Time-course paper

Carsten O. Daub
Albin Sandelin
Erik Arner

Version: February 10th, 2014

Sections

1. Introduction
2. Data descriptor/Resource/novel stuff – Fig 1
   - Broad coverage of state change
     - In particular, new and dynamic enhancers are observed
   - Dynamic promoters/enhancers
3. Immediate Early Response – Fig 2 on promoter level, Figure 3 on enhancer level
   - High resolution
   - Sanity check (we see known IER genes)
   - We observe large diversity in ER genes between time courses
   - Respnse patters of enahcners close to IER genes (how many etc)
   - Clustering of enhancers and charaterization of super-early enhancers

4. General overview of typical response patterns for promoters and enhancers over multiple time courses
   - Rule-based method to classify expression profiles over time into 7 cases shows…
   - Clear difference between regulators and other types of genes

5. Dynamics in promoter-enhancer interaction – Fig 4. Short and long term?
   - CAGE allows for simultaneous study of promoter and enhancer temporal dynamics at high resolution
   - Timed order of enhancers, TFs, promoters. Can we classify these based on motif context (machine learning?)
   - Driver TFs of enhancer/promoter dynamics (MARA)

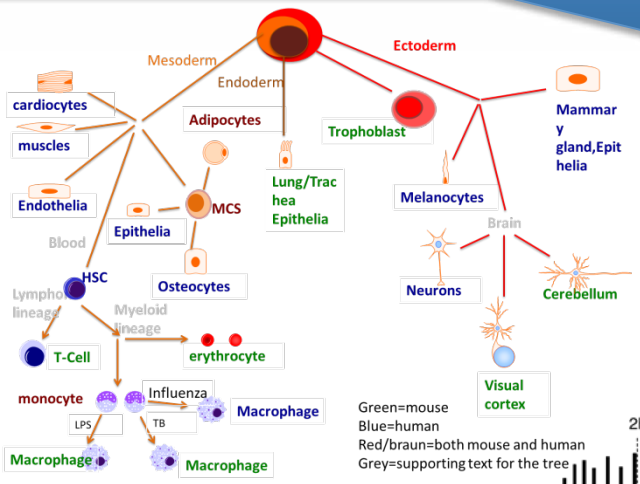
6: Case stories . Figure 5
   1. SRF antisense (time course?)
   2. Domain loss over time in LPS (Berit)

Figure 1

- Section: Resource
  - Panel 1: Differentiation tree of our systems
    - **Andreas**
  - Panel 2: MDS plot (3D) of phase 2 data in the context of Phase 1
    - Plus zoomed in 3D view of adipogenesis and MCF-7 time courses
    - **Carsten/Robin/Morana**
  - Panel 3: Mini plots of all time courses
    - number of expressed promoters/enhancers/TFs
    - number of DE expressed promoters/enhancers/TFs
    - **Carsten**

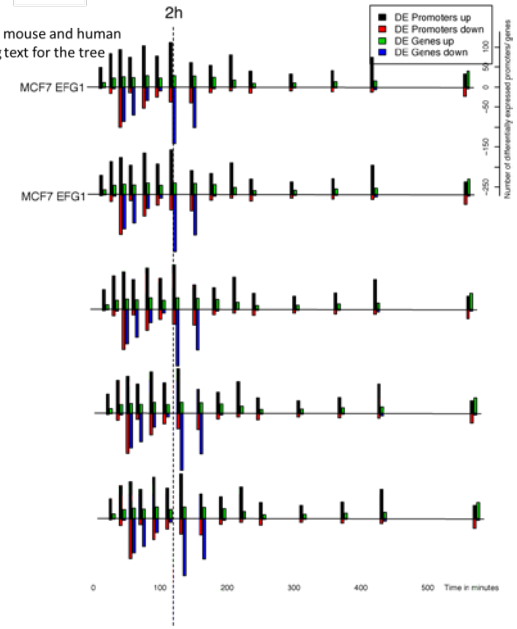
Figure 1 – mock up

Overall takehome message:
Broad and diverse time course studies, and their relation to phase 1



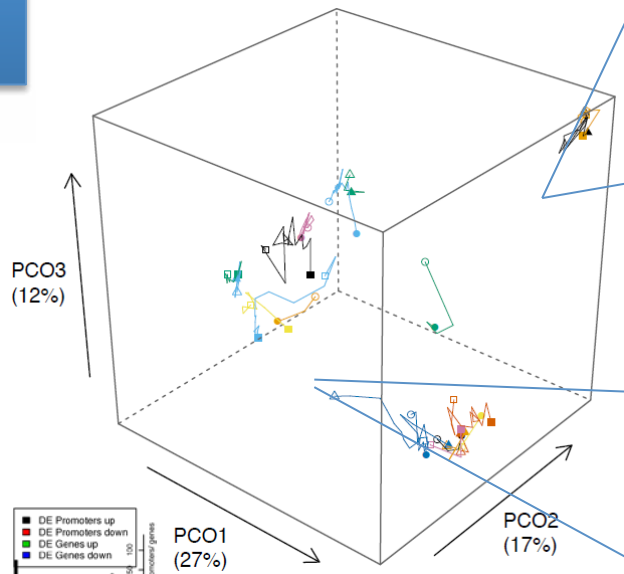
Panel 1

Green=mouse
Blue=human
Red/braun=both mouse and human
Grey=supporting text for the tree

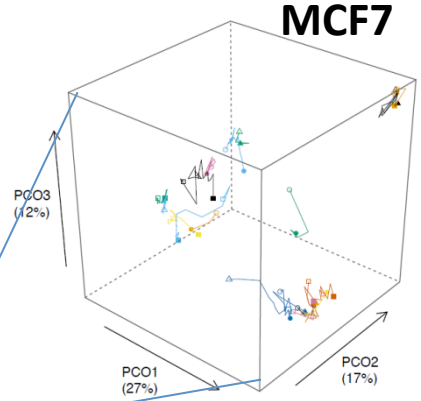


Panel 3

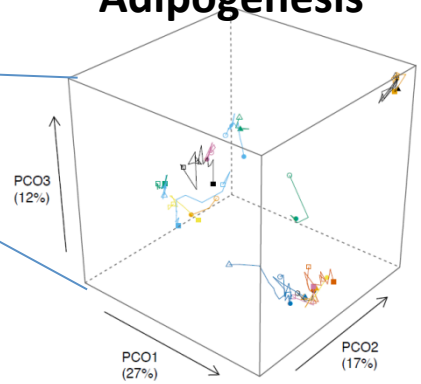
All Phase 1 + 2
Phase 1 gray
Phase 2 highlighted



MCF7



Adipogenesis



Panel 2

Figure 2: IER promoter response

- Section: Immediate Early Response
  - Panel 1: Expression profile of known IER promoters for ~ 4 time courses
    - The rest in supplement figure
    - **Carsten/Erik**
  - Panel 2: Heat map of data driven identification of IER promoters
    - Visualizes the number of time courses each promoter is immediate early in
    - Sorted from highest to lowest number of TCs
    - Human (mouse in supplement)
    - **Erik**
  - Panel 2 and 3 may be merged. Panel 4 may be moved to supplement

Figure 2 – mock up

Panel 1 **Panel 2** **Panel 3** **Panel 4**

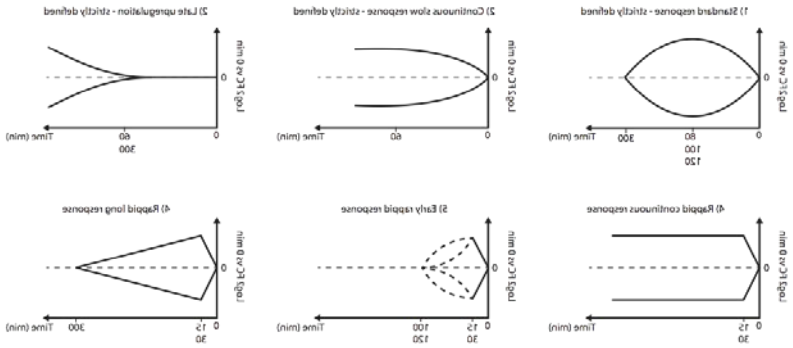
Overall takehome message:
Partially shared but also diverse IER across time series. Also shows IER enhancers around IER genes (and by themselves) as an intro to next sections

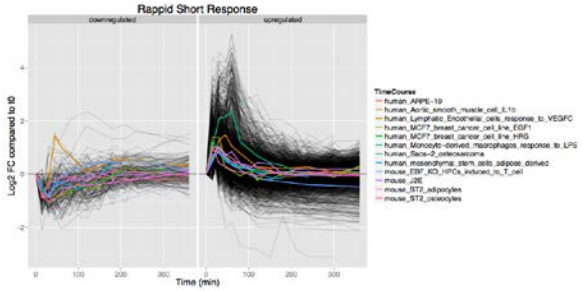
Figure 3: Enhacners IER

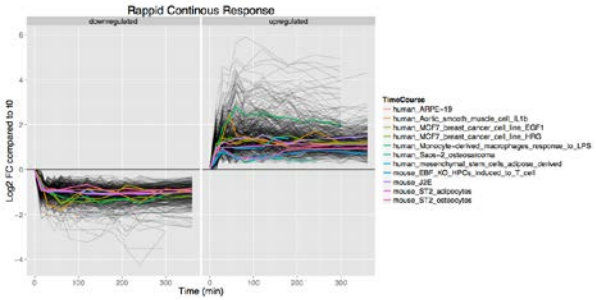
- Panel 1: Heat map of immediate early status of enhancer closest to promoter by same ordering as panel 2
  - Human (mouse in supplement)
  - **Albin**
- Panel 2: Heat map of data driven identification of IER enhancers
  - As panel 2. Or just clusters.
  - **Erik**
- Panel 3-4: characterization of very early dropping enhancers(Kristoffer/Robin/Morana). Examples, motifs and euler diagram

Figure 4: Expression trends over multiple time series

- Expansion of early response concept
- It is possible to classify most (80%?) of expression profilesin time series to 7 generic patterns
- This means that we can compare time courses
  - Same meta-patterns in each?
  - Same genes do same thing in each, or is it differentgenes/enhancers
  - Gene class differences




Rapid Short Response
downregulated
upregulated
Log2 FC compared to t0
Time (min)
TimeCourse
human_ARPE-19
human_Aortic_smooth_muscle_cell_IL1b
human_Lymphatic_Endothelial_cells_response_to_VEGFC
human_MCF7_breast_cancer_cell_line_EGF1
human_MCF7_breast_cancer_cell_line_HRG
human_Monocyte-derived_macrophages_response_to_LPS
human_Saos-2_osteosarcoma
human_mesenchymal_stem_cells_adipose_derived
mouse_EBF_KO_HPCs_induced_to_T_cell
mouse_J2E
mouse_ST2_adipocytes
mouse_ST2_osteocytes


Rapid Continous Response
downregulated
upregulated
Log2 FC compared to t0
Time (min)
TimeCourse
human_ARPE-19
human_Aortic_smooth_muscle_cell_IL1b
human_MCF7_breast_cancer_cell_line_EGF1
human_MCF7_breast_cancer_cell_line_HRG
human_Monocyte-derived_macrophages_response_to_LPS
human_Saos-2_osteosarcoma
human_mesenchymal_stem_cells_adipose_derived
mouse_EBF_KO_HPCs_induced_to_T_cell
mouse_J2E
mouse_ST2_adipocytes
mouse_ST2_osteocytes

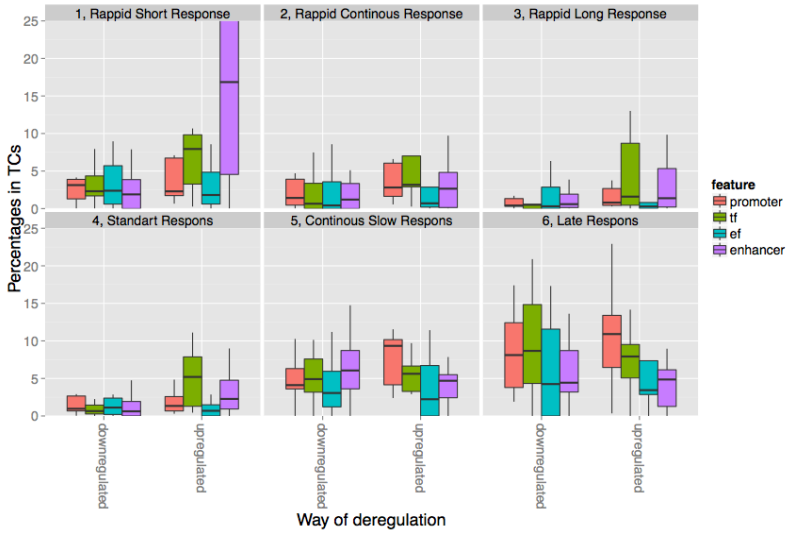
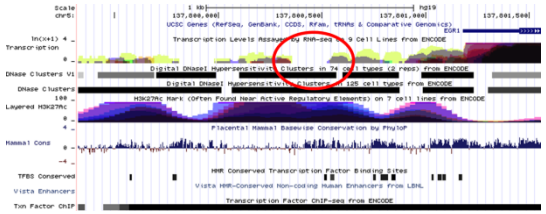

1, Rapid Short Response
2, Rapid Continous Response
3, Rapid Long Response
4, Standart Respons
5, Continous Slow Respons
6, Late Respons
Percentages in TCs
downregulated
upregulated
Way of deregulation
feature
promoter
tf
ef
enhancer

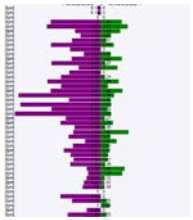
Figure 5: eRNA and promoter interactions

- Section: Transcriptional dynamics of promoters and enhancers
  - Panel 1: Genome browser + expression profile view of known enhancer/ promoter pair, where expression timing is similar
    - **Erik**
  - Panel 2: Genome browser + expression profile view of known enhancer/ promoter pair, where expression timing is shifted
    - **Erik**
  - Panel 3: Cumulative distributions of number of differentially expressed promoters/enhancers
    - **Erik**
  - Panel 4: Distributions of lag between enhancer/promoter peak expression
    - **Robin**
  - Panel 5: the same, but from an enhancer perspective (Kristoffer)
  - Panel 6: Drivers of transcriptional activities
    - Examples of aligned and shifted motif activities in same/different time courses
    - **Erik**

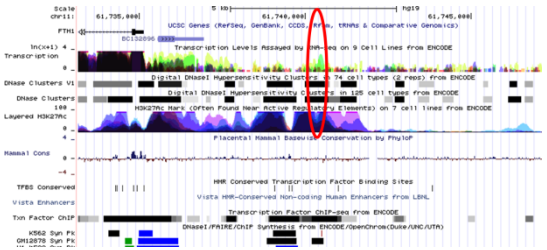
Overall takehome message:
Diversity in timing difference between enhancers and promoters, also at the regulatory level

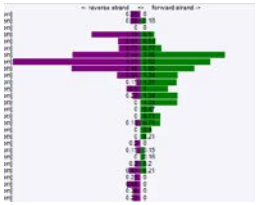
Figure 5 – mock up



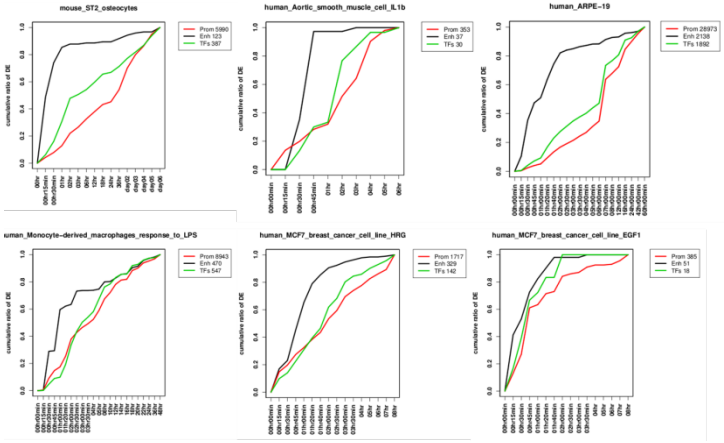


Panel 1

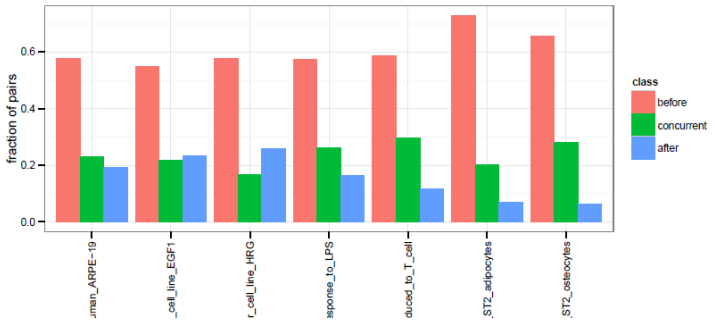


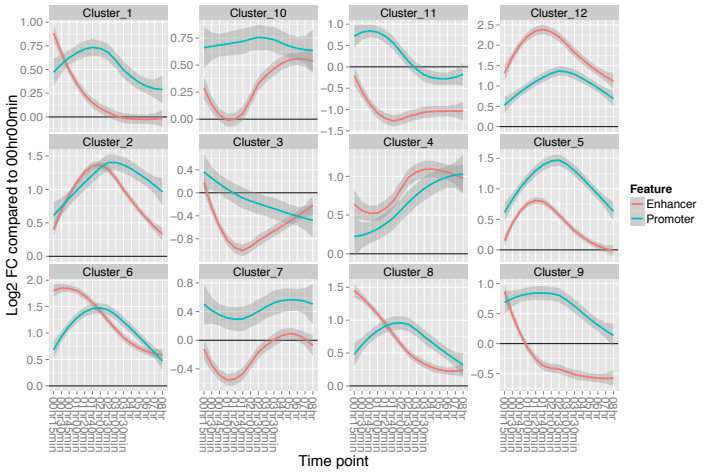


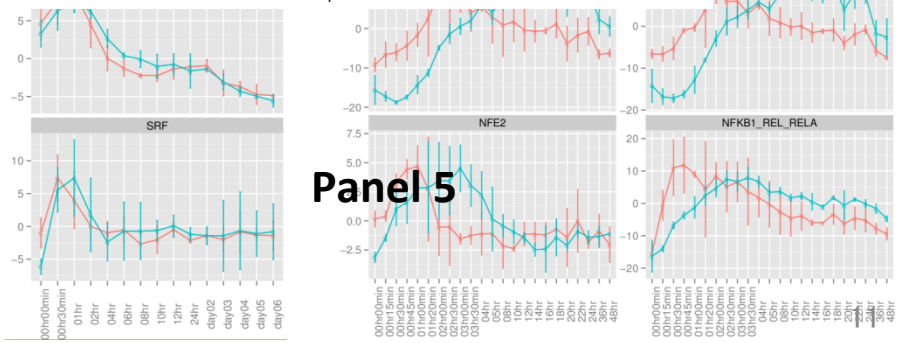
Panel 2



Panel 3







Panel 5

Figure 6: case stories

- SRF story
- Protein domain loss story
- More?
- I think 2-4 would be good.