

Matching the Pemetrexed Heatmap

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1 Executive Summary

1.1 Introduction

Hsu et al. [3] construct a signature for pemetrexed using the NCI-60 cell lines. They note that pemetrexed and cisplatin sensitivity appear to be inversely correlated in NSCLC, suggesting that patients resistant to one would likely respond to the other. In this report, we outline our reconstruction of the heatmap provided, and our inferences about the specific genes and cell lines involved.

1.2 Methods

We loaded two previously constructed Rda files: novartisA and hsuReportedGeneLists. We extracted quantifications for the reported probesets, and examined heatmaps to see if there was clear separation of sensitive and resistant cell lines. We repeated this procedure after “offsetting” the probesets by one row to account for possible problems with binreg. We then constructed pairwise sample correlation matrices to suggest the specific cell lines used in each group. Starting from this initial guess, we then examined all other sets of cell lines in a local “neighborhood” and assigned each set a “score” of the number of reported probesets (offset or not) that were matched. We shifted to the set with the highest score in the neighborhood and repeated the process until a local maximum was reached. This scoring makes use of Matlab scripts which call the binreg software; the primary file is buildPemetrexedHeatmap.m.

1.3 Results

Using probesets “off-by-one” from those reported, we were able to perfectly reconstruct the heatmap reported, thus identifying the specific genes and cell lines involved. The cell lines are
Resistant (8): K-562, MOLT-4, HL-60(TB), MCF7, HCC-2998, HCT-116, NCI-H460, and TK-10,
Sensitive (10): SNB-19, HS 578T, MDA-MB-231/ATCC, MDA-MB-435, NCI-H226, M14, MALME-3M, SKMEL-2, SK-MEL-28, and SN12C. We match all 85 of the genes reported after offsetting.

The various intermediate files and gene lists for pemetrexed are saved in RDataObjects as pemetrexedAll.Rda.

1.4 Conclusions

The reported signature for pemetrexed is incorrect due to an off-by-one indexing error.

2 Options and Libraries

```
> options(width = 80)
```

3 Loading and Parsing Data

3.1 Earlier Rda Files

We begin by loading two Rda files assembled earlier: novartisA and hsuReportedGenelists.

```
> rdaList <- c("novartisA", "hsuReportedGenelists")
> for (rdaFile in rdaList) {
+   rdaFullFile <- file.path("RDataObjects", paste(rdaFile, "Rda",
+     sep = "."))
+   if (file.exists(rdaFullFile)) {
+     cat("loading ", rdaFullFile, " from cache\n")
+     load(rdaFullFile)
+   }
+   else {
+     cat("building ", rdaFullFile, " from raw data\n")
+     Stangle(file.path("RNowebSource", paste("buildRda", rdaFile,
+       "Rnw", sep = ".")))
+     source(paste("buildRda", rdaFile, "R", sep = "."))
+   }
+ }
```

```
loading RDataObjects/novartisA.Rda from cache
loading RDataObjects/hsuReportedGenelists.Rda from cache
```

4 Matching the Reported Genes

Hsu et al. [3] used 18 cell lines to form their pemetrexed signature: 8 resistant and 10 sensitive. From these, the binreg software was used to select the 85 genes having the most extreme two-sample t-test values separating resistant from sensitive.

We loaded the list of reported genes above. We now check that all of these genes reported are present in the novartisA data matrix.

```
> unmatchedRows <- which(is.na(match(pemetrexedReportedProbesets[,
+   "probesetID"], rownames(novartisA))))
> unmatchedRows

integer(0)

> matchedPemetrexedProbesets <- rownames(pemetrexedReportedProbesets)
```

We match all 85 of the reported probesets.

5 Drawing Heatmaps of the Reported (and Offset) Genes

5.1 A Heatmap of the Reported Genes

We now draw a heatmap showing the expression levels of the reported genes across all of the samples. Since these genes were chosen specifically to separate one group of cell lines from another, we expect to see

some clear differential structure. We center and scale the results for each row (probeset) before display (the heatmap function in R does this scaling by default). We also use an analog of the Matlab jet colormap. The heatmap is shown in Figure 1. There is essentially no separating structure visible.

5.2 A Heatmap of the Reported Genes, Offset

Coombes et al. [1] noted that all of the gene lists initially reported by Potti et al. [4] had been “offset by one” due to an indexing error. We try introducing the same type of offset (e.g., replacing 1100_at with 1101_at) and redrawing the heatmap. This heatmap is shown in Figure 2. There is now clearly visible structure separating groups of cell lines. This suggests that the probesets shown were part of the “true” signature, and that the reported list is incorrect due to the same indexing error that affected the initial gene lists reported by Potti et al. [4].

6 Using Correlation to Guess Starting Cell Lines

We know of no simple analytic way of determining which cell lines were involved, and the names are not given in Hsu et al. [3] or in their supplementary material. We rely instead on a combination of informed guessing and brute force. We begin by looking at correlations between samples using the expression values for the offset genes identified above. A heatmap is shown in Figure 3. Looking at the correlation heatmap suggests some clear candidates for the larger (sensitive) group: the 12 samples in the cluster at the top right. Reading from the top, these are SNB-75, HS 578T, SNB-19, SF-268, NCI-H226, SK-MEL-2, M14, MALME-3M, SK-MEL-28, MDA-MB-231/ATCC, SN12C, and MDA-MB-435. Likewise, the 10 samples in the cluster at the bottom left are good candidates for the smaller (resistant) group. Reading from the top, these are SW-620, NCI-H460, KM12, HCT-116, HCC-2998, K-562, CCRF-CEM, HL-60(TB), MCF7, and MOLT-4.

```
> startingSensitiveLines <- c("SNB-75", "HS 578T", "SNB-19", "SF-268",
+   "NCI-H226", "SK-MEL-2", "M14", "MALME-3M", "SK-MEL-28", "MDA-MB-231/ATCC",
+   "SN12C", "MDA-MB-435")
> startingResistantLines <- c("SW-620", "NCI-H460", "KM12", "HCT-116",
+   "HCC-2998", "K-562", "CCRF-CEM", "HL-60(TB)", "MCF7", "MOLT-4")
```

The starting lists involve 12 and 10 cell lines, respectively, whereas Hsu et al. [3] use 10 and 8.

7 Steepest Ascent with Binreg

In order to improve our guess, we use a process of steepest ascent with the binreg software used by Potti et al. [4] Specifically, we give each set of cell lines a score corresponding to the number of target probesets we can match. From our starting set, we score all sets that can be reached by changing the status of at most one cell line (e.g., from sensitive to resistant, from sensitive to excluded, from excluded to resistant). We then shift our central location to the set in the neighborhood with the highest score and repeat until a local maximum is reached.

7.1 Exporting the Novartis A NCI-60 Data

To conduct our search, we first export the novartisA NCI-60 in a format usable by binreg.

```

> tempMat <- log2(novartisA[matchedPemetrexedProbesets, ])
> source(file.path("Scripts", "jet.colors.R"))
> heatmap(as.matrix(tempMat), col = jet.colors(64), margins = c(7,
+ 4), cexRow = 0.45, cexCol = 0.65)

```

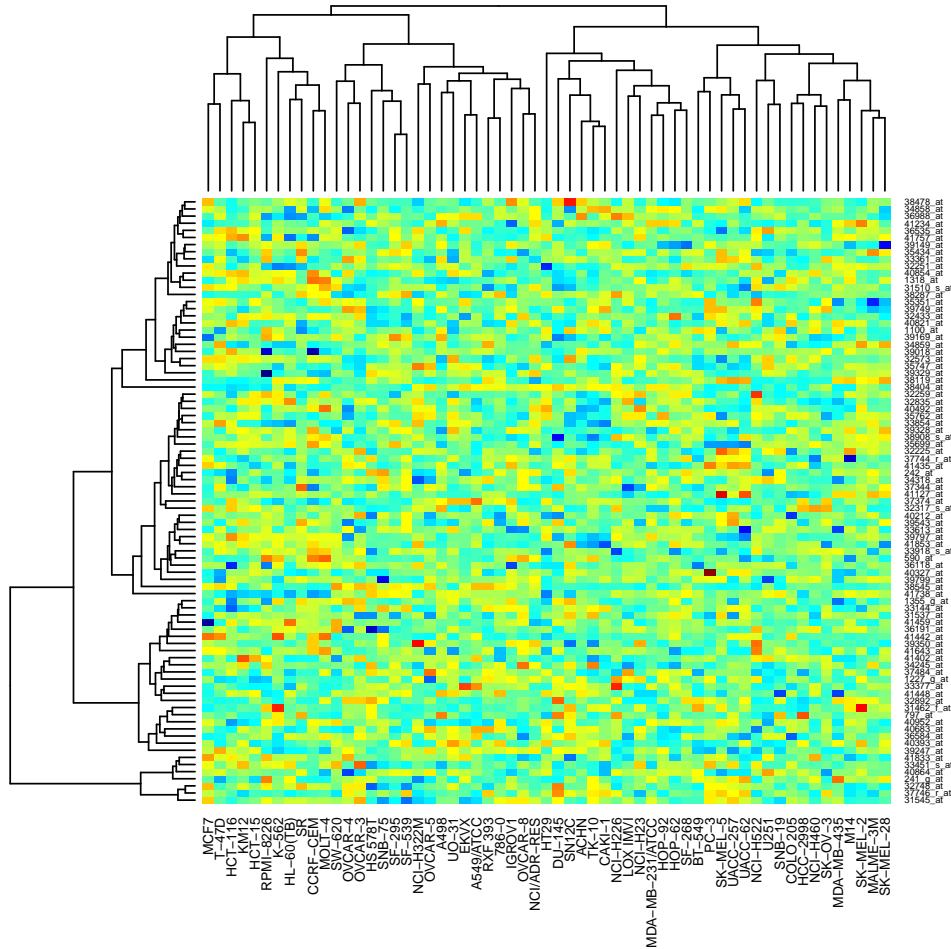


Figure 1: Heatmap of centered expression values from the Novartis A set expression data for the pemetrexed probesets reported by Hsu et al. [3] As these genes were chosen to separate sensitive from resistant lines, we expect to see fairly pervasive structure separating two subgroups. We do not see this structure.

```

> offsetPemetrexedProbesets <- rownames(novartisA)[match(matchedPemetrexedProbesets,
+   rownames(novartisA)) + 1]
> tempMat <- log2(novartisA[offsetPemetrexedProbesets, ])
> heatmap(as.matrix(tempMat), col = jet.colors(64), margins = c(7,
+   4), cexRow = 0.45, cexCol = 0.65)

```

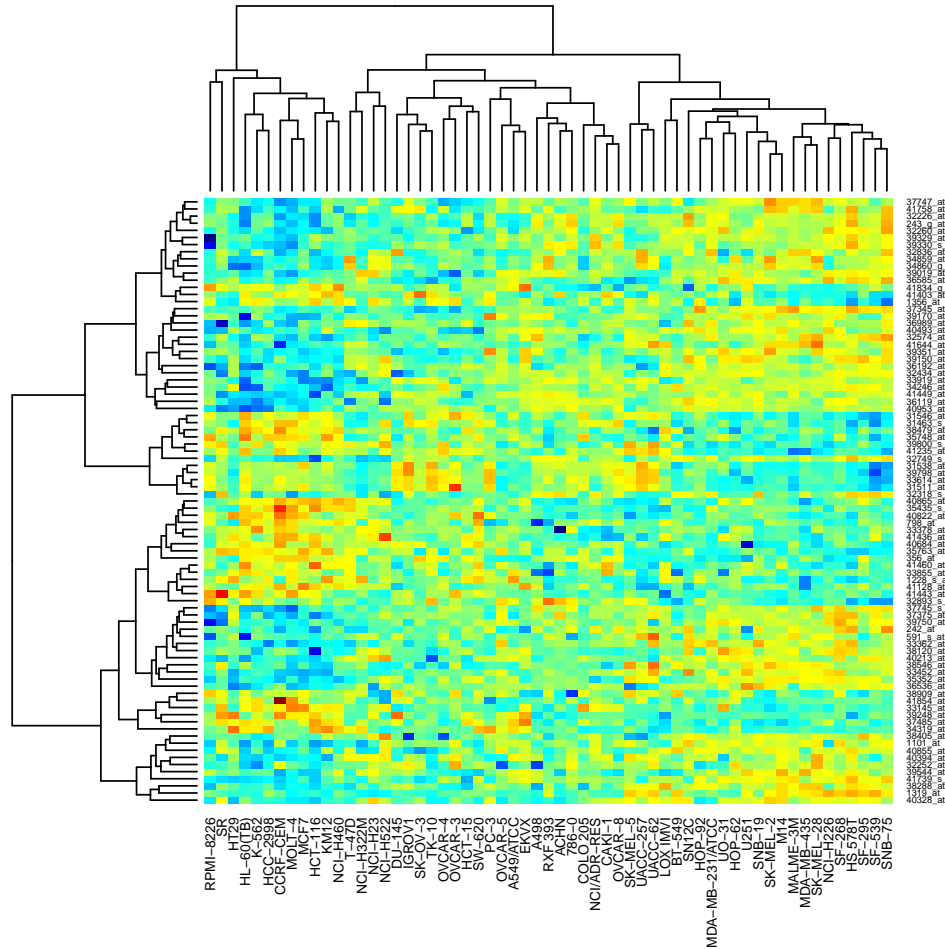


Figure 2: Heatmap of centered expression values from the Novartis A set expression data for the probesets reported by Hsu et al. [3] after “offsetting” by one row. As genes were chosen to separate sensitive from resistant lines, we expect to see fairly pervasive structure separating two subgroups. We see this structure here, suggesting that the reported list is incorrect due to an indexing error.

```
> pemetrexedCor <- cor(t(scale(t(tempMat))))
> heatmap(pemetrexedCor, scale = "none", margins = c(7, 7), cexCol = 0.7,
+       cexRow = 0.7, col = jet.colors(64))
```

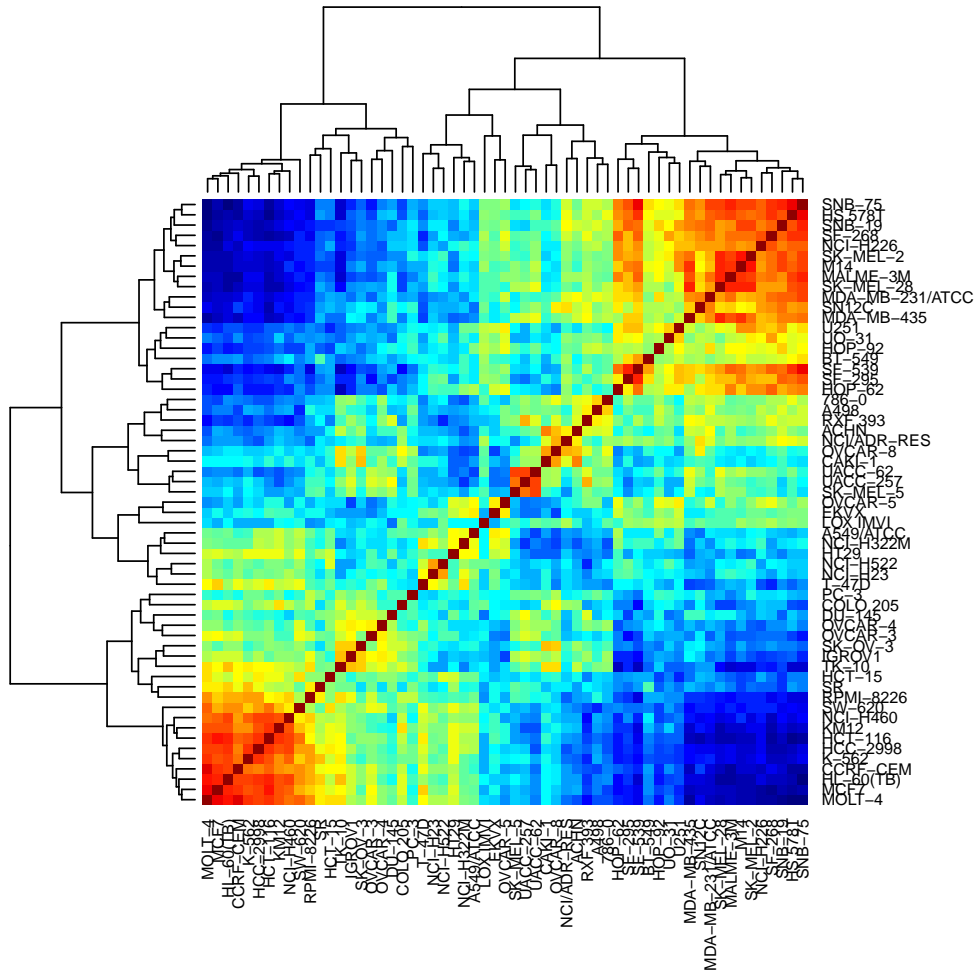


Figure 3: Heatmap of correlations between samples using the offset probesets from Figure 2. The clearest groups of cell lines are those in the upper right and lower left.


```

> affyControlRows = grep("^AFFX", rownames(novartisA))
> write.table(novartisA[-affyControlRows, ], file = file.path("MatlabFiles",
+   "NCI60Data", "nci60_numbers.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE)
> write.table(rownames(novartisA)[-affyControlRows], file = file.path("MatlabFiles",
+   "NCI60Data", "nci60_probesets.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE, quote = FALSE)
> write.table(colnames(novartisA), file = file.path("MatlabFiles",
+   "NCI60Data", "nci60_samples.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE, quote = FALSE)

```

7.2 Exporting the Starting Guess

We likewise export our starting guesses for the resistant and sensitive cell lines, and the target probeset ids that we want to match.

```

> write.table(startingResistantLines, file = file.path("MatlabFiles",
+   "Pemetrexed", "startingResistantLines.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE, quote = FALSE)
> write.table(startingSensitiveLines, file = file.path("MatlabFiles",
+   "Pemetrexed", "startingSensitiveLines.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE, quote = FALSE)
> write.table(offsetPemetrexedProbesets, file = file.path("MatlabFiles",
+   "Pemetrexed", "targetProbesets.csv"), sep = ",", row.names = FALSE,
+   col.names = FALSE, quote = FALSE)

```

7.3 Invoking Matlab

The main Matlab script is buildPemetrexedHeatmap.m. This script iteratively explores the neighborhood to increase the score until a maximum is found. At each iteration, it produces a figure indicating how the current guess should be changed. For pemetrexed, this search and change process takes seven steps, as illustrated in Figures 4-10. The baseline score is 58 in agreement. The biggest jump (to 66) is seen when we add TK-10 to the resistant group. The biggest jump in the second neighborhood (to 71) is seen when we drop SW-620 from the resistant group. The biggest jump in the third neighborhood (to 73) is seen when we drop SNB-75 from the sensitive group. There is no change in the fourth neighborhood that causes an increase, and only one alteration to the list that leaves things at 73 – dropping KM12 from the resistant group (we make this alteration). The biggest jump in the fifth neighborhood (and there is one, to 77) is seen when we drop SF-268 from the sensitive group. The biggest jump in the sixth neighborhood (to 85, a perfect score) is seen when we drop CCRF-CEM from the resistant group. Exploring the seventh neighborhood shows that we are indeed at a maximum; any further alteration of the list drops the score. The numbers of resistant and sensitive lines now match those shown by Hsu et al. [3]

After reaching a local maximum, we produce a heatmap using the final set of cell lines selected. This heatmap, shown in Figure 11, perfectly matches the one shown in Figure 1B of Hsu et al. [3]

8 Loading Matlab Output and Comparing Gene Lists

8.1 Loading Scores from Each Iteration

We begin by loading the numerical scores and starting vectors for each iteration of the fitting procedure.

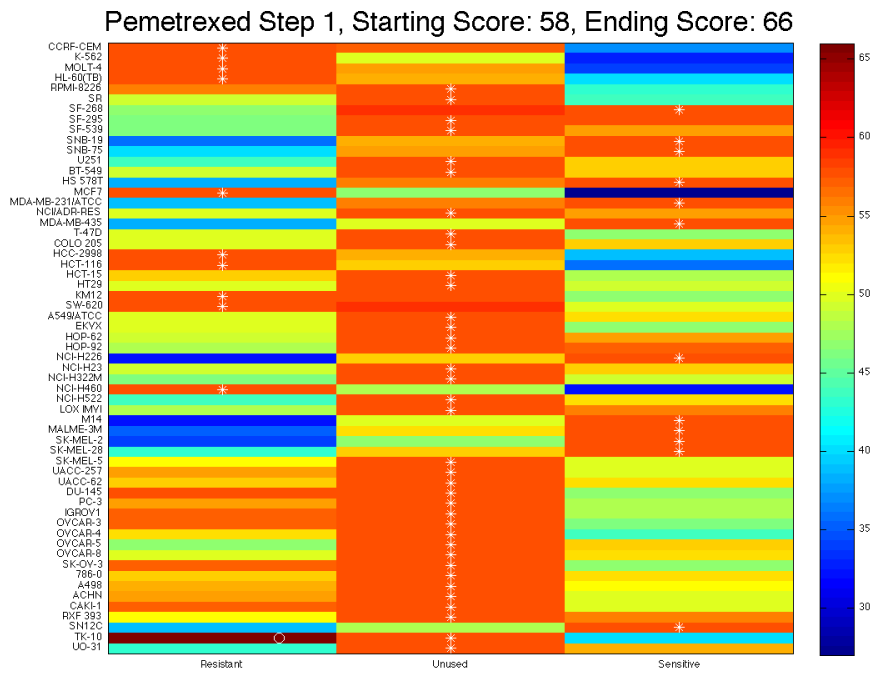


Figure 4: First iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving TK-10 from Unused to Resistant) is indicated with an offset circle. This shift increases the score from 58 to 66.

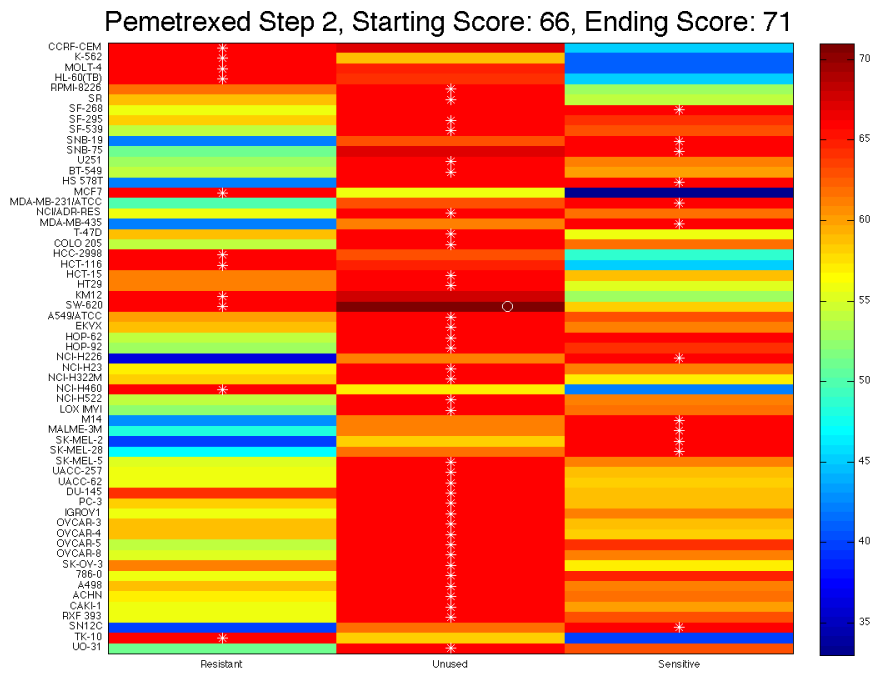


Figure 5: Second iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving SW-620 from Resistant to Unused) is indicated with an offset circle. This shift increases the score from 66 to 71.

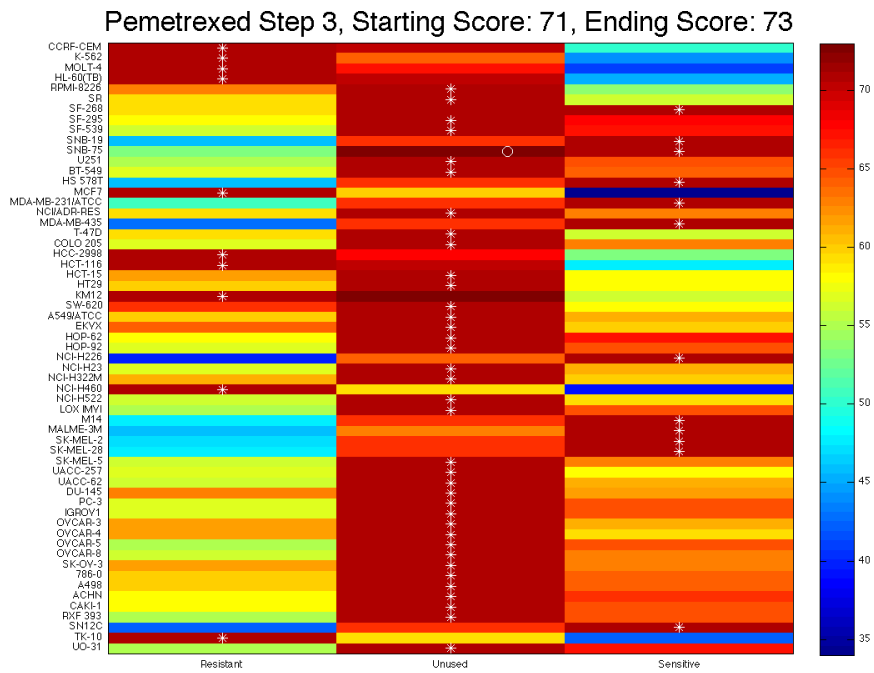


Figure 6: Third iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving SNB-75 from Sensitive to Unused) is indicated with an offset circle. This shift increases the score from 71 to 73.

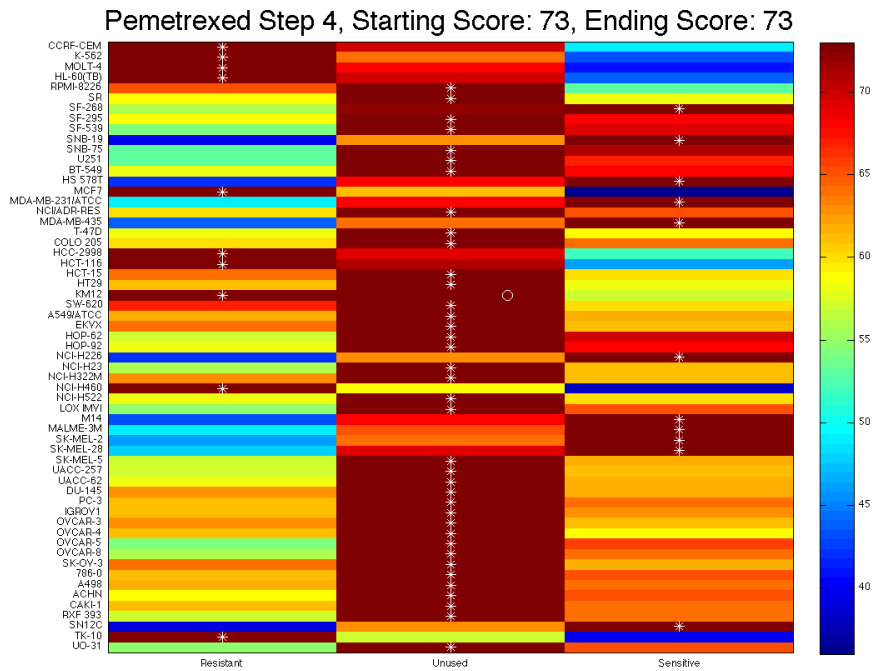


Figure 7: Fourth iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving KM12 from Resistant to Unused) is indicated with an offset circle. This shift leaves the score unchanged at 73.



Figure 8: Fifth iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving SF-258 from Sensitive to Unused) is indicated with an offset circle. This shift increases the score from 73 to 77.



Figure 9: Sixth iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. The shift producing the maximum score (moving CCRF-CEM from Resistant to Unused) is indicated with an offset circle. This shift increases the score from 77 to 85.

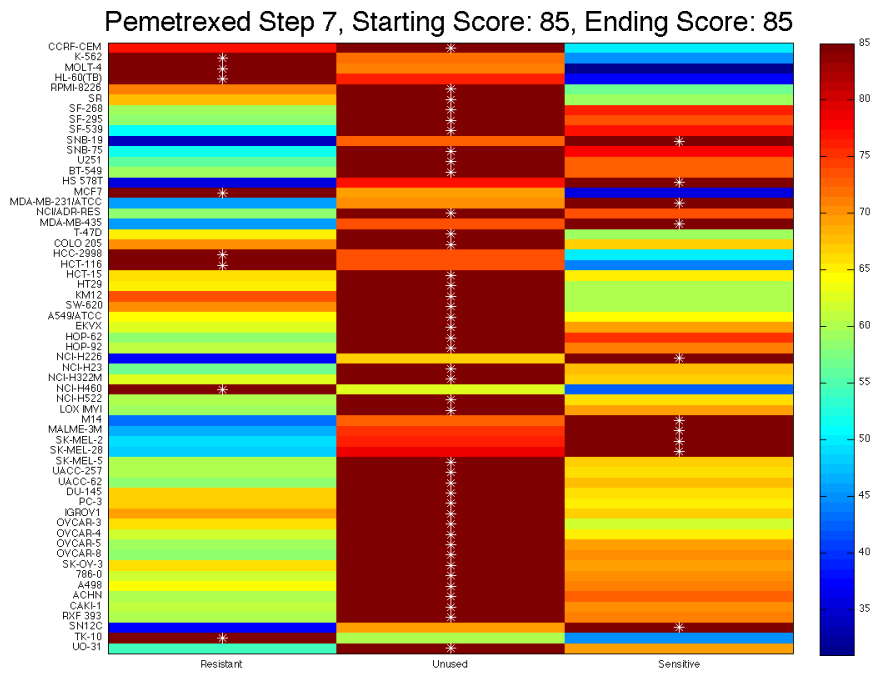


Figure 10: Seventh iteration to find an overall maximum for pemetrexed. White asterisks indicate the status of each cell line using the starting guess, and colors indicate how the score increases or decreases as a given change is made. Any shift from the current guess decreases the score. Our best score is 85 (a perfect match).

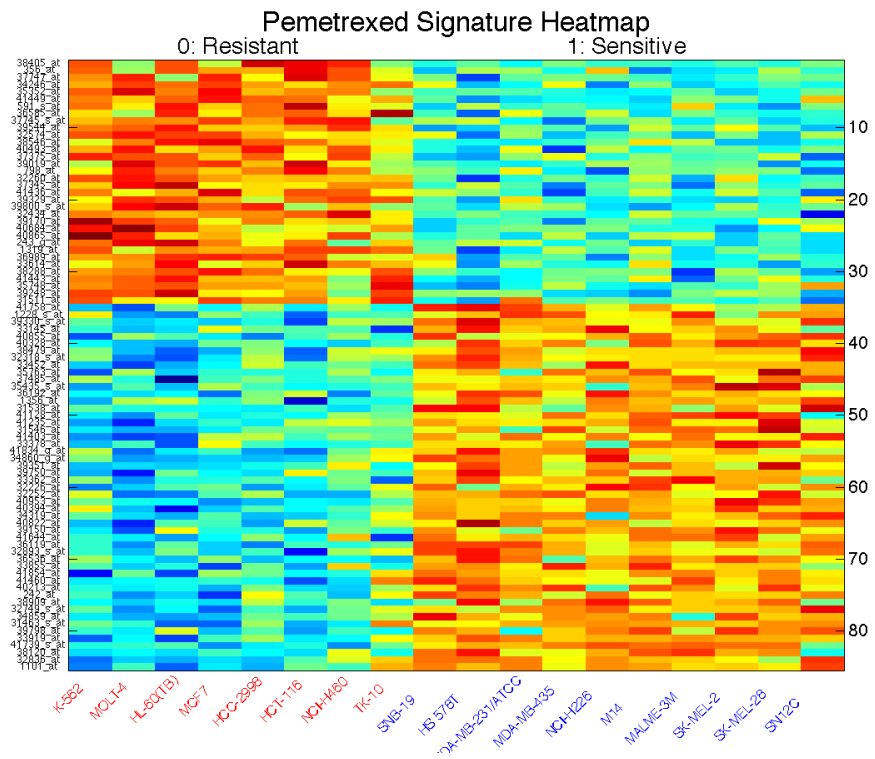


Figure 11: Heatmap for the pemetrexed signature using the final set of cell lines obtained through our search procedure. This heatmap is a perfect match for that in Figure 1B of Hsu et al. [3], indicating that these are the cell lines and genes involved.

```

> pemetrexedIteration1 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration1.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration2 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration2.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration3 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration3.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration4 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration4.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration5 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration5.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration6 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration6.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration7 <- read.table(file.path("MatlabFiles", "Pemetrexed",
+      "pemetrexedIteration7.csv"), header = TRUE, sep = ",", row.names = 1)
> pemetrexedIteration7[1:5, ]

```

	startStatus	Resistant	Unused	Sensitive
CCRF-CEM	Unused	77	85	50
K-562	Resistant	85	72	45
MOLT-4	Resistant	85	71	31
HL-60(TB)	Resistant	85	76	37
RPMI-8226	Unused	71	85	57

8.2 Extracting the Cell Lines Used

Next, we extract the cell lines used to obtain the perfectly matching heatmap.

```

> pemetrexedResistantLines <- rownames(pemetrexedIteration3)[pemetrexedIteration7[,
+   "startStatus"] == "Resistant"]
> pemetrexedSensitiveLines <- rownames(pemetrexedIteration3)[pemetrexedIteration7[,
+   "startStatus"] == "Sensitive"]
> pemetrexedResistantLines

[1] "K-562"      "MOLT-4"     "HL-60(TB)" "MCF7"       "HCC-2998"   "HCT-116"
[7] "NCI-H460"  "TK-10"

> pemetrexedSensitiveLines

[1] "SNB-19"      "HS 578T"      "MDA-MB-231/ATCC" "MDA-MB-435"
[5] "NCI-H226"    "M14"          "MALME-3M"       "SK-MEL-2"
[9] "SK-MEL-28"  "SN12C"

```

8.3 Loading the Heatmap Genes

Next, we load the probesets used in the final heatmap.

```

> softwarePemetrexedProbesets <- read.table(file.path("MatlabFiles",
+   "Pemetrexed", "topPemetrexedGenesInHeatmapOrder.txt"), header = FALSE,
+   sep = ",", strip.white = TRUE)
> softwarePemetrexedProbesets <- as.character(softwarePemetrexedProbesets[,

```

```

+     1])
> sort(softwarePemetrexedProbesets)

 [1] "1101_at"    "1228_s_at"  "1319_at"    "1356_at"    "242_at"
 [6] "243_g_at"   "31463_s_at" "31511_at"   "31538_at"   "31546_at"
[11] "32226_at"   "32252_at"   "32260_at"   "32318_s_at" "32434_at"
[16] "32574_at"   "32749_s_at" "32836_at"   "32893_s_at" "33145_at"
[21] "33362_at"   "33378_at"   "33452_at"   "33614_at"   "33855_at"
[26] "33919_at"   "34246_at"   "34319_at"   "34859_at"   "34860_g_at"
[31] "35352_at"   "35435_s_at" "356_at"     "35748_at"   "35763_at"
[36] "36119_at"   "36192_at"   "36536_at"   "36585_at"   "36989_at"
[41] "37345_at"   "37375_at"   "37485_at"   "37745_s_at" "37747_at"
[46] "38120_at"   "38288_at"   "38405_at"   "38479_at"   "38546_at"
[51] "38909_at"   "39019_at"   "39150_at"   "39170_at"   "39248_at"
[56] "39329_at"   "39330_s_at" "39351_at"   "39544_at"   "39750_at"
[61] "39798_at"   "39800_s_at" "40213_at"   "40328_at"   "40394_at"
[66] "40493_at"   "40684_at"   "40822_at"   "40855_at"   "40865_at"
[71] "40953_at"   "41128_at"   "41235_at"   "41403_at"   "41436_at"
[76] "41443_at"   "41449_at"   "41460_at"   "41644_at"   "41739_s_at"
[81] "41758_at"   "41834_g_at" "41854_at"   "591_s_at"   "798_at"

```

8.4 Comparing Gene Lists

Now we see which genes we can and cannot match.

```

> sum(!is.na(match(offsetPemetrexedProbesets, softwarePemetrexedProbesets)))

 [1] 85

> setdiff(softwarePemetrexedProbesets, offsetPemetrexedProbesets)

character(0)

```

As noted above, the software output matches the offset gene list perfectly.

9 Save Rda File

Finally, we save the data associated with our examination of the pemetrexed signature.

```

> save(pemetrexedCor, pemetrexedIteration1, pemetrexedIteration2,
+      pemetrexedIteration3, pemetrexedIteration4, pemetrexedIteration5,
+      pemetrexedIteration6, pemetrexedIteration7, pemetrexedReportedProbesets,
+      pemetrexedResistantLines, pemetrexedSensitiveLines, pemetrexedTable,
+      matchedPemetrexedProbesets, offsetPemetrexedProbesets, softwarePemetrexedProbesets,
+      file = file.path("RDataObjects", "pemetrexedAll.Rda"))

```

10 Appendix

10.1 File Location

```
> getwd()
[1] "/Users/kabagg/ReproRsch/AnnAppStat"
```

10.2 Saves

10.3 SessionInfo

```
> sessionInfo()

R version 2.9.1 (2009-06-26)
i386-apple-darwin8.11.1

locale:
en_US.UTF-8/en_US.UTF-8/C/C/en_US.UTF-8/en_US.UTF-8

attached base packages:
[1] stats      graphics  grDevices  utils      datasets  methods    base

other attached packages:
[1] geneflotter_1.22.0 lattice_0.17-25  annotate_1.22.0
[4] AnnotationDbi_1.6.1 Biobase_2.4.1    XML_2.6-0

loaded via a namespace (and not attached):
[1] DBI_0.2-4      grid_2.9.1      KernSmooth_2.23-2 RColorBrewer_1.0-2
[5] RSQLite_0.7-1 xtable_1.5-5
```

References

- [1] Coombes KR, Wang J, Baggerly KA: Microarrays: retracing steps. *Nat Med*, **13**:1276-7, 2007. Author reply, 1277-8.
- [2] Györfy B, Surowiak P, Kiesslich O, et al.: Gene expression profiling of 30 cancer cell lines predicts resistance towards 11 anticancer drugs at clinically achieved concentrations. *Int J Cancer*, **118**:1699-712, 2006.
- [3] Hsu DS, Balakumaran BS, Acharya CR, et al.: Pharmacogenomic strategies provide a rational approach to the treatment of cisplatin-resistant patients with advanced cancer. *J Clin Oncol*, **25**:4350-4357, 2007
- [4] Potti A, Dressman HK, Bild A, et al: Genomic signatures to guide the use of chemotherapeutics. *Nat Med*, **12**:1294-1300, 2006.