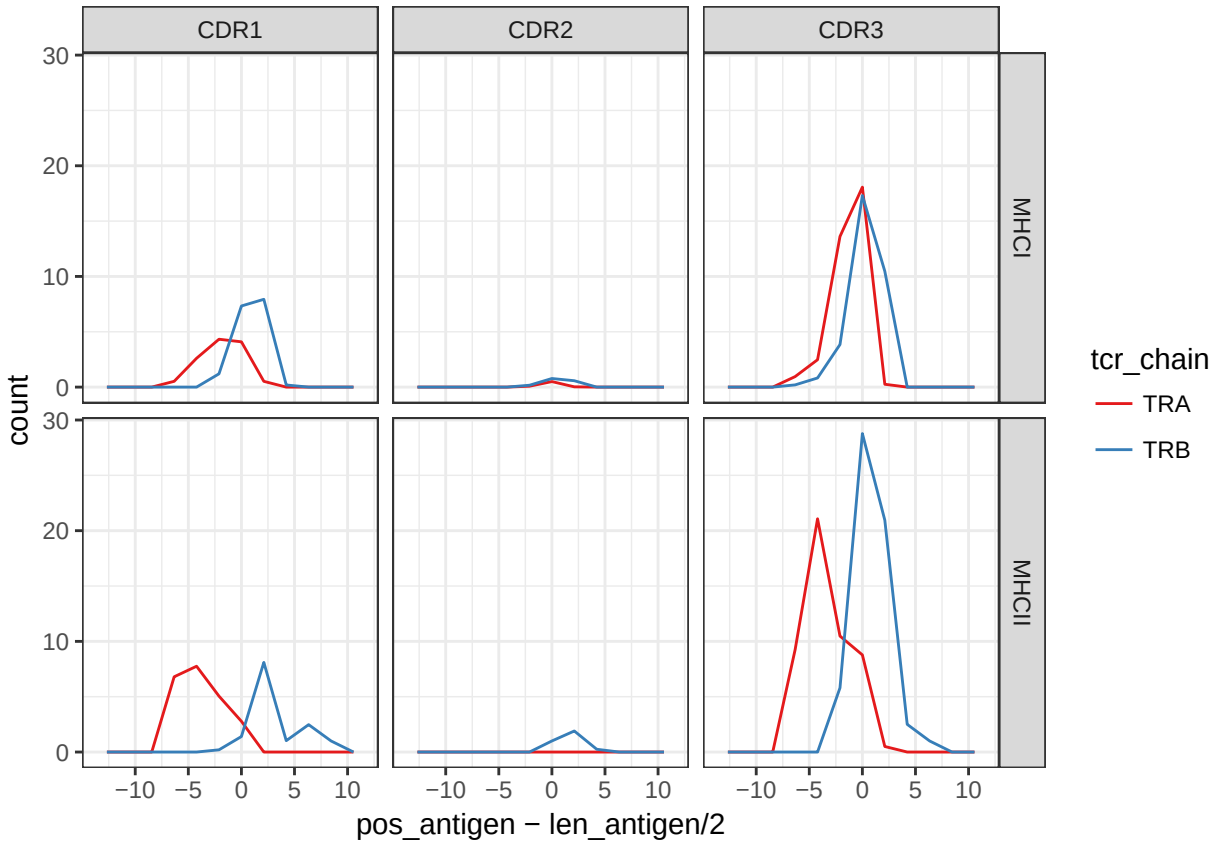
```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = contacts ~ tcr_chain * tcr_region * mhc_type, data = df.contact.sum)
##
## $`tcr_chain:tcr_region`
##                           diff        lwr        upr     p adj
## TRB:CDR1-TRA:CDR1 -0.7078242 -1.6577655  0.2421171 0.2732468
## TRA:CDR2-TRA:CDR1 -2.4499303 -3.4019897 -1.4978710 0.0000000
## TRB:CDR2-TRA:CDR1 -2.0620171 -3.0119584 -1.1120758 0.0000000
## TRA:CDR3-TRA:CDR1  3.8672566  2.9173153  4.8171979 0.0000000
## TRB:CDR3-TRA:CDR1  4.5665121  3.6165708  5.5164534 0.0000000
## TRA:CDR2-TRB:CDR1 -1.7421061 -2.6941655 -0.7900468 0.0000034
## TRB:CDR2-TRB:CDR1 -1.3541930 -2.3041343 -0.4042517 0.0007328
## TRA:CDR3-TRB:CDR1  4.5750808  3.6251395  5.5250221 0.0000000
## TRB:CDR3-TRB:CDR1  5.2743363  4.3243950  6.2242776 0.0000000
## TRB:CDR2-TRA:CDR2  0.3879132 -0.5641462  1.3399725 0.8535634
## TRA:CDR3-TRA:CDR2  6.3171869  5.3651276  7.2692463 0.0000000
## TRB:CDR3-TRA:CDR2  7.0164424  6.0643831  7.9685018 0.0000000
## TRA:CDR3-TRB:CDR2  5.9292738  4.9793325  6.8792151 0.0000000
## TRB:CDR3-TRB:CDR2  6.6285292  5.6785879  7.5784706 0.0000000
## TRB:CDR3-TRA:CDR3  0.6992555 -0.2506858  1.6491968 0.2864734
```

Filter TCRs with no contacts

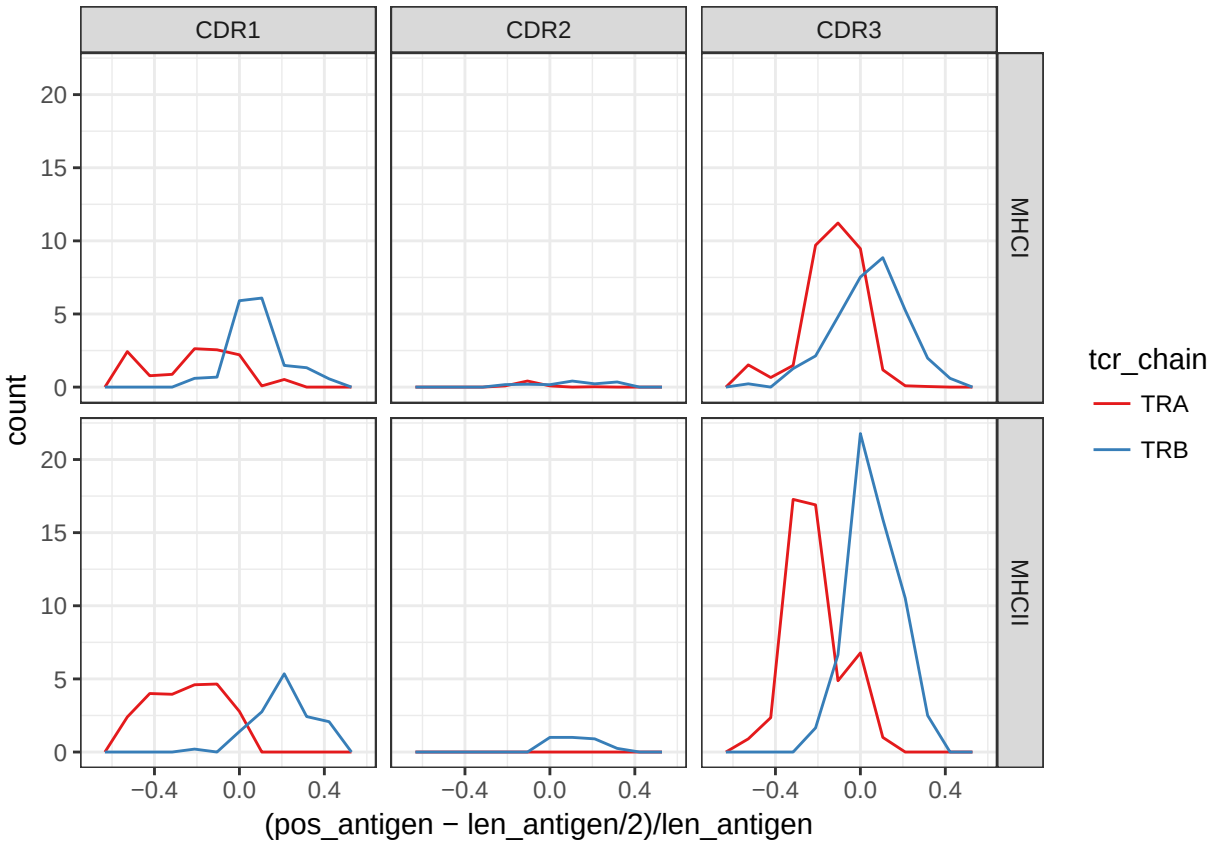
```
df = df[pdb_id %in% df.contact.sum.pdb$pdb_id ]
```

Contact distribution on antigen

```
df.contact.dist.ag = df[,
                        .(contacts = sum(contact), total.pdb = length(unique(pdb_id))),
                        by=.(tcr_chain, tcr_region, mhc_type, pos_antigen, len_antigen)]

ggplot(df.contact.dist.ag, aes(x = pos_antigen - len_antigen / 2, weight = contacts / total.pdb, color =
  geom_freqpoly(bins=10) +
  facet_grid(mhc_type~tcr_region) +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```

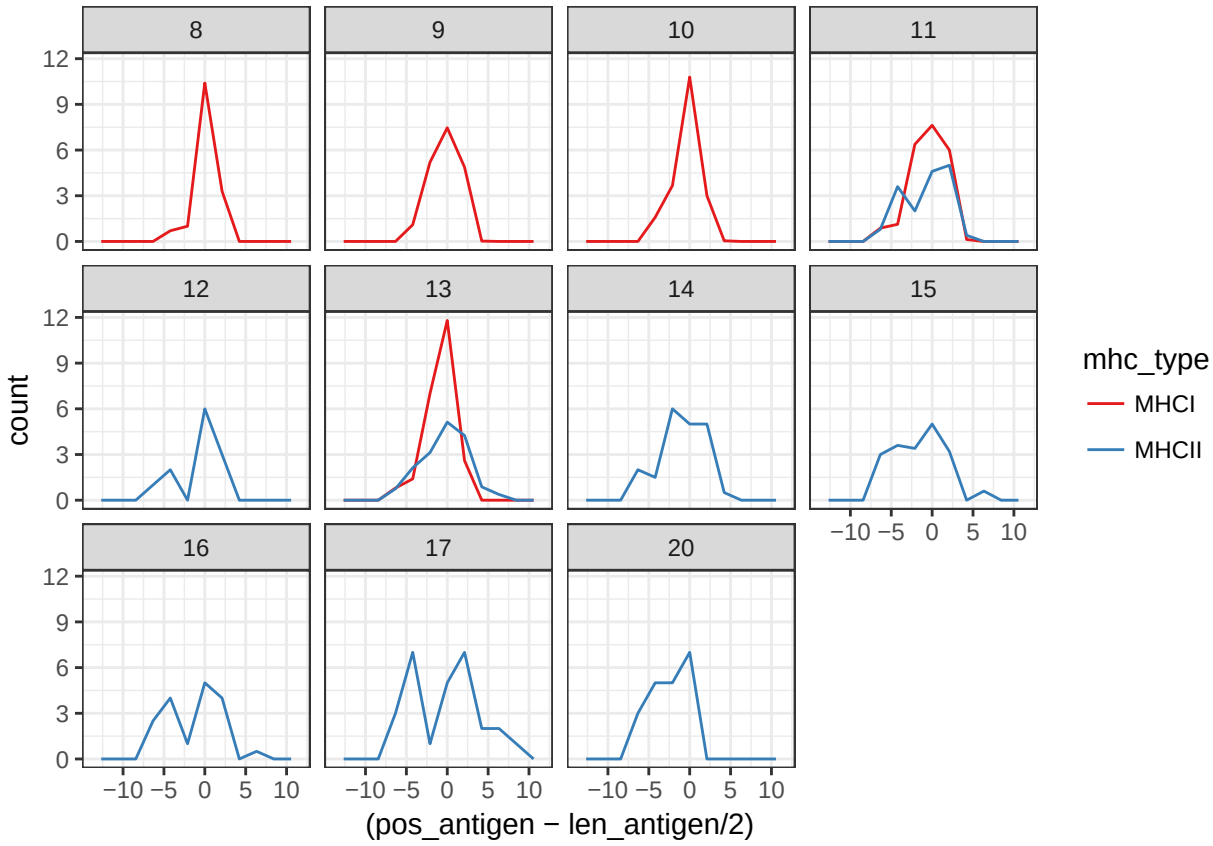



```
ggplot(df.contact.dist.ag, aes(x = (pos_antigen - len_antigen / 2) / len_antigen, weight = contacts / t
  geom_freqpoly(bins=10) +
  facet_grid(mhc_type~tcr_region) +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```



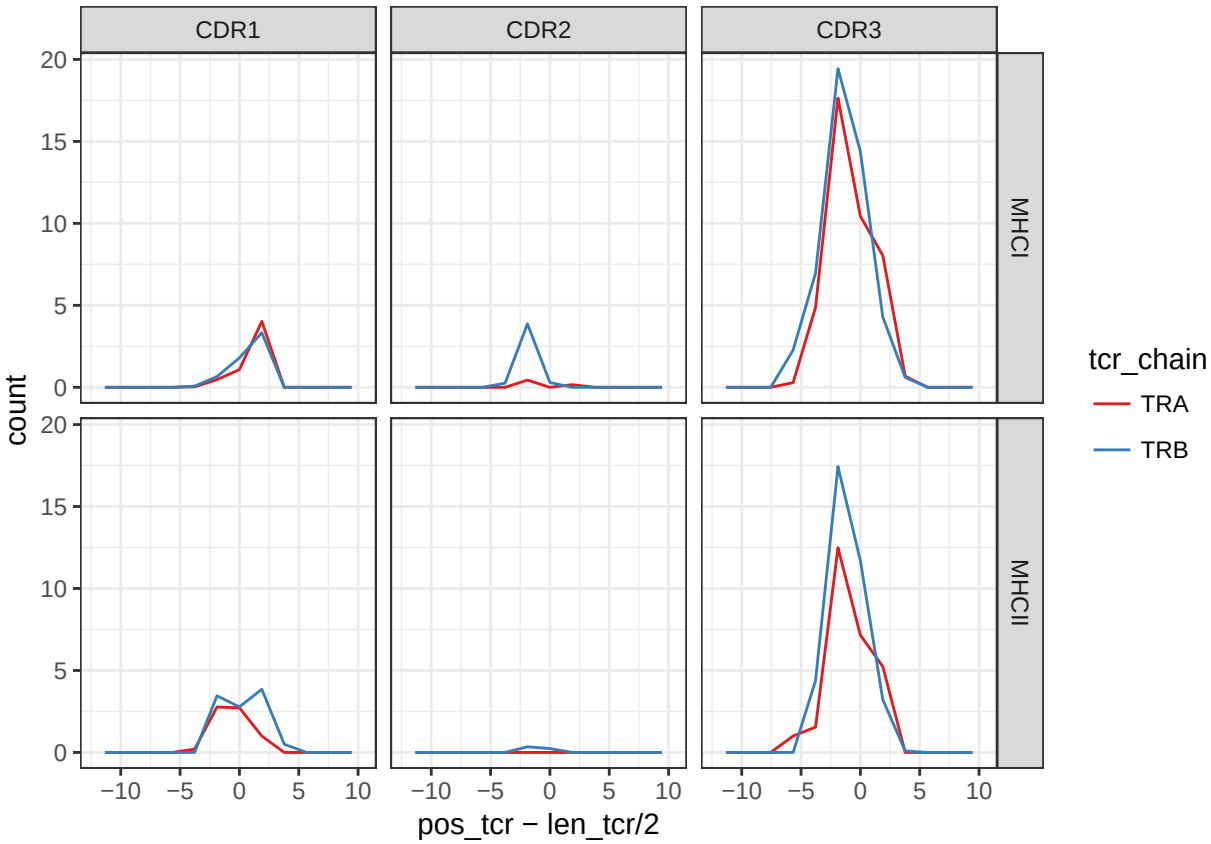

vs antigen length

```
df.contact.dist.ag.len = df[,
                        .(contacts = sum(contact), total.pdb = length(unique(pdb_id))),
                        by=.(pos_antigen, len_antigen, mhc_type)]

ggplot(df.contact.dist.ag.len, aes(x = (pos_antigen - len_antigen / 2), group = paste(len_antigen,mhc_ty
                                   weight = contacts / total.pdb, color = mhc_type)) +
  geom_freqpoly(bins=10) +
  facet_wrap(~len_antigen) +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```

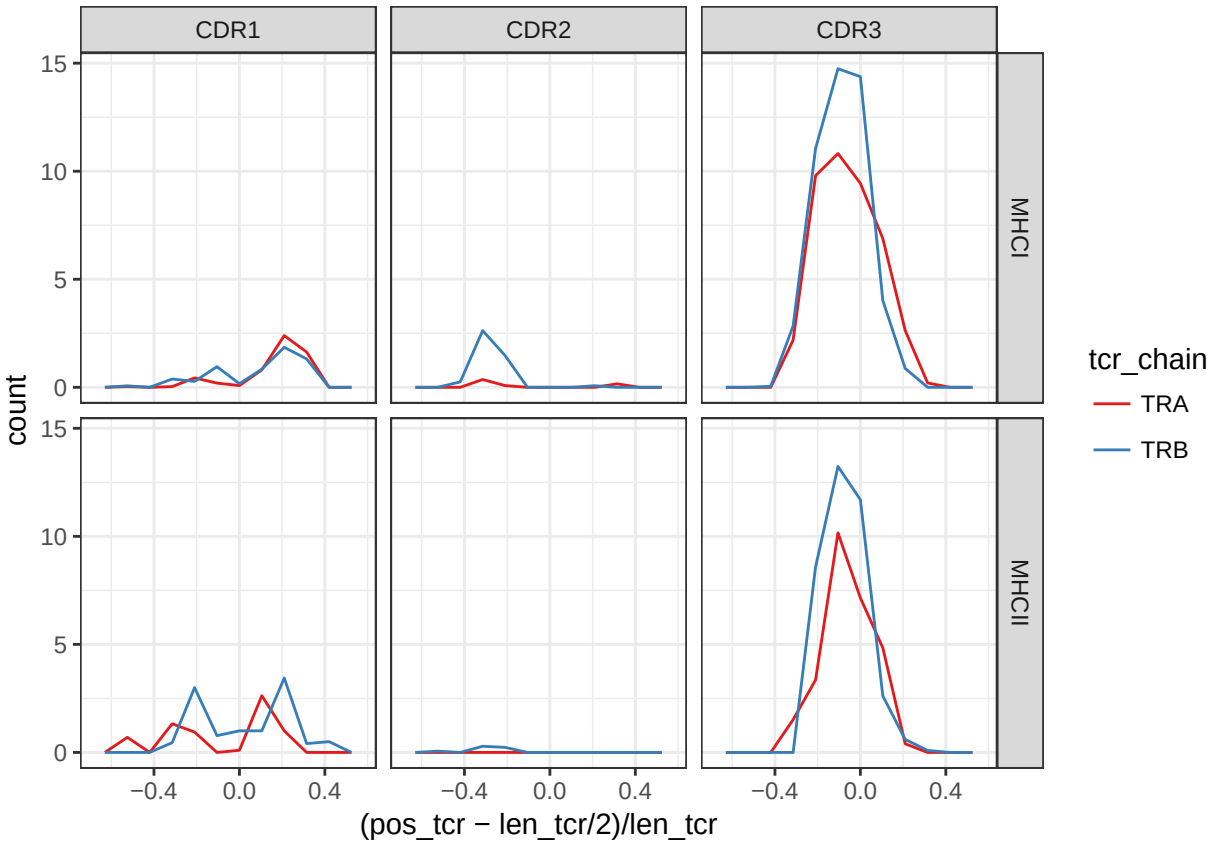



Contact distribution on TCR

```
df.contact.dist.tcr = df[,
                         .(contacts = sum(contact), total.pdb = length(unique(pdb_id))),
                         by=.(tcr_chain, tcr_region, mhc_type, pos_tcr, len_tcr)]

ggplot(df.contact.dist.tcr, aes(x = pos_tcr - len_tcr / 2, weight = contacts / total.pdb, color = tcr_cl
  geom_freqpoly(bins=10) +
  facet_grid(mhc_type~tcr_region) +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```

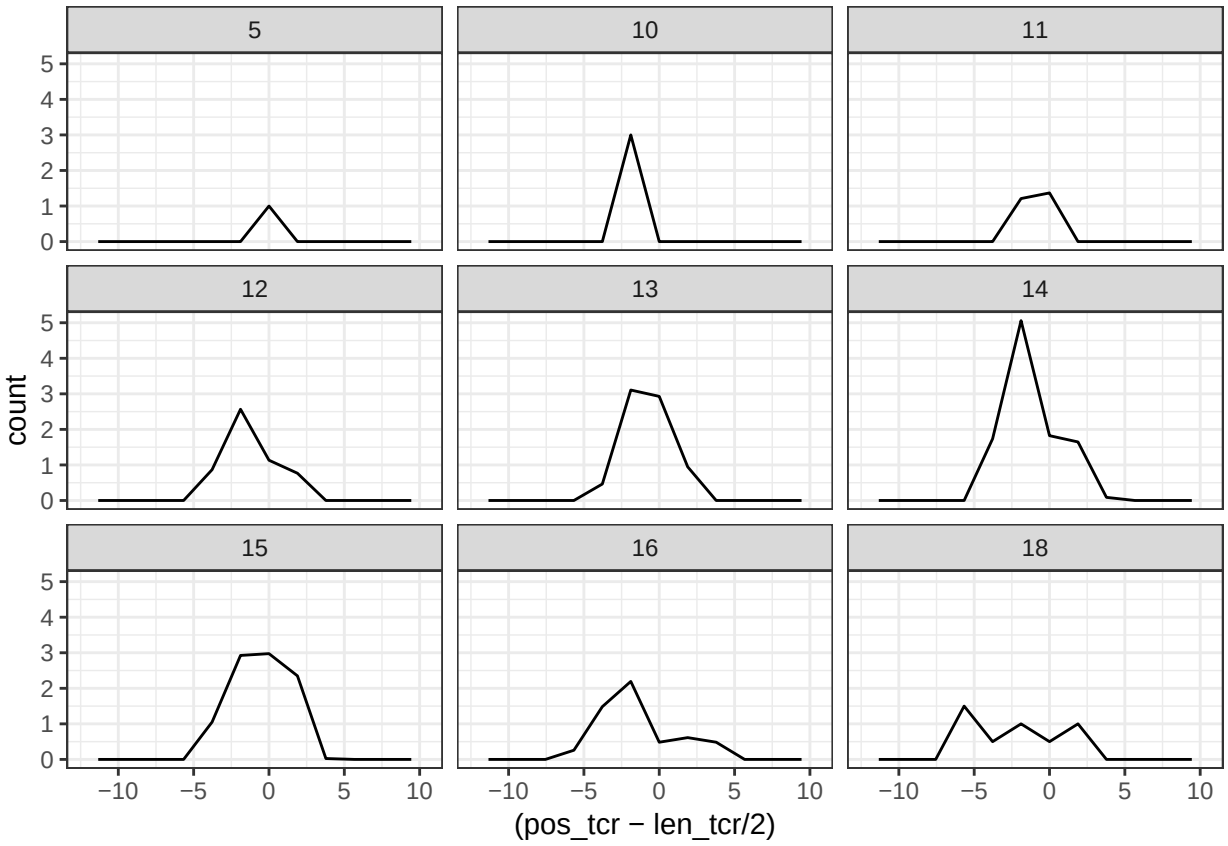



```
ggplot(df.contact.dist.tcr, aes(x = (pos_tcr - len_tcr / 2) / len_tcr, weight = contacts / total.pdb, c
  geom_freqpoly(bins=10) +
  facet_grid(mhc_type~tcr_region) +
  scale_color_brewer(palette = "Set1") +
  theme_bw()
```




vs CDR3 len

```
df.contact.dist.tcr.len = df[tcr_region == "CDR3",
                         .(contacts = sum(contact), total.pdb = length(unique(pdb_id))),
                         by=.(pos_tcr, len_tcr)]

ggplot(df.contact.dist.tcr.len, aes(x = (pos_tcr - len_tcr / 2), group = len_tcr, weight = contacts / to
  geom_freqpoly(bins=10) +
  facet_wrap(~len_tcr) +
  theme_bw()
```




### Amino acid pairs in contacts

## Modelling

Center coordinates

```
df.pred = df
df.pred$pos_tcr_c = with(df.pred, pos_tcr - round(len_tcr/2))
df.pred$pos_antigen_c = with(df.pred, pos_antigen - round(len_antigen/2))
```

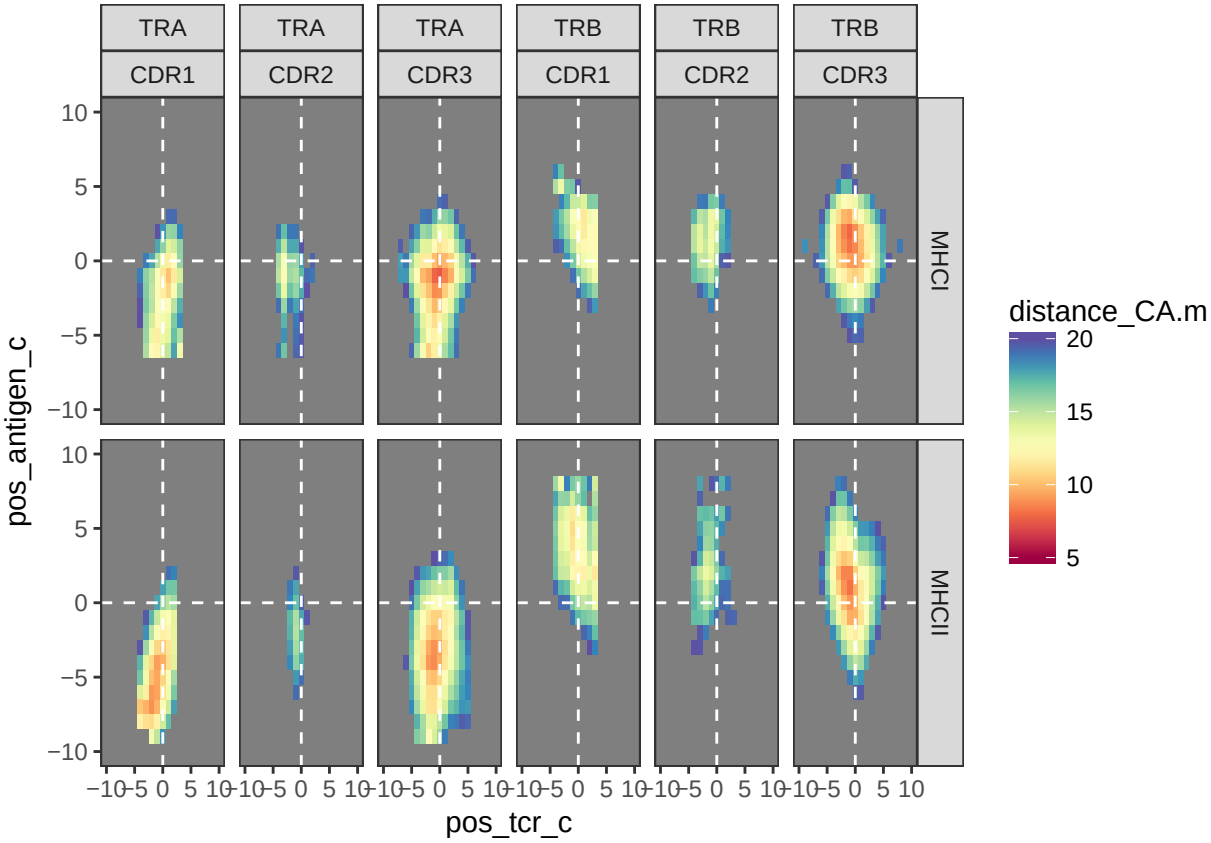
### Calpha distance model

#### Simple mean model

Mean Calpha distances for centered coordinates

```
df.ca.mean = df.pred[,.(distance_CA.m = mean(distance_CA)),
                        by=.(tcr_chain, tcr_region, mhc_type, pos_tcr_c, pos_antigen_c)]

ggplot(df.ca.mean, aes(x=pos_tcr_c, y=pos_antigen_c, fill=distance_CA.m)) +
  geom_tile() +
  geom_vline(xintercept = 0, linetype = "dashed", color = "white") +
  geom_hline(yintercept = 0, linetype = "dashed", color = "white") +
  facet_grid(mhc_type~tcr_chain+tcr_region) +
  scale_x_continuous(limits=c(-10,10)) +
```

```
  scale_y_continuous(limits=c(-10,10)) +
  scale_fill_gradientn(colors=colorRampPalette(brewer.pal(11, 'Spectral'))(32), limits=c(5, 20)) +
  theme_bw() +
  theme(panel.background = element_rect(fill = 'grey50'),
        panel.grid.major = element_blank(), panel.grid.minor = element_blank())
```




### Checking the model

Add mean distance values

```
df.pred = df.pred[as.data.table(df.ca.mean), on = .(tcr_chain, tcr_region, mhc_type, pos_tcr_c, pos_anti
```

Compare to true Calpha distance values

```
ggplot(df.pred, aes(x=round(distance_CA.m), group = round(distance_CA.m), y = distance_CA)) +
  geom_boxplot() +
  geom_abline(slope = 1, intercept = 0, color = "red", linetype = "dashed") +
  scale_x_continuous(limits=c(5,20)) +
  scale_y_continuous(limits=c(5,20)) +
  facet_grid(mhc_type~tcr_chain+tcr_region) +
  theme_bw()
```

```
## Warning: Removed 22609 rows containing non-finite values (stat_boxplot).
```

```
## Warning: Removed 1 rows containing missing values (geom_segment).
```

```
## Warning: Removed 1 rows containing missing values (geom_segment).
```

```
## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

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## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).

## Warning: Removed 1 rows containing missing values (geom_segment).
```
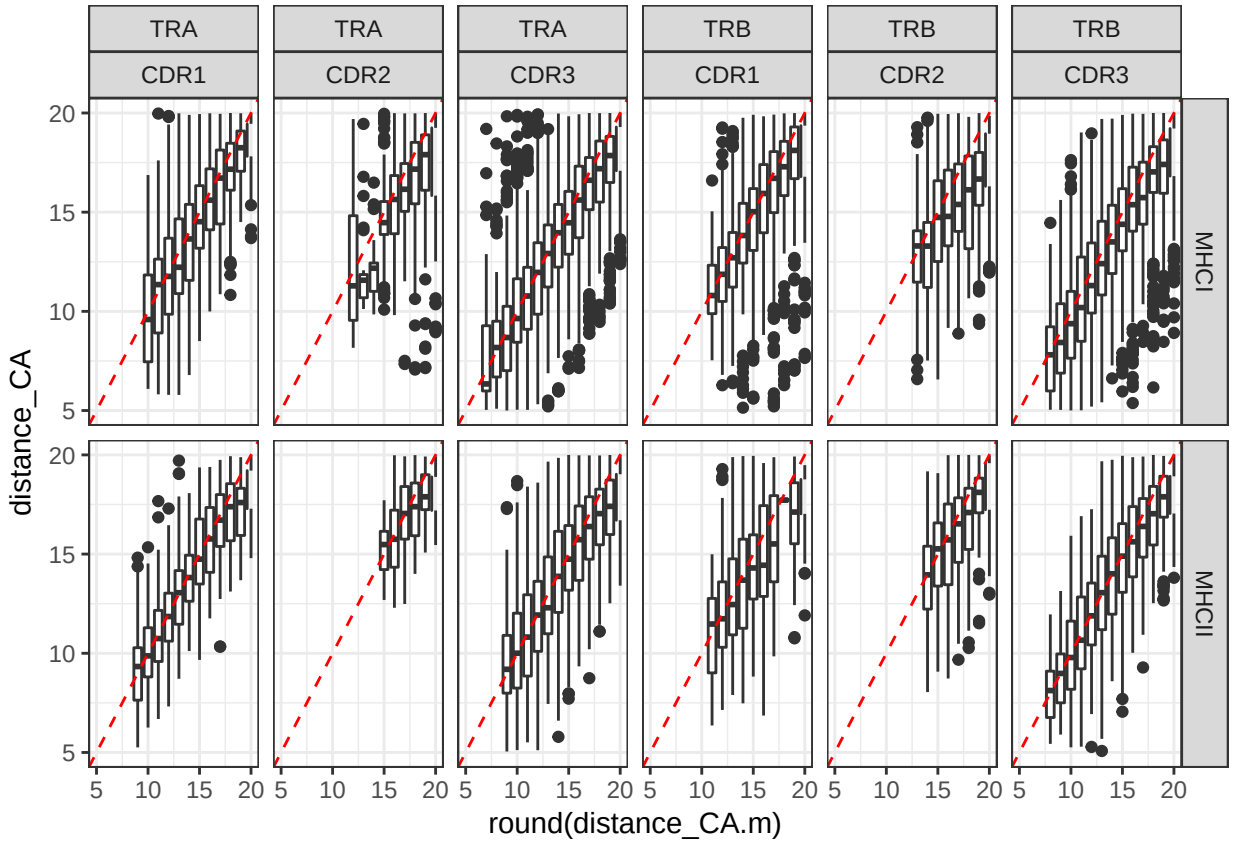




```
summary(lm(distance_CA ~ distance_CA.m, df.pred))
```

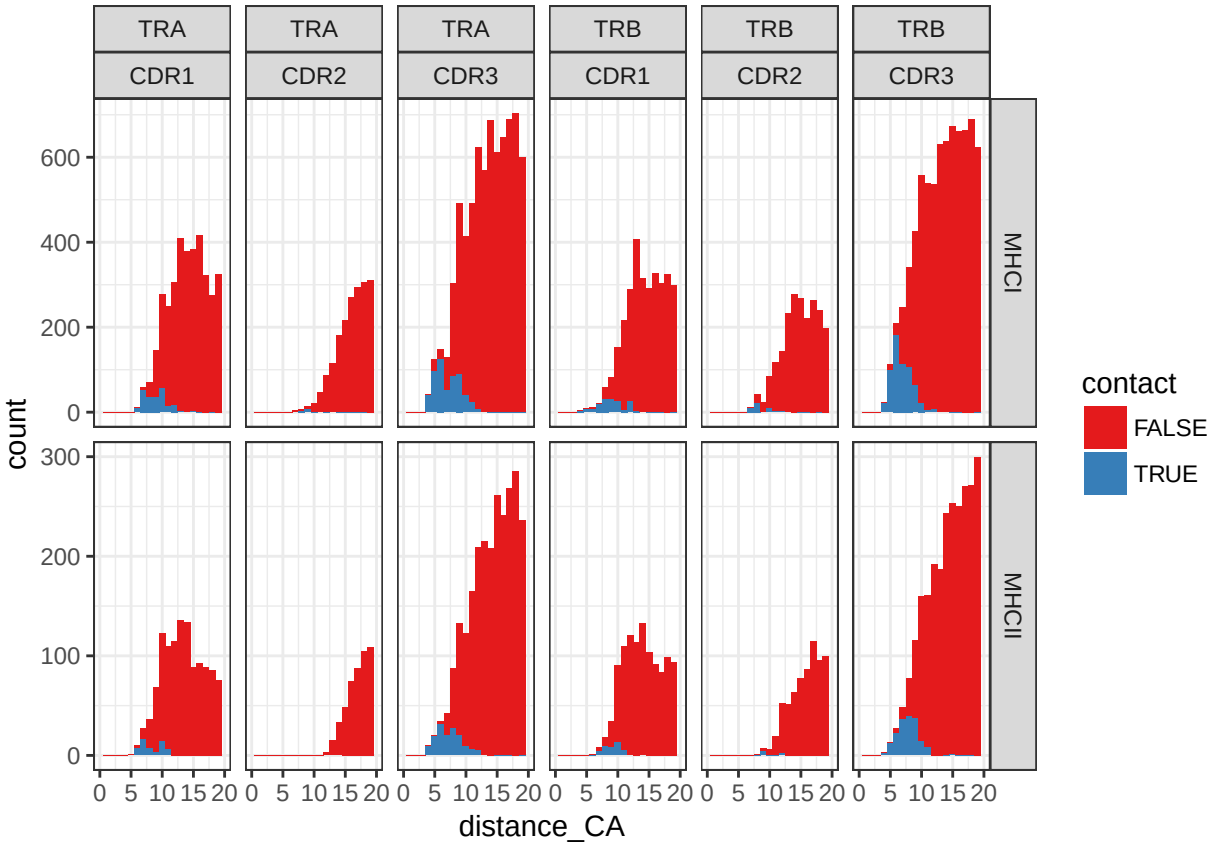
```
##
## Call:
## lm(formula = distance_CA ~ distance_CA.m, data = df.pred)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
```

```
## -13.994  -1.898  -0.134   1.658  40.683
##
## Coefficients:
##                  Estimate Std. Error t value Pr(>|t|)
## (Intercept)   -2.031e-12  4.828e-02     0.0        1
## distance_CA.m  1.000e+00  2.557e-03   391.1   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 3.262 on 55887 degrees of freedom
## Multiple R-squared:  0.7324, Adjusted R-squared:  0.7324
## F-statistic: 1.529e+05 on 1 and 55887 DF,  p-value: < 2.2e-16
```

Plot distance distribution for contacts and non-contacts, for real and estimated distances:

```
ggplot(df.pred, aes(x = distance_CA, fill = contact)) +
  geom_histogram(binwidth = 1) +
  facet_grid(mhc_type~tcr_chain+tcr_region, scales="free_y") +
  scale_x_continuous(limits=c(0,20))+
  scale_fill_brewer(palette = "Set1") +
  theme_bw()
```

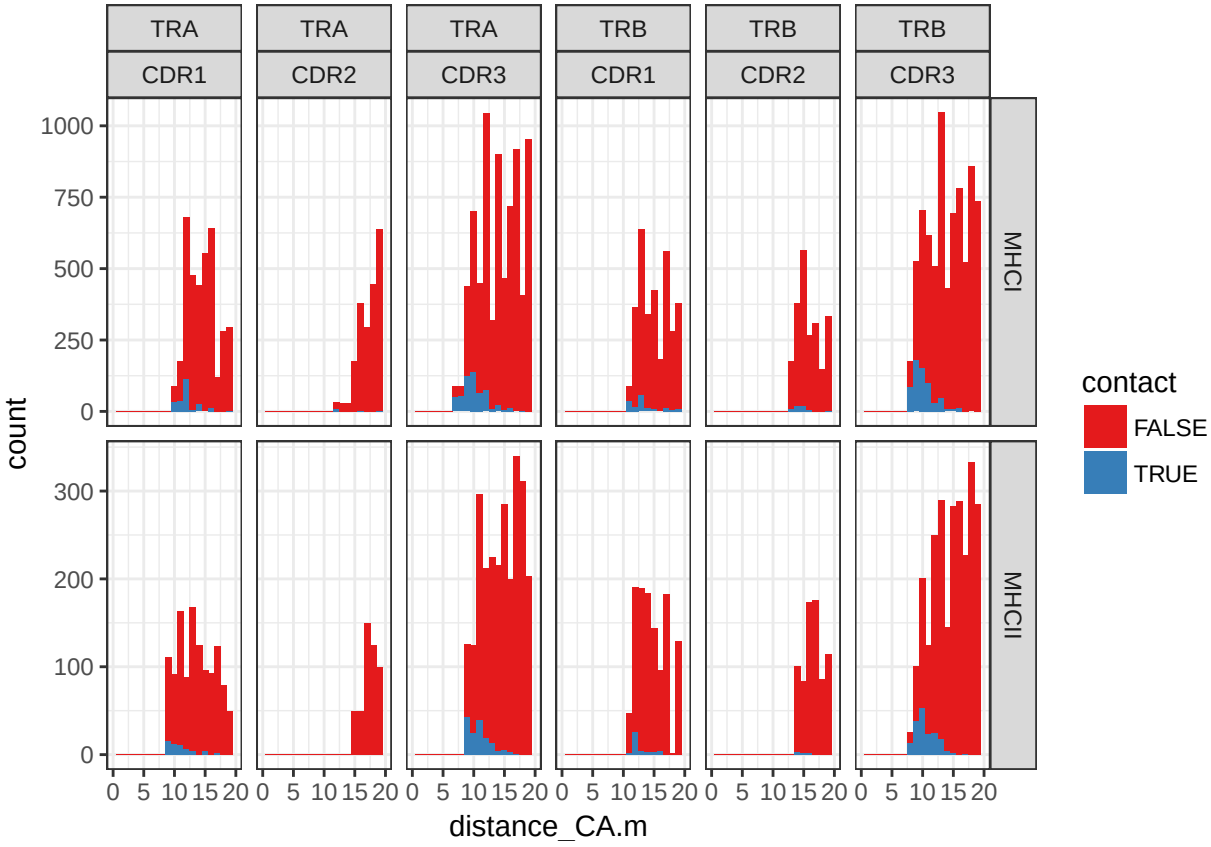
```
## Warning: Removed 20140 rows containing non-finite values (stat_bin).
```




```
ggplot(df.pred, aes(x = distance_CA.m, fill = contact)) +
  geom_histogram(binwidth = 1) +
  facet_grid(mhc_type~tcr_chain+tcr_region, scales="free_y") +
  scale_x_continuous(limits=c(0,20))+
  scale_fill_brewer(palette = "Set1") +
```

```
  theme_bw()
```

```
## Warning: Removed 19288 rows containing non-finite values (stat_bin).
```




## Amino acid preferences and Calpha distance

Using a generalized linear model to fit contacts, operate with amino acid pairs, ignoring which one is in TCR and which one comes from antigen.

```
res = glm(contact ~ distance_CA + aa_pair + 0, family = binomial(), data = df.pred)
```

```
## Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

```
summary(res)
```

```
##
## Call:
## glm(formula = contact ~ distance_CA + aa_pair + 0, family = binomial(),
##     data = df.pred)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -3.2988  -0.0306  -0.0024  -0.0001   3.5854
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## distance_CA   -1.1641     0.0239 -48.697  < 2e-16 ***
```

```
## aa_pairA_A     7.4506     0.6490  11.480  < 2e-16 ***
## aa_pairA_C    -5.0823   780.4740  -0.007 0.994804
## aa_pairA_D     6.5046     1.0711   6.073 1.25e-09 ***
## aa_pairA_E     8.0084     0.6800  11.778  < 2e-16 ***
## aa_pairA_F     8.0345     0.5030  15.973  < 2e-16 ***
## aa_pairA_G     6.2345     0.4301  14.495  < 2e-16 ***
## aa_pairA_H    10.6128     0.7373  14.394  < 2e-16 ***
## aa_pairA_I     7.6925     0.7669  10.031  < 2e-16 ***
## aa_pairA_K     9.5920     0.7834  12.244  < 2e-16 ***
## aa_pairA_L     8.8465     0.3937  22.473  < 2e-16 ***
## aa_pairA_M    -5.9568  1130.5277  -0.005 0.995796
## aa_pairA_N     7.3236     0.5978  12.251  < 2e-16 ***
## aa_pairA_P     7.2898     0.6451  11.300  < 2e-16 ***
## aa_pairA_Q     9.8584     0.3929  25.089  < 2e-16 ***
## aa_pairA_R     8.9961     0.4562  19.718  < 2e-16 ***
## aa_pairA_S     6.5389     0.4515  14.482  < 2e-16 ***
## aa_pairA_T     7.2314     0.4943  14.629  < 2e-16 ***
## aa_pairA_V     8.3448     0.5171  16.138  < 2e-16 ***
## aa_pairA_W     8.1996     0.7161  11.451  < 2e-16 ***
## aa_pairA_Y     9.6342     0.4171  23.100  < 2e-16 ***
## aa_pairC_C     5.5391  2779.5674   0.002 0.998410
## aa_pairC_D    -6.8313  1132.6530  -0.006 0.995188
## aa_pairC_E    -2.0493   926.5239  -0.002 0.998235
## aa_pairC_F    -0.7815   797.9707  -0.001 0.999219
## aa_pairC_G     9.2124     1.2538   7.348 2.02e-13 ***
## aa_pairC_H    -4.3174  2039.2983  -0.002 0.998311
## aa_pairC_I    -3.0568   862.9445  -0.004 0.997174
## aa_pairC_K     4.2483  1806.6199   0.002 0.998124
## aa_pairC_L    -3.0819   592.3562  -0.005 0.995849
## aa_pairC_M    -2.1508  1908.9111  -0.001 0.999101
## aa_pairC_N    -6.7657  1332.2014  -0.005 0.995948
## aa_pairC_P    -2.0699   697.2333  -0.003 0.997631
## aa_pairC_Q    -4.5411   848.1169  -0.005 0.995728
## aa_pairC_R    10.4997     2.7515   3.816 0.000136 ***
## aa_pairC_S     8.5894     1.5813   5.432 5.58e-08 ***
## aa_pairC_T    -5.3605   850.3332  -0.006 0.994970
## aa_pairC_V    -2.0320   802.1970  -0.003 0.997979
## aa_pairC_W    14.6097    15.2080   0.961 0.336724
## aa_pairC_Y    11.5405     1.1727   9.841  < 2e-16 ***
## aa_pairD_D    -8.4260  1885.3630  -0.004 0.996434
## aa_pairD_E     8.8254     0.8749  10.088  < 2e-16 ***
## aa_pairD_F     7.6371     0.4809  15.881  < 2e-16 ***
## aa_pairD_G     7.7062     0.4204  18.332  < 2e-16 ***
## aa_pairD_H    10.5940     1.2362   8.570  < 2e-16 ***
## aa_pairD_I     8.3684     1.0899   7.678 1.61e-14 ***
## aa_pairD_K    11.3968     0.6166  18.485  < 2e-16 ***
## aa_pairD_L     8.0172     0.5329  15.044  < 2e-16 ***
## aa_pairD_M    10.5306     0.7343  14.341  < 2e-16 ***
## aa_pairD_N    10.5382     0.5275  19.977  < 2e-16 ***
## aa_pairD_P     8.5002     0.5117  16.611  < 2e-16 ***
## aa_pairD_Q     9.8007     0.5269  18.602  < 2e-16 ***
## aa_pairD_R    10.2193     0.4511  22.654  < 2e-16 ***
## aa_pairD_S     8.5882     0.3648  23.542  < 2e-16 ***
## aa_pairD_T     9.4943     0.5013  18.940  < 2e-16 ***
```

```
## aa_pairD_V     7.6737     0.8521   9.005  < 2e-16 ***
## aa_pairD_W    10.0487     0.5646  17.798  < 2e-16 ***
## aa_pairD_Y    12.5331     0.4058  30.886  < 2e-16 ***
## aa_pairE_E    -4.1498  1179.5758  -0.004 0.997193
## aa_pairE_F     9.3895     0.8108  11.580  < 2e-16 ***
## aa_pairE_G     8.5642     0.3830  22.361  < 2e-16 ***
## aa_pairE_H    -5.4856  1406.6838  -0.004 0.996889
## aa_pairE_I     8.9068     1.0515   8.471  < 2e-16 ***
## aa_pairE_K    12.4610     0.5940  20.980  < 2e-16 ***
## aa_pairE_L     8.6543     0.5354  16.164  < 2e-16 ***
## aa_pairE_M    -4.6918  1639.6501  -0.003 0.997717
## aa_pairE_N     8.1989     0.7943  10.322  < 2e-16 ***
## aa_pairE_P     7.6073     1.1323   6.718 1.84e-11 ***
## aa_pairE_Q    11.8648     0.4099  28.947  < 2e-16 ***
## aa_pairE_R    11.3891     0.4742  24.018  < 2e-16 ***
## aa_pairE_S     8.6229     0.5590  15.425  < 2e-16 ***
## aa_pairE_T     7.7773     0.6697  11.614  < 2e-16 ***
## aa_pairE_V    10.1429     0.6650  15.253  < 2e-16 ***
## aa_pairE_W    10.4254     0.9237  11.287  < 2e-16 ***
## aa_pairE_Y    12.3228     0.4422  27.870  < 2e-16 ***
## aa_pairF_F    -3.2224   771.2796  -0.004 0.996666
## aa_pairF_G     7.9085     0.3799  20.818  < 2e-16 ***
## aa_pairF_H    -5.1197  1246.1192  -0.004 0.996722
## aa_pairF_I     9.2106     0.5143  17.907  < 2e-16 ***
## aa_pairF_K    10.2473     1.0648   9.623  < 2e-16 ***
## aa_pairF_L     8.6929     0.5704  15.239  < 2e-16 ***
## aa_pairF_M     9.6971     0.9663  10.035  < 2e-16 ***
## aa_pairF_N     8.5956     0.5080  16.920  < 2e-16 ***
## aa_pairF_P     9.6564     0.4587  21.052  < 2e-16 ***
## aa_pairF_Q     9.9189     0.4133  23.999  < 2e-16 ***
## aa_pairF_R    10.9736     0.4013  27.347  < 2e-16 ***
## aa_pairF_S     8.6672     0.3586  24.168  < 2e-16 ***
## aa_pairF_T     9.9687     0.4255  23.430  < 2e-16 ***
## aa_pairF_V     7.8259     1.1200   6.987 2.80e-12 ***
## aa_pairF_W     9.7643     0.6815  14.328  < 2e-16 ***
## aa_pairF_Y    10.6024     0.4121  25.727  < 2e-16 ***
## aa_pairG_G     6.4114     0.2999  21.378  < 2e-16 ***
## aa_pairG_H     8.8415     0.6071  14.564  < 2e-16 ***
## aa_pairG_I     7.3621     0.3630  20.282  < 2e-16 ***
## aa_pairG_K     9.3725     0.4510  20.782  < 2e-16 ***
## aa_pairG_L     8.0443     0.2913  27.618  < 2e-16 ***
## aa_pairG_M     8.8593     0.3993  22.187  < 2e-16 ***
## aa_pairG_N     8.2034     0.3522  23.290  < 2e-16 ***
## aa_pairG_P     7.3596     0.3688  19.958  < 2e-16 ***
## aa_pairG_Q     9.2003     0.3126  29.432  < 2e-16 ***
## aa_pairG_R    10.0279     0.3850  26.045  < 2e-16 ***
## aa_pairG_S     6.6783     0.3075  21.721  < 2e-16 ***
## aa_pairG_T     7.5166     0.3074  24.449  < 2e-16 ***
## aa_pairG_V     7.1543     0.3496  20.465  < 2e-16 ***
## aa_pairG_W     8.9571     0.4065  22.033  < 2e-16 ***
## aa_pairG_Y     8.3490     0.3134  26.640  < 2e-16 ***
## aa_pairH_H    -5.9571  4189.8593  -0.001 0.998866
## aa_pairH_I    -5.3697  1577.0481  -0.003 0.997283
## aa_pairH_K    -6.6937  2098.9520  -0.003 0.997455
```

```
## aa_pairH_L    -7.0644   843.9878  -0.008 0.993322
## aa_pairH_M    -5.8359  2692.4847  -0.002 0.998271
## aa_pairH_N    10.2543     0.9601  10.681  < 2e-16 ***
## aa_pairH_P    -7.4070  1291.9322  -0.006 0.995426
## aa_pairH_Q     9.1952     0.7813  11.769  < 2e-16 ***
## aa_pairH_R    -4.2777  1719.6820  -0.002 0.998015
## aa_pairH_S    -6.6240  1059.3532  -0.006 0.995011
## aa_pairH_T     8.9645     0.6992  12.821  < 2e-16 ***
## aa_pairH_V     9.4917     1.1789   8.051 8.21e-16 ***
## aa_pairH_W    11.0727     1.1758   9.417  < 2e-16 ***
## aa_pairH_Y    10.5947     0.6673  15.876  < 2e-16 ***
## aa_pairI_I    -5.1068  1264.5330  -0.004 0.996778
## aa_pairI_K     9.6424     1.1858   8.131 4.25e-16 ***
## aa_pairI_L    10.0496     0.5433  18.498  < 2e-16 ***
## aa_pairI_M     9.1956     0.7545  12.187  < 2e-16 ***
## aa_pairI_N     8.8260     0.4763  18.531  < 2e-16 ***
## aa_pairI_P     8.8625     1.1070   8.006 1.19e-15 ***
## aa_pairI_Q     9.7686     0.4811  20.303  < 2e-16 ***
## aa_pairI_R    10.3780     0.7608  13.641  < 2e-16 ***
## aa_pairI_S     8.9292     0.4018  22.225  < 2e-16 ***
## aa_pairI_T     9.2663     0.4067  22.784  < 2e-16 ***
## aa_pairI_V     9.4079     0.5409  17.392  < 2e-16 ***
## aa_pairI_W     9.4824     0.7782  12.186  < 2e-16 ***
## aa_pairI_Y    10.7984     0.4302  25.102  < 2e-16 ***
## aa_pairK_K    -4.4266  2144.6153  -0.002 0.998353
## aa_pairK_L     8.9371     0.9337   9.571  < 2e-16 ***
## aa_pairK_M    -4.1309  1973.7639  -0.002 0.998330
## aa_pairK_N    10.2295     0.5343  19.147  < 2e-16 ***
## aa_pairK_P     9.0716     0.6459  14.044  < 2e-16 ***
## aa_pairK_Q     9.8796     0.7776  12.706  < 2e-16 ***
## aa_pairK_R     9.6186     0.9726   9.889  < 2e-16 ***
## aa_pairK_S    10.4602     0.4901  21.343  < 2e-16 ***
## aa_pairK_T     9.8153     0.6671  14.712  < 2e-16 ***
## aa_pairK_V     9.0919     0.8868  10.252  < 2e-16 ***
## aa_pairK_W    -6.4313  2300.2325  -0.003 0.997769
## aa_pairK_Y    10.5764     0.7582  13.949  < 2e-16 ***
## aa_pairL_L     8.4956     0.5063  16.779  < 2e-16 ***
## aa_pairL_M    10.1232     0.5793  17.476  < 2e-16 ***
## aa_pairL_N     9.2011     0.3892  23.641  < 2e-16 ***
## aa_pairL_P     9.4667     0.4228  22.392  < 2e-16 ***
## aa_pairL_Q    11.1273     0.3417  32.561  < 2e-16 ***
## aa_pairL_R    11.0384     0.4089  26.996  < 2e-16 ***
## aa_pairL_S     8.1457     0.3843  21.198  < 2e-16 ***
## aa_pairL_T     8.2599     0.3723  22.188  < 2e-16 ***
## aa_pairL_V     8.7641     0.5618  15.599  < 2e-16 ***
## aa_pairL_W    10.1963     0.6578  15.500  < 2e-16 ***
## aa_pairL_Y    10.5892     0.3733  28.365  < 2e-16 ***
## aa_pairM_M    -4.2232  3270.1334  -0.001 0.998970
## aa_pairM_N     9.7992     0.8052  12.170  < 2e-16 ***
## aa_pairM_P    11.2941     0.5793  19.497  < 2e-16 ***
## aa_pairM_Q     9.1321     0.6825  13.380  < 2e-16 ***
## aa_pairM_R    10.2472     1.1014   9.304  < 2e-16 ***
## aa_pairM_S    10.3857     0.6830  15.206  < 2e-16 ***
## aa_pairM_T    10.4871     0.5915  17.729  < 2e-16 ***
```

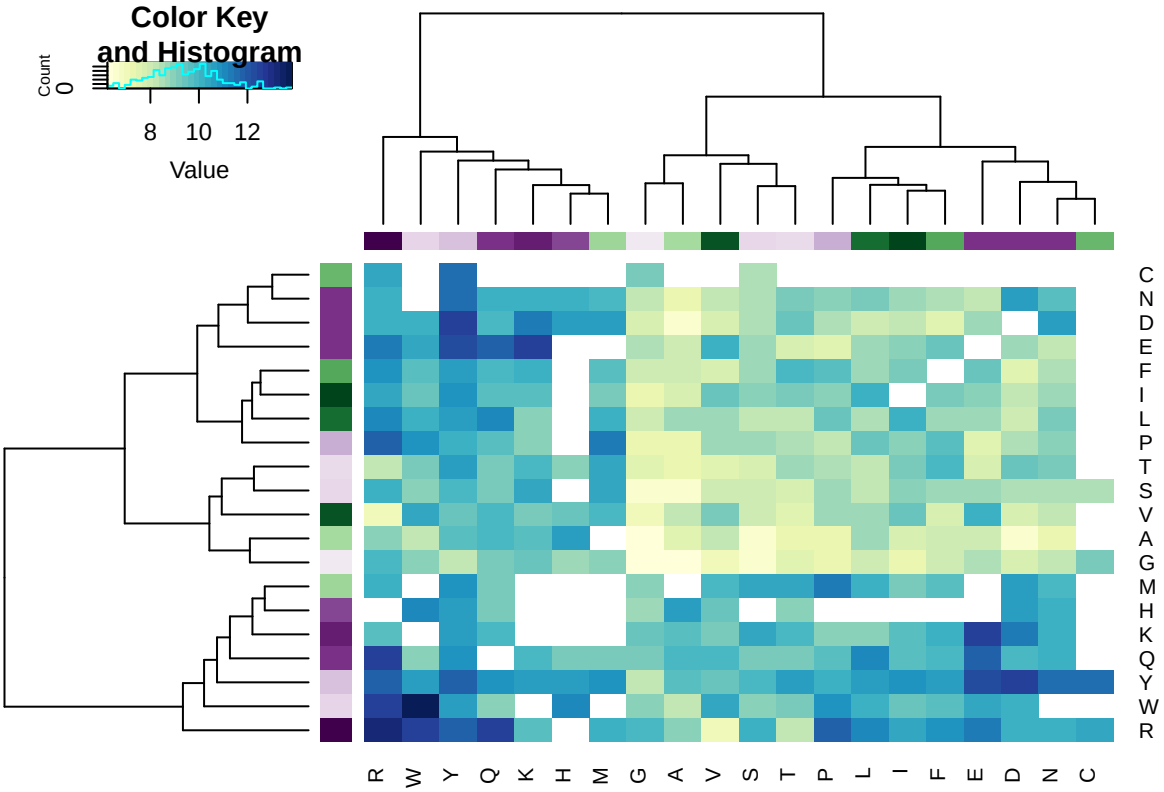
```
## aa_pairM_V    10.0076     0.7358  13.602  < 2e-16 ***
## aa_pairM_W    -1.3742  2890.8807   0.000 0.999621
## aa_pairM_Y    10.8579     0.5073  21.402  < 2e-16 ***
## aa_pairN_N     9.7526     0.7056  13.822  < 2e-16 ***
## aa_pairN_P     9.0655     0.4420  20.509  < 2e-16 ***
## aa_pairN_Q    10.1333     0.4000  25.332  < 2e-16 ***
## aa_pairN_R    10.1765     0.5927  17.168  < 2e-16 ***
## aa_pairN_S     8.5840     0.5222  16.440  < 2e-16 ***
## aa_pairN_T     9.1378     0.4950  18.461  < 2e-16 ***
## aa_pairN_V     8.3114     0.6490  12.806  < 2e-16 ***
## aa_pairN_W    -8.4428  1476.7351  -0.006 0.995438
## aa_pairN_Y    11.5988     0.4668  24.845  < 2e-16 ***
## aa_pairP_P     8.3694     1.0895   7.682 1.57e-14 ***
## aa_pairP_Q     9.7304     0.5615  17.328  < 2e-16 ***
## aa_pairP_R    11.7045     0.4296  27.242  < 2e-16 ***
## aa_pairP_S     8.7843     0.3882  22.630  < 2e-16 ***
## aa_pairP_T     8.5350     0.4719  18.087  < 2e-16 ***
## aa_pairP_V     8.6306     0.6433  13.417  < 2e-16 ***
## aa_pairP_W    10.9156     0.4580  23.832  < 2e-16 ***
## aa_pairP_Y    10.1015     0.4318  23.395  < 2e-16 ***
## aa_pairQ_Q    -4.6743  1285.0453  -0.004 0.997098
## aa_pairQ_R    12.4911     0.5125  24.373  < 2e-16 ***
## aa_pairQ_S     9.0880     0.4056  22.409  < 2e-16 ***
## aa_pairQ_T     9.2985     0.4610  20.172  < 2e-16 ***
## aa_pairQ_V     9.8137     0.4857  20.206  < 2e-16 ***
## aa_pairQ_W     9.0369     0.9533   9.479  < 2e-16 ***
## aa_pairQ_Y    10.9516     0.4023  27.225  < 2e-16 ***
## aa_pairR_R    13.3130     0.8040  16.559  < 2e-16 ***
## aa_pairR_S    10.2157     0.4588  22.268  < 2e-16 ***
## aa_pairR_T     8.2202     0.5519  14.895  < 2e-16 ***
## aa_pairR_V     7.0930     1.0785   6.577 4.80e-11 ***
## aa_pairR_W    12.5928     0.6466  19.475  < 2e-16 ***
## aa_pairR_Y    11.7568     0.4875  24.117  < 2e-16 ***
## aa_pairS_S     8.0212     0.7304  10.983  < 2e-16 ***
## aa_pairS_T     7.7769     0.6008  12.944  < 2e-16 ***
## aa_pairS_V     8.1070     0.4649  17.438  < 2e-16 ***
## aa_pairS_W     8.8810     0.5756  15.428  < 2e-16 ***
## aa_pairS_Y     9.9924     0.3501  28.540  < 2e-16 ***
## aa_pairT_T     8.7818     0.5402  16.256  < 2e-16 ***
## aa_pairT_V     7.4450     0.5503  13.530  < 2e-16 ***
## aa_pairT_W     9.3202     0.5622  16.579  < 2e-16 ***
## aa_pairT_Y    10.6287     0.4068  26.128  < 2e-16 ***
## aa_pairV_V     9.2680     0.8291  11.179  < 2e-16 ***
## aa_pairV_W    10.3870     0.9506  10.927  < 2e-16 ***
## aa_pairV_Y     9.4449     0.5751  16.422  < 2e-16 ***
## aa_pairW_W    13.8331     1.2502  11.065  < 2e-16 ***
## aa_pairW_Y    10.6918     0.3910  27.347  < 2e-16 ***
## aa_pairY_Y    11.8573     0.4829  24.552  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 77478.6  on 55889  degrees of freedom
```

```
## Residual deviance:  5776.2  on 55678  degrees of freedom
## AIC: 6198.2
##
## Number of Fisher Scoring iterations: 19
```

Explore results

```
coef = res$coefficients
pvalue = coef(summary(res))[,4]
coef = ifelse(pvalue < 0.05, coef, NA)
names(coef) = str_split_fixed(names(coef), "aa_pair", 2)[,2]

df.aa.coef = data.frame(coef = coef,
                        aa_tcr = str_split_fixed(names(coef), "_", 2)[, 1],
                        aa_antigen = str_split_fixed(names(coef), "_", 2)[ ,2]) %>%
  filter(aa_tcr != "" & aa_antigen != "") %>%
  droplevels

df.aa.coef.diag = df.aa.coef
df.aa.coef.diag$aa_pair = with(df.aa.coef.diag,
  as.factor(ifelse(as.character(aa_tcr) < as.character(aa_antigen), paste(aa_tcr, aa_antigen, sep = "_"

df.aa.coef.diag = df.aa.coef.diag %>% select(aa_pair, coef)

df.aa.coef.rev = df.aa.coef
df.aa.coef.rev$aa_tcr = df.aa.coef$aa_antigen
df.aa.coef.rev$aa_antigen = df.aa.coef$aa_tcr

df.aa.coef = rbind(df.aa.coef, df.aa.coef.rev) %>% unique()

# transform to matrix and plot heatmap.2

aa_pair_mat = dcast(df.aa.coef, aa_tcr ~ aa_antigen, value.var = "coef", fun.aggregate = mean)
rownames(aa_pair_mat) = aa_pair_mat$aa_tcr
aa_pair_mat$aa_tcr = NULL
aa_pair_mat = as.matrix(aa_pair_mat)

df.hydro <- data.frame(
  aa = strsplit("I V L F C M A W G T S Y P H N D Q E K R", " ")[[1]],
  hydrop = strsplit("4.5 4.2 3.8 2.8 2.5 1.9 1.8 -0.9 -0.4 -0.7 -0.8 -1.3 -1.6 -3.2 -3.5 -3.5 -3.5 -3.5
)

df.hydro = df.hydro %>%
  mutate(hydrop = as.numeric(as.character(hydrop))) %>%
  arrange(hydrop) %>%
  mutate(hydrop.sc = round(100 * (hydrop - min(hydrop)) / (max(hydrop) - min(hydrop))))

df.hydro$color = colorRampPalette(brewer.pal(11, 'PRGn'))(101)[df.hydro$hydrop.sc + 1]

aa_colors = df.hydro$color
names(aa_colors) = df.hydro$aa

heatmap.2(aa_pair_mat,
          hclustfun = function(x) hclust(x, method = "ward.D2"),
          RowSideColors = aa_colors[rownames(aa_pair_mat)],
```

```
          ColSideColors = aa_colors[colnames(aa_pair_mat)],
          trace = "none",
          #breaks = seq(-16, -7, length.out = 101),
          col=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32))
```



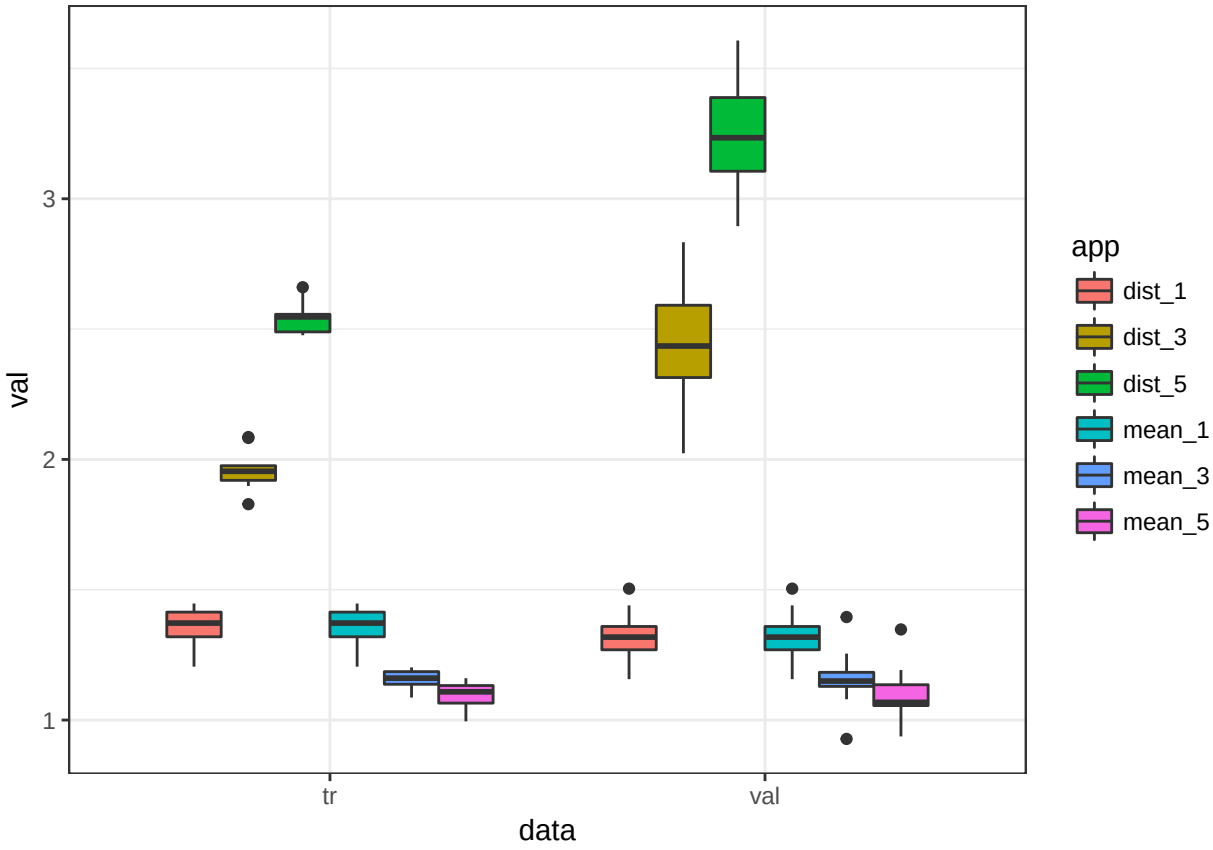

**Impute missing values**

```
kidera = t(data.frame(lapply(strsplit("A,-1.56,-1.67,-0.97,-0.27,-0.93,-0.78,-0.2,-0.08,0.21,-0.48;R,0.1

kidera[,2:ncol(kidera)] = lapply(kidera[,2:ncol(kidera)], function (col) (col - min(col)) / (max(col) -
row.names(kidera) = kidera$amino.acid
kidera = as.matrix(kidera[,-1])


generate_data <- function (.mat, .train_size = .7, .cv = 10, .seed = 42) {
  melted = melt(.mat)[melt(upper.tri(.mat, diag = T))[,3],]
  melted[,1] = as.character(melted[,1])
  melted[,2] = as.character(melted[,2])
  train_data = melted[!is.na(melted[,3]), ]
  test_data = melted[is.na(melted[,3]), ]

  med = median(train_data[,3])

  hi_logic = train_data[,3] >= med
  lo_logic = train_data[,3] < med

  train_size = round(.train_size * nrow(train_data))
```

```
  train_inds = list()
  val_inds = list()

  set.seed(.seed)
  for (i in 1:.cv) {
    hi_inds = sample(which(hi_logic), train_size / 2, F)
    lo_inds = sample(which(lo_logic), train_size / 2, F)
    train_inds[[i]] = sample(c(hi_inds, lo_inds))

    val_inds[[i]] = sample(c(setdiff(which(hi_logic), hi_inds), setdiff(which(lo_logic), lo_inds)))
  }

  res = matrix(0, nrow(train_data), 10)
  for (i in 1:nrow(res)) {
    res[i,] = (kidera[train_data[i,1], ] + kidera[train_data[i,2], ]) / 2
  }
  row.names(res) = paste0(train_data[,1], train_data[,2])

  res_tst = matrix(0, nrow(test_data), 10)
  for (i in 1:nrow(res_tst)) {
    res_tst[i,] = (kidera[test_data[i,1], ] + kidera[test_data[i,2], ]) / 2
  }
  row.names(res_tst) = paste0(test_data[,1], test_data[,2])

  list(X = res, y = train_data[,3], X_test = res_tst, train = train_inds, val = val_inds)
}


impute_knn_mean <- function (X_train, y_train, X_val, y_val, X_test, .k) {
  res_tr = sapply(1:nrow(X_train), function (row_i) {
    tmp = sapply(1:nrow(X_train), function (row_j) {
      if (row_i != row_j) { sqrt(sum((X_train[row_i, ] - X_train[row_j, ]) ^ 2))
      }
      else { 20 }
    })
    mean(y_train[order(tmp)[1:.k]])
  })

  res_val = sapply(1:nrow(X_val), function (row_i) {
    tmp = sapply(1:nrow(X_train), function (row_j) {
      sqrt(sum((X_val[row_i, ] - X_train[row_j, ]) ^ 2))
    })
    mean(y_train[order(tmp)[1:.k]])
  })

  merged = rbind(X_train, X_val)
  merged_y = c(y_train, y_val)
  imp_tst = sapply(1:nrow(X_test), function (row_i) {
    tmp = sapply(1:nrow(merged), function (row_j) {
      sqrt(sum((X_test[row_i, ] - merged[row_j, ]) ^ 2))
    })
    mean(merged_y[order(tmp)[1:.k]])
  })
```

```
  list(res_tr, res_val, imp_tst)
}


impute_knn_dist <- function (X_train, y_train, X_val, y_val, X_test, .k) {
  res_tr = sapply(1:nrow(X_train), function (row_i) {
    tmp = sapply(1:nrow(X_train), function (row_j) {
      if (row_i != row_j) { sqrt(sum((X_train[row_i, ] - X_train[row_j, ]) ^ 2)) }
      else { 20 }
    })
    mean((min(tmp[order(tmp)[1:.k]]) / tmp[order(tmp)[1:.k]]) ^ 2 * y_train[order(tmp)[1:.k]])
  })

  res_val = sapply(1:nrow(X_val), function (row_i) {
    tmp = sapply(1:nrow(X_train), function (row_j) {
      sqrt(sum((X_val[row_i, ] - X_train[row_j, ]) ^ 2))
    })
    mean((min(tmp[order(tmp)[1:.k]]) / tmp[order(tmp)[1:.k]]) ^ 3 * y_train[order(tmp)[1:.k]])
  })

  merged = rbind(X_train, X_val)
  merged_y = c(y_train, y_val)
  imp_tst = sapply(1:nrow(X_test), function (row_i) {
    tmp = sapply(1:nrow(merged), function (row_j) {
      sqrt(sum((X_test[row_i, ] - merged[row_j, ]) ^ 2))
    })
    mean(merged_y[order(tmp)[1:.k]])
  })

  list(res_tr, res_val, imp_tst)
}


eval_model <- function (.data, .fun, ...) {
  .scorer <- function (ytrue, ypred) {
    sqrt(mean((ytrue - ypred) ^ 2))
  }

  res_tr = c()
  res_val = c()
  for (i in 1:length(.data$train)) {
    tmp = .fun(.data$X[.data$train[[i]], ],
               .data$y[.data$train[[i]]],
               .data$X[.data$val[[i]], ],
               .data$y[.data$val[[i]]],
               .data$X_test, ...)
    res_tr  = c(res_tr,  .scorer(tmp[[1]], .data$y[.data$train[[i]]]))
    res_val = c(res_val, .scorer(tmp[[2]], .data$y[.data$val[[i]]]))
  }
  list(tr = res_tr, val = res_val)
}
```

```
aa_data = generate_data(aa_pair_mat, .cv = 10)
imp_res = list()
imp_res[["mean_1"]] = eval_model(aa_data, impute_knn_mean, .k = 1)
imp_res[["mean_3"]] = eval_model(aa_data, impute_knn_mean, .k = 3)
imp_res[["mean_5"]] = eval_model(aa_data, impute_knn_mean, .k = 5)
imp_res[["dist_1"]] = eval_model(aa_data, impute_knn_dist, .k = 1)
imp_res[["dist_3"]] = eval_model(aa_data, impute_knn_dist, .k = 3)
imp_res[["dist_5"]] = eval_model(aa_data, impute_knn_dist, .k = 5)
imp_res = melt(imp_res)
colnames(imp_res) = c("val", "data", "app")
qplot(x = data, y = val, fill = app, data = imp_res, geom = "boxplot") + theme_bw()
```

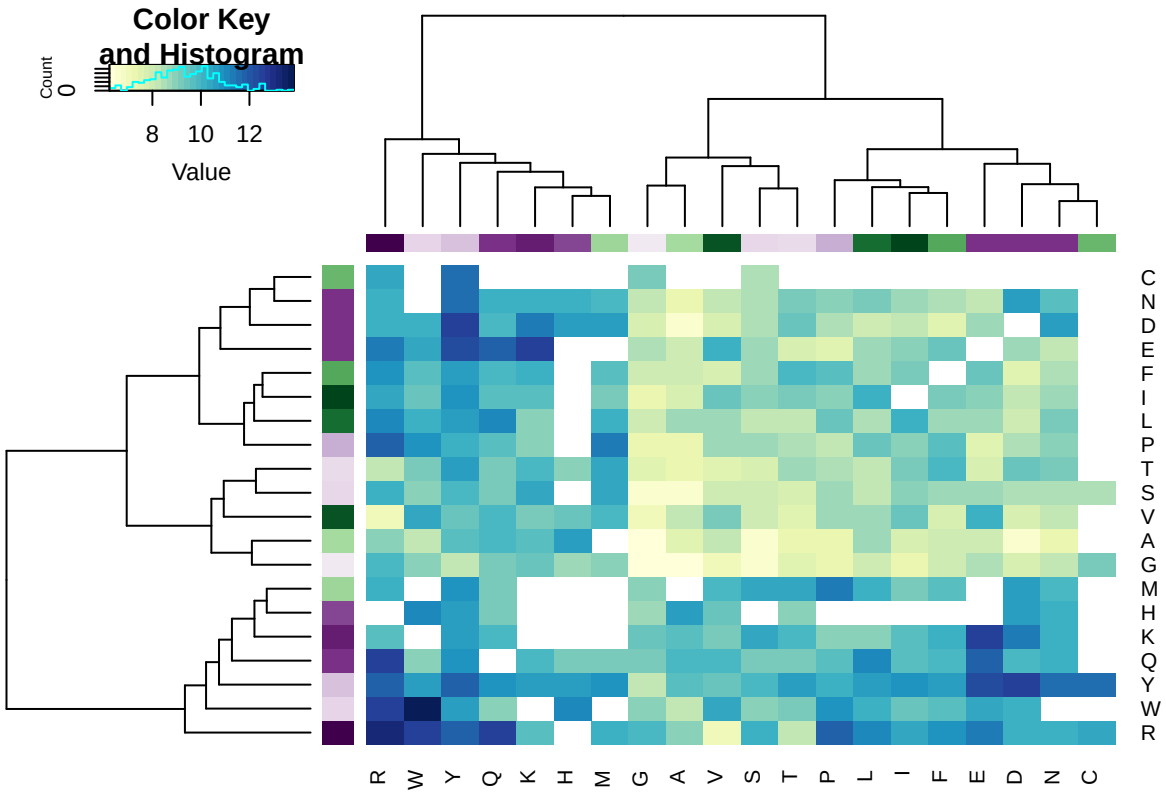



```
melted = melt(aa_pair_mat)[melt(upper.tri(aa_pair_mat, T))[,3],]
melted[,1] = as.character(melted[,1])
melted[,2] = as.character(melted[,2])
test_data = melted[is.na(melted[,3]), ]

imputed = impute_knn_mean(aa_data$X[aa_data$train[[1]], ],
                          aa_data$y[aa_data$train[[1]]],
                          aa_data$X[aa_data$val[[1]], ],
                          aa_data$y[aa_data$val[[1]]],
                          aa_data$X_test, .k = 5)[[3]]

aa_pair_mat_imp = aa_pair_mat
for (r in 1:nrow(test_data)) {
  aa_pair_mat_imp[test_data[r,1], test_data[r,2]] = imputed[r]
  aa_pair_mat_imp[test_data[r,2], test_data[r,1]] = imputed[r]
```

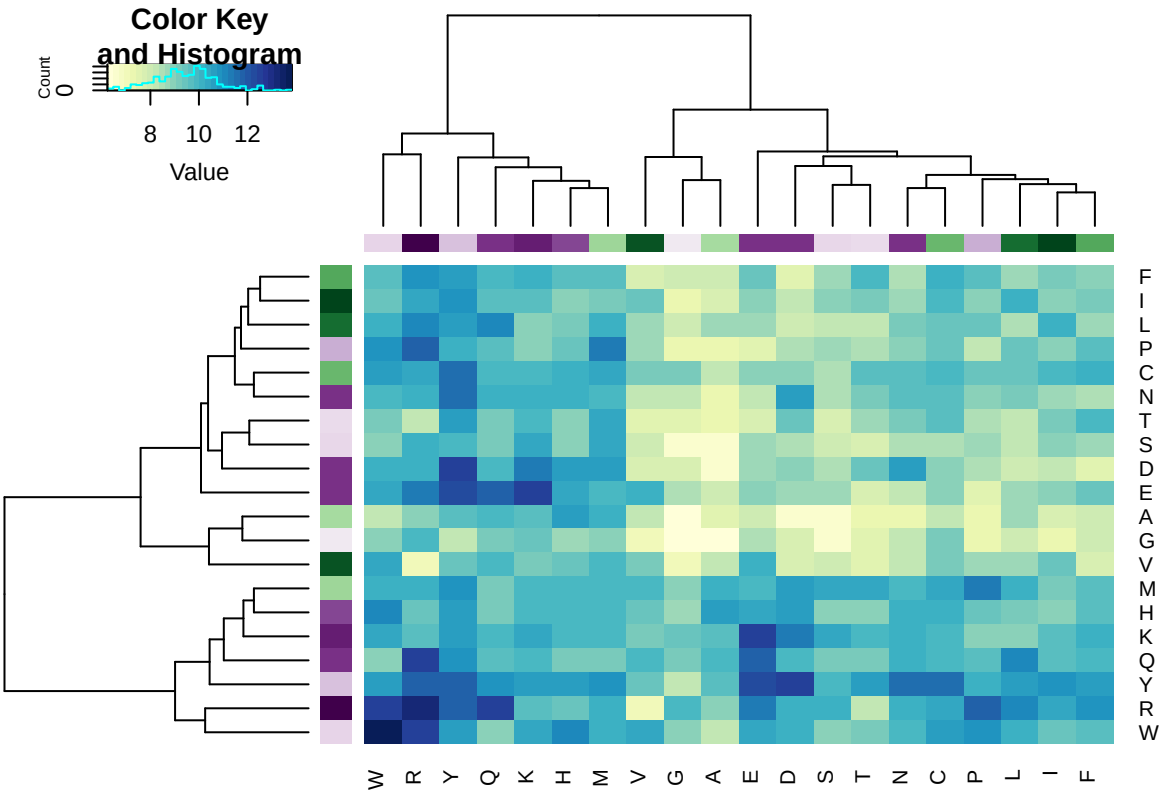
```
}
```

### Imputed amino acids

```
p2 = heatmap.2(aa_pair_mat,
          hclustfun = function(x) hclust(x, method = "ward.D2"),
          RowSideColors = aa_colors[rownames(aa_pair_mat)],
          ColSideColors = aa_colors[colnames(aa_pair_mat)],
          trace = "none",
          #breaks = seq(-16, -7, length.out = 101),
          col=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32))
```




```
p2 = heatmap.2(aa_pair_mat_imp,
          hclustfun = function(x) hclust(x, method = "ward.D2"),
          RowSideColors = aa_colors[rownames(aa_pair_mat)],
          ColSideColors = aa_colors[colnames(aa_pair_mat)],
          trace = "none",
          #breaks = seq(-16, -7, length.out = 101),
          col=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32))
```




### Discard distant amino acids

Append amino acid distance coefficients

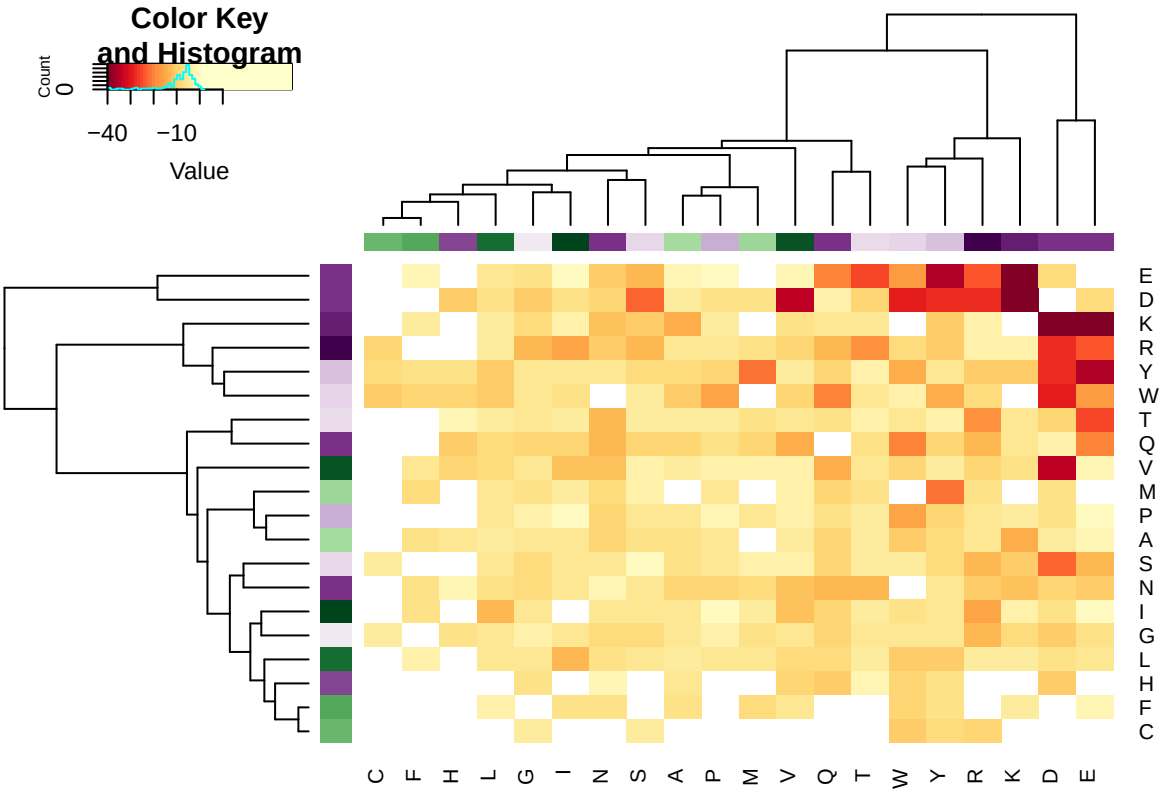
```
df.pred = df.pred[df.aa.coef.diag, on = "aa_pair"]
df.pred.trimmed = df.pred[distance_CA <= 15] # discard AAs that are too far away for training
```

## Contact energies

Compute mean GROMACS energies

```
df.energies = df[contact == T, .(energy.mean = mean(ifelse(energy > 0 , 0, energy))), by = "aa_pair"]
df.energies$aa_tcr = str_split_fixed(as.character(df.energies$aa_pair), "_", 2)[, 1]
df.energies$aa_antigen = str_split_fixed(as.character(df.energies$aa_pair), "_", 2)[, 2]

df.energies.tmp = df.energies
df.energies.tmp$aa_tcr = df.energies$aa_antigen
df.energies.tmp$aa_antigen = df.energies$aa_tcr

df.energies = rbind(df.energies, df.energies.tmp) %>% unique()

# transform to matrix and plot heatmap.2

aa_pair_energy_mat = dcast(df.energies, aa_tcr ~ aa_antigen, value.var = "energy.mean", fun.aggregate =
rownames(aa_pair_energy_mat) = aa_pair_energy_mat$aa_tcr
aa_pair_energy_mat$aa_tcr = NULL
aa_pair_energy_mat = as.matrix(aa_pair_energy_mat)
```

```
heatmap.2(aa_pair_energy_mat,
          hclustfun = function(x) hclust(x, method = "ward.D2"),
          RowSideColors = aa_colors[rownames(aa_pair_mat)],
          ColSideColors = aa_colors[colnames(aa_pair_mat)],
          trace = "none",
          breaks = seq(-40, 2, length.out = 33),
          col=rev(colorRampPalette(brewer.pal(9, 'YlOrRd'))(32)))
```




## Building and testing a predictor

Final generalized linear model to fit contacts.

```
# Train on a trimmed dataset
contact_glm = glm(contact ~ distance_CA.m + coef, family = binomial(), data = df.pred.trimmed)

summary(contact_glm)
```

```
##
## Call:
## glm(formula = contact ~ distance_CA.m + coef, family = binomial(),
##     data = df.pred.trimmed)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.1271  -0.4980  -0.3149  -0.1694   3.7497
##
## Coefficients:
```

```
##                Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -0.68268    0.19461  -3.508 0.000452 ***
## distance_CA.m -0.47137    0.01239 -38.044  < 2e-16 ***
## coef           0.47245    0.01844  25.624  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 13079  on 18252  degrees of freedom
## Residual deviance: 10668  on 18250  degrees of freedom
##   (596 observations deleted due to missingness)
## AIC: 10674
##
## Number of Fisher Scoring iterations: 6
```

```
df.pred.trimmed$p = predict(contact_glm, df.pred.trimmed, type="response")
df.pred$p = predict(contact_glm, df.pred, type="response")

df.pred = df.pred[df.energies, on = .(aa_tcr, aa_antigen)]
```

Save model for further evaluation:

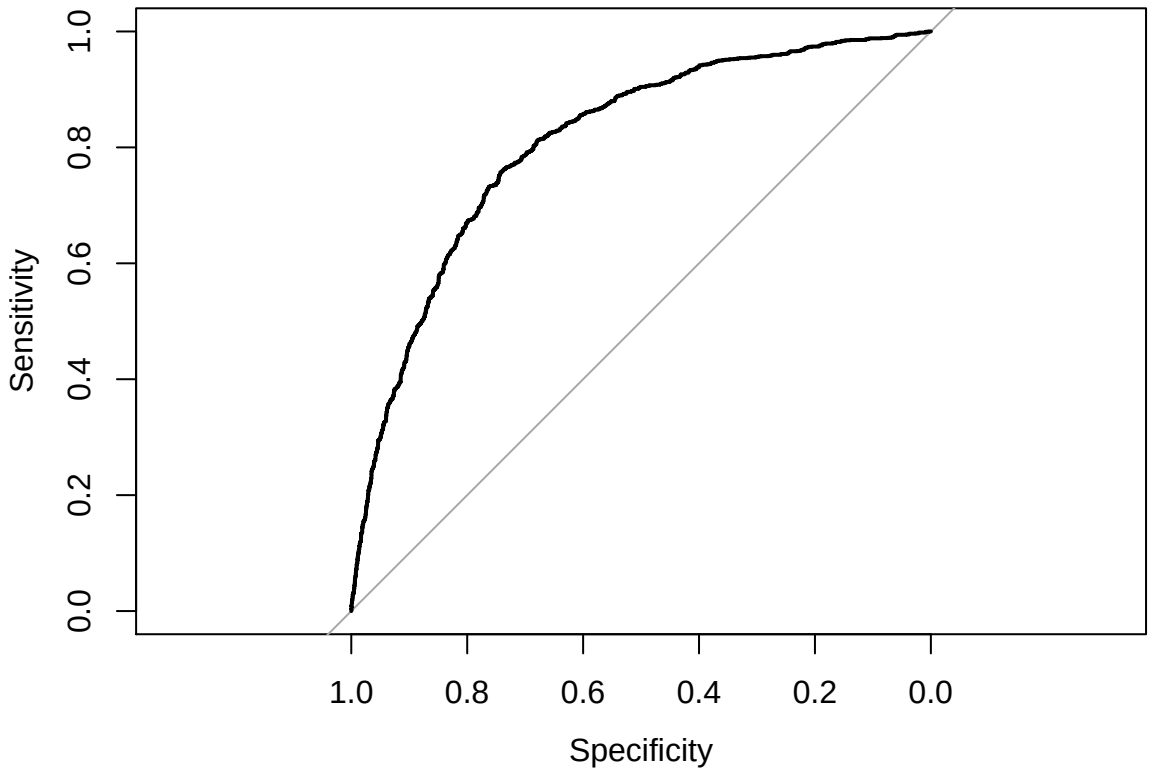
```
save(df.ca.mean, df.aa.coef, contact_glm, df.energies, file="eval/model_simple.RData")
write.table(df.ca.mean, "eval/ca_dist_mean.txt", sep="\t", quote=F, row.names = F)
write.table(df.aa.coef, "eval/aa_pairwise_contact_coef.txt", sep="\t", quote=F, row.names = F)
write.table(df.energies, "eval/aa_pairwise_energy.txt", sep="\t", quote=F, row.names = F)
```

## Check accuracy

### General

ROC curve

```
rocobj = plot.roc(as.data.frame(df.pred.trimmed)[,"contact"], df.pred.trimmed$p, ci=T)
```



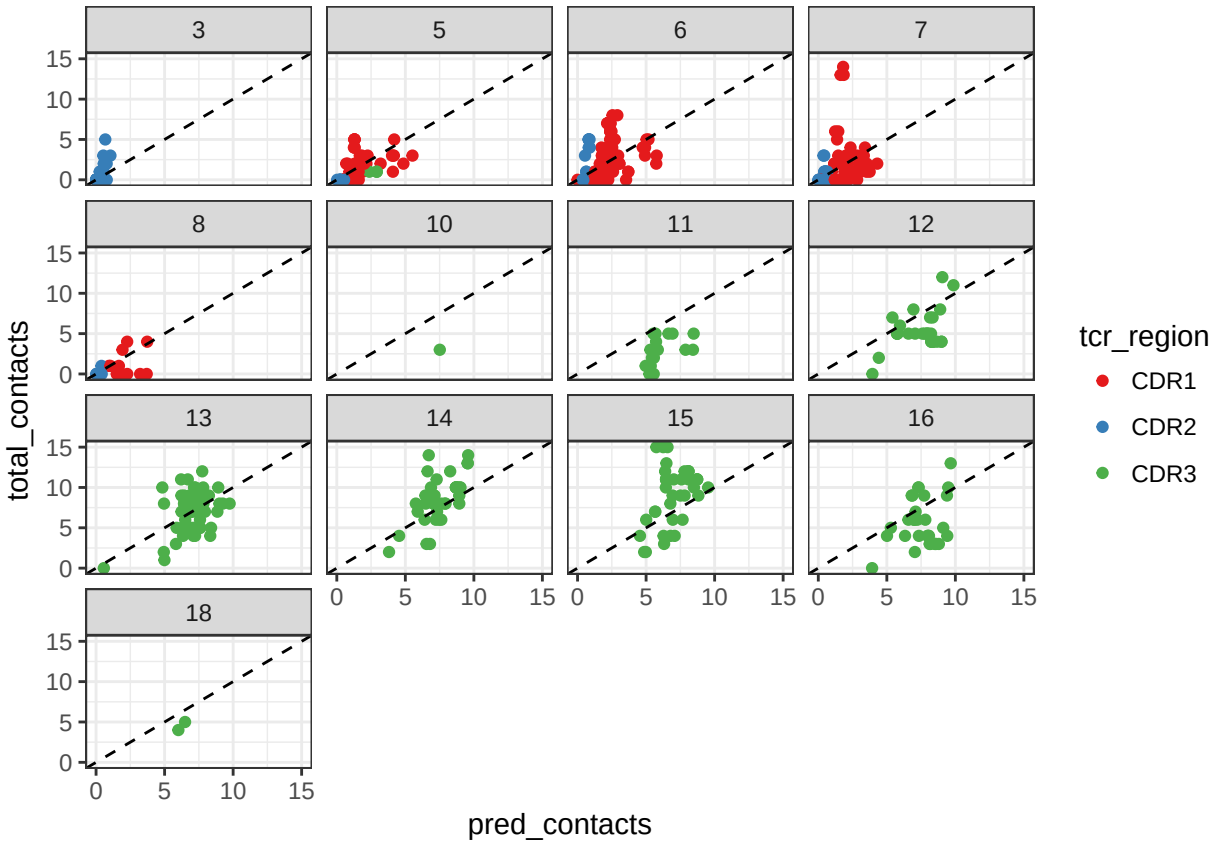

```
rocobj
```

```
##
## Call:
## plot.roc.default(x = as.data.frame(df.pred.trimmed)[, "contact"],     predictor = df.pred.trimmed$p,
##
## Data: df.pred.trimmed$p in 16141 controls (as.data.frame(df.pred.trimmed)[, "contact"] FALSE) < 2112
## Area under the curve: 0.809
## 95% CI: 0.7994-0.8185 (DeLong)
```

Compute true and estimated total number of contacts

```
df.pred.contsum = df.pred.trimmed[, .(total_contacts = sum(contact), pred_contacts = sum(p, na.rm=T)), l

ggplot(df.pred.contsum, aes(x=pred_contacts, y=total_contacts, color = tcr_region)) +
  geom_point() +
  geom_abline(slope = 1, intercept = 0, linetype = "dashed") +

  scale_x_continuous(limits=c(0,15)) +
  scale_y_continuous(limits=c(0,15)) +
  scale_color_brewer(palette = "Set1") +
  facet_wrap(~len_tcr) +
  theme_bw()
```

```
## Warning: Removed 2 rows containing missing values (geom_point).
```




```
lfit = lm(total_contacts ~ pred_contacts + len_tcr + tcr_region - 1, df.pred.contsum)
summary(lfit)
```

```
##
## Call:
## lm(formula = total_contacts ~ pred_contacts + len_tcr + tcr_region -
##     1, data = df.pred.contsum)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -5.9314 -1.2572 -0.1719  0.7878 11.7296
##
## Coefficients:
##                 Estimate Std. Error t value Pr(>|t|)
## pred_contacts    0.84078    0.08811   9.542  < 2e-16 ***
## len_tcr          0.26766    0.06048   4.426 1.13e-05 ***
## tcr_regionCDR1 -1.12580    0.40841  -2.757 0.006005 **
## tcr_regionCDR2 -0.96886    0.28759  -3.369 0.000799 ***
## tcr_regionCDR3 -2.74663    0.93172  -2.948 0.003314 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 2.306 on 650 degrees of freedom
## Multiple R-squared:  0.7816, Adjusted R-squared:  0.7799
## F-statistic: 465.2 on 5 and 650 DF,  p-value: < 2.2e-16
```

```r
anova(lfit)
```

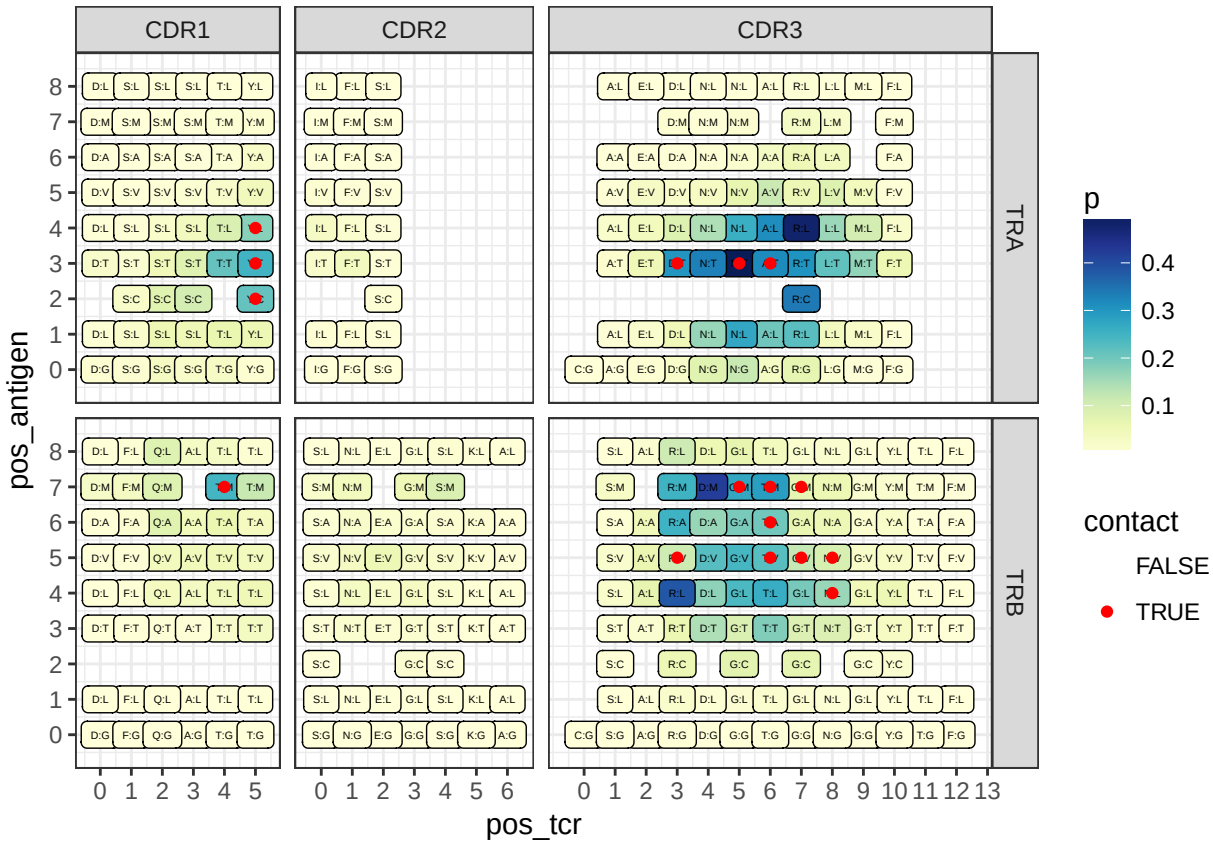
```
## Analysis of Variance Table
##
## Response: total_contacts
##                Df  Sum Sq Mean Sq   F value    Pr(>F)
## pred_contacts   1 12243.6 12243.6 2302.7585 < 2.2e-16 ***
## len_tcr         1    56.5    56.5   10.6301  0.001171 **
## tcr_region      3    65.8    21.9    4.1279  0.006493 **
## Residuals     650  3456.0     5.3
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

### Examples from the train data

Check for a couple of antigens, GLCTLVAML

```r
df.pred.glc = df.pred %>%
  filter(antigen_seq == "GLCTLVAML") %>%
  droplevels()

ggplot(df.pred.glc, aes(x=pos_tcr, y=pos_antigen)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=1.3) +
  geom_point(aes(color=contact)) +
  scale_x_continuous(breaks=0:20) +
  scale_y_continuous(breaks=0:20) +
  #scale_fill_gradient("P",
  #                    low="white", high="#045a8d") +
  scale_color_manual(values = c(NA, "red")) +
  scale_fill_gradientn(colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(tcr_chain ~ tcr_region, scales="free", space="free") +
  theme_bw()
```

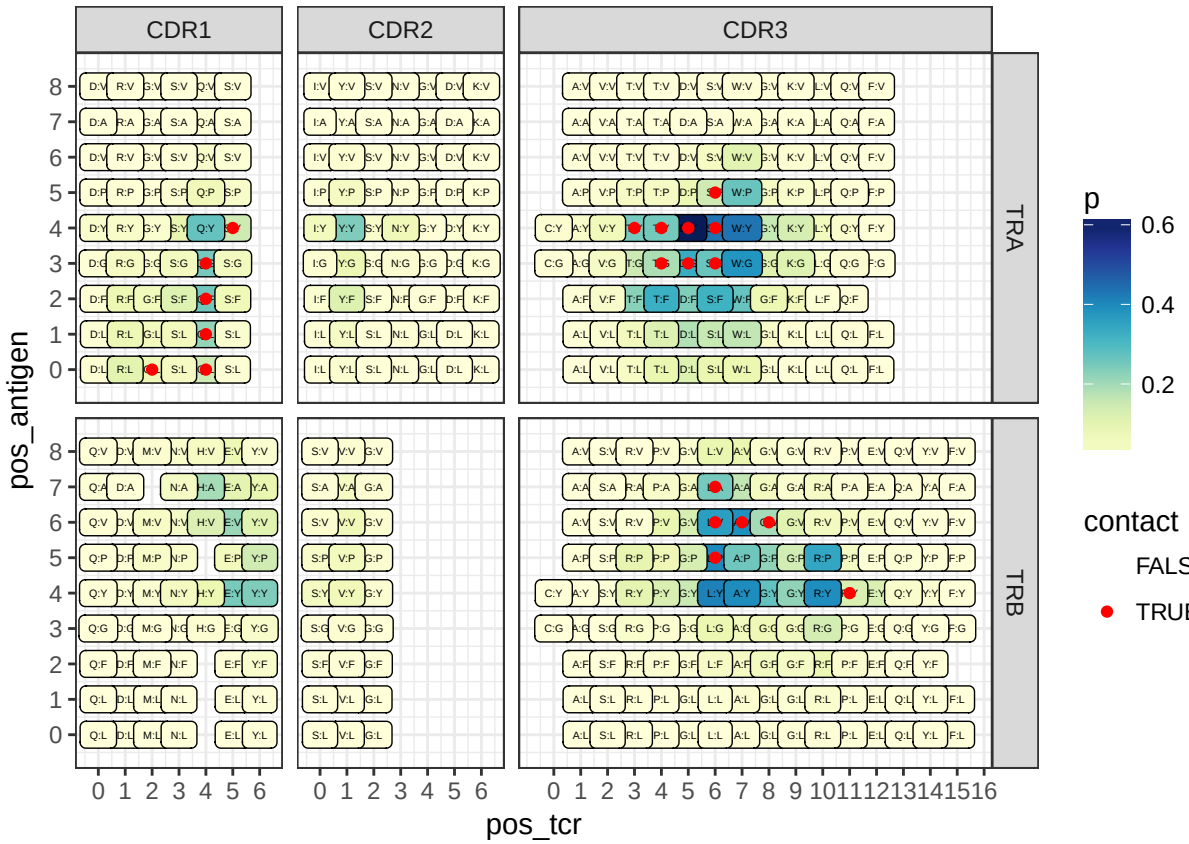
```
## Warning: Removed 343 rows containing missing values (geom_point).
```




and LLFGYPVAV

```
df.pred.llf = df.pred %>%
  filter(antigen_seq == "LLFGYPVAV") %>%
  droplevels()

ggplot(df.pred.llf, aes(x=pos_tcr, y=pos_antigen)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=1.3) +
  geom_point(aes(color=contact)) +
  scale_x_continuous(breaks=0:20) +
  scale_y_continuous(breaks=0:20) +
  #scale_fill_gradient("P",
  #                    low="white", high="#045a8d") +
  scale_color_manual(values = c(NA, "red")) +
  scale_fill_gradientn(colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(tcr_chain ~ tcr_region, scales="free", space="free") +
  theme_bw()
```

```
## Warning: Removed 427 rows containing missing values (geom_point).
```




# Independent validation

Computing contact map from fitted model for a specified TCR:pMHC setup

```
compute_contact_map = function(mhc_type, tcr_chain, tcr_region, cdr_seq, ag_seq, id = "tmp") {
  cdr_seq = as.character(cdr_seq)
  ag_seq = as.character(ag_seq)
  df.cdr = data.frame(aa_tcr = strsplit(cdr_seq, "")[[1]],
                      pos_tcr = 1:nchar(cdr_seq) - 1)
  df.ag = data.frame(aa_antigen = strsplit(ag_seq, "")[[1]],
                     pos_antigen = 1:nchar(ag_seq) - 1)

  df.pairs = expand.grid(df.cdr$pos_tcr, df.ag$pos_antigen)
  colnames(df.pairs) = c("pos_tcr", "pos_antigen")

  df.pairs = merge(df.pairs, df.cdr)
  df.pairs = merge(df.pairs, df.ag)

  df.pairs$aa_pair = with(df.pairs,
                      as.factor(ifelse(as.character(aa_tcr) < as.character(aa_antigen),
                                       paste(aa_tcr, aa_antigen, sep = "_"), paste(aa_antigen, aa_tcr,

  df.pairs$mhc_type = mhc_type
  df.pairs$tcr_chain = tcr_chain
  df.pairs$tcr_region = tcr_region
```

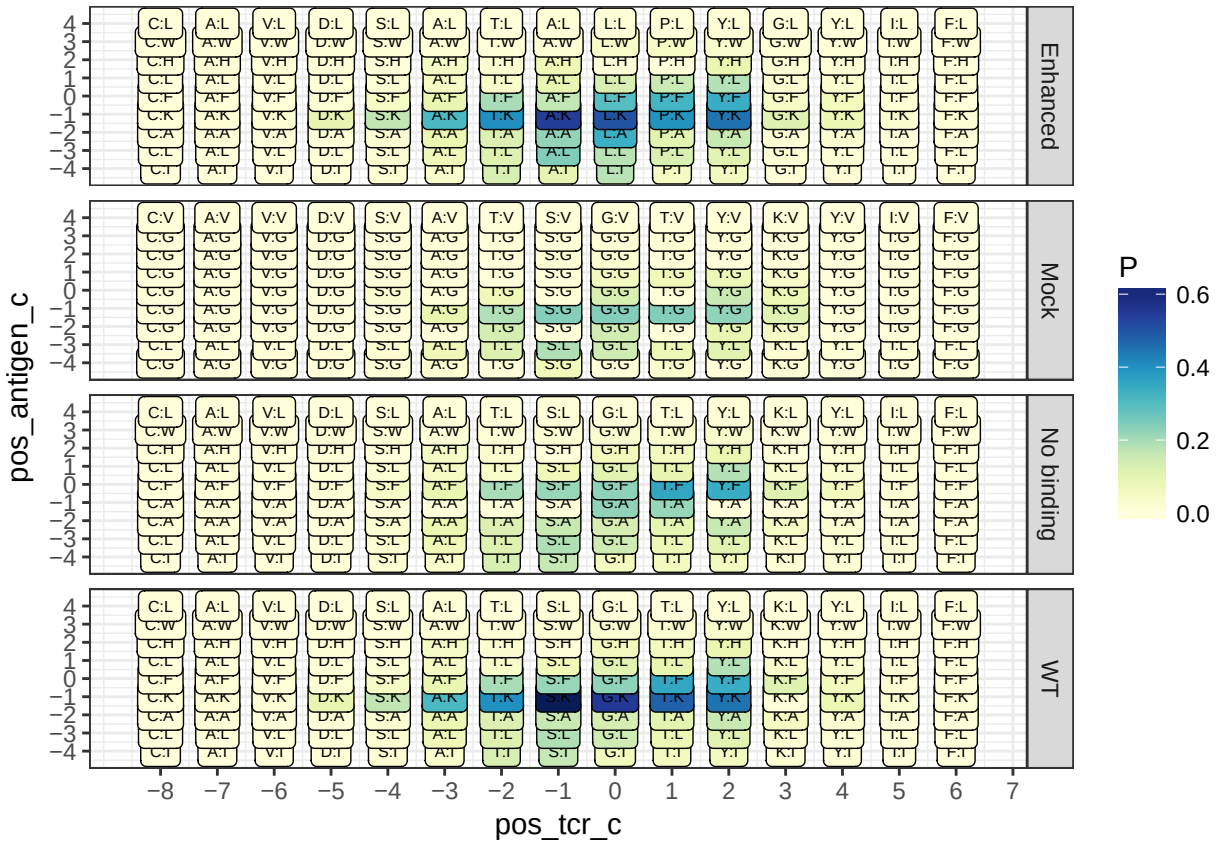
```
  df.pairs$len_tcr = nchar(cdr_seq)
  df.pairs$len_antigen = nchar(ag_seq)

  df.pairs$pos_tcr_c = with(df.pairs, pos_tcr - round(len_tcr / 2))
  df.pairs$pos_antigen_c = with(df.pairs, pos_antigen - round(len_antigen / 2))

  df.pairs$id = id # ! id can be anything to group the complex, e.g. clonotype id in sample

  df.res = merge(df.pairs %>% select(id, mhc_type, tcr_chain, tcr_region, pos_tcr_c, pos_antigen_c, aa_a
        df.pred %>% select(mhc_type, tcr_chain, tcr_region, pos_tcr_c, pos_antigen_c, aa_pair, p, energy
        unique()

  df.res$p[is.na(df.res$p)] = 0
  df.res$energy.mean[is.na(df.res$energy.mean)] = 0

  df.res
}
```

Testing - example 1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681418/ - engeneered peptide

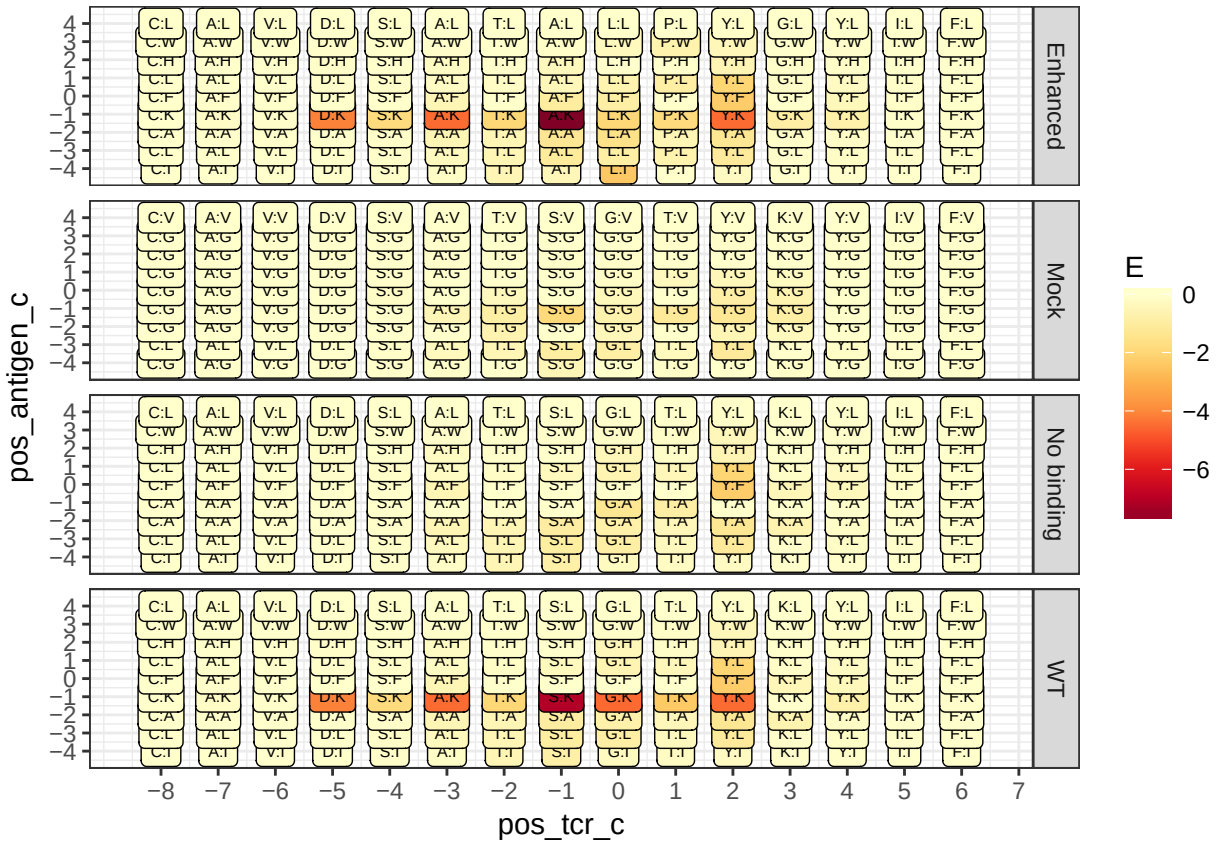
```
cm.tmp = compute_contact_map("MHCI","TRA","CDR3","CAVDSATSGTYKYIF","ILAKFLHWL","WT")
cm.tmp = rbind(cm.tmp, compute_contact_map("MHCI","TRA","CDR3","CAVDSATSGTYKYIF","ILAAFLHWL","No bindin
cm.tmp = rbind(cm.tmp, compute_contact_map("MHCI","TRA","CDR3","CAVDSATSGTYKYIF","GLGGGGGGV","Mock"))
cm.tmp = rbind(cm.tmp, compute_contact_map("MHCI","TRA","CDR3","CAVDSATALPYGYIF","ILAKFLHWL", "Enhanced

print(cm.tmp %>% group_by(id) %>% summarize(contacts = sum(p), energy = sum(p * energy.mean)))
```

```
## # A tibble: 4 × 3
##           id contacts    energy
##        <chr>    <dbl>     <dbl>
## 1   Enhanced 8.269807 -58.66817
## 2       Mock 3.350889 -18.29960
## 3 No binding 5.165294 -24.74191
## 4         WT 7.955917 -54.55842
```

```
ggplot(cm.tmp, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("P", colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```




```
ggplot(cm.tmp, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p * energy.mean), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("E", colors=rev(colorRampPalette(brewer.pal(9, 'YlOrRd'))(32))) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```

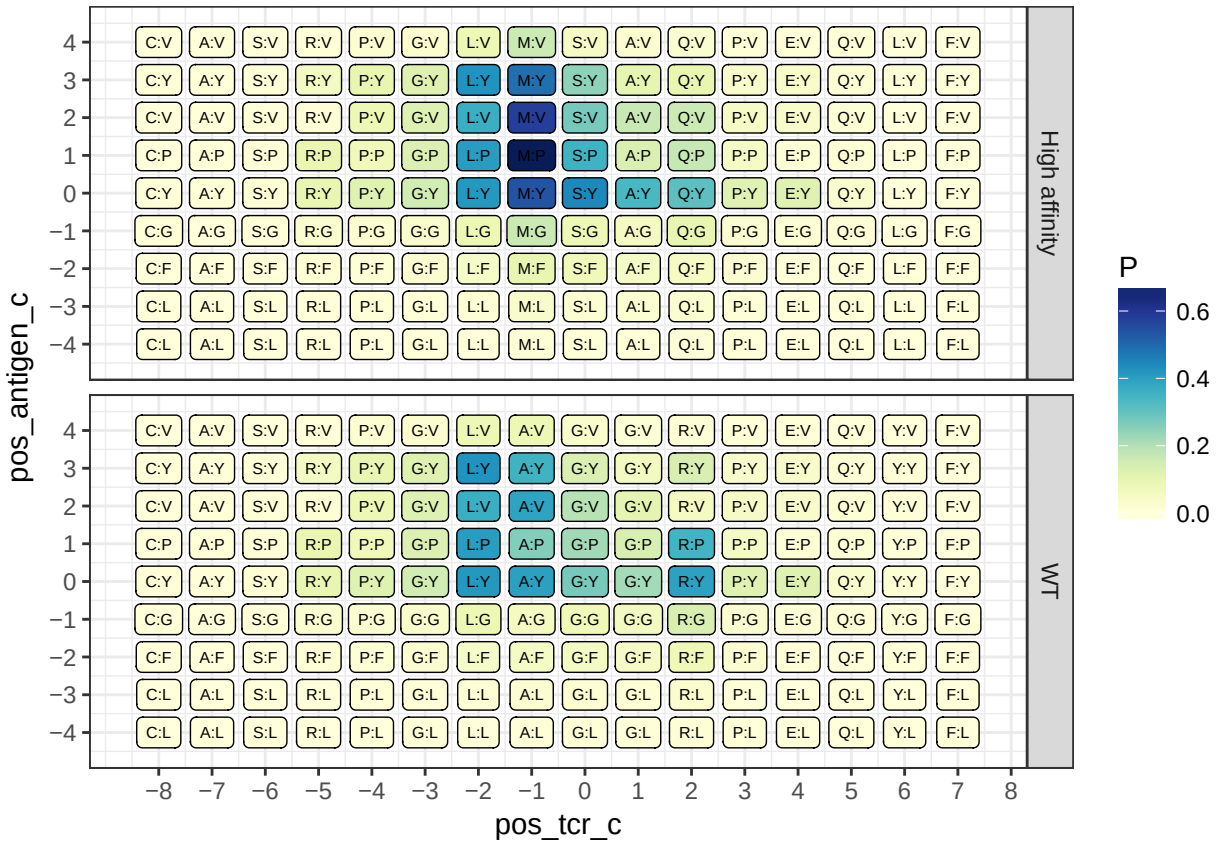



Testing - example 2 http://www.nature.com/articles/ncomms6223, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049343/ - high affinity Tax mutant

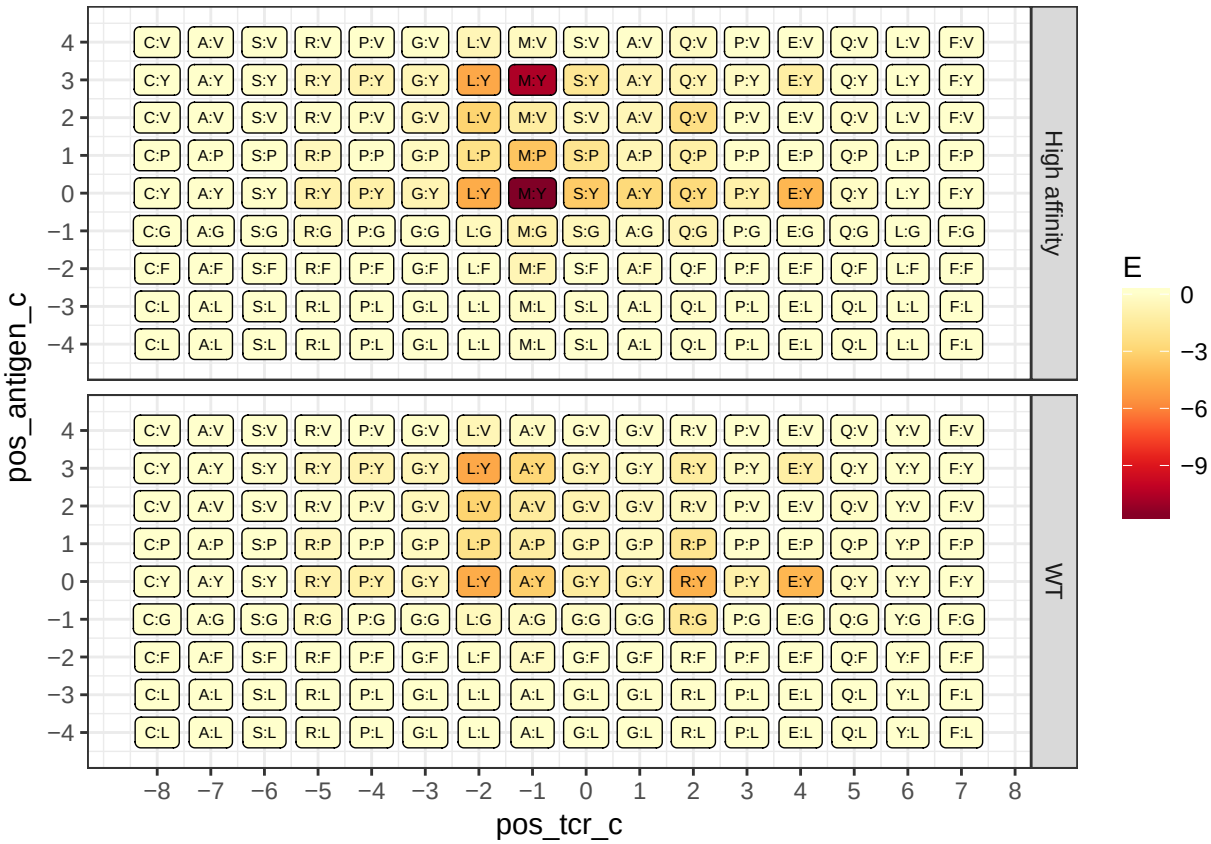
```
cm.tmp = compute_contact_map("MHCI","TRB","CDR3","CASRPGLAGGRPEQYF","LLFGYPVYV","WT")
cm.tmp = rbind(cm.tmp, compute_contact_map("MHCI","TRB","CDR3","CASRPGLMSAQPEQLF","LLFGYPVYV","High affi

print(cm.tmp %>% group_by(id) %>% summarize(contacts = sum(p), energy = sum(p * energy.mean)))
```

```
## # A tibble: 2 × 3
##               id contacts    energy
##            <chr>    <dbl>     <dbl>
## 1 High affinity 9.841837 -84.70442
## 2            WT 8.145584 -59.29974
```

```
ggplot(cm.tmp, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("P", colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```




```
ggplot(cm.tmp, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p * energy.mean), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("E", colors=rev(colorRampPalette(brewer.pal(9, 'YlOrRd'))(32))) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```

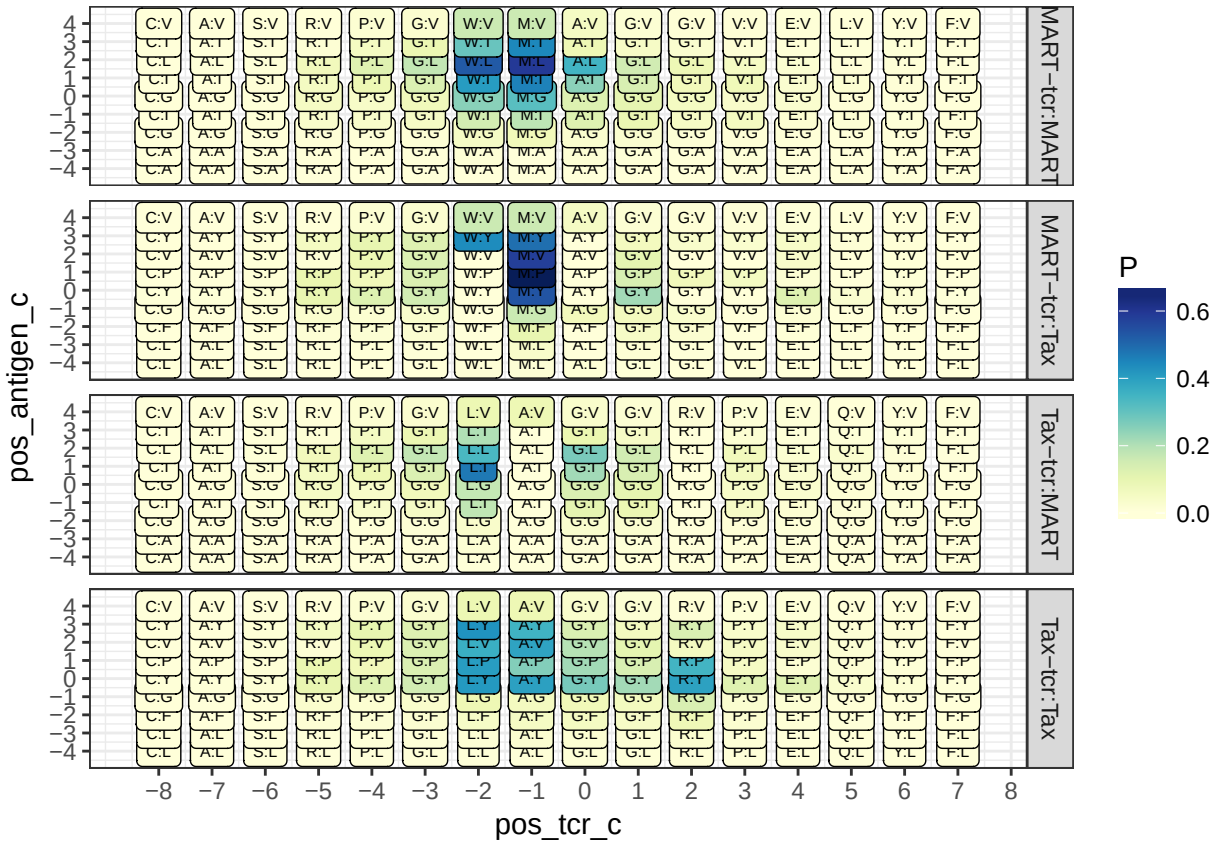



Testing - example 3 same as above - comparing Tax specific vs Tax and MART specific vs MART + cross-comparison. We compare CDR3beta of A6 (wild-type Tax-specific variant) and a MART-specific TCR derived from A6 by direct evolution.

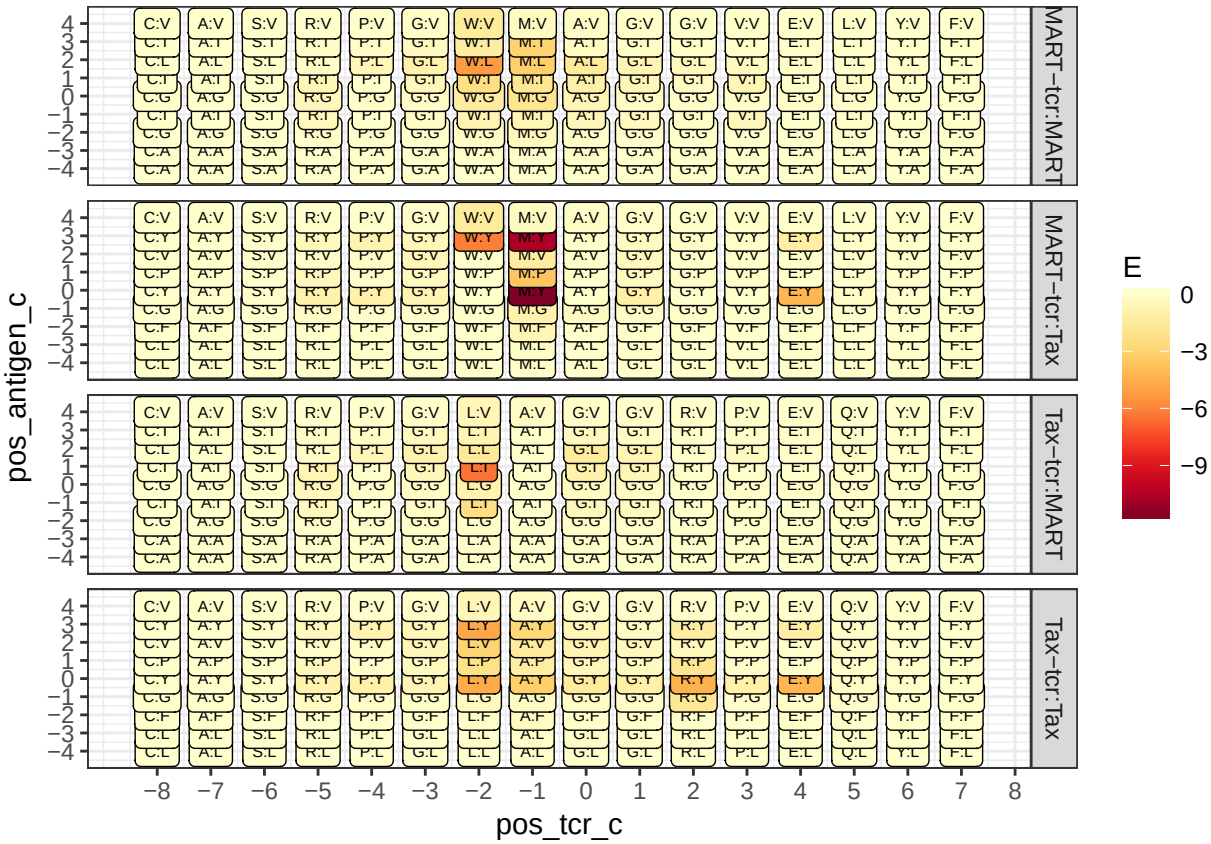
```
cm.tmp.1 = compute_contact_map("MHCI","TRB","CDR3","CASRPGLAGGRPEQYF","LLFGYPVYV","Tax-tcr:Tax")
cm.tmp.1 = rbind(cm.tmp.1, compute_contact_map("MHCI","TRB","CDR3","CASRPGLAGGRPEQYF","AAGIGILTV","Tax-
cm.tmp.1 = rbind(cm.tmp.1, compute_contact_map("MHCI","TRB","CDR3","CASRPGWMAGGVELYF","LLFGYPVYV","MART
cm.tmp.1 = rbind(cm.tmp.1, compute_contact_map("MHCI","TRB","CDR3","CASRPGWMAGGVELYF","AAGIGILTV","MART

print(cm.tmp.1 %>% group_by(id) %>% summarize(contacts = sum(p), energy = sum(p * energy.mean)))
```

```
## # A tibble: 4 × 3
##              id contacts    energy
##           <chr>    <dbl>     <dbl>
## 1 MART-tcr:MART 7.354818 -42.77908
## 2  MART-tcr:Tax 5.984228 -55.59605
## 3  Tax-tcr:MART 4.488071 -28.21870
## 4   Tax-tcr:Tax 8.145584 -59.29974
```

```
ggplot(cm.tmp.1, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("P", colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```




```
ggplot(cm.tmp.1, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p * energy.mean), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("E", colors=rev(colorRampPalette(brewer.pal(9, 'YlOrRd'))(32))) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```

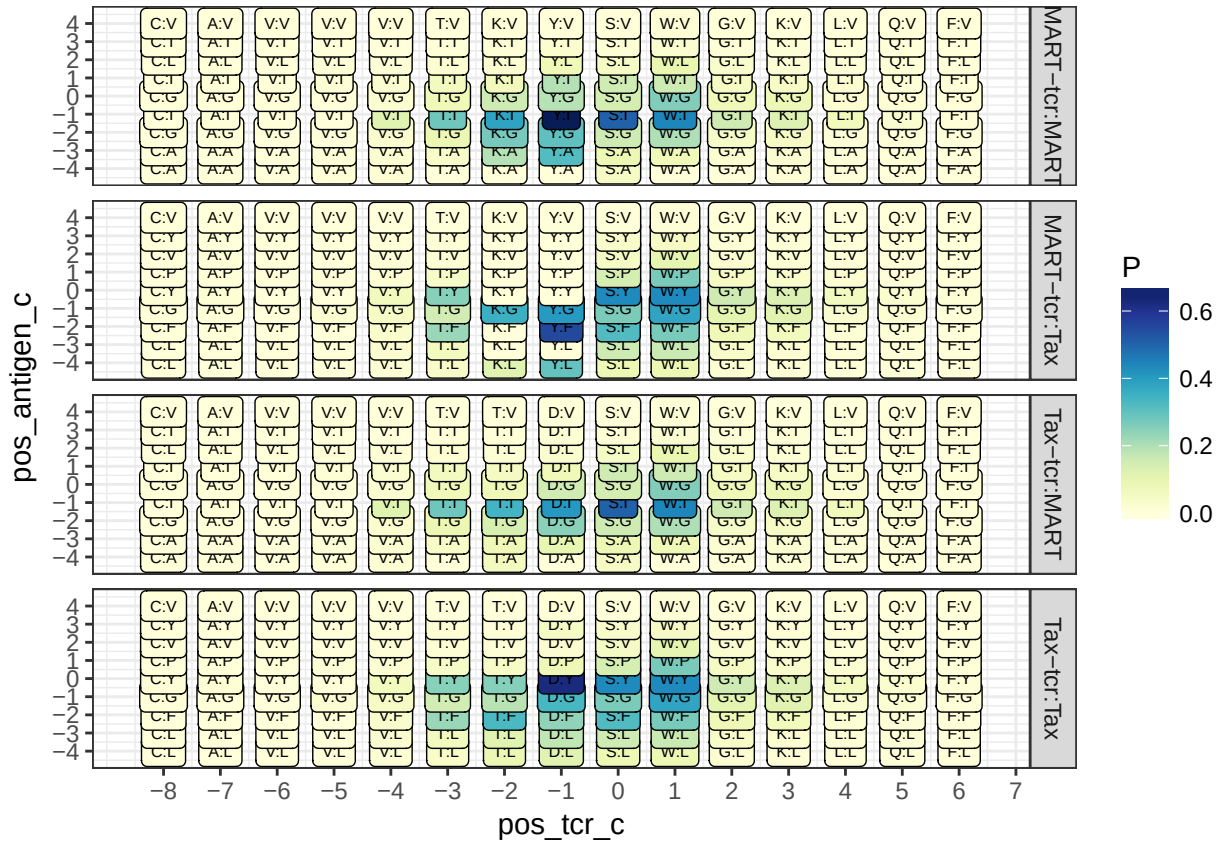



Same as above for alpha chains

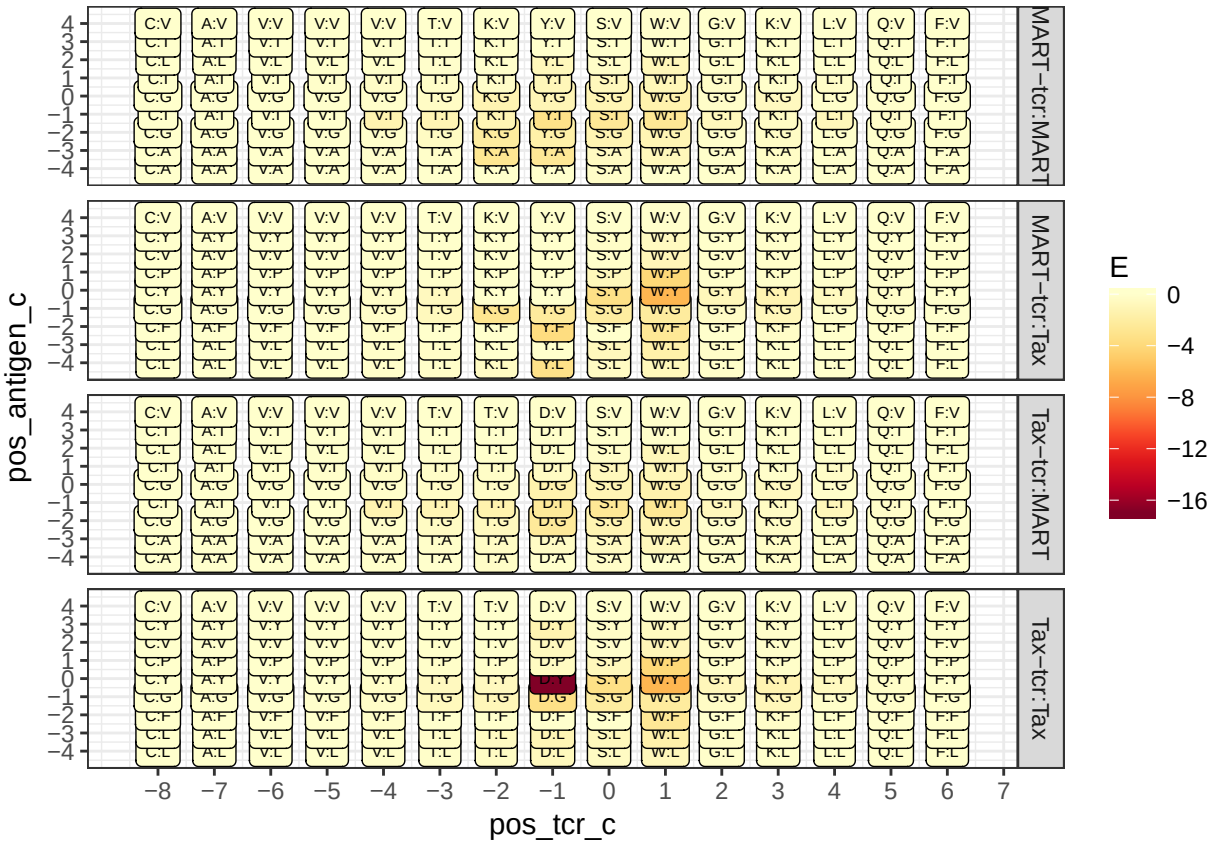
```
cm.tmp.2 = compute_contact_map("MHCI","TRA","CDR3","CAVVVTTDSWGKLQF","LLFGYPVYV","Tax-tcr:Tax")
cm.tmp.2 = rbind(cm.tmp.2, compute_contact_map("MHCI","TRA","CDR3","CAVVVTTDSWGKLQF","AAGIGILTV","Tax-t
cm.tmp.2 = rbind(cm.tmp.2, compute_contact_map("MHCI","TRA","CDR3","CAVVVTKYSWGKLQF","LLFGYPVYV","MART-
cm.tmp.2 = rbind(cm.tmp.2, compute_contact_map("MHCI","TRA","CDR3","CAVVVTKYSWGKLQF","AAGIGILTV","MART-

print(cm.tmp.2 %>% group_by(id) %>% summarize(contacts = sum(p), energy = sum(p * energy.mean)))
```

```
## # A tibble: 4 × 3
##              id contacts    energy
##           <chr>    <dbl>     <dbl>
## 1 MART-tcr:MART 6.857838 -42.29902
## 2  MART-tcr:Tax 6.942484 -48.31163
## 3  Tax-tcr:MART 5.729772 -34.90383
## 4   Tax-tcr:Tax 7.862019 -62.86467
```

```
ggplot(cm.tmp.2, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("P", colors=colorRampPalette(brewer.pal(9, 'YlGnBu'))(32)) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```




```
ggplot(cm.tmp.2, aes(x=pos_tcr_c, y=pos_antigen_c)) +
  geom_tile(fill=NA) +
  geom_label(aes(label=paste(aa_tcr, aa_antigen, sep=":"), fill = p * energy.mean), cex=2) +
  scale_x_continuous(breaks=-8:9) +
  scale_y_continuous(breaks=-5:5) +
  scale_fill_gradientn("E", colors=rev(colorRampPalette(brewer.pal(9, 'YlOrRd'))(32))) +
  facet_grid(id~., scales="free", space="free") +
  theme_bw()
```




Summarize alpha and beta chains

```
print(rbind(cm.tmp.1, cm.tmp.2) %>% group_by(id) %>% summarize(contacts = sum(p), energy = sum(p * energ
```

```
## # A tibble: 4 × 3
##              id contacts     energy
##           <chr>    <dbl>      <dbl>
## 1 MART-tcr:MART 14.21266  -85.07810
## 2  MART-tcr:Tax 12.92671 -103.90768
## 3  Tax-tcr:MART 10.21784  -63.12253
## 4   Tax-tcr:Tax 16.00760 -122.16441
```