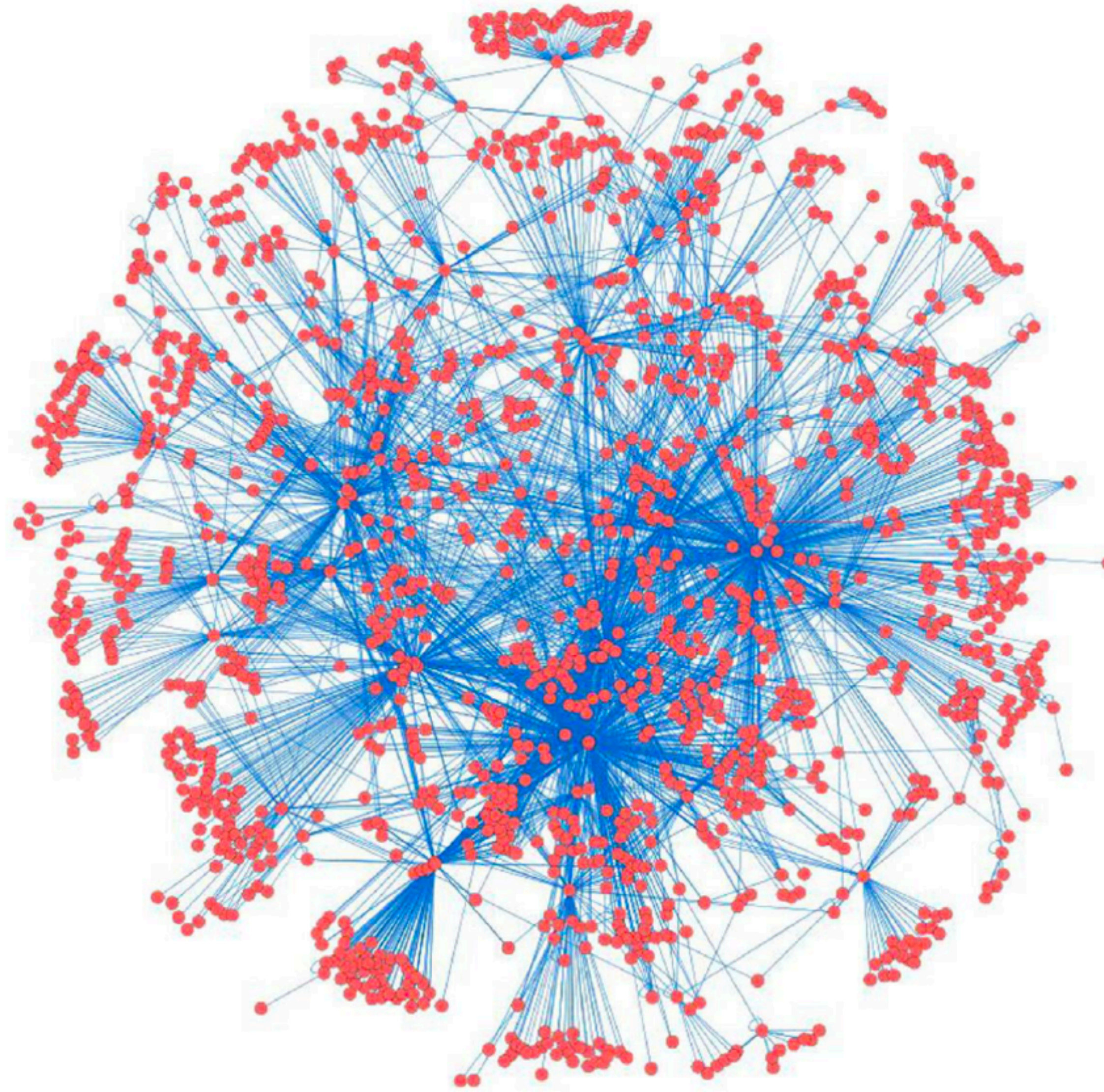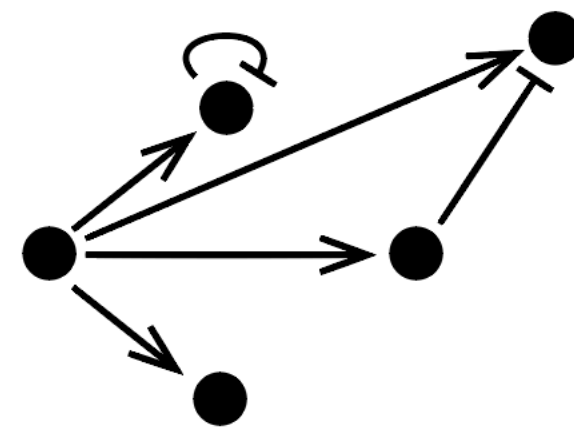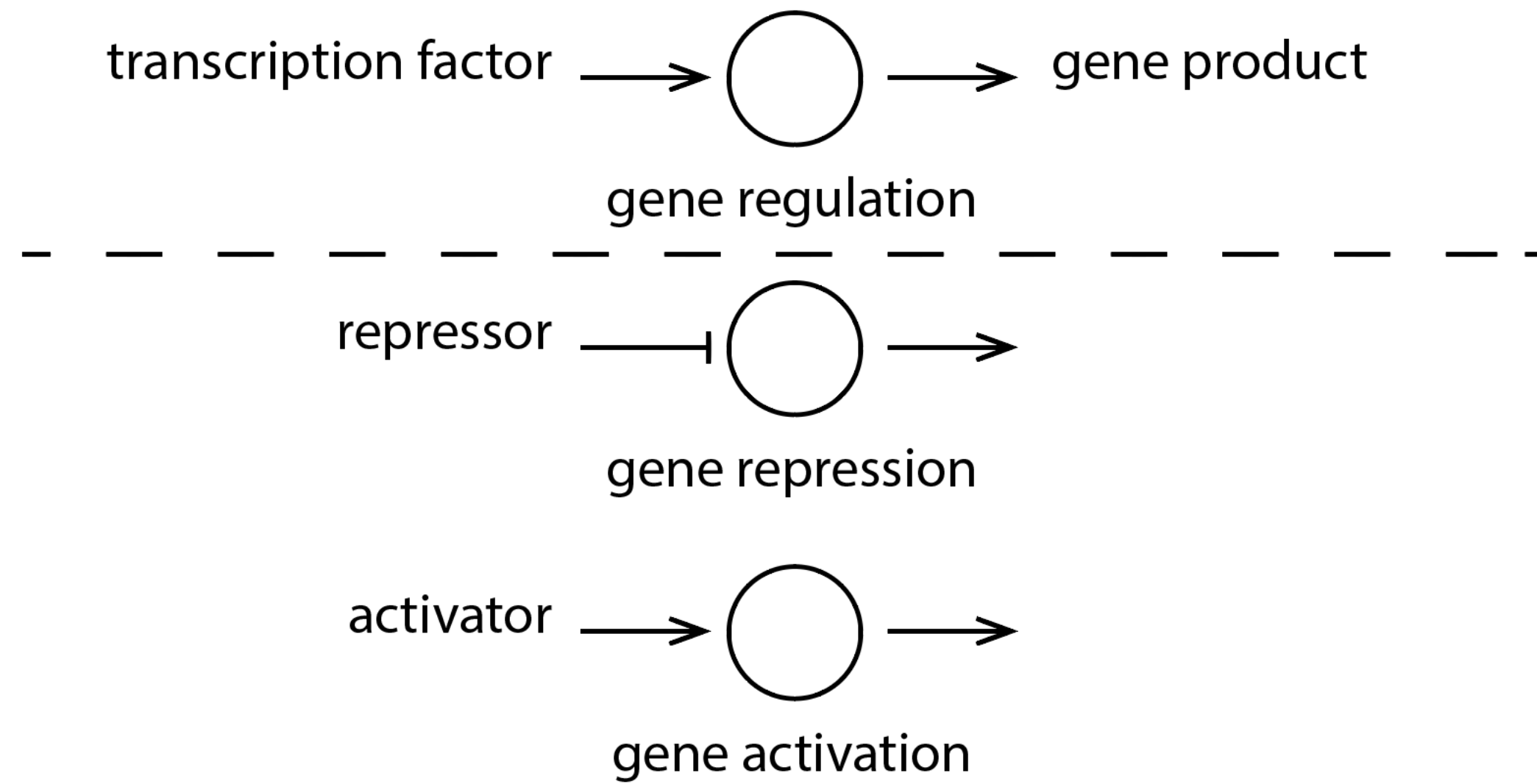# LECTURE 6
REGULATION **MOTIFS**

Gene regulation
Time constants of gene regulation
Gene repression
Separation of fast and slow
Dissociation constant
EC50
Hill coefficient
Boolean approximation
Gene activation
Gene regulatory network model
Multidimensional promoters (AND, OR)

E. coli network
5M bp, 4000 genes, 300 TFs (DoFs)
20% network (Shen-Orr 2002)
N=420, E=520
Erdos random network, p = E/N^2
Motif
Single node motifs

p_{self} = 1/N, $<n_{self}>$ = var = E/N
NAR motif
approximate model
steady state normalization
rise time, T_r = K/2/Vmax
comparison with unregulated model
speed up module
robustness module
PAR motif
approximate model
rise time
delay module

EXERCISE
create a random GRN (N=10,E=10)
make direction and sign binomially dist
make Km uniform between 0 and 1
let Vmax = 1
choose input and output at random
generate ensemble of 1e6 step resp

BIONUMBERS
(https://bionumbers.hms.harvard.edu/)
Transcription rate (20-40nt/sec)
mRNA export time (1-10min)
Translation rate (5-10 codons/sec)
Folding time (10-30min/protein)
Diffusion time yeast (0.5sec)
Diffusion rate in cytoplasm (8um^2/sec)
Diffusion rate in water (100um^2/sec)
ER flux yeast (460molecules/sec)
Secretion time (~20min)

transcription factor → ◯ → gene product

gene regulation

- - - - - - - - - - - - - - - - - - - -

repressor —⊣ ◯ →

gene repression

activator → ◯ →

gene activation

transcriptional regulatory network

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ODE model
(gene repression)

Chemical Reaction Network:

gene expression $\qquad G \xrightarrow{k_1} G + P$

degradation $\qquad P \xrightarrow{k_2} \emptyset$

repression $\qquad G + I \underset{k_4}{\overset{k_3}{\rightleftharpoons}} G^*$

Full ODE:

$$\dot{G} = k_4 G^* - k_3 G I^n$$
$$\dot{G^*} = k_3 G I^n - k_4 G^*$$
$$\dot{P} = k_1 G - k_2 P$$

Mass Conservation:

$$G + G^* = G_T \ (\text{constant})$$

Reduced ODE:

$$\dot{G} = k_4(G_T - G) - k_3 G I^n$$
$$\quad = k_4 G_T - G(k_4 + k_3 I^n)$$
$$\dot{P} = k_1 G - k_2 P$$

Time scale separation:

Fast dynamics $\Rightarrow$ gene regulation $\sim$ sec

Slow dynamics $\Rightarrow$ gene expression $\sim$ 10min

Fully reduced ODE:

$$\tilde{k}_4 = \frac{k_4}{\varepsilon}, \quad \tilde{k}_3 = \frac{k_3}{\varepsilon}$$

$$\dot{G} = \frac{\tilde{k}_4}{\varepsilon} G_T^* - G(\tilde{k}_4 + \tilde{k}_3 I^n)/\varepsilon$$
$$\varepsilon \dot{G} = \tilde{k}_4 G_T - G(\tilde{k}_4 + \tilde{k}_3 I^n)$$

pseudo eq. $\Rightarrow$

$$G = \frac{\tilde{k}_4 G_T}{\tilde{k}_4 + \tilde{k}_3 I^n}$$

$$= \frac{G_T}{1 + \left(\frac{I}{\sqrt[n]{\frac{\tilde{k}_4}{\tilde{k}_3}}}\right)^n} \leftarrow \text{hill coef.}$$

$$= \frac{G_T}{1 + \left(\frac{I}{K_d}\right)^n} \leftarrow \text{diss. constant}$$

as $n \to \infty$ more like true logic gate

what is the activation ODE?

how would you model the multi-input gene below?

input 1

input 2

multi-input example

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