Human Regulatory Networks

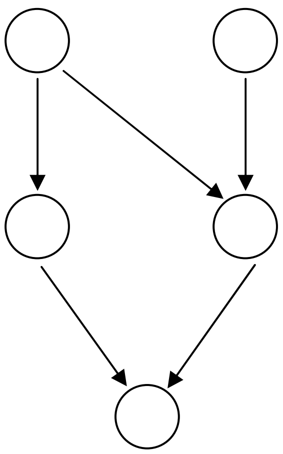
Lecture 14
6.874J/7.90J/6.807

David Gifford

(Q1) How can we explain complex experimental data with models?

The Model Spectrum

Diagram removed for copyright reasons.
Complex process chart.



Detailed Coarse

Fragile Robust

Alternative data representations

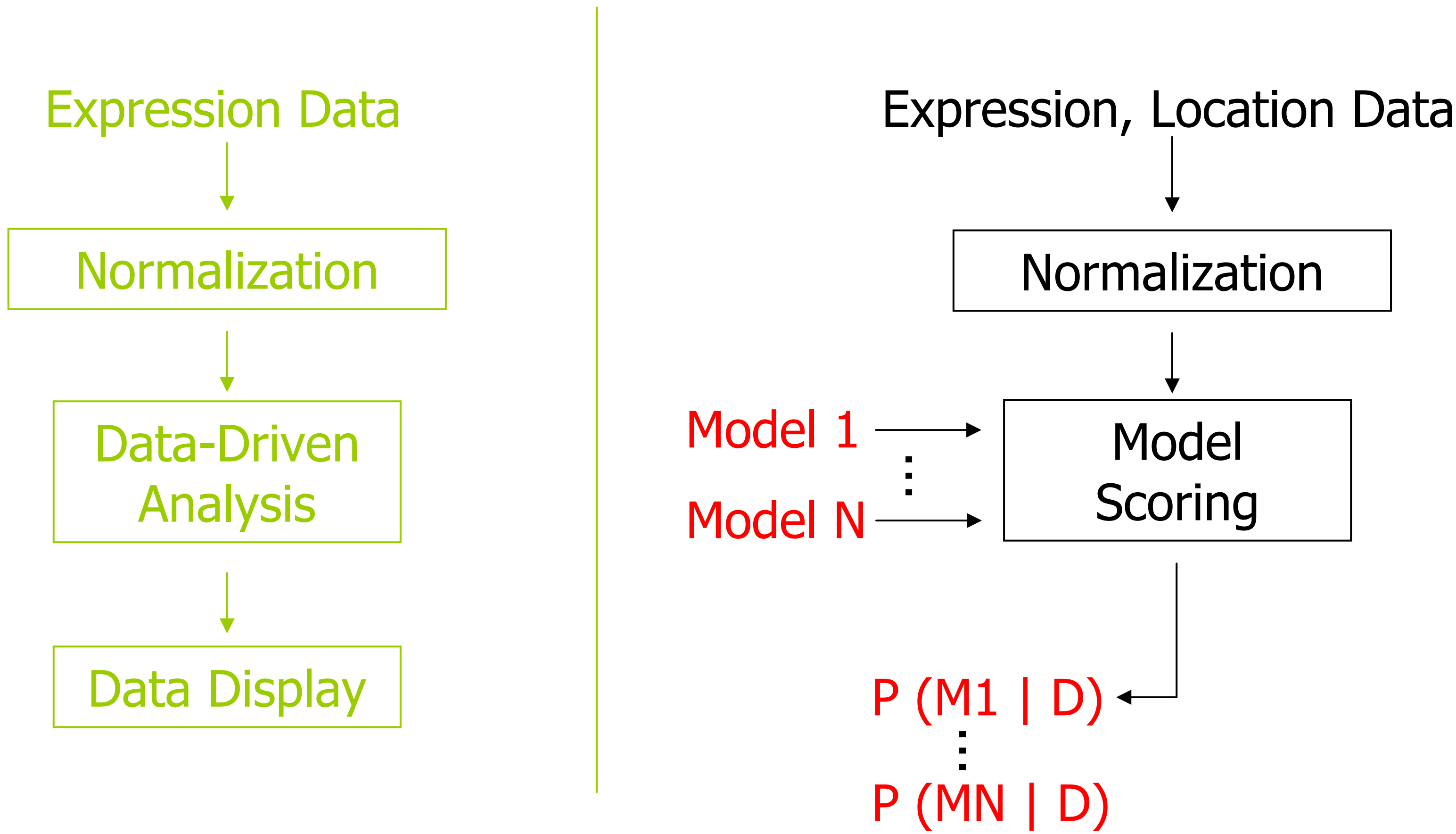
Two diagrams removed for copyright reasons.

Why graphical models?

- Handle imperfect data and imperfect theory robustly
- Biologically interpretable and familiar
- Permit arbitrary (more than pair-wise) interactions
- Produce results with statistical significance
- Remain methodologically principled
- Combinable for network reassembly

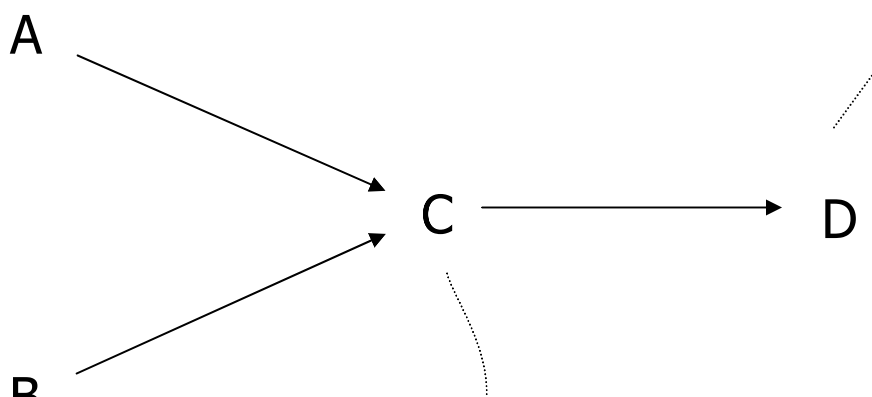
(Q2) How can we judge the significance of models?

Comparing alternative network structures



We can easily compute P(D | S, θ)

P(A=1) = 0.6



P(B=1) = 0.8

P(D=1|C=0) = 0.8
P(D=1|C=1) = 0.3

Parameters θ

P(C=1|A=0,B=0) = 0.1
P(C=1|A=0,B=1) = 0.1
P(C=1|A=1,B=0) = 0.1
P(C=1|A=1,B=1) = 0.8

How can we score models without parameters?

- P(S | D) P(D) = P(D | S) P(S)

$$\text{Score} = \log P(S \mid D)$$
$$= \log P(D \mid S) + \log P(S) + c$$

- Likelihood term is computed as an average with a distribution over parameter settings θ :

$$P(D \mid S) = \int P(D \mid \theta, S) P(\theta \mid S) d\theta$$

Scores need to be interpreted properly

- Scores are not absolute, relative comparisons are needed
- May not have informative data to distinguish models
- Relevant variables may not be represented
- It’s just science… an iterative process

Human Regulatory Pathways

Human Biology

- The organism and its components
- Motivation: improved understanding of health and disease

Gene Expression Regulatory Pathways

- Cell division cycle
- Tissue-specific gene expression programs
- Immune response
- Cell-cell signaling pathways
- Development

What are the big problems, key questions and challenges?

Human Tissues

Brain and Spinal Cord

Cerebrum
Cerebellum
Ganglia & nerves

Circulatory System

Heart
Vascular system

Digestive System

Esophagus
Stomach
Intestines
Liver
Pancreas

Urinary System

Kidney
Urinary tract

Respiratory System

Airways
Lungs

Reproductive Organs

Ovary
Uterus
Breast
Testis

Skeletal and Muscular

Bone
Muscle
Cartilage

Hematopoietic System

Bone marrow
Blood
Embryonic Liver

Immune System

Thymus
Spleen
Lymph nodes

Sensory Organs

Eye
Ear
Olfactory
Skin
Tongue

Transcription Factors Implicated in Disease

<u>Diabetes</u>
Hnf1α, Hnf1β, Hnf4α, Pdx1, NeuroD1

<u>Obesity</u>
PPARγ, SIM1

<u>Hypertension</u>
NR3C2, GCCR

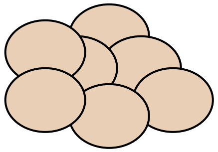
<u>Cancer</u>
AML1, p53, PLZF, PML, Rb, WT1

<u>Developmental Defects</u>
GATA1, VDR, CRX, CBP, MeCP2

<u>Immunological Defects</u>
RFX5, WHN

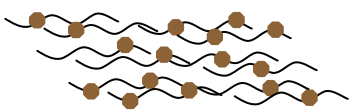
<u>CNS Disorders</u>
PAX3, EGR-1, EGR-2, OCT6, SOX family

Genome-wide Expression Analysis Reveals Changes in Global Gene Expression



Isolate total RNA from cells

Enzymatic amplification to generate biotin-labeled cRNA (50-100 fold amplification)



Hybridize to Array (45^oC overnight)

Photo of array removed for copyright reasons.

Wash & Stain

Photo of array removed for copyright reasons.

Image Capture

16 bit TIFF image

Data Extraction

#	UniqueID	Function	Accession	Clone	Ratio	Ratio 1	Ratio 2	Ratio 3
1	380	(D00710) heat-shock protein [	MEN	4h08f1	6.55	7.32	7.75	5.20
2	6651	heat shock protein 101 (HSP101	pIW24	pIW24	6.19	7.46	4.70	6.32
3	5168	(Y11828) heat shock protein [	MEN	58g08f1	5.79	6.82	6.57	4.35
4	1258	HEAT SHOCK PROTEIN 81-2 (HSP8	MEN	14a10f1	5.54	5.20	5.63	5.66
5	5309	BETA-AMYLASE (1 4-ALPHA-D-GL	MEN	61c05f1	5.47	6.25	4.10	6.36
6	2280	hypothetical protein T9E8.150	MEN	25f12f1	5.29	7.07	4.33	4.78
7	6267	heat shock protein 101 (HSP101	pIW24	pIW24	5.15	5.65	4.99	4.90
8	6290	HSP70-3cyt	HSP70-3cyt	sIW217	5.08	5.53	4.20	4.42
9	5584	(AC003105) unknown protein [A	MEN	73b04f1	4.87	4.74	4.06	5.53
10	1234	(AC002337) putative galactino	MEN	13g10f1	4.57	5.15	3.99	3.88

Fluidics

Scanner

Genome-wide Location Analysis Reveals Physical Interactions Between Regulators and DNA

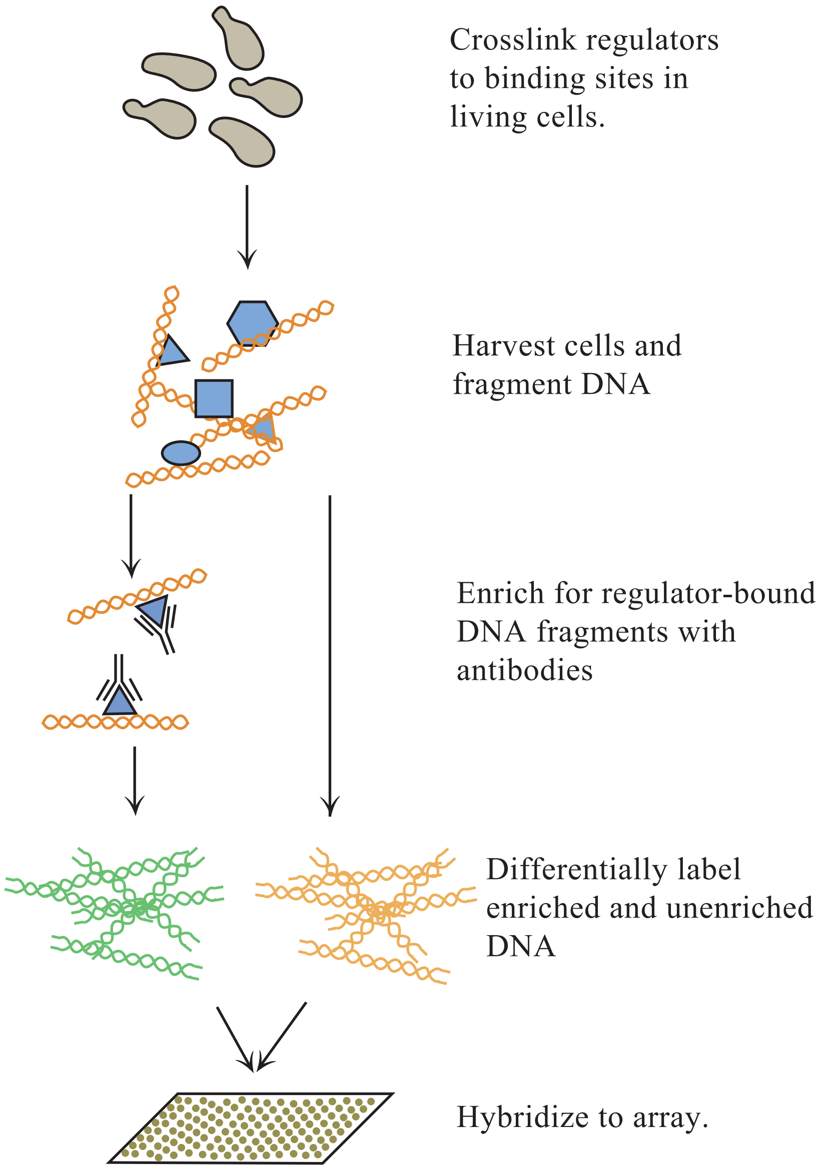


Figure by MIT OCW.

Bing Ren, Francois Robert, John Wyrick
Science 290: 2306 (2000)

Human Regulatory Pathways

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Gene Expression Regulatory Pathways

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- Immune response
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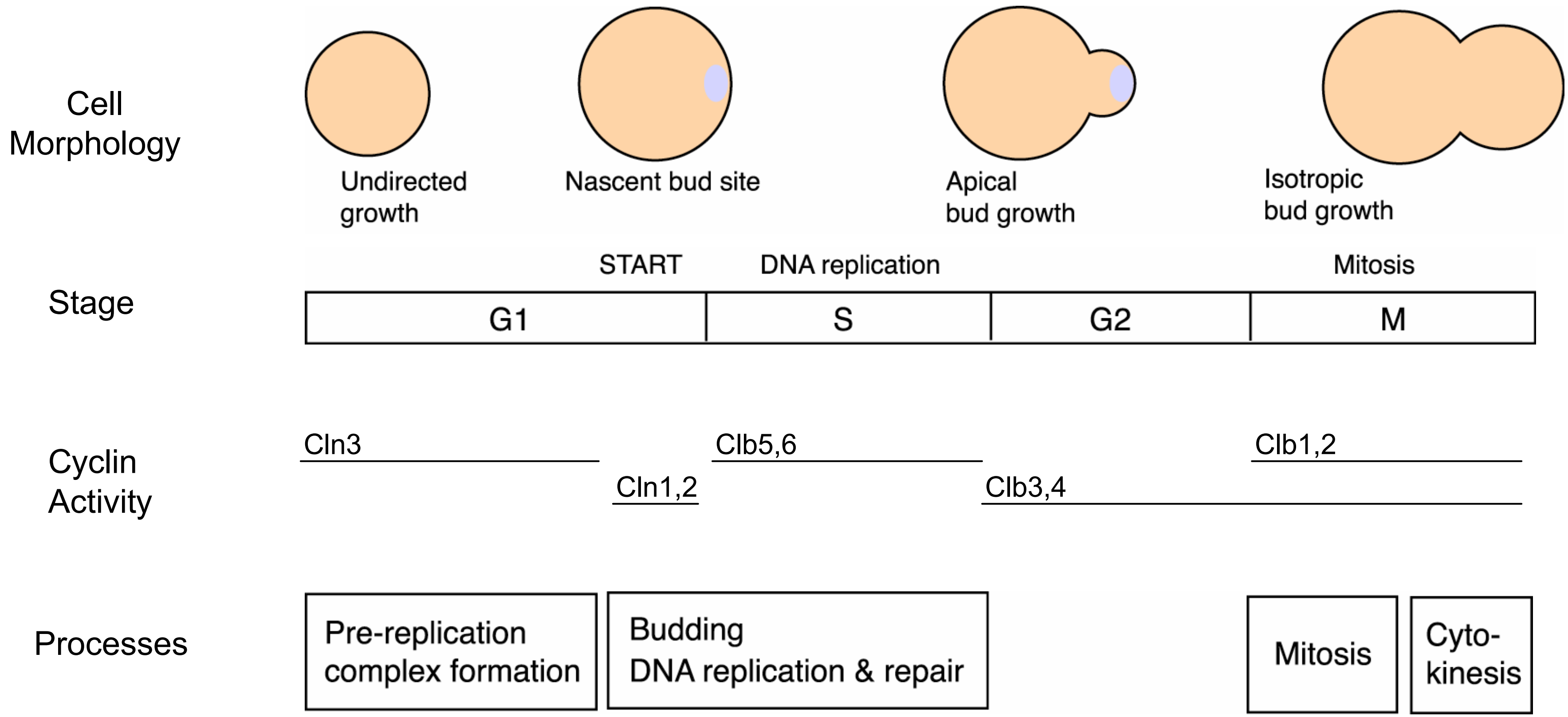
- Development

Major Events in Yeast Cell Cycle



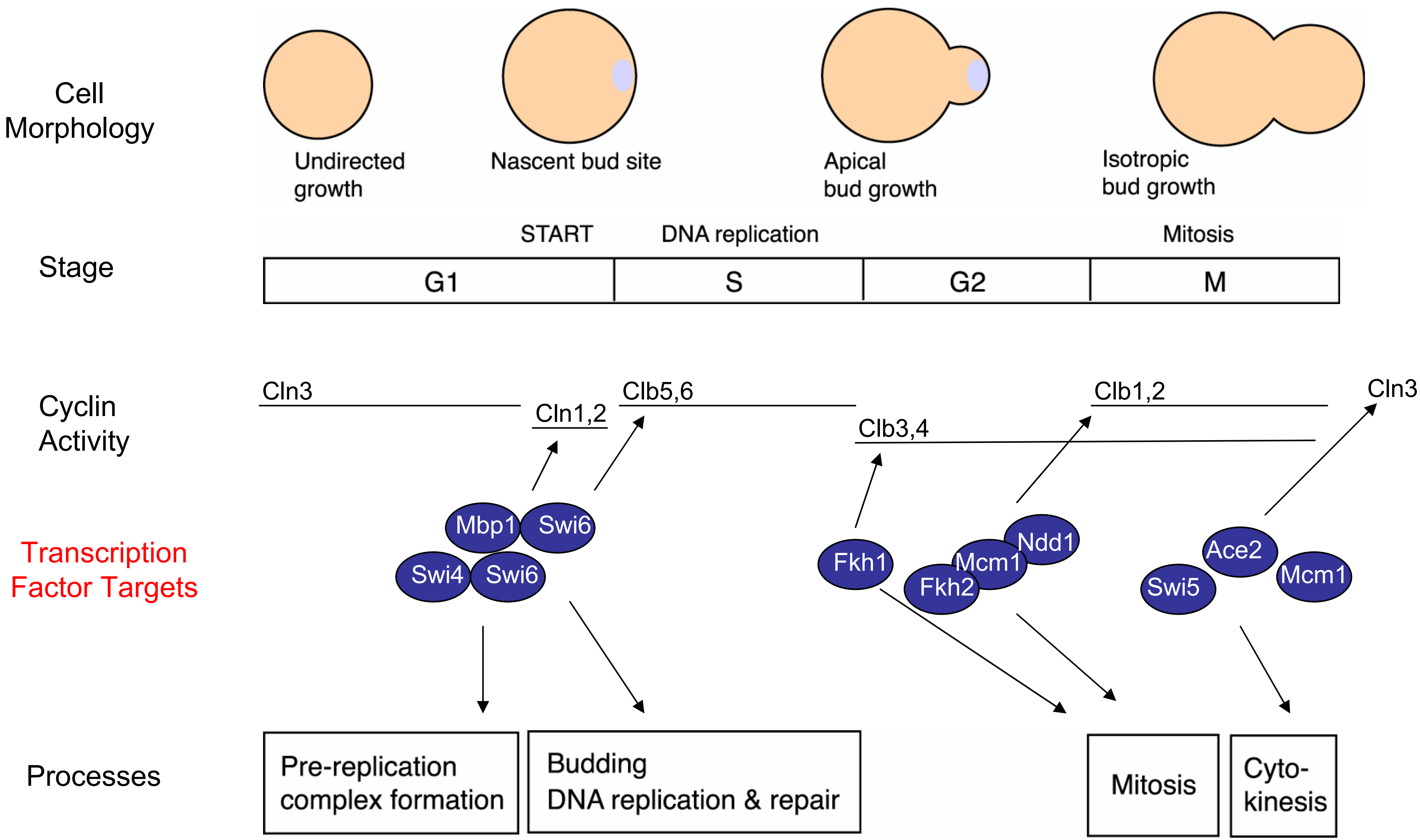
How is transcription of cyclin and other cell cycle genes regulated?

Transcriptional Regulation of Yeast Cell Cycle

Image removed for copyright reasons.

See Figure 2A in Simon et al., *Cell* 106: 697 (2001).

Transcriptional Regulation of Cyclins and Cell Cycle Processes



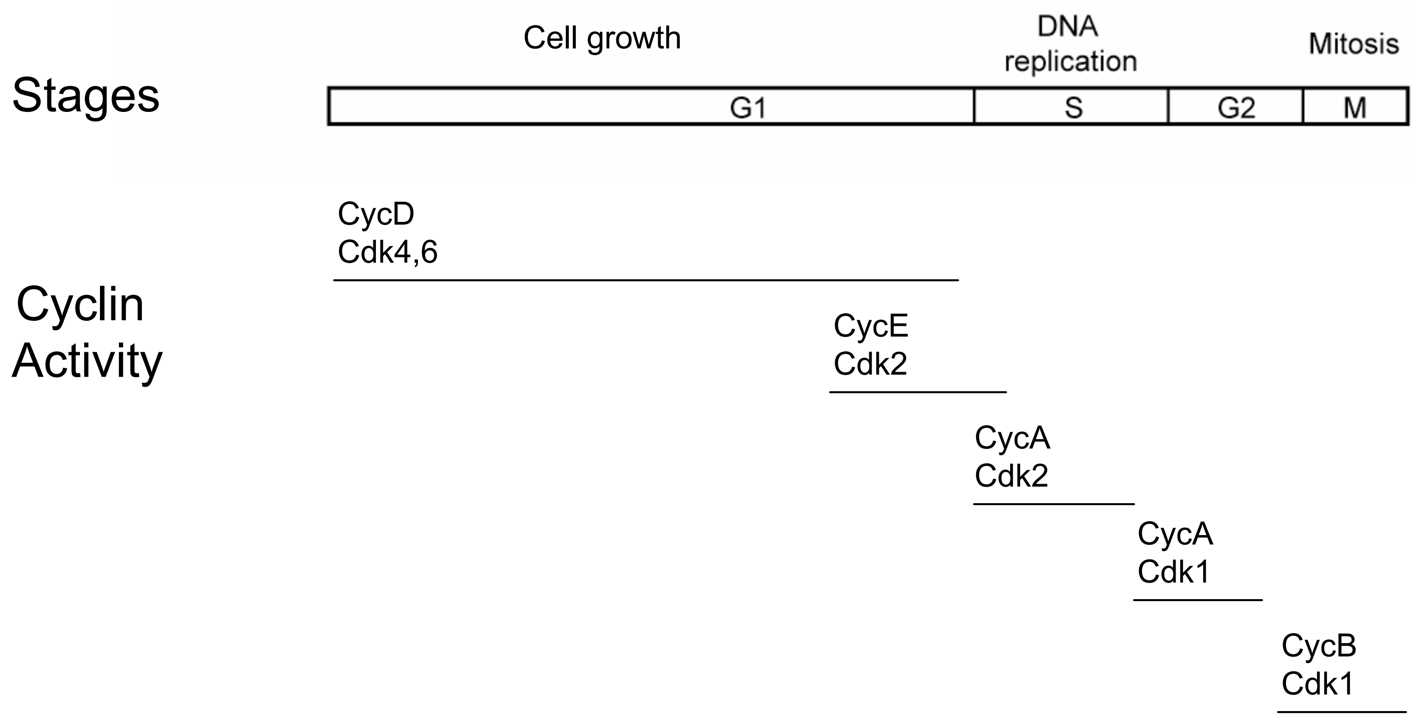
Cell Cycle Transcriptional Regulatory Network

Image removed for copyright reasons.

See Figure 3B in Simon et al., *Cell* 106: 697 (2001).

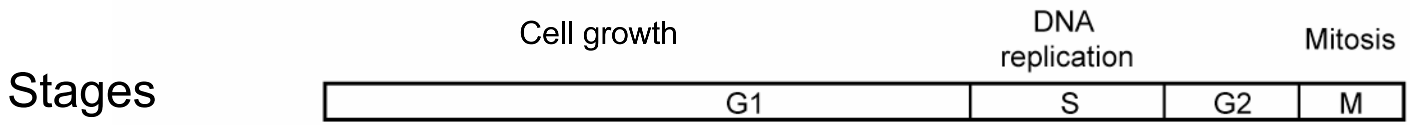
Activators that function during one stage of the cell cycle regulate activators that function during the next stage

Human Cell Cycle Regulation



How is transcription of cyclin and other cell cycle genes regulated?

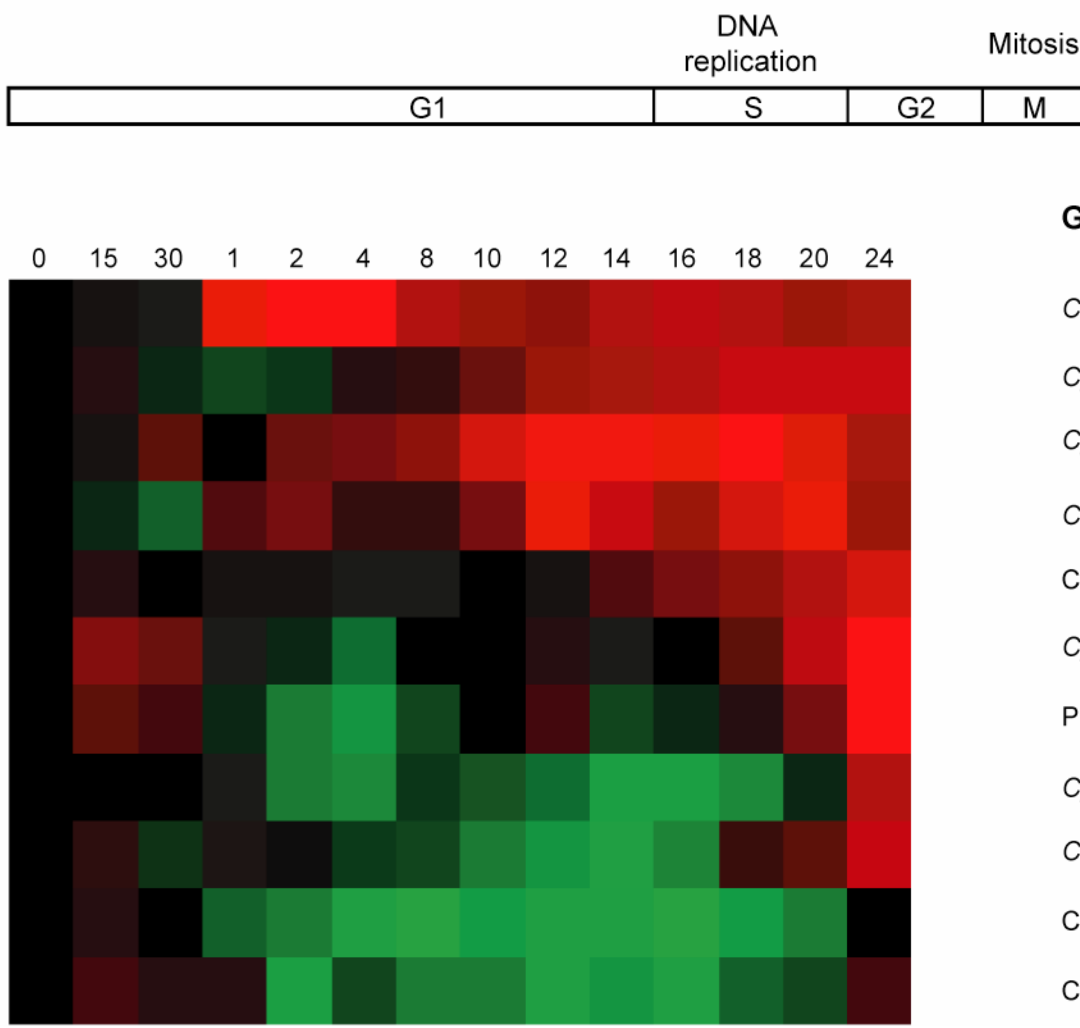
Human Cell Cycle Transcriptional Regulation



Challenges:

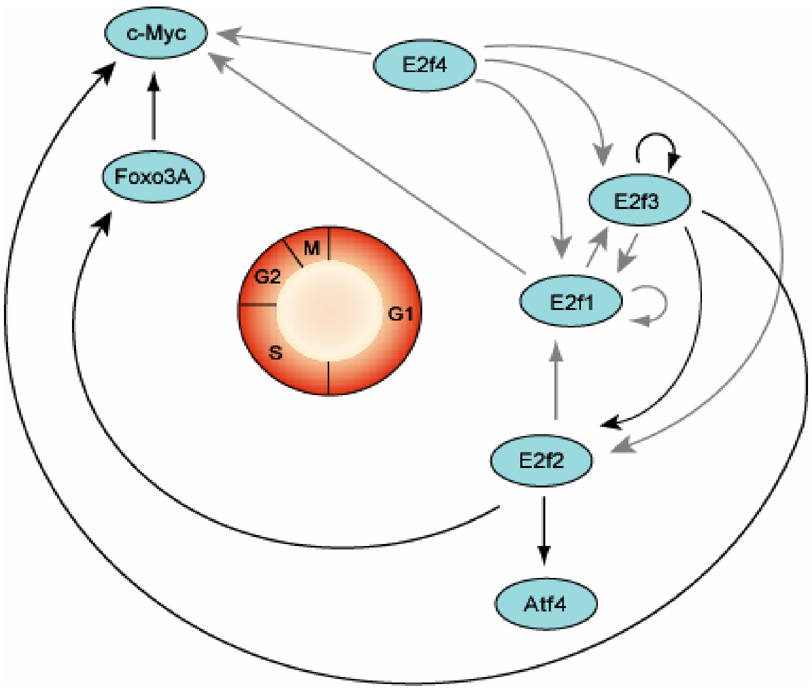
1) Few cell cycle transcriptional regulators known (E2F1,2,3,4,5, Fox03A).
2) What cells should be used? (most normal cells exist in G0)
3) Genome sequence not fully annotated.

Transcriptional Regulation of Key CDKs and Their Regulators



Gene	Bound by
Cdk7	E2f2
Cyclin D	
Cyclin E	
CDC25A	E2f3, E2f4
Cdk2	
Cyclin A	E2f4
PLK	E2f4, Foxo3A
Cyclin B	E2f4, Foxo3A
CDK1	E2f4, E2f1
CDC25B	E2f4
CDC25C	E2f4

Cell Cycle Transcriptional Regulatory Network



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Gene Expression in Selected Human Tissues

<u>Brain and Spinal Cord</u>

Cerebrum
Cerebellum
Ganglia & nerves

<u>Circulatory System</u>

Heart
Vascular system

<u>Digestive System</u>

Esophagus
Stomach
Intestines
Liver
Pancreas

<u>Urinary System</u>

Kidney
Urinary tract

<u>Respiratory System</u>

Airways
Lungs

<u>Reproductive Organs</u>

Ovary
Uterus
Breast
Testis

<u>Skeletal and Muscular</u>

Bone
Muscle
Cartilage

<u>Hematopoietic System</u>

Bone marrow
Blood
Embryonic Liver

<u>Immune System</u>

Thymus
Spleen
Lymph nodes

<u>Sensory Organs</u>

Eye
Ear
Olfactory
Skin
Tongue

What genes are expressed and what are silent in each cell type?
How are all these genes regulated?

Master Regulators of Human Transcription

Misregulation results in developmental problems and/or adult disease

<u>Brain and Spinal Cord</u>
SOX1-18, OCT6, MeCP2
CBP, NGN, NEUROD
Cerebrum
Cerebellum
Ganglia & nerves

<u>Circulatory System</u>
Myocardin, GATA4, TBX5,
NKX2.5, MEF2, HAND
Heart
Vascular system

<u>Digestive System</u>
HNF1, HNF4, HNF6, CBP,
PGC1, FOXA, PDX1, GATA,
MAFA, NKX2.2
Esophagus
Stomach
Intestines
Liver
Pancreas

<u>Urinary System</u>
HNF1B, HNF4, CDX, FTF
C/EBP, FOXA, GATA
Kidney
Urinary tract

<u>Respiratory System</u>
HNF-3, NKX2.1 and GATA6
Airways
Lungs

<u>Reproductive Organs</u>
ESR1, SERM, C/EBPβ
Ovary
Uterus
Breast
Testis

<u>Skeletal and Muscular</u>
MYOD, MEF2, MRF4, MYF5
Bone
Muscle
Cartilage

<u>Hematopoietic System</u>
TAL1, LMO1, LMO2, E2A,
XBP1, AFT6, PAX5, BCL6
Bone marrow
Blood
Embryonic Liver

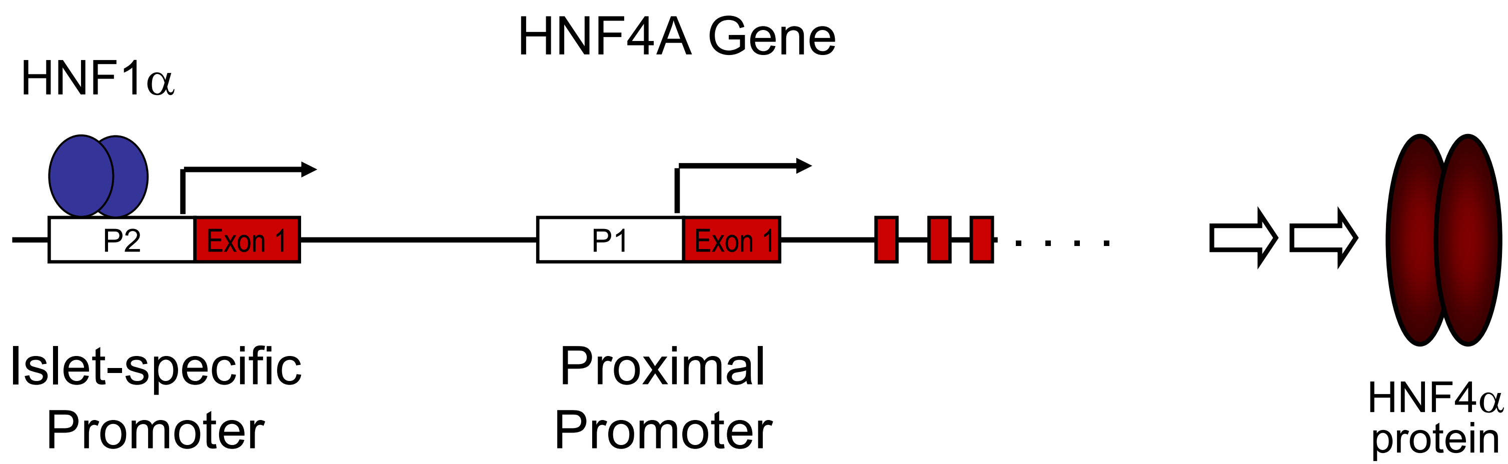
<u>Immune System</u>
AML1, MLL1, HP1, HOXA7,
HOXA9, HOXC8, C/EBPA,
NFkB family
Thymus
Spleen
Lymph nodes

<u>Sensory Organs</u>
SOX1-18, OCT6, PAX3,
PAX6, NGN, SKIN1
Eye
Ear
Olfactory
Skin
Tongue

Maturity Onset Diabetes of the Young

MODY type	**Causative Gene**	**Protein Class**	% Cases
MODY 1	***HNF-4α***	Orphan nuclear receptor protein	1
MODY 2	Glucokinase	Key enzyme in glucose sensing	20
MODY 3	***HNF-1α***	POU-homeodomain protein	60
MODY 4	***IPF1/PDX1***	Homeodomain protein	1
MODY 5	***HNF-1β***	POU-homeodomain protein	1
MODY 6	***NeuroD1***	Basic helix-loop-helix protein	1

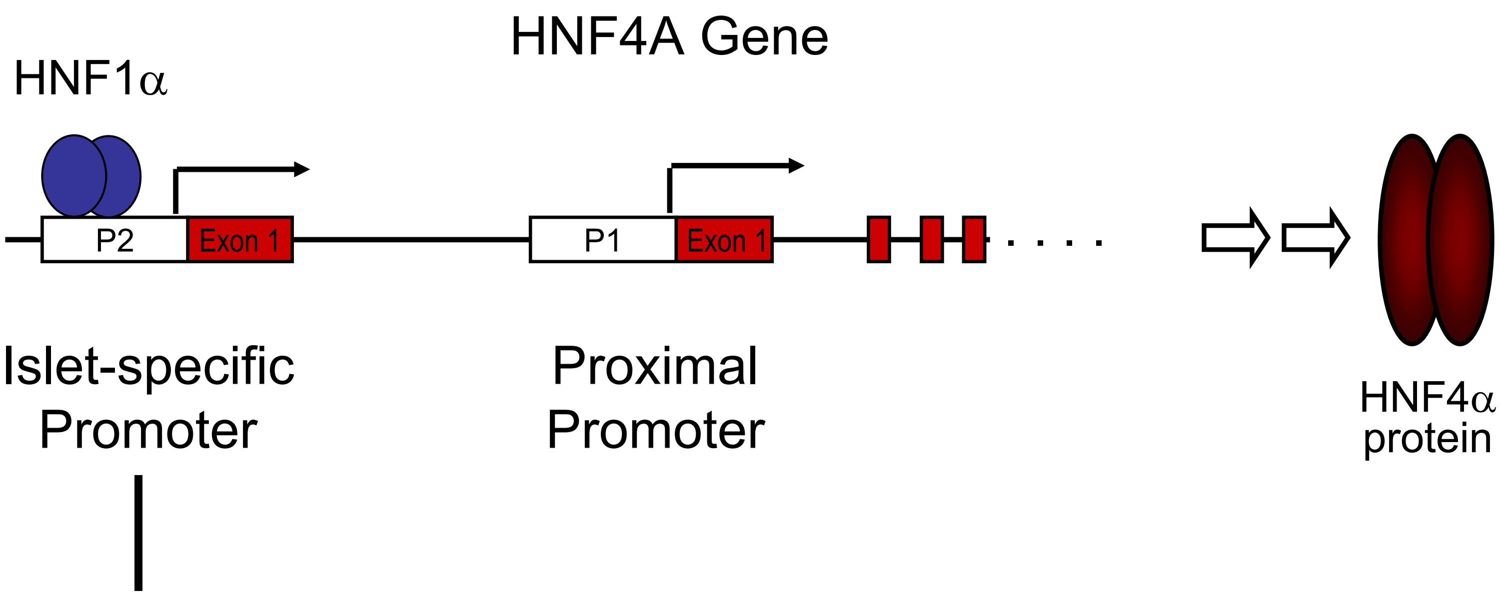
New Insights into Pancreatic Gene Regulation and MODY Diabetes



HNF1α regulates the HNF4A gene

Odom et al. Science 2004

New Insights into Type II Adult-Onset Diabetes



Polymorphisms in the P2 promoter region are associated with susceptibility to type II diabetes in diverse human populations.

Love-Gregory et al. Diabetes 2004
Silander et al. Diabetes 2004

Surprise: Large-scale Role for HNF4α in Liver and Pancreatic Islets

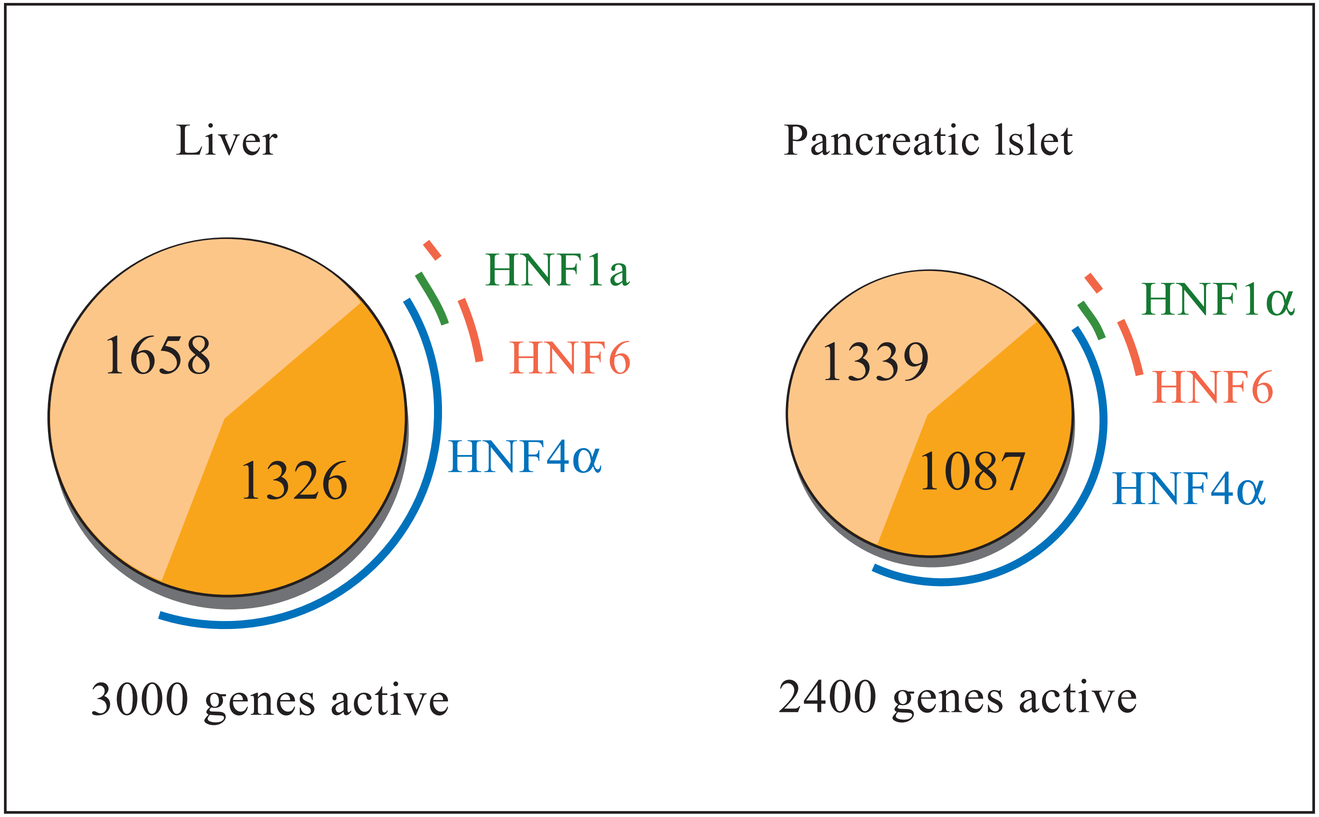


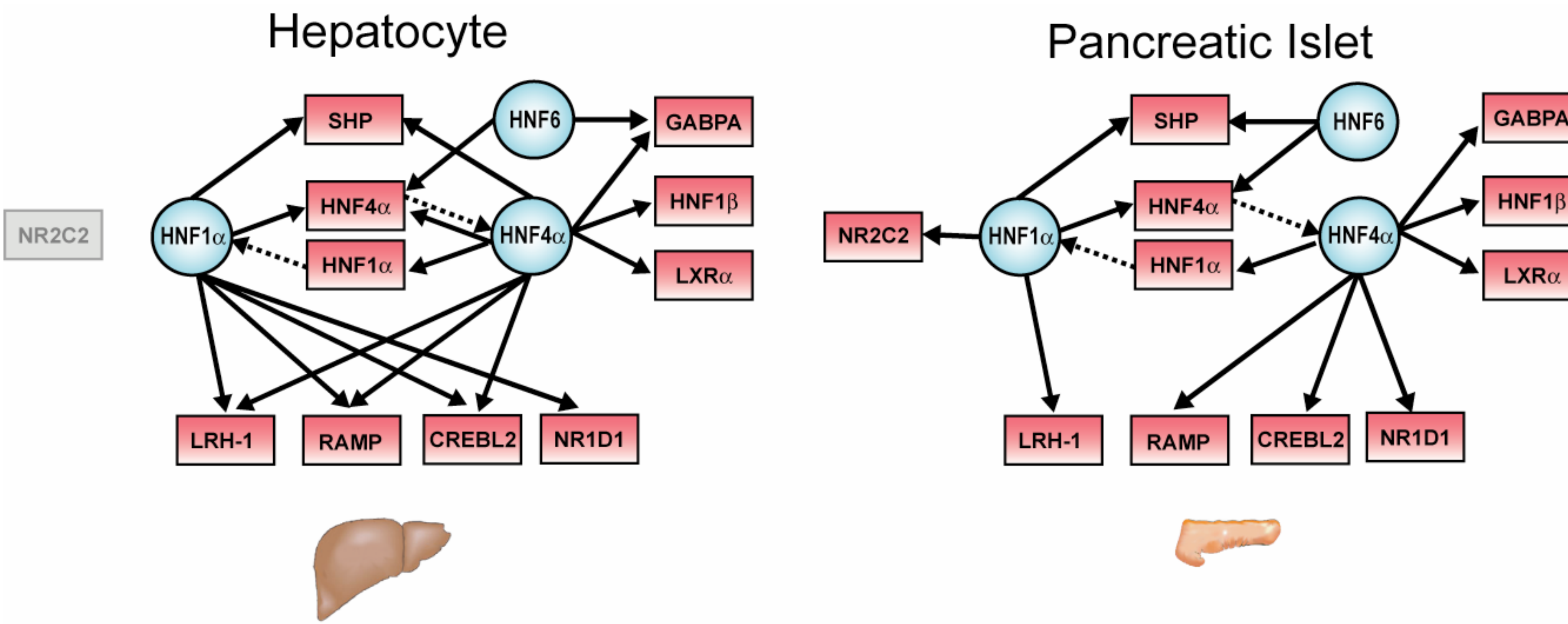
Figure by MIT OCW.

HNF4α occupies over 40% of the genes expressed in these tissues.

Abnormal levels of HNF4α may cause MODY by destabilizing transcriptome.

Odom et al. Science 2004

Transcriptional Regulatory Networks Controlled by HNF1α and HNF4α



- Identification of downstream transcriptional regulators reveals factors for further profiling of tissues

- Challenge: cell type hererogeneity

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