

# **BIOMENG 261**

## **TISSUE AND BIOMOLECULAR ENGINEERING**

*Module I: Reaction kinetics and systems biology*

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# MODULE OVERVIEW

Reaction kinetics and systems biology (*Oliver Maclaren*)  
**[11 lectures/3 tutorials/2 labs]**

*1. Basic principles: modelling with reaction kinetics* [4 lectures]

Conservation, directional and constitutive principles. Mass action. Enzyme kinetics. Enzyme regulation. Mathematical/graphical tools for analysis and fitting.

*2. Systems biology I: signalling and metabolic systems* [2 lectures]

Overview of systems biology. Modelling signalling systems using reaction kinetics. Introduction to parameter estimation. Modelling metabolic systems using reaction kinetics. Flux balance analysis and constraint-based methods.

*3. Systems biology II: genetic systems* [3 lectures]

Modelling genes and gene regulation using reaction kinetics. Gene regulatory networks, transcriptomics and analysis of microarray data.

# LECTURE 11: MICROARRAY DATA

- Brief overview of microarray data
- Data organisation
- Experiment and analysis types

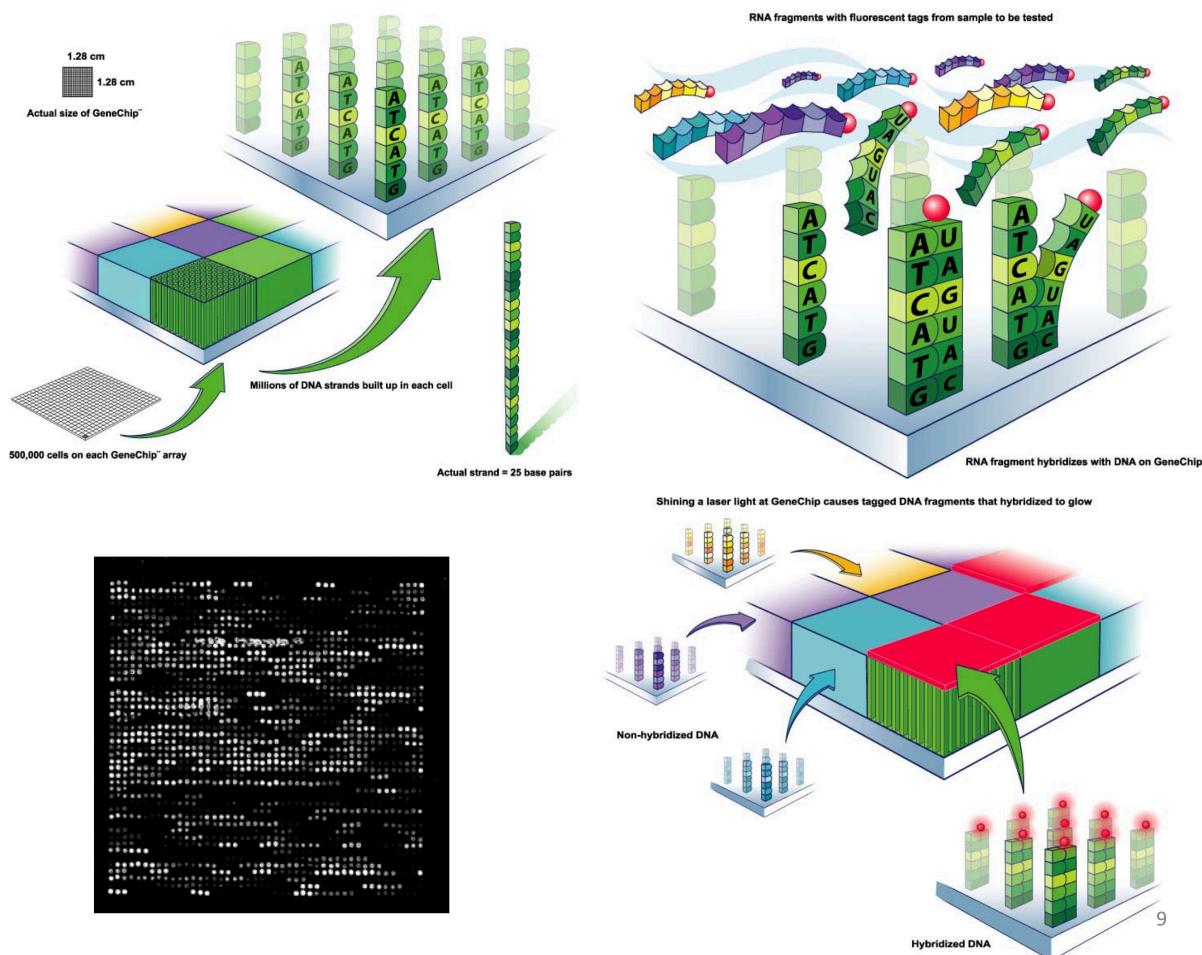
Note: there are many images stolen from the internet in what follows...

# MICROARRAYS

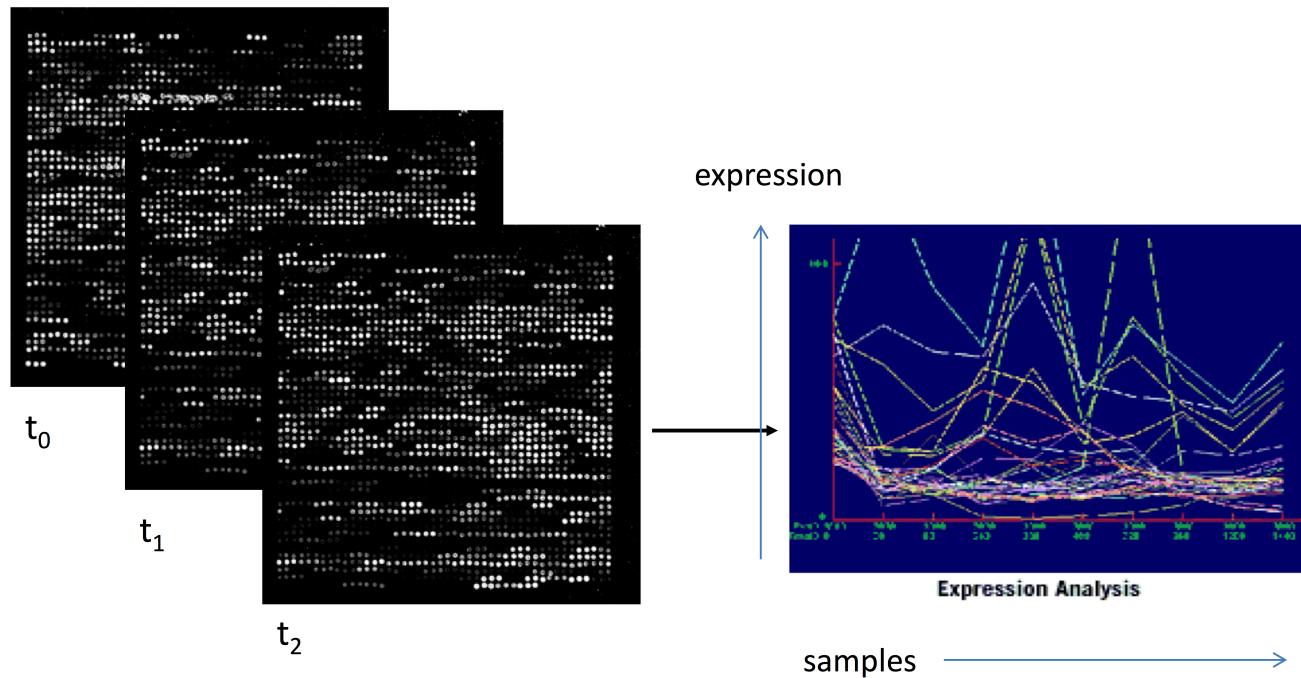


For a video intro: see e.g. <http://www.youtube.com/watch?v=VNsThMNjKhM>

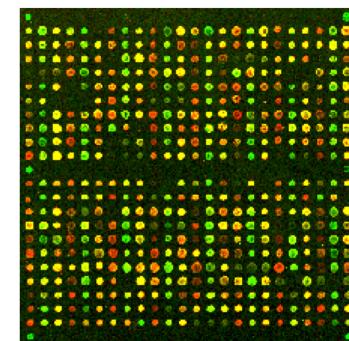
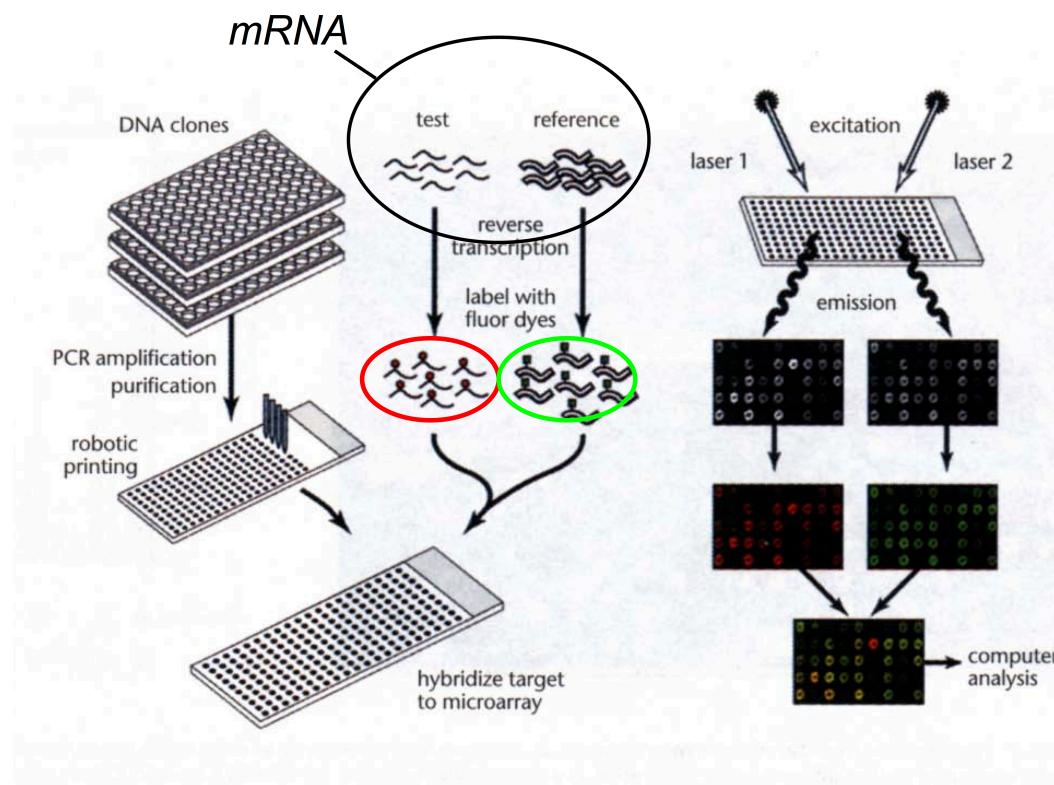
# MICROARRAYS



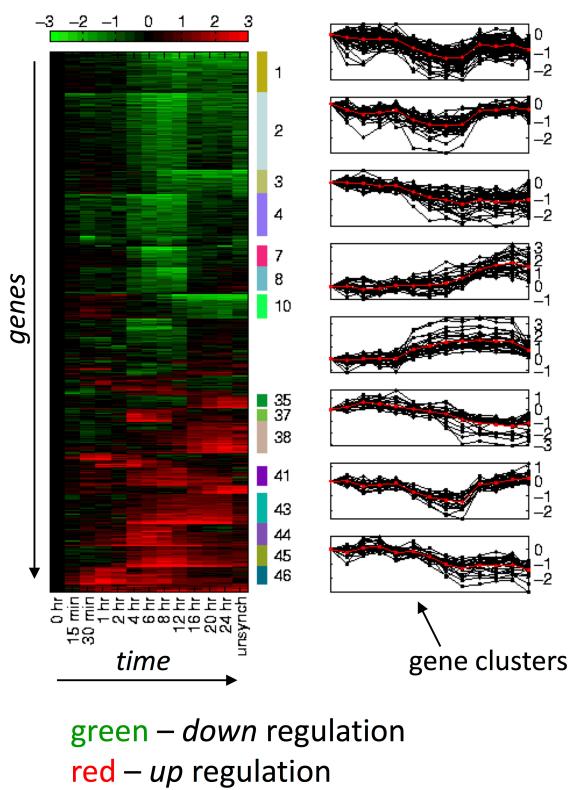
# MICROARRAYS: TIME SERIES



# MICROARRAYS: COMPARATIVE EXPRESSION



# MICROARRAYS: RELATIVE EXPRESSION OVER TIME



# DATA ANALYSIS: STATISTICAL/MACHINE LEARNING

Clustering, unsupervised and supervised learning etc. see:

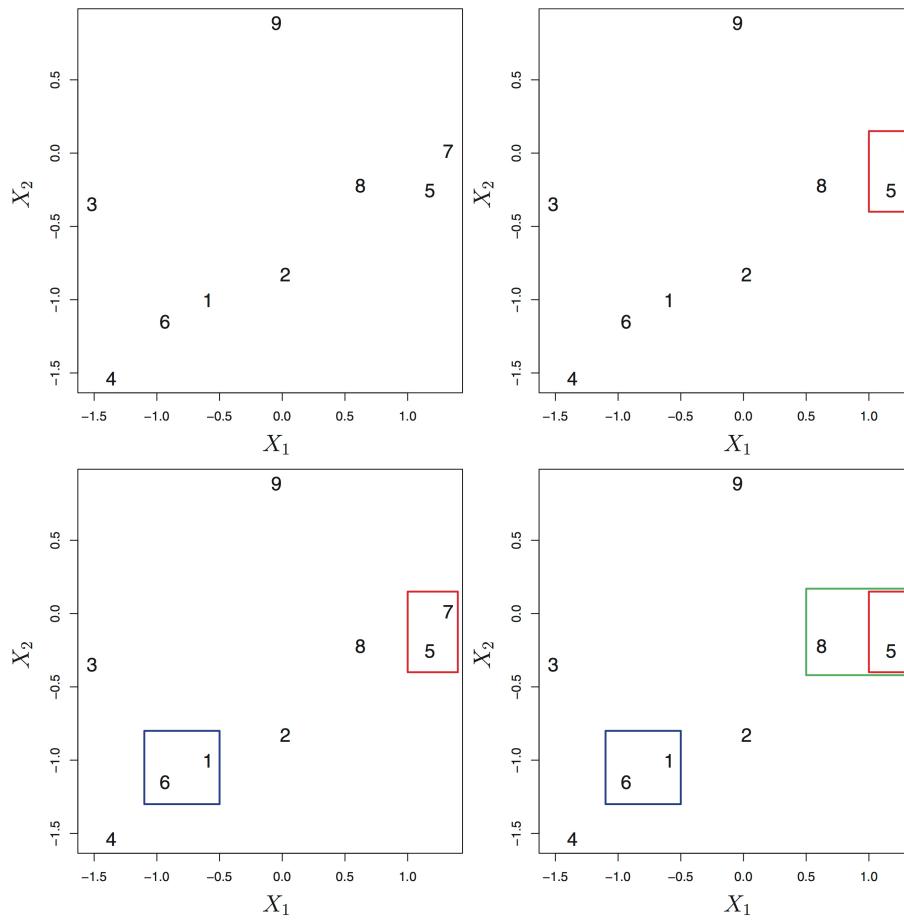
- James et al. 'An Introduction to Statistical Learning'
  - Available at: <http://www-bcf.usc.edu/~gareth/ISL/>
- Hastie et. al 'Elements of Statistical Learning: Data Mining, Inference and Prediction'
  - Available at:  
<http://web.stanford.edu/~hastie/ElemStatLearn/>

# CLUSTERING

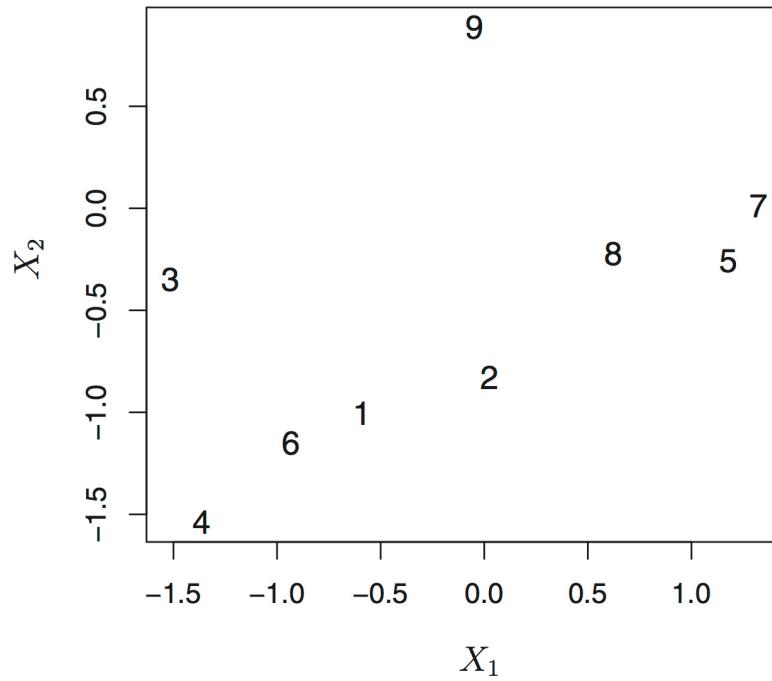
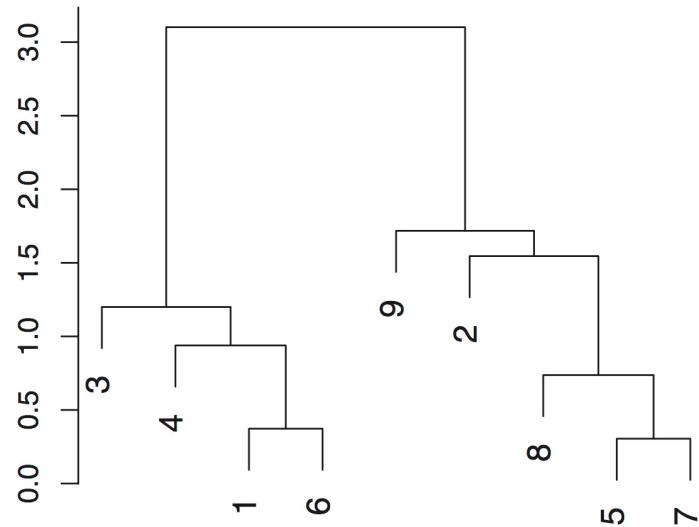
- An *unsupervised learning* method for *pattern discovery*
- Two popular algorithms are
  - K-means
  - Hierarchical clustering

See James et al. Chapter 10 for detailed algorithms. We will look at *hierarchical clustering* here.

# HIERARCHICAL CLUSTERING EXAMPLE (JAMES ET AL.)



# HIERARCHICAL CLUSTERING: DENDROGRAMS



# PERTURBATION APPROACH FOR INFERRING REGULATORY MATRICES/NETWORKS

- Perturb *transcription rates* for *each gene in turn*
- Measure changes in *steady-state expression levels* for all genes (including self)
- Gives indication of underlying *regulatory network*
- Summarise in *regulatory strength matrix or network diagram.*

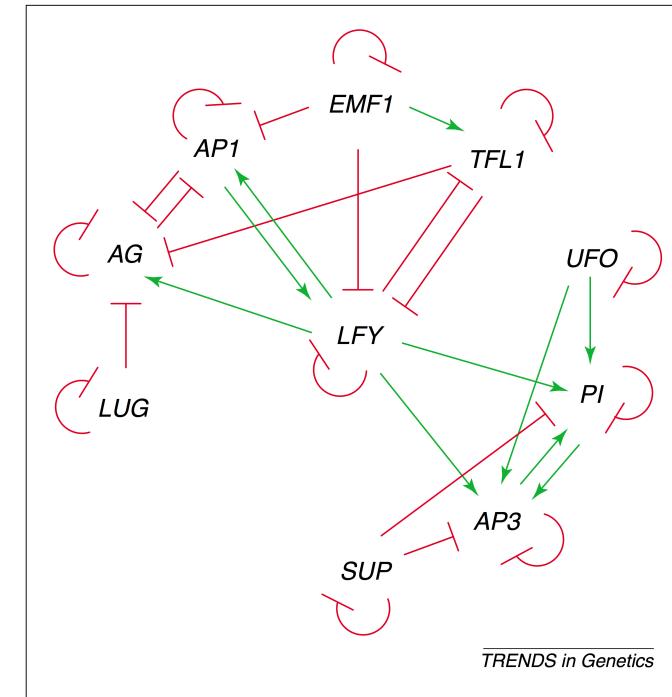
See de la Fuente et al. (2002) 'Linking the genes' (on Canvas)

# PERTURBATION APPROACH FOR INFERRING REGULATORY MATRICES/NETWORKS

Example: flower morphogenesis (see de la Fuente et al. 2002 for details):

LUG	AG	AP1	EMF1	TFL1	LFY	SUP	A3P	PI	UFO	
-1	0	0	0	0	0	0	0	0	0	Rd =
-0.579	-1.14	-0.184	-0.002	-0.112	0.114	0	0	0	0	LUG
-0.009	-0.894	-1.14	-0.109	-0.002	0.124	0	0	0	0	AG
0	0	0	-1	0	0	0	0	0	0	AP1
0	0	0	0.094	-1.09	-0.973	0	0	0	0	EMF1
-0.002	-0.005	0.053	-0.103	-0.107	-1.09	0	0	0	0	TFL1
0	0	0	0	0	0	-1	0	0	0	LFY
0	0	0	-0.001	-0.001	0.135	-0.119	-1.04	0.192	0.109	SUP
0	0	0	-0.001	-0.001	0.135	-0.119	0.192	-1.04	0.109	A3P
0	0	0	0	0	0	0	0	0	-1	PI
0	0	0	0	0	0	0	0	0	0	UFO

TRENDS in Genetics



# EXAMPLE PAST QUESTIONS

- (b) DNA microarrays are used are used to simultaneously measure the expression of many different genes in a sample. Explain briefly the difference between *time series* and *comparative* microarray measurements.
- (4 marks)
- (c) In a series of experiments, the amounts of mRNA for different genes are perturbed and the changes in mRNA of all genes of interest (namely A, B and C) are measured. A set of ‘co-control coefficients’ was calculated and organised into the ‘Regulatory Strength’ matrix,  $Rd$ , given below

$$Rd = \begin{bmatrix} & A & B & C \\ A & -0.5 & 0 & 0 \\ B & 0.1 & 0 & 1.2 \\ C & 0.8 & -0.1 & 1 \end{bmatrix}$$

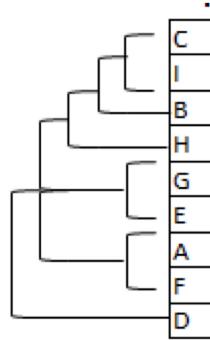
Using the information in  $Rd$  sketch a qualitative regulatory network showing how each gene regulates the expression of all genes (including itself). Use arrows ( $\rightarrow$ ) to show positive regulation and blunt arrows ( $\overleftarrow{\phantom{x}}$ ) to indicate negative regulation.

(5 marks)

# EXAMPLE PAST QUESTIONS

5)

- a) In a microarray experiment, the expression of 8 genes was measured as a function of time and the data were analysed to create the following dendrogram:



State if the following statements are TRUE, FALSE or INDETERMINATE.

- i) Genes C and I show similar expression patterns at the different time points.

(1 mark)

- ii) The Euclidean distance between genes C and I is less than the Euclidean distance between genes I and B.

(1 mark)