

Analysis of TP53 Data

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To install the gpsim software, Antti suggests the following:

```
mkdir ~/R-libs
cd ~/mlprojects/gpsim/R
R CMD INSTALL --library=~/R-libs .
```

First we load in the raw cel files and process using mmgmos. This takes about 20 minutes to run. There is normalization done by multi-mgMOS which is median based. Just as a sanity check we can have a quick look at this normalization.

Perform clustering on data with 11 clusters,

	Length	Class	Mode
y	1	-none-	list
yvar	1	-none-	list
times	13	-none-	numeric
genes	22690	-none-	character
scale	22690	-none-	numeric
ratioData	4	-none-	list

1 Targets Suggested by TSNI

First experiment; we take the top 9 predicted targets from TSNI. We try and explain these through the GPSIM model. Targets taken from [?] (Supplementary Table 1). We initialize the model setting sensitivities to -1 if a target is repressed, and setting the length scale to reflect the fact that time points are taken every 20 minutes.

Gaussian process single input motif model:

Number of time points:

Number of genes: 9

Basal transcription rate:

Gene 1: 1.65673654935152

Gene 2: 2.7628399246217

Gene 3: 1.94234696280137

Gene 4: 2.28788172492768

Gene 5: 3.2111972230618

Gene 6: 3.74787723593359

Gene 7: 2.77775620446388

Gene 8: 2.04583104038801

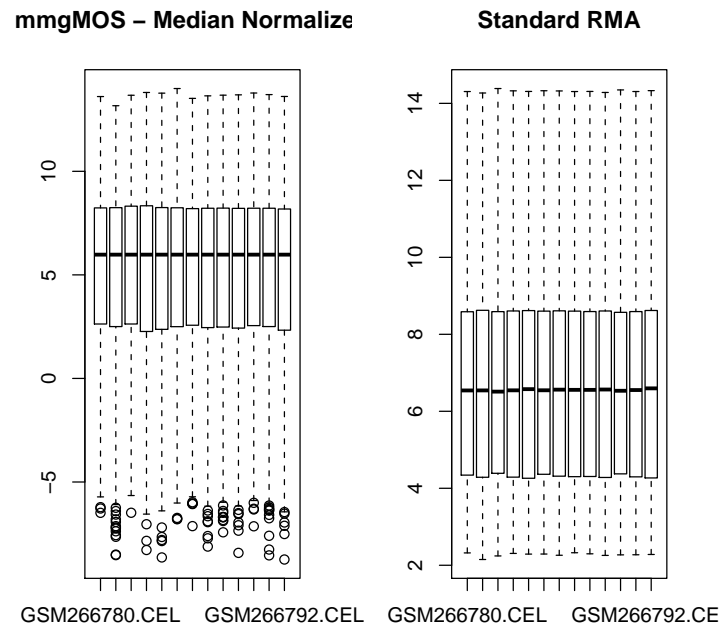


Figure 1: Left: multi-mgMOS normalization of expression data. Right: standard RMA normalization of expression data.

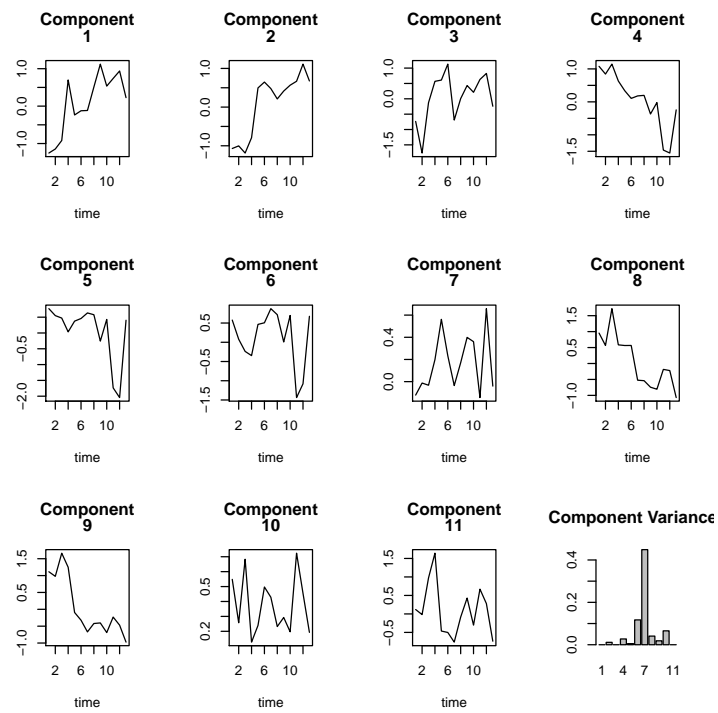


Figure 2: Clustering of the data using pumaClust using 11 components.

Gene 9: 2.98317478812787

Kernel:

Multiple output block kernel:

Block 1

RBF inverse width: 0.0025 (length scale 20)

RBF variance: 1

Block 2

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: 1

Block 3

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 4

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 5

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: 1

Block 6

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 7

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 8

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 9

Non-stationary version of the kernel

Sensitivities allowed to be negative.
 SIM decay: 1
 SIM inverse width: 0.0025 (length scale 20)
 SIM Sensitivity: -1
 Block 10
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1
 SIM inverse width: 0.0025 (length scale 20)
 SIM Sensitivity: -1

Now we optimise the model for a maximum of 1000 iterations with scaled conjugate gradient [?]. Below are the parameters of the optimized model.

Optimizing genes 1419728_at 1417065_at 1420350_at 1419215_at 1432032_a_at 1418355_at 14508

Finished.

Gaussian process single input motif model:

Number of time points:
 Number of genes: 9
 Basal transcription rate:
 Gene 1: 0.638280304071994
 Gene 2: 3.67766918194326
 Gene 3: 2.6363630851479
 Gene 4: 1.40171856777711
 Gene 5: 3.61693406919537
 Gene 6: 4.34819978938802
 Gene 7: 3.20541655018555
 Gene 8: 2.53840997388237
 Gene 9: 3.56847185316651

Kernel:

Multiple output block kernel:
 Block 1
 RBF inverse width: 0.001194142 (length scale 28.93823)
 RBF variance: 1
 Block 2
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.509086
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: 1.563712
 Block 3
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.341618
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.2417944
 Block 4
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.

SIM decay: 0.888961
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.9322217
 Block 5
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.211666
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: 1.049817
 Block 6
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.9397985
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.6777505
 Block 7
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.922723
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.9231063
 Block 8
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.8290811
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.9090726
 Block 9
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.8124591
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.8746456
 Block 10
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.9168052
 SIM inverse width: 0.001194142 (length scale 28.93823)
 SIM Sensitivity: -0.903592

In Figure 3 we show the inferred transcription factor activity and the implied gene expression for the top nine targets of TSNI.

2 ChIP Induced Targets

Now we create a different model using targets given by ChIP binding experiments.

Gaussian process single input motif model:
 Number of time points:

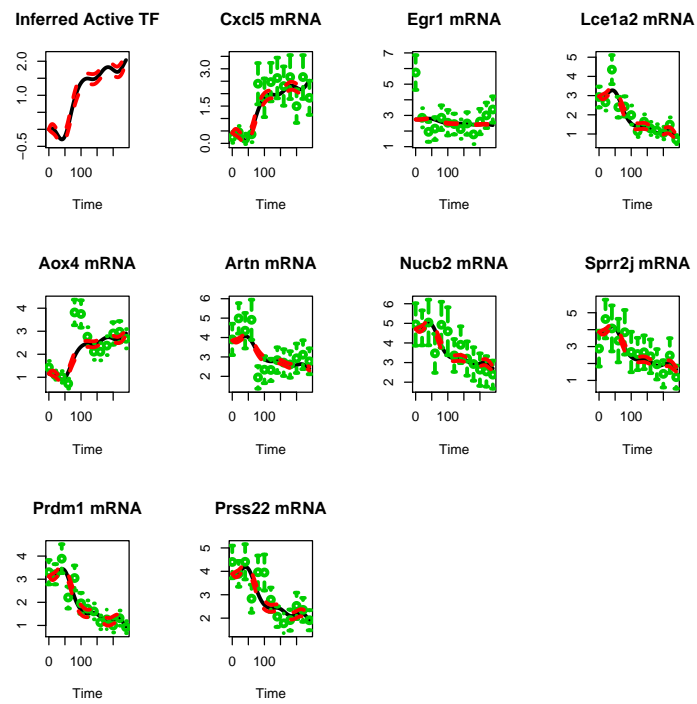


Figure 3: Estimated transcription factor activity and gene expression derived from that activity for TSNI identified targets.

Number of genes: 9

Basal transcription rate:

- Gene 1: 2.71727073880032
- Gene 2: 4.42764740913062
- Gene 3: 3.54983809814947
- Gene 4: 3.12428126185475
- Gene 5: 3.16368068669093
- Gene 6: 4.49770509968614
- Gene 7: 2.79678475727662
- Gene 8: 2.05172174865338
- Gene 9: 1.61445962141905

Kernel:

Multiple output block kernel:

Block 1

- RBF inverse width: 0.0025 (length scale 20)
- RBF variance: 1

Block 2

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1
- SIM inverse width: 0.0025 (length scale 20)
- SIM Sensitivity: 1

Block 3

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1
- SIM inverse width: 0.0025 (length scale 20)
- SIM Sensitivity: 1

Block 4

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1
- SIM inverse width: 0.0025 (length scale 20)
- SIM Sensitivity: -1

Block 5

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1
- SIM inverse width: 0.0025 (length scale 20)
- SIM Sensitivity: 1

Block 6

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1
- SIM inverse width: 0.0025 (length scale 20)
- SIM Sensitivity: 1

Block 7

- Non-stationary version of the kernel
- Sensitivities allowed to be negative.
- SIM decay: 1


```

SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: 1
Block 8
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: 1
Block 9
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 10
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1

```

Now we optimise the model for a maximum of 1000 iterations with scaled conjugate gradient [?]. Below are the parameters of the optimized model.

Optimizing genes 1449876_at 1420851_at 1427537_at 1450055_at 1424842_a_at 1418488_s_at 145
Finished.

Gaussian process single input motif model:

```

Number of time points:
Number of genes: 9
Basal transcription rate:
Gene 1: 2.10093131270225
Gene 2: 3.04677377924095
Gene 3: 4.04622238537271
Gene 4: 1.75716373607305
Gene 5: 2.73118385139885
Gene 6: 4.18838369962362
Gene 7: 1.63974541872706
Gene 8: 1.15673842007403
Gene 9: 2.62835509472822

```

Kernel:

```

Multiple output block kernel:
Block 1
RBF inverse width: 0.001236036 (length scale 28.44359)
RBF variance: 1
Block 2
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1.413685
SIM inverse width: 0.001236036 (length scale 28.44359)

```

SIM Sensitivity: 0.8953301
 Block 3
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.986706
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 1.242598
 Block 4
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.8875609
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: -0.9317456
 Block 5
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.9963758
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 1.249836
 Block 6
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.21884
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 0.9693802
 Block 7
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.197184
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 1.006858
 Block 8
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.088448
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 1.303119
 Block 9
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.667704
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: 2.059236
 Block 10
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.672141
 SIM inverse width: 0.001236036 (length scale 28.44359)
 SIM Sensitivity: -0.4684839

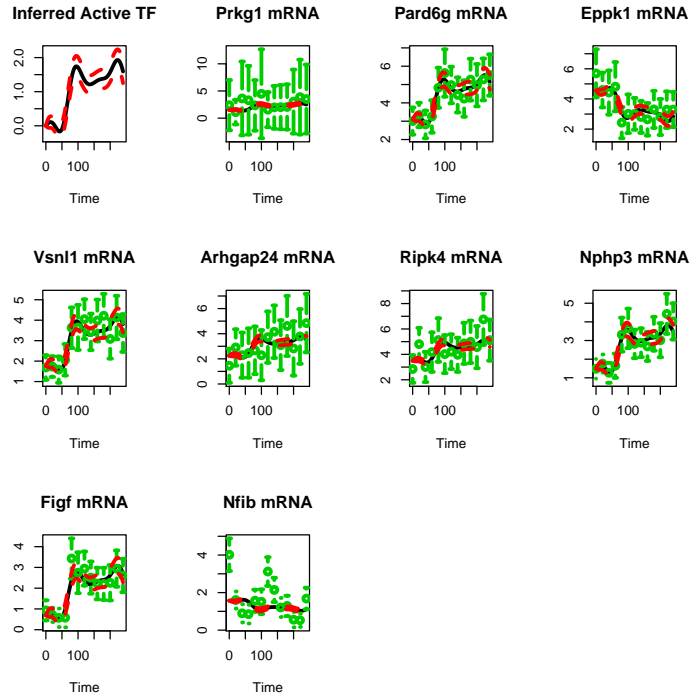


Figure 4: Estimated transcription factor activity and gene expression derived from that activity for ChIP identified targets.

In Figure 4 we show the inferred transcription factor activity and the implied gene expression for the top nine targets according to ChIP binding strength.

3 Independently Confirmed Literature Targets

Finally we create a further model using targets identified by the literature, in two separate papers. There are 12 of these, interestingly they are all cases where TP63 acts as a repressor, but for the other models we had several cases of activation.

Gaussian process single input motif model:

Number of time points:

Number of genes: 12

Basal transcription rate:

Gene 1: 2.62607572083916

Gene 2: 2.09713845900778

Gene 3: 3.2111972230618

Gene 4: 3.45060158580463

Gene 5: 2.12541883504727

Gene 6: 2.20149800962417

Gene 7: 2.01009948373733

Gene 8: 1.55244837111471
 Gene 9: 2.39777171736749
 Gene 10: 1.19597137683305
 Gene 11: 4.15273339554879
 Gene 12: 2.42420764408452

Kernel:

Multiple output block kernel:

Block 1

RBF inverse width: 0.0025 (length scale 20)

RBF variance: 1

Block 2

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 3

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 4

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 5

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 6

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 7

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

SIM inverse width: 0.0025 (length scale 20)

SIM Sensitivity: -1

Block 8

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1

```

SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 9
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 10
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 11
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 12
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1
Block 13
Non-stationary version of the kernel
Sensitivities allowed to be negative.
SIM decay: 1
SIM inverse width: 0.0025 (length scale 20)
SIM Sensitivity: -1

```

Now we optimise the model for a maximum of 1000 iterations with scaled conjugate gradient [?]. Below are the parameters of the optimized model.

Optimizing genes 1450014_at 1449519_at 1432032_a_at 1418350_at 1416916_at 1448694_at 14230

Finished.

Gaussian process single input motif model:

```

Number of time points:
Number of genes: 12
Basal transcription rate:
Gene 1: 2.67051899676575
Gene 2: 2.52663481316057
Gene 3: 4.16655214560397
Gene 4: 4.21110047880415
Gene 5: 2.61905212937489
Gene 6: 2.70210065340353
Gene 7: 2.51191334340965

```

Gene 8: 2.92227395516449
 Gene 9: 1.98478878723145
 Gene 10: 1.60482292424213
 Gene 11: 4.39320297879432
 Gene 12: 3.16459814875772

Kernel:

Multiple output block kernel:

Block 1

RBF inverse width: 0.0007863732 (length scale 35.66035)

RBF variance: 1

Block 2

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 0.7596348

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.7838613

Block 3

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 0.8499611

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.8689609

Block 4

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1.055300

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.9467449

Block 5

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 1.028656

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.8125815

Block 6

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 0.8171976

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.988543

Block 7

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 0.8868582

SIM inverse width: 0.0007863732 (length scale 35.66035)

SIM Sensitivity: -0.8760437

Block 8

Non-stationary version of the kernel

Sensitivities allowed to be negative.

SIM decay: 0.8269738

SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -0.971253
 Block 9
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 1.180809
 SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -1.251162
 Block 10
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.6146354
 SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -0.654024
 Block 11
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.7538652
 SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -0.7989634
 Block 12
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.8273999
 SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -1.071594
 Block 13
 Non-stationary version of the kernel
 Sensitivities allowed to be negative.
 SIM decay: 0.959274
 SIM inverse width: 0.0007863732 (length scale 35.66035)
 SIM Sensitivity: -0.9593601

In Figure 5 we show the inferred transcription factor activity and the implied gene expression for the twelve targets taken from the literature.

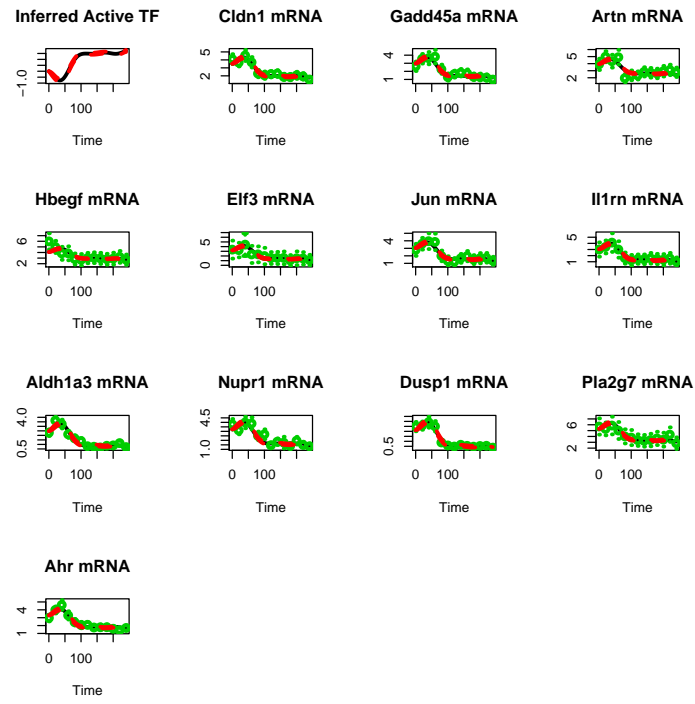


Figure 5: Estimated transcription factor activity and gene expression derived from literature targets.