Biology of the *noisy* gene

Universidad Autónoma de Madrid

Jan 2008

Juan F. Poyatos

Logic of Genomic Systems laboratory

Spanish National Biotechnology Centre (CNB)

day V: noisy eukaryotes
2) yeast

- Systemic view of noise.
- A general scaling of noise.

Logs laboratory

Systemic studies of noise I

Previous studies limited to very specific genes, generalizability?

Experiment: 43 *S. cerevisiae* proteins under 11 experimental conditions.
        In contrast to previous studies there was no synthetic modification
        of transcription/translation rates.

    - Focused on correlation of noise and mean expression level (abundance)
    - Different mean-expression levels associated to different gene classes:

            - stress
            - proteasome
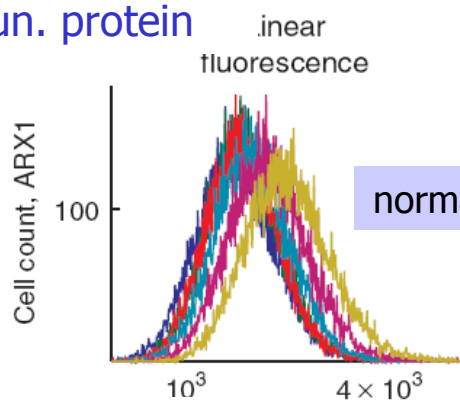   - ergosterol
            - rRNA processing

MAIN RESULT: Expression variance roughly proportional to mean.
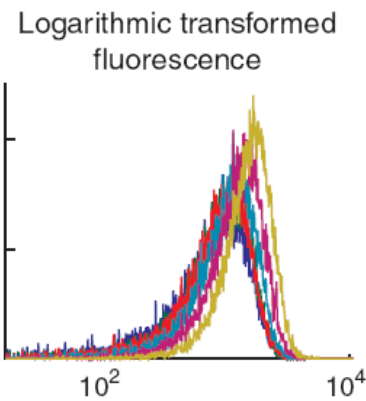
Noise *vs.* mean protein abundance
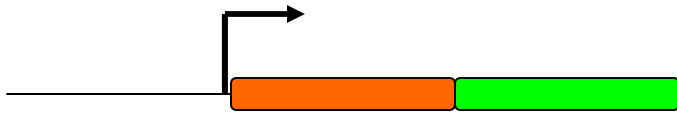
Cells expressing GFP-fused version of each prot.
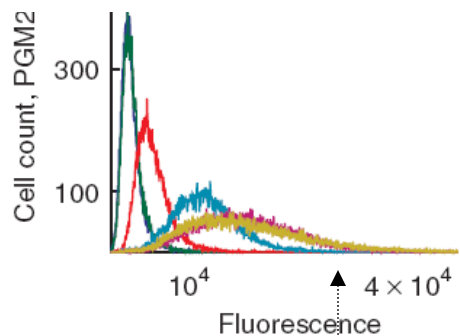11 environmental conditions
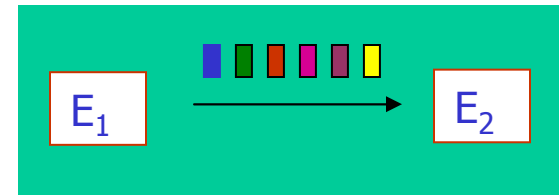Flow citometry measurements

low-abun. protein

Linear fluorescence
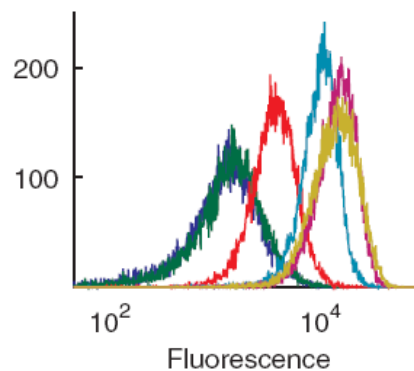
b Logarithmic transformed fluorescence

Cell count, ARX1

normality

high-abun

d

Cell count, PGM2

Fluorescence

Fluorescence

deviation from normality

E_1 → E_2

Noise *vs.* mean protein abundance

points before E change
(steady state conditions)

different conditions

Auto-fluorescence
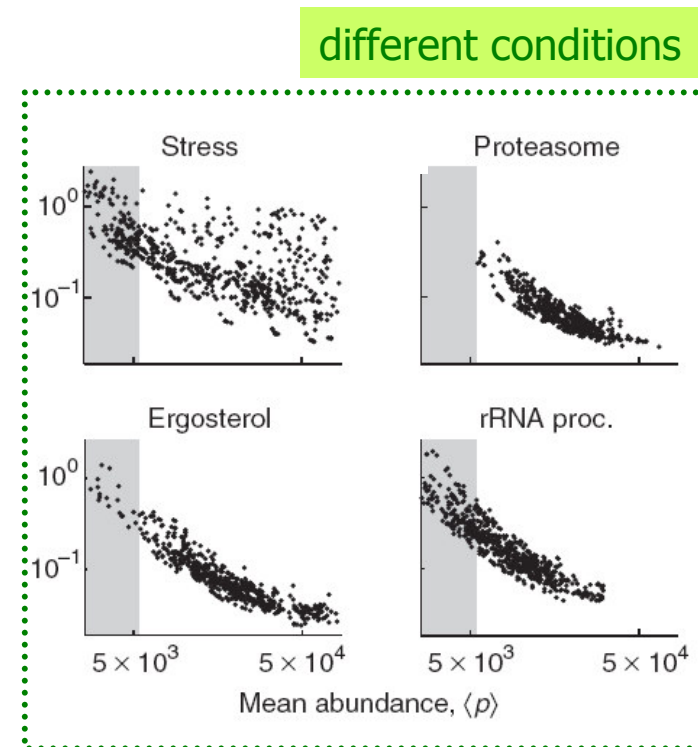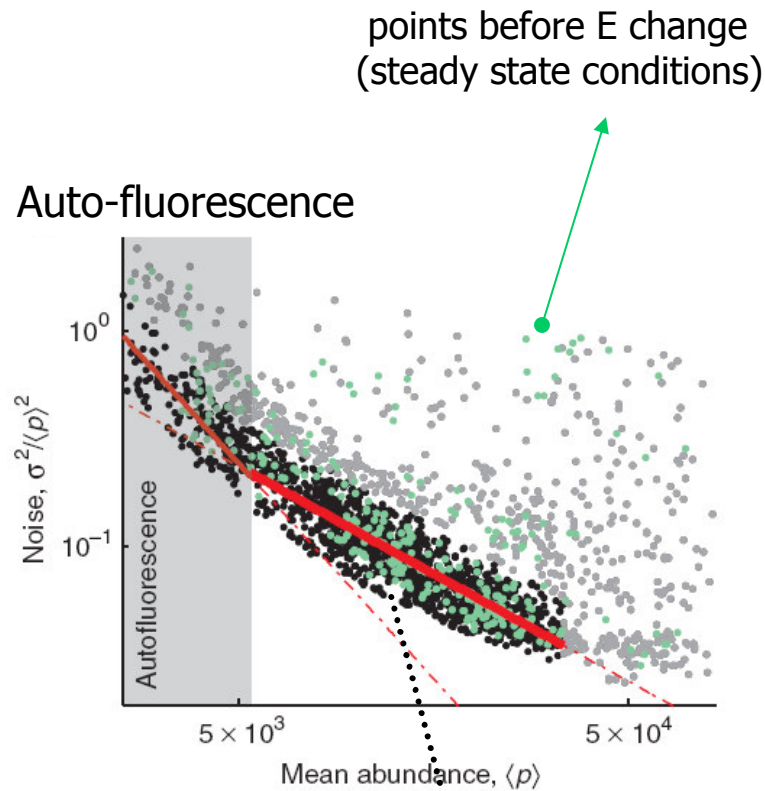
$$\eta_p^2 = C/\langle p\rangle,\ \text{with}\ C \approx 1{,}200$$

Recall, poissonian → CV² $= \eta_p^2 = 1/\langle p\rangle$

Noise *vs.* mean protein abundance; theoretical analysis
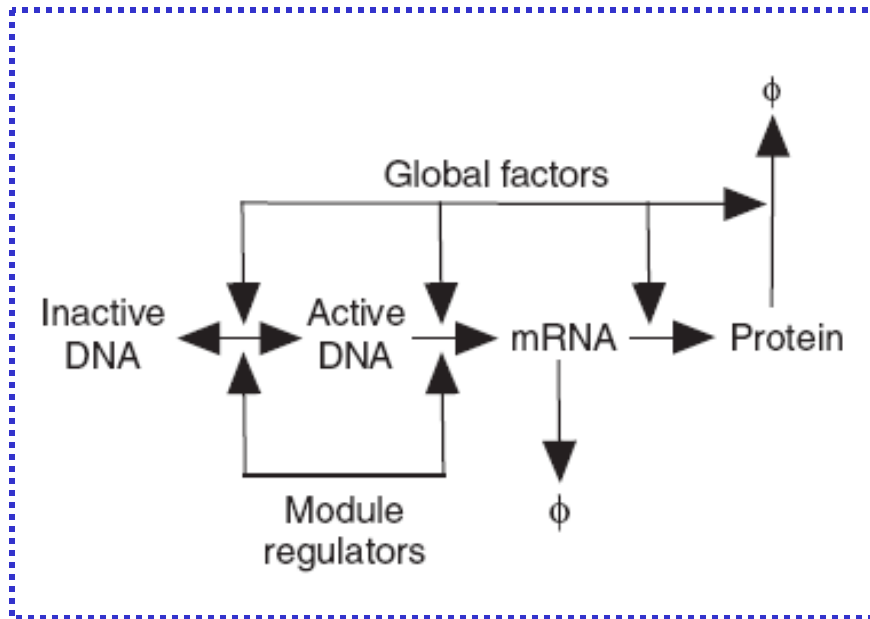
- Is noise driven by global factors explaining this trend?

- Is noise driven by mRNA fluctuations explaining this trend?

- Is noise driven by promoter fluctuations explaining this trend?

Can global factors explain the variance/abundance correlation?

-Protein production depend on level of independent upstream component $\boxed{X}$
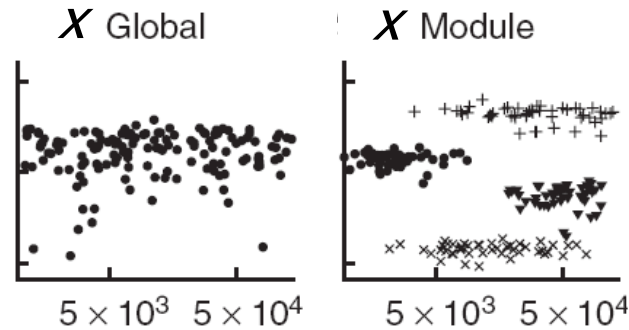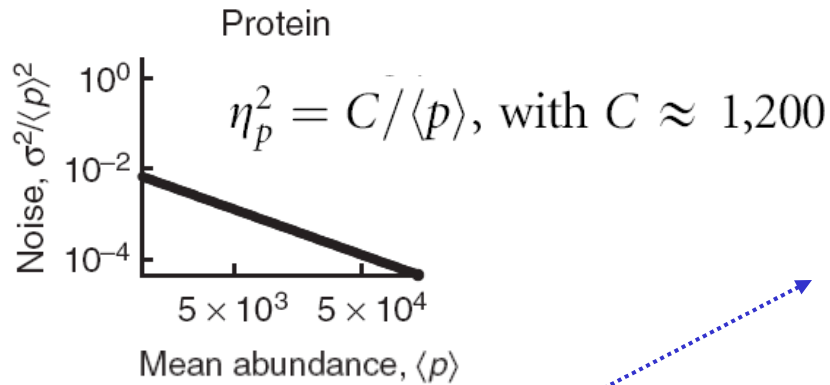

$$\eta_p^2 \approx \underbrace{\frac{1}{H_{PP}} \times \frac{1}{\langle p \rangle}}_{\text{spontaneous}} + \underbrace{\eta_x^2 \times \frac{H_{xp}^2}{H_{PP}^2} \times \frac{H_{pp}/\tau_p}{H_{pp}/\tau_p + H_{xx}/\tau_x}}_{\text{x-influence}}$$

Noise in upstream comp.

Elasticities; sharpess of nonlinearities;
Susceptibility to upstream noise

Average lifetimes
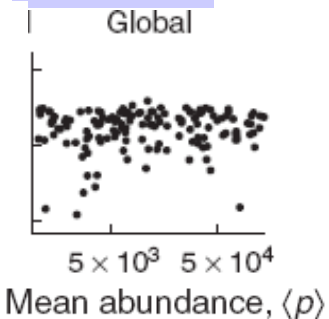
Can global factors explain the variance/abundance correlation?
(specific pathway)

Protein

$$\eta_p^2 = C/\langle p \rangle, \text{ with } C \approx 1{,}200$$

Noise, $\sigma^2/\langle p \rangle^2$

10^0 10^{-2} 10^{-4}

5×10^3 5×10^4

Mean abundance, $\langle p \rangle$

same qualitative scaling but to get scaling constant -> unrealistic small elastic.

$$\eta_p^2 \approx \frac{1}{H_{PP}} \times \frac{1}{\langle p \rangle} + \eta_x^2 \times \frac{H_{xp}^2}{H_{pp}^2} \times \frac{H_{pp}/\tau_p}{H_{pp}/\tau_p + H_{xx}/\tau_x}$$
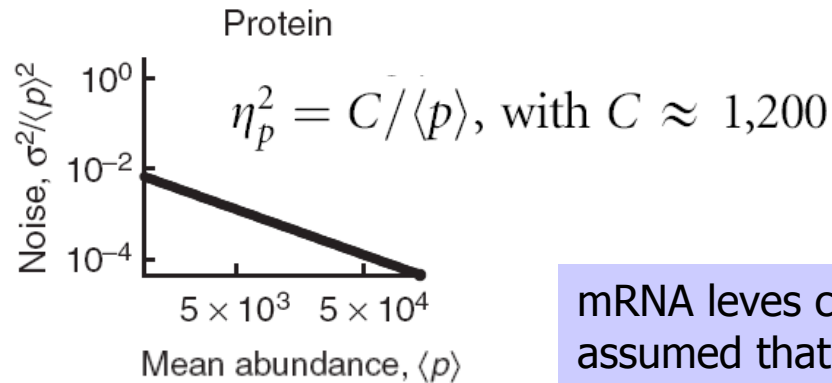
constant

Global

5×10^3 5×10^4

Mean abundance, $\langle p \rangle$

To explain this, changes in lifetime should dominate, why?

how strongly x affects p
why should it correlate with abundance?

Can mRNA noise explain the variance/abundance correlation?

Protein

$$\eta_p^2 = C/\langle p \rangle, \text{ with } C \approx 1{,}200$$

Noise, $\sigma^2/\langle p \rangle^2$

10^0

10^{-2}

10^{-4}

$5 \times 10^3 \quad 5 \times 10^4$

Mean abundance, $\langle p \rangle$

mRNA leves changes for each gene
assumed that mRNA is short-lived with respect to proteins

$$C \approx \lambda_p \tau_{\mathrm{mRNA}}$$

$$\eta_p^2 = \eta_{\mathrm{mRNA}}^2 \times \frac{1/\tau_p}{1/\tau_p + 1/\tau_{\mathrm{mRNA}}} \approx \eta_{\mathrm{mRNA}}^2 \times \frac{\tau_{\mathrm{mRNA}}}{\tau_p} \approx C/\langle p \rangle$$

$$\eta_{\mathrm{mRNA}}^2 = 1/\langle \mathrm{mRNA} \rangle \qquad \langle p \rangle = \langle \mathrm{mRNA} \rangle \lambda_p \tau_{p}$$

$$\langle \mathrm{mRNA} \rangle = \lambda_{\mathrm{mRNA}} \tau_{\mathrm{mRNA}}$$

Can mRNA noise explain the variance/abundance correlation?

Protein

$$\eta_p^2 = C/\langle p \rangle, \text{ with } C \approx 1{,}200$$

Noise, $\sigma^2/\langle p \rangle^2$

10^0
10^{-2}
10^{-4}

$5 \times 10^3 \quad 5 \times 10^4$
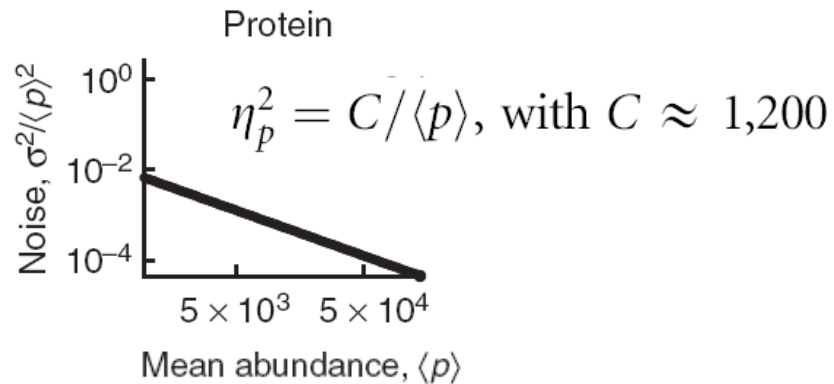
Mean abundance, $\langle p \rangle$

If $\quad \eta_p^2 = C/\langle p \rangle \quad \longleftarrow \cdots \bullet \quad C \approx \lambda_p \tau_{\text{mRNA}}$

→ average prot. per transcript similar for all genes/conditions in data

mean C ≈ 1300

→ differences in prot. abundance mainly due to chances in transcription

→ finally, gene activation could also play a role in a regime where genes are mostly OFF. These mechanisms are however not sufficiently characterized

Intrinsic noise

- Two-reporter assays for 4 proteins of intermediate (PWP1, TPS1, PRE9) and high abundance (ACS2)
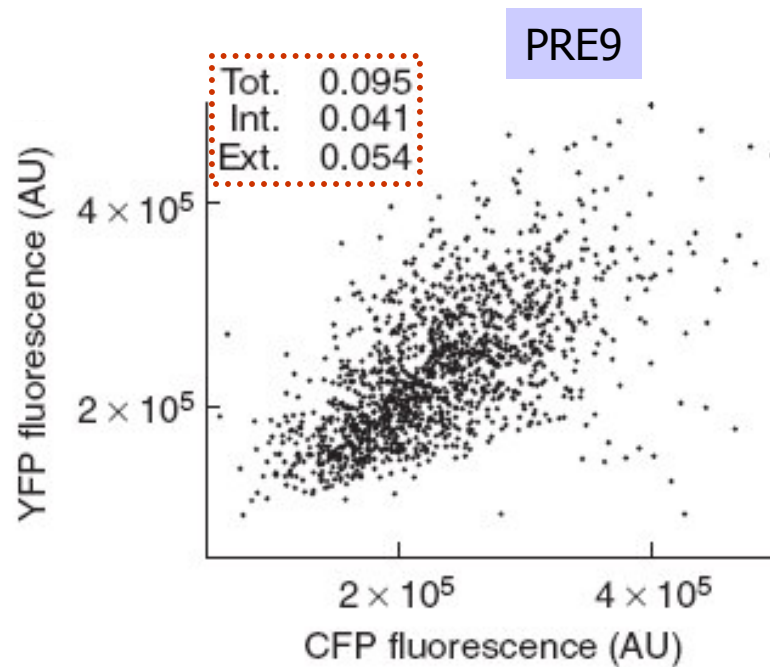
- For proteins of intermediate abundance → substancial contribution of internal noise.

Systemic studies of noise II

Previous studies limited to very specific genes, generalizability?

Experiment: >2500 *S. cerevisiae* proteins in **rich** and **minimal** media
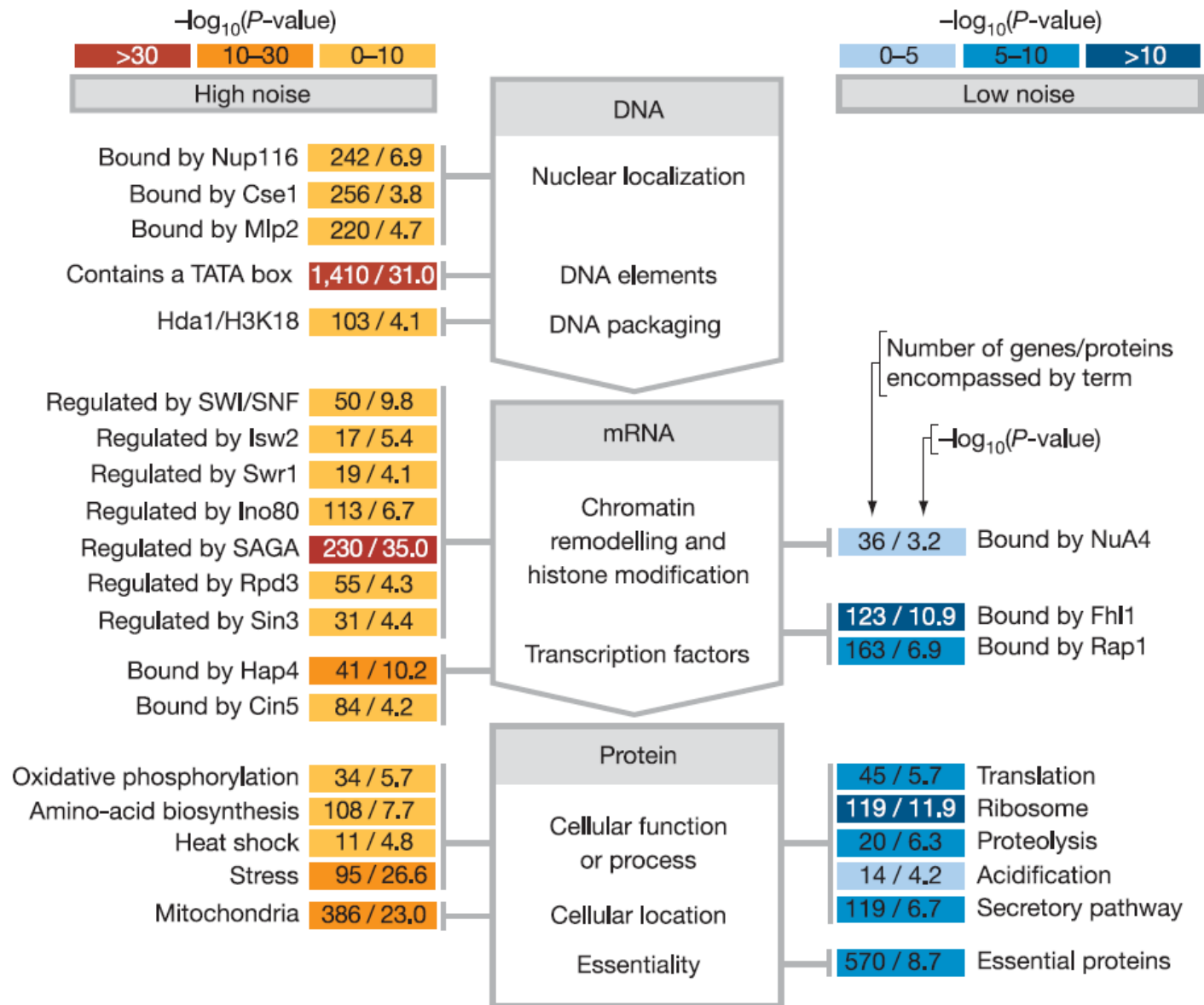   In contrast to previous studies there was no synthetic modification
   of transcription/translation rates.

   - Focused on correlation of noise and mean expression level (abundance)
   -

MAIN RESULT: Noise in protein expression is dominated by stochastic
       production/destruction of mRNAs
       Dramatic protein-specific differences in noise

Factors contributing to noise

Factors contributing to noise

Cellular properties correlated with variation

Property	Test	$-\log_{10}(P\text{-value})$
Gene proximity	Dist. vs DM or CV	0.2–2.7
mRNA copy number	mRNA per cell vs CV	109.0
mRNA half-life	mRNA $t_{1/2}$ vs DM	3.0
mRNA variation	mRNA σ vs DM	67.0
CAI score	CAI vs DM	3.0
Ribosome density	Ribos. dens. vs DM	6.5
No. of proteins/mRNA	No. prot./mRNA vs DM	5.9
Protein copy number	Protein per cell vs CV	321.0
Protein interactions	No. PPI vs DM	0.5

Correlation 0–3 3–5 5–10 >10