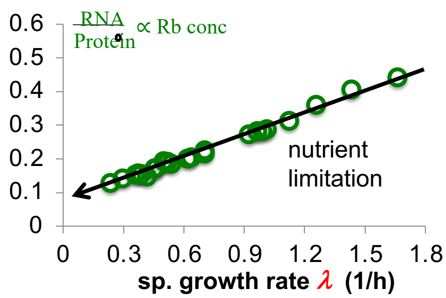
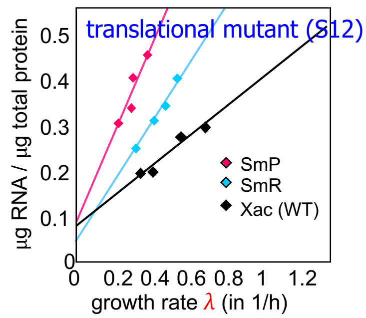
Microbial growth law [Ole Maaloe et al, 1950s - 70s]





Model of bacterial growth

- assume all ribosomes efficiently engaged in protein synthesis

rate protein mass accum. = rate Rb elongation

⇑ ⇑

$$\underbrace{\dot{M}_{tot} = \lambda \cdot M_{tot} \qquad \gamma \cdot M_{Rb}}$$

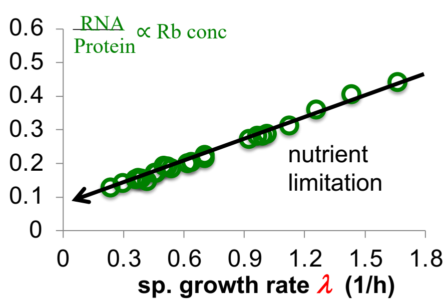
$$\phi_R \equiv \frac{M_{Rb}}{M_{tot}} = \lambda / \gamma$$

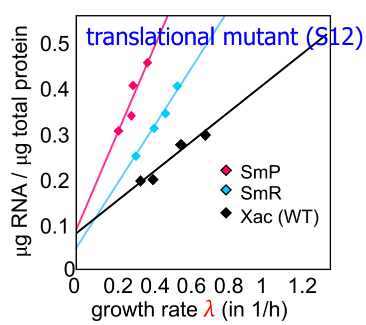
λ : specific growth rate

γ : Rb elongation rate (~20 aa/s or 10 Rb/hr)

1

Microbial growth law [Ole Maaloe et al, 1950s - 70s]





Model of bacterial growth

- assume all ribosomes efficiently engaged in protein synthesis

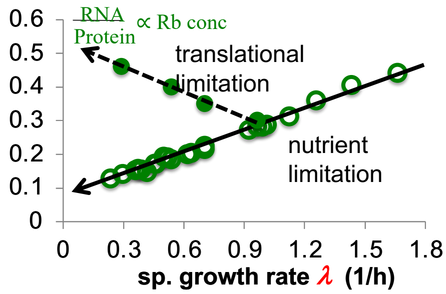
➔ higer ribosomal content is required for fast growth

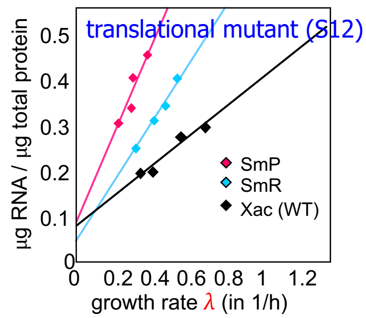
➔ protein expressions are <u>globally coupled</u> if most ribosomes are engaged in translation

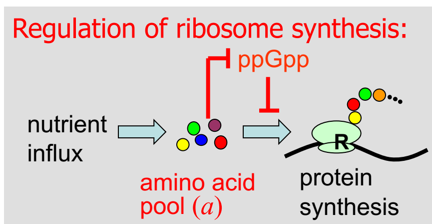
2

Microbial growth law [Ole Maaloe et al, 1950s - 70s]

Orthogonal perturbations [Scott et al, Science 2010]







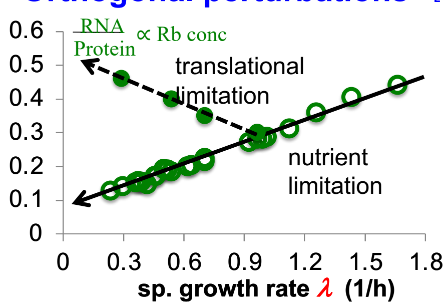
Q: but why linear increase of ϕ_R?

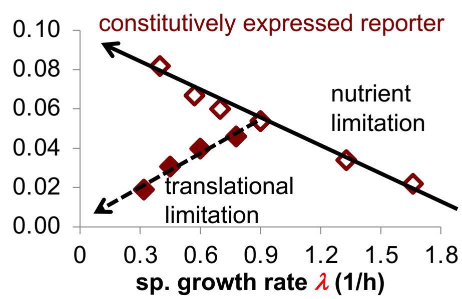
increased Rb synthesis must come at expense of reduction in the synthesis of other proteins

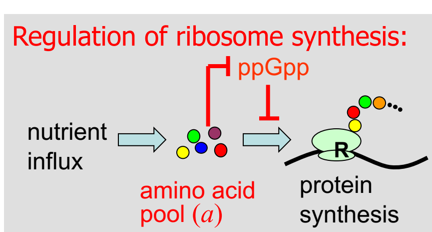
3

Microbial growth law [Ole Maaloe et al, 1950s - 70s]

Orthogonal perturbations [Scott et al, Science 2010]







Q: but why linear increase of ϕ_R?

increased Rb synthesis must come at expense of reduction in the synthesis of other proteins

➔ Examine the response of various metabolic enzymes

4

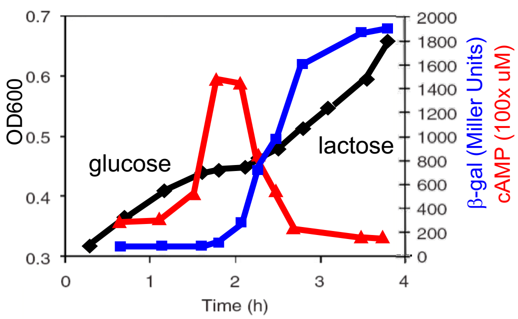
Catabolite repression & carbon hierarchy

- glucose effect: ability of glucose to inhibit the synthesis of certain enzymes
- all glucose-sensitive enzymes can convert their substrates to metabolites which can also be obtained more readily by the metabolism of glucose

➔ "catabolites" formed rapidly from glucose would accumulate and repress the formation of enzymes whose activity would augment the already large intracellular pools of these compounds [B. Magasanik, 1961]

carbon hierarchy (e.g., glucose-lactose diauxie)

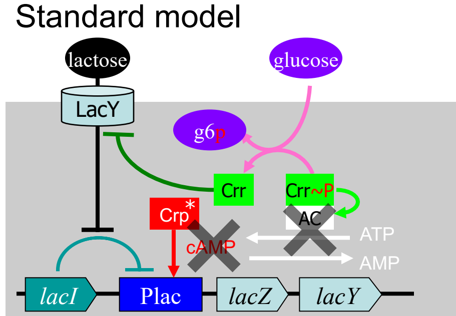
cAMP as a messenger ("inverse" of "catabolites")



8

Catabolite repression & carbon hierarchy

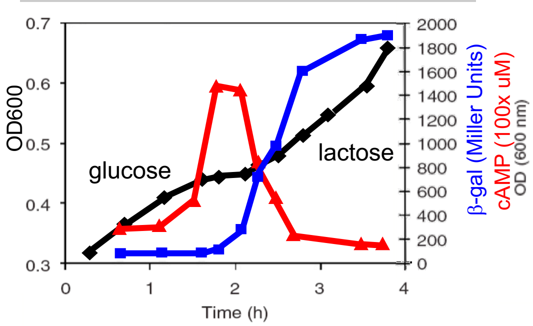
Standard model

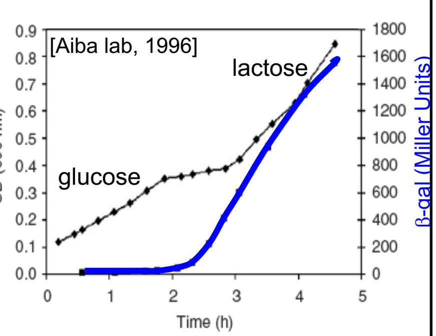


Problems with the standard model

- diauxie does not require cAMP

(mediated by "inducer exclusion"; later)

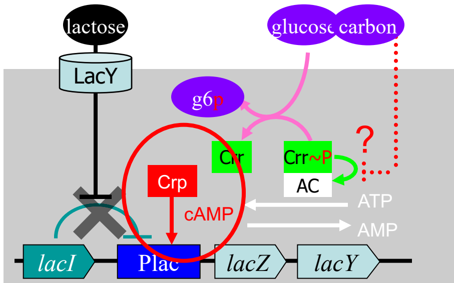




9

Catabolite repression

Standard model



Problems with the standard model
- diauxie does not require cAMP
  (mediated by "inducer exclusion"; later)
- effect not specific to glucose

Q1: how is cAMP level controlled?
Q2: what are the "catabolites"?
Q3: physiological function?
Q4: what about carbon hierarchy?

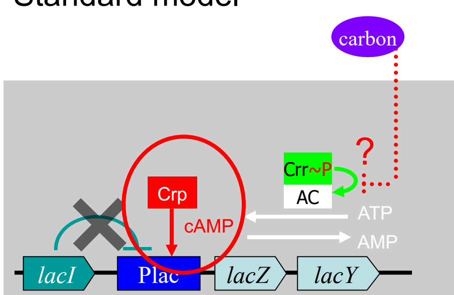
[J. Mandelstam, 1962]

Carbon source	β-Galactosidase (units/mg. dry wt.)	Doubling time (min.)
Lactose	136	45
Glucose	200	48
Gluconate	260	50
Galactose	432	54
Glycerol	499	60
Succinate	600	65
Fructose	613	67
Lactate	816	65

10

Catabolite repression

Standard model



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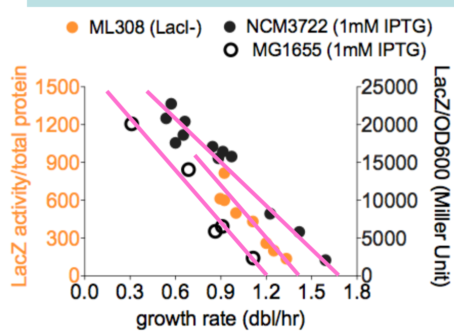


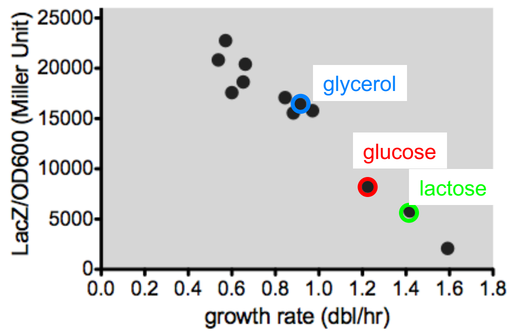
12

Physiological study of catabolite repression

E. coli K-12 NCM3722
(1mM IPTG)

C-source	dbl rate (dbl/h)	β-gal (Miller)
glucose6p +gluconate	1.59	2085
lactose	1.42	5803
glucose	1.22	8225
maltose	0.97	15789
glycerol	0.91	16431
pyruvate	0.88	15557
fructose	0.84	17080
succinate	0.66	20406
sorbitol	0.65	18636
mannose	0.60	17586
arabinose	0.57	22757
acetate	0.54	20834

[You et al, Nature 2013]



13

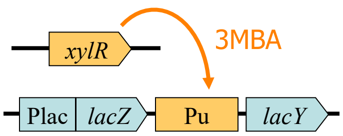
Physiological study of catabolite repression

E. coli K-12 NCM3722
(1mM IPTG)

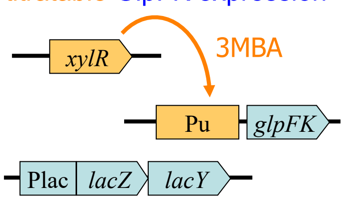
➔ Up-regulation in response to reduced C-flux

Q: what about other types of growth limitation?
no effect according to known regulation

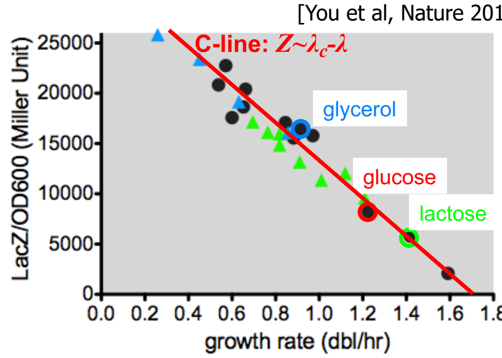
titratable LacY expression



titratable GlpFK expression



[You et al, Nature 2013]



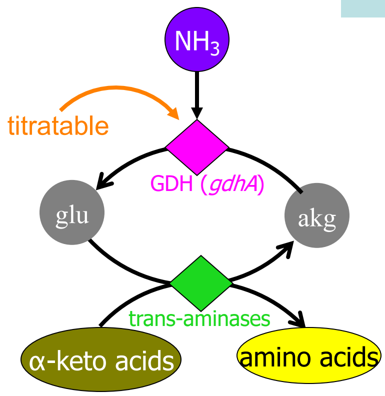
▲ lactose with titratable LacY expression
▲ glycerol with titratable GlpFK expression

14

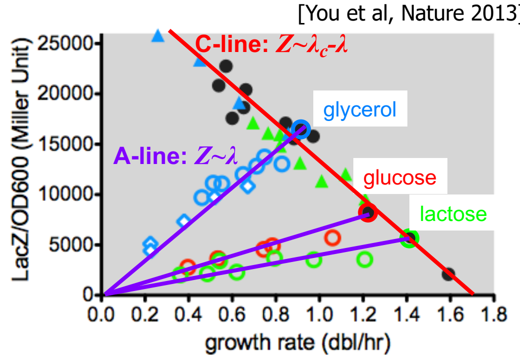
Physiological study of catabolite repression

E. coli K-12 NCM3722
(1mM IPTG)

➔ Up-regulation in response to reduced C-flux
➔ Down-regulation of catabolism
upon other nutrient limitations (A-lines)



[You et al, Nature 2013]



▲ lactose with titratable LacY expression
▲ glycerol with titratable GlpFK expression

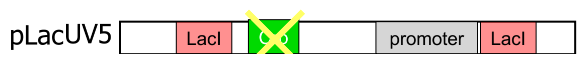
○○○ ΔgltD; titratable GDH; various C-sources
◇ S-limited chemostat; glycerol

17

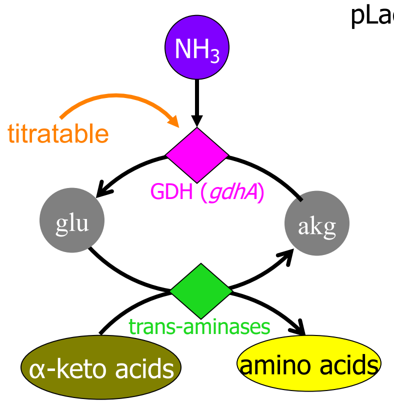
Physiological study of catabolite repression

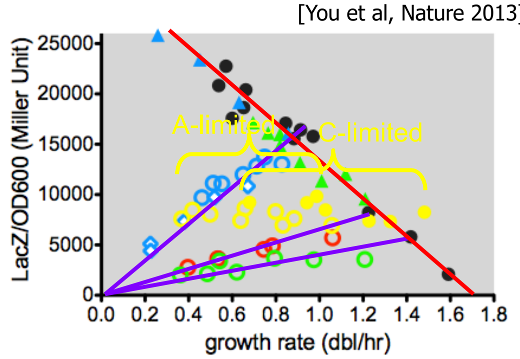
E. coli K-12 NCM3722
(1mM IPTG)

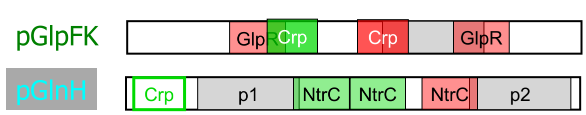
Dependence on Crp-cAMP?
➔ both C- and A- lines require Crp-cAMP



[You et al, Nature 2013]







18

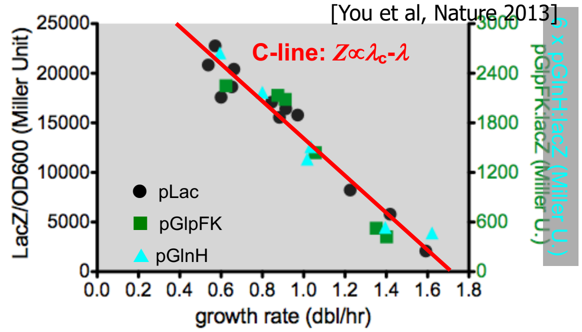
Physiological study of catabolite repression

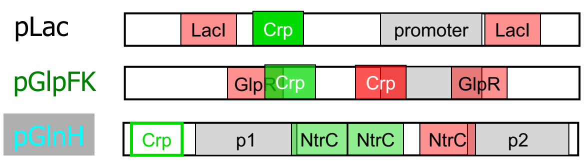
Strain: NCM3722
(1mM IPTG)

C-source	dbl rate (dbl/h)	β-gal (Miller)
glucose6p +gluconate	1.59	2085
lactose	1.42	5803
glucose	1.22	8225
maltose	0.97	15789
glycerol	0.91	16431
pyruvate	0.88	15557
fructose	0.84	17080
succinate	0.66	20406
sorbitol	0.65	18636
mannose	0.60	17586
arabinose	0.57	22757
acetate	0.54	20834

Dependence on Crp-cAMP?
➔ both C- and A- lines require Crp-cAMP
➔ same C-line (λ_c) from different promoters

[You et al, Nature 2013]

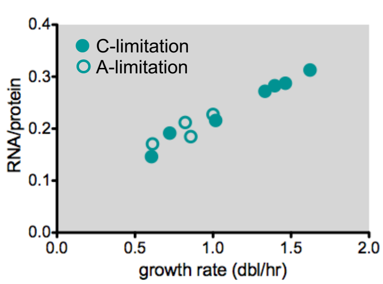


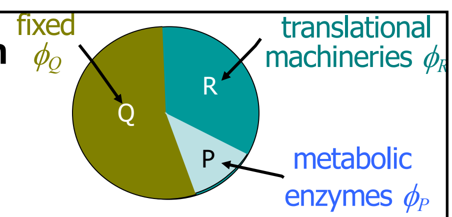


19

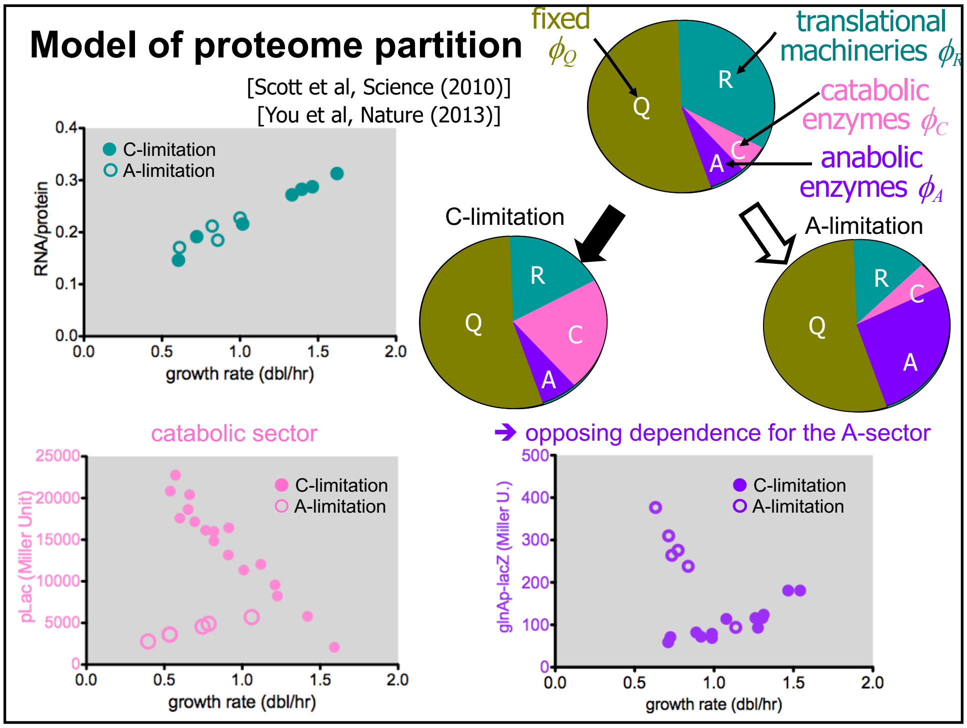
Model of proteome partition

[Scott et al, Science (2010)]



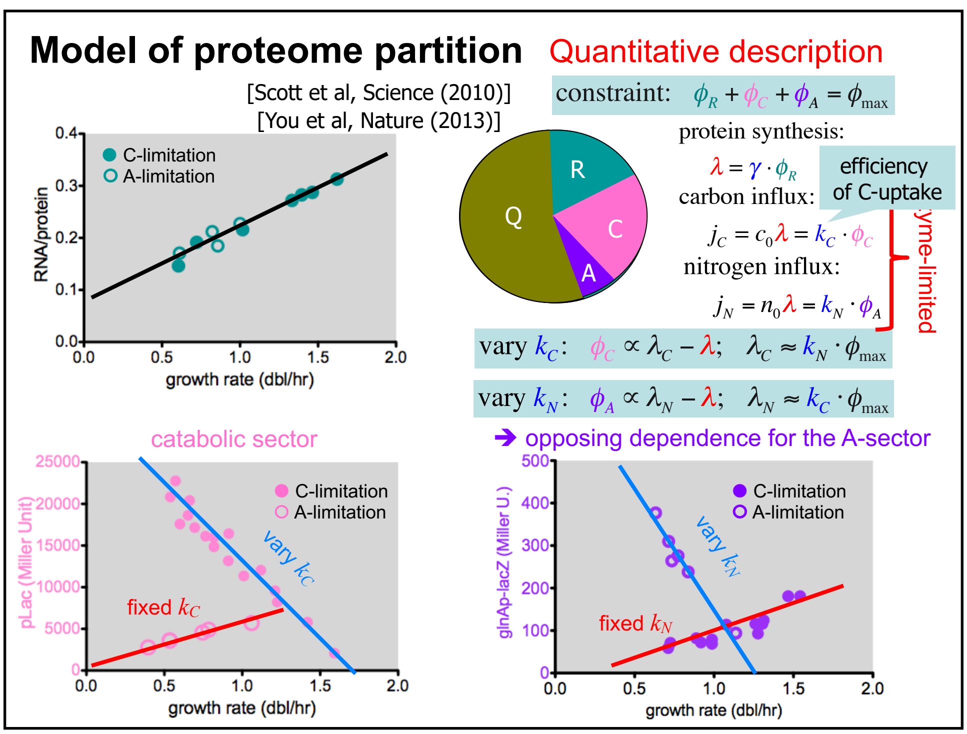


23



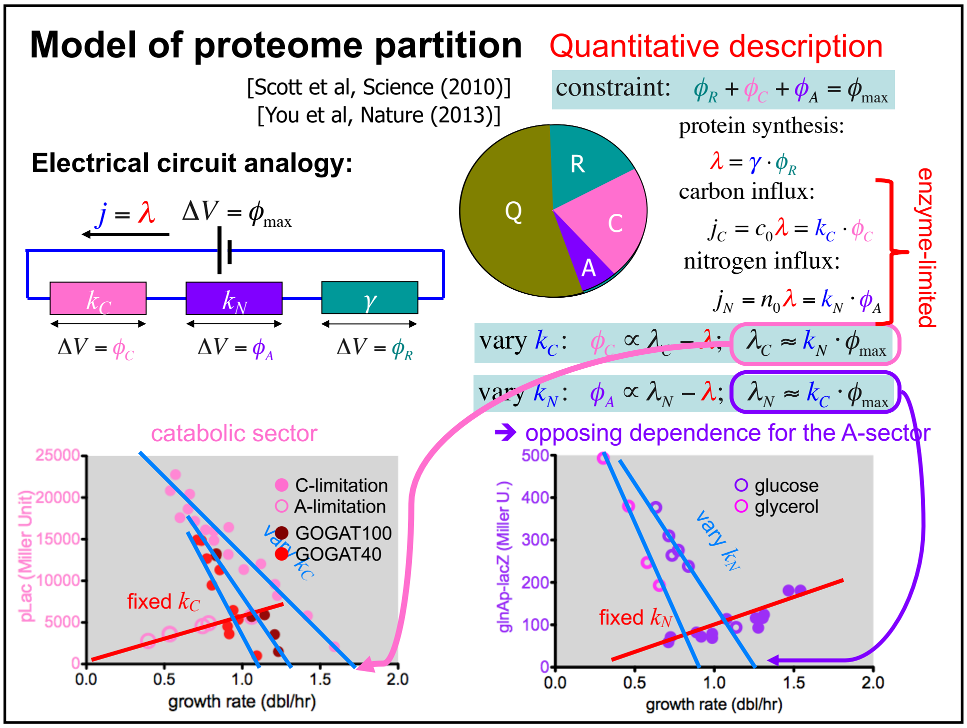
Model of proteome partition
[Scott et al, Science (2010)]
[You et al, Nature (2013)]
fixed ϕ_Q
translational machineries ϕ_R
catabolic enzymes ϕ_C
anabolic enzymes ϕ_A
Q
R
C
A
C-limitation
A-limitation
RNA/protein
growth rate (dbl/hr)
catabolic sector
pLac (Miller Unit)
→ opposing dependence for the A-sector
glnAp-lacZ (Miller U.)

24

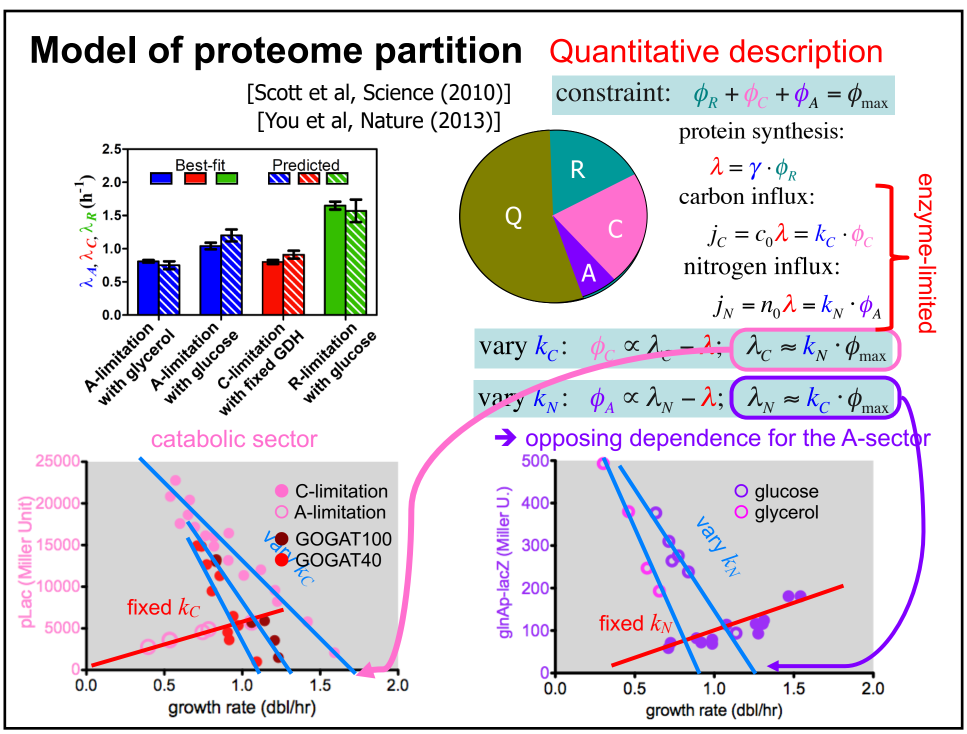


Model of proteome partition
Quantitative description
[Scott et al, Science (2010)]
[You et al, Nature (2013)]
constraint: $\phi_R + \phi_C + \phi_A = \phi_{\max}$
protein synthesis:
$\lambda = \gamma \cdot \phi_R$
efficiency of C-uptake
carbon influx:
$j_C = c_0 \lambda = k_C \cdot \phi_C$
nitrogen influx:
$j_N = n_0 \lambda = k_N \cdot \phi_A$
yme-limited
vary k_C: $\phi_C \propto \lambda_C - \lambda$; $\lambda_C \approx k_N \cdot \phi_{\max}$
vary k_N: $\phi_A \propto \lambda_N - \lambda$; $\lambda_N \approx k_C \cdot \phi_{\max}$
Q
R
C
A
C-limitation
A-limitation
RNA/protein
growth rate (dbl/hr)
catabolic sector
pLac (Miller Unit)
vary k_C
fixed k_C
→ opposing dependence for the A-sector
glnAp-lacZ (Miller U.)
vary k_N
fixed k_N

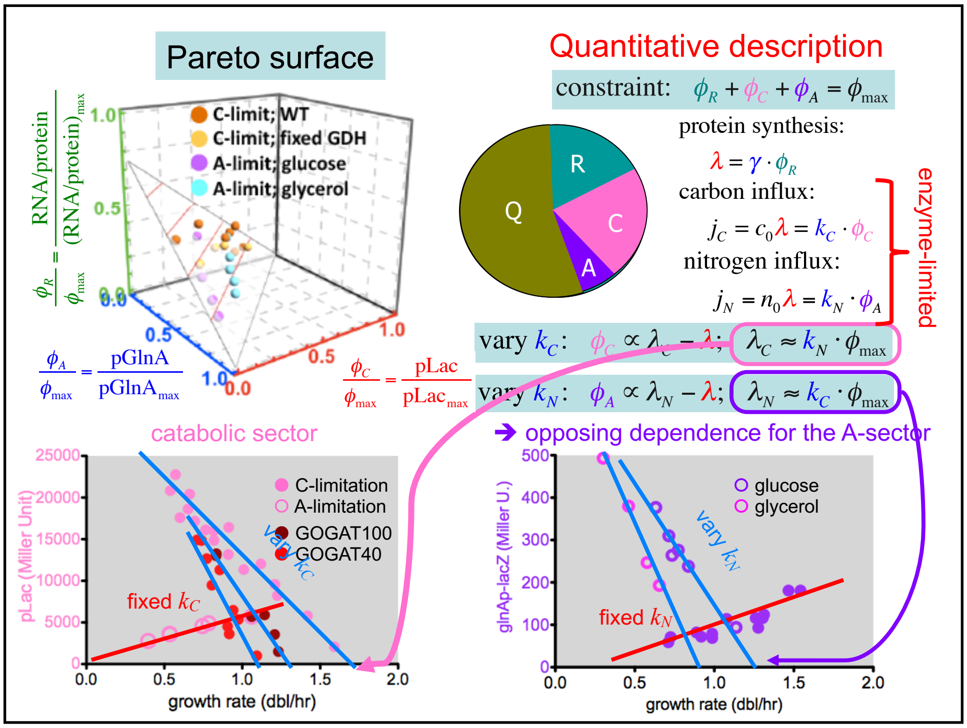
25


Model of proteome partition
Quantitative description
[Scott et al, Science (2010)]
[You et al, Nature (2013)]
Electrical circuit analogy:
$j = \lambda$
$\Delta V = \phi_{max}$
k_C
k_N
γ
$\Delta V = \phi_C$
$\Delta V = \phi_A$
$\Delta V = \phi_R$
constraint: $\phi_R + \phi_C + \phi_A = \phi_{max}$
R
Q
C
A
protein synthesis:
$\lambda = \gamma \cdot \phi_R$
carbon influx:
$j_C = c_0 \lambda = k_C \cdot \phi_C$
nitrogen influx:
$j_N = n_0 \lambda = k_N \cdot \phi_A$
enzyme-limited
vary k_C: $\phi_C \propto \lambda_C - \lambda$; $\lambda_C \approx k_N \cdot \phi_{max}$
vary k_N: $\phi_A \propto \lambda_N - \lambda$; $\lambda_N \approx k_C \cdot \phi_{max}$
opposing dependence for the A-sector
catabolic sector
pLac (Miller Unit)
C-limitation
A-limitation
GOGAT100
GOGAT40
vary k_C
fixed k_C
growth rate (dbl/hr)
glnAp-lacZ (Miller U.)
glucose
glycerol
vary k_N
fixed k_N
growth rate (dbl/hr)

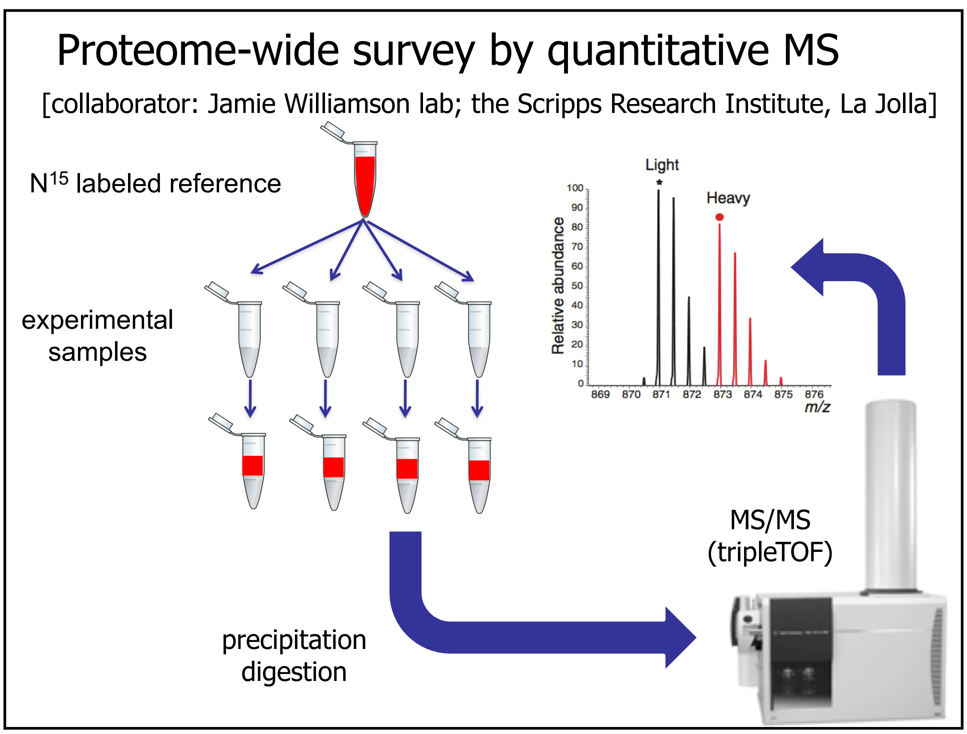
26


Model of proteome partition
Quantitative description
[Scott et al, Science (2010)]
[You et al, Nature (2013)]
Best-fit
Predicted
$\lambda_A, \lambda_C, \lambda_R$ (h^{-1})
A-limitation with glycerol
A-limitation with glucose
C-limitation with fixed GDH
R-limitation with glucose
constraint: $\phi_R + \phi_C + \phi_A = \phi_{max}$
R
Q
C
A
protein synthesis:
$\lambda = \gamma \cdot \phi_R$
carbon influx:
$j_C = c_0 \lambda = k_C \cdot \phi_C$
nitrogen influx:
$j_N = n_0 \lambda = k_N \cdot \phi_A$
enzyme-limited
vary k_C: $\phi_C \propto \lambda_C - \lambda$; $\lambda_C \approx k_N \cdot \phi_{max}$
vary k_N: $\phi_A \propto \lambda_N - \lambda$; $\lambda_N \approx k_C \cdot \phi_{max}$
opposing dependence for the A-sector
catabolic sector
pLac (Miller Unit)
C-limitation
A-limitation
GOGAT100
GOGAT40
vary k_C
fixed k_C
growth rate (dbl/hr)
glnAp-lacZ (Miller U.)
glucose
glycerol
vary k_N
fixed k_N
growth rate (dbl/hr)

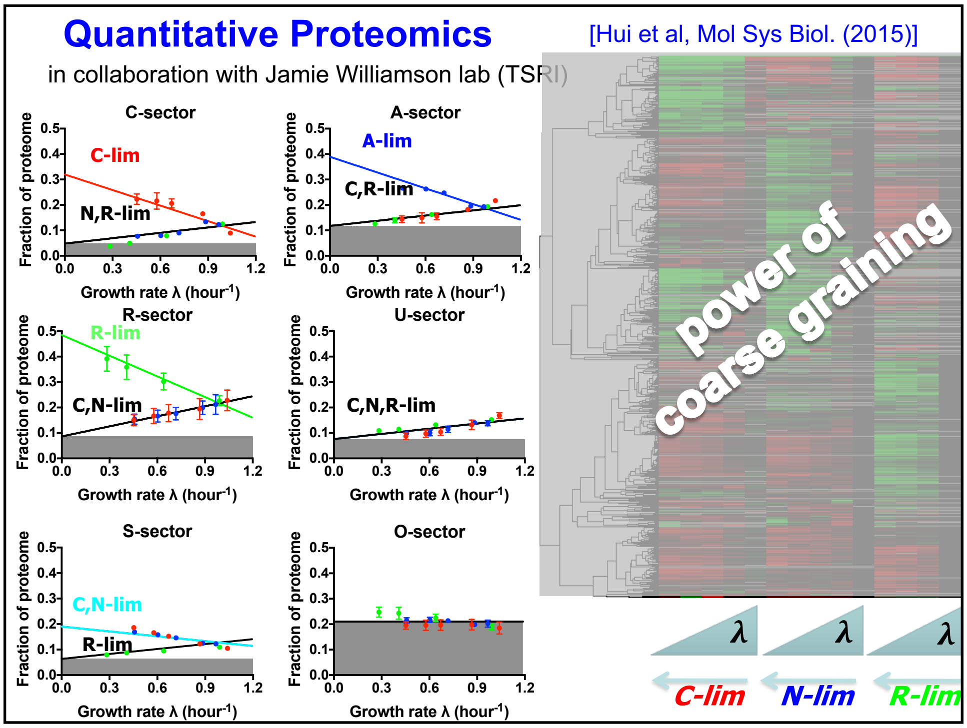
27


Pareto surface
Quantitative description
constraint: $\phi_R + \phi_C + \phi_A = \phi_{max}$
protein synthesis:
$\lambda = \gamma \cdot \phi_R$
carbon influx:
$j_C = c_0 \lambda = k_C \cdot \phi_C$
nitrogen influx:
$j_N = n_0 \lambda = k_N \cdot \phi_A$
enzyme-limited
vary k_C: $\phi_C \propto \lambda_C - \lambda$; $\lambda_C \approx k_N \cdot \phi_{max}$
vary k_N: $\phi_A \propto \lambda_N - \lambda$; $\lambda_N \approx k_C \cdot \phi_{max}$
→ opposing dependence for the A-sector
C-limit; WT
C-limit; fixed GDH
A-limit; glucose
A-limit; glycerol
$\frac{\phi_R}{\phi_{max}} = \frac{\text{RNA/protein}}{(\text{RNA/protein})_{max}}$
$\frac{\phi_A}{\phi_{max}} = \frac{\text{pGlnA}}{\text{pGlnA}_{max}}$
$\frac{\phi_C}{\phi_{max}} = \frac{\text{pLac}}{\text{pLac}_{max}}$
R
C
A
Q
catabolic sector
C-limitation
A-limitation
GOGAT100
GOGAT40
vary k_C
fixed k_C
pLac (Miller Unit)
growth rate (dbl/hr)
glucose
glycerol
vary k_N
fixed k_N
glnAp-lacZ (Miller U.)
growth rate (dbl/hr)

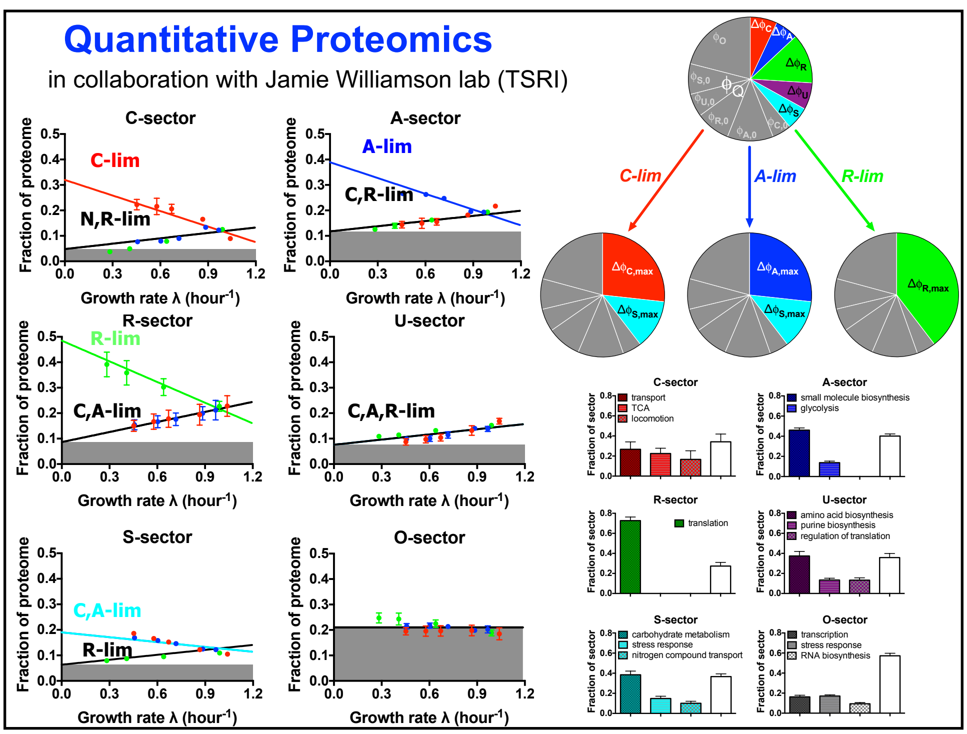
28


Proteome-wide survey by quantitative MS
[collaborator: Jamie Williamson lab; the Scripps Research Institute, La Jolla]
N15 labeled reference
experimental samples
precipitation digestion
MS/MS (tripleTOF)
Light
Heavy
Relative abundance
m/z

29


Quantitative Proteomics
[Hui et al, Mol Sys Biol. (2015)]
in collaboration with Jamie Williamson lab (TSRI)
C-sector
C-lim
N,R-lim
A-sector
A-lim
C,R-lim
R-sector
R-lim
C,N-lim
U-sector
C,N,R-lim
S-sector
C,N-lim
R-lim
O-sector
Fraction of proteome
Growth rate λ (hour-1)
power of coarse graining
λ
C-lim
N-lim
R-lim

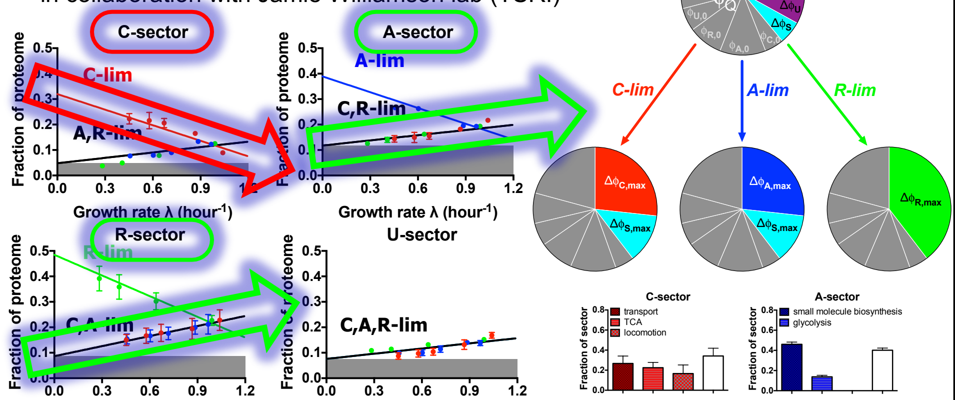
31


Quantitative Proteomics
in collaboration with Jamie Williamson lab (TSRI)
C-sector
C-lim
N,R-lim
A-sector
A-lim
C,R-lim
R-sector
R-lim
C,A-lim
U-sector
C,A,R-lim
S-sector
C,A-lim
R-lim
O-sector
Fraction of proteome
Growth rate λ (hour-1)
C-lim
A-lim
R-lim
Fraction of sector
transport
TCA
locomotion
small molecule biosynthesis
glycolysis
translation
amino acid biosynthesis
purine biosynthesis
regulation of translation
carbohydrate metabolism
stress response
nitrogen compound transport
transcription
stress response
RNA biosynthesis

32

Quantitative Proteomics

in collaboration with Jamie Williamson lab (TSRI)



Q3: Physiological function of catabolite repression

A: proteome/metabolic coordination

When C-influx is high, trade catabolic proteins for the ribosomal and anabolic proteins which are necessary for fast growth

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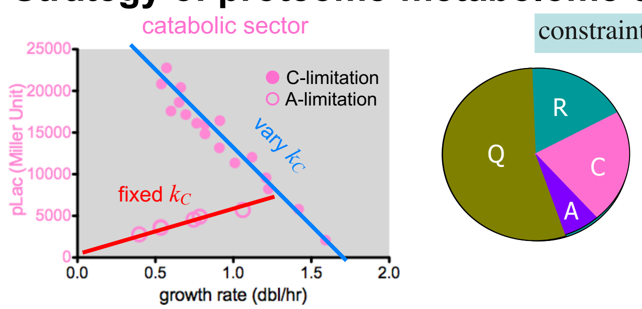
Strategy of proteome-metabolome coordination



constraint: $\phi_R + \phi_C + \phi_A = \phi_{max}$

protein synthesis:

$\lambda = \gamma \cdot \phi_R$

carbon influx:

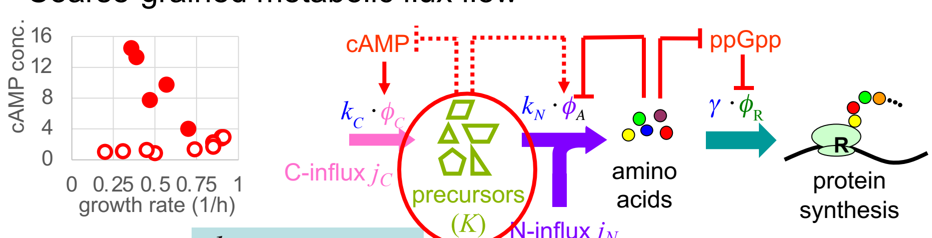
$j_C = c_0 \lambda = k_C \cdot \phi_C$

nitrogen influx:

$j_N = n_0 \lambda = k_N \cdot \phi_A$

enzyme-limited

Coarse-grained metabolic flux flow



$$\frac{d}{dt} K = j_C - j_N$$

integral feedback

($j_C = j_N$ in steady state)

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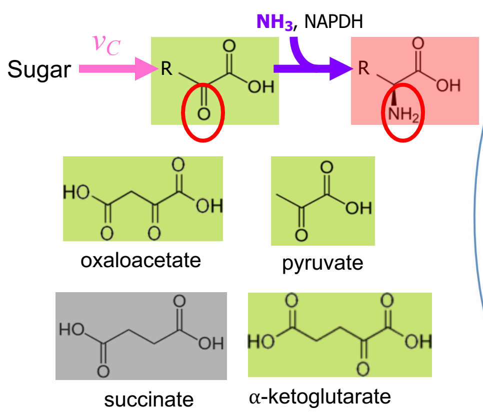
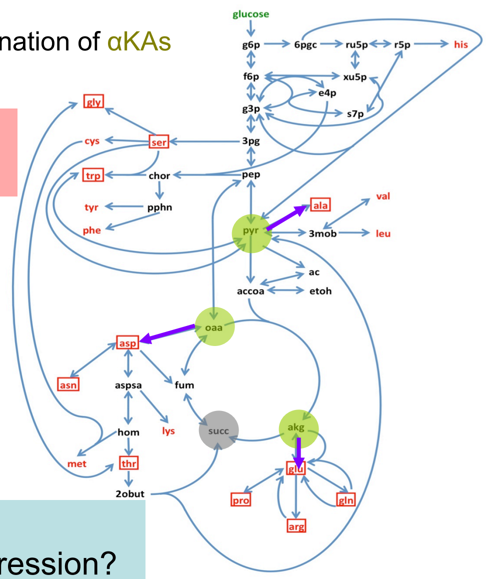
Strategy of proteome metabolic coordination

Simplest scenario: feedback by α-ketoacids (αKA)

All amino acids synthesized from amination of αKAs





Test: does the addition of αKA affect catabolic gene expression?

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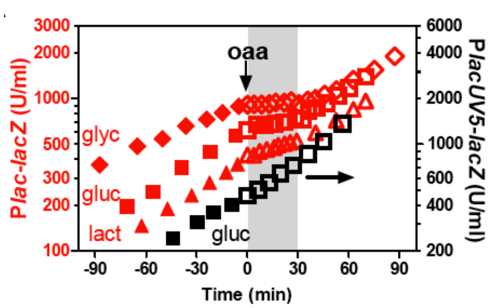
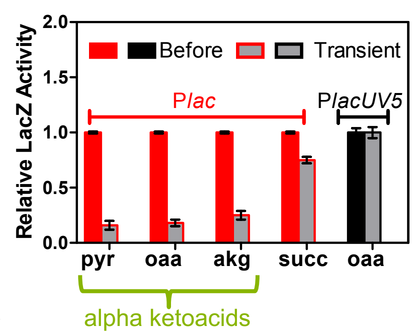
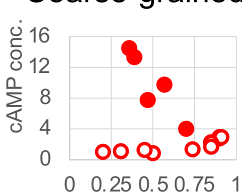
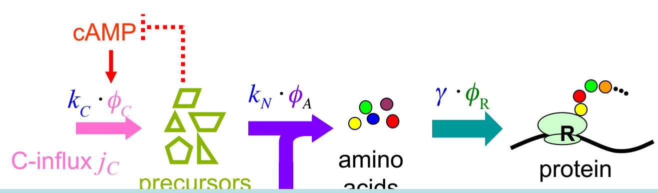
Testing the carbon precursor feedback model





Coarse-grained metabolic flux flow





Q2: What are the “catabolites?

A: alpha ketoacids

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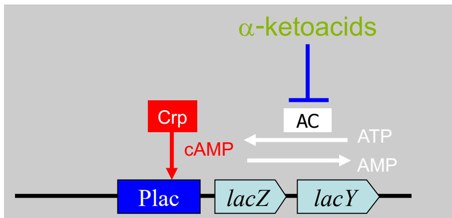
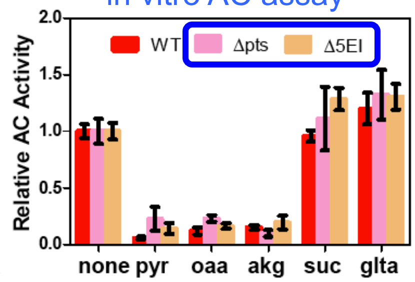
Testing the carbon precursor feedback model

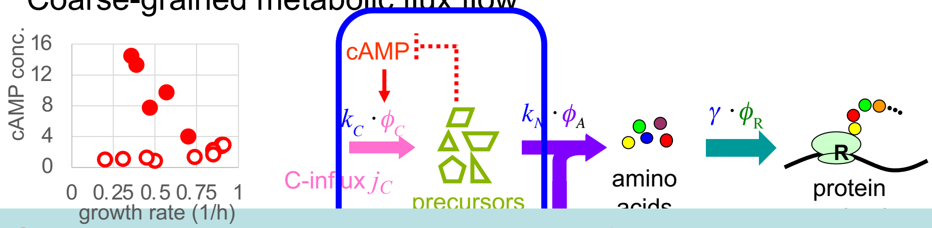
mechanism? PTS not necessary



in vitro AC assay



Coarse-grained metabolic flux flow



Q1: How is cAMP level controlled?

A: direct inhibition of AC activity by alpha ketoacids

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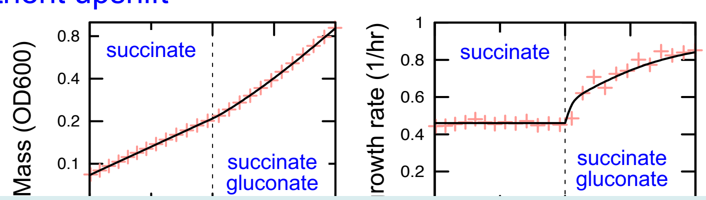
Growth transition kinetics

[Erickson et al, Nature (2017)]

Nutrient upshift



Coarse-grained kinetic model requiring only

-- single ordinary differential equation

-- values of the initial and final growth rates (to define C quality)

-- steady-state growth laws

➔ describes gene expression and growth curve throughout the course of the transition

➔ no need for kinetic parameters; no fitting parameter

➔ works both for nutrient upshifts and downshifts

➔ same theory describes growth inhibition by antibiotics

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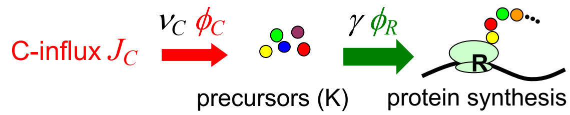
Growth transition kinetics

[Erickson et al, Nature (2017)]

coarse-grained metabolism

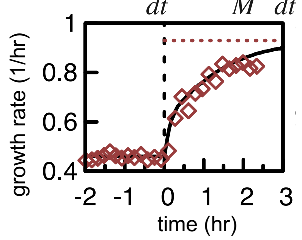


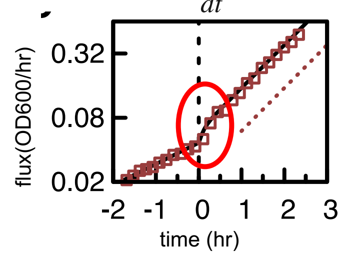
steady-state growth laws: protein synthesis: $\lambda = \gamma \cdot \phi_R$; carbon uptake: $\lambda = \nu_C \cdot \phi_C$

adiabatic approximation: $\cancel{\dfrac{d\lambda}{dt} = \lambda(t)\cdot\left[\nu_C\phi_C(\lambda) - \lambda(t)\right]}$

$\lambda(t) \equiv \dfrac{d\ln(M)}{dt} = \dfrac{1}{M}\dfrac{dM}{dt}$

$J(t) \equiv \dfrac{dM}{dt}$





➔ fast underlying kinetics manifested by biomass flux

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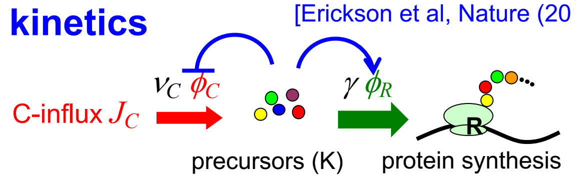
Growth transition kinetics

[Erickson et al, Nature (2017)]

coarse-grained metabolism



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fast kinetics: regulation by precursors (K)

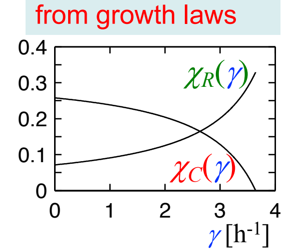
$$\frac{dK}{dt} = K(t)\cdot\left[\nu_C\chi_C(K) - \gamma(K)\chi_R(K)\right]$$

… but requires MANY molecular parameters

➔ capture fast kinetics by following $\gamma(K(t))$

$$\frac{d\gamma}{dt} = \gamma\cdot\left[\nu_C\chi_C(\gamma) - \gamma\chi_R(\gamma)\right]$$

regulatory functions from growth laws



➔ take reg functions $\chi_i(\gamma)$ as given by steady state: $\chi_i(\gamma(\lambda)) = \phi_i(\lambda)$

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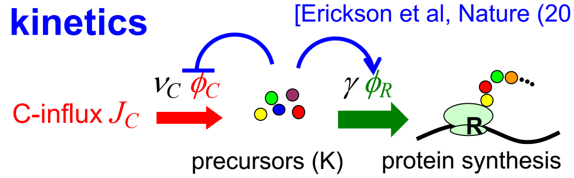
Growth transition kinetics

[Erickson et al, Nature (2017)]

coarse-grained metabolism



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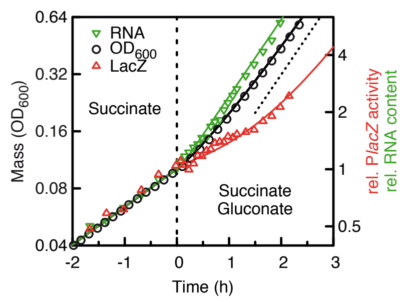
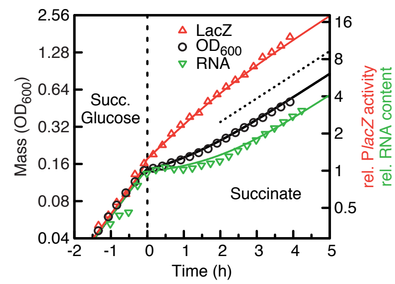
$$\frac{d\gamma}{dt} = \gamma\cdot\left[\nu_C\chi_C(\gamma) - \gamma\chi_R(\gamma)\right] \quad ➔ \quad M(t),\ M_R(t),\ M_C(t)$$

- exact solution; completely determined by λ_i, λ_f

nutrient upshift



nutrient downshift



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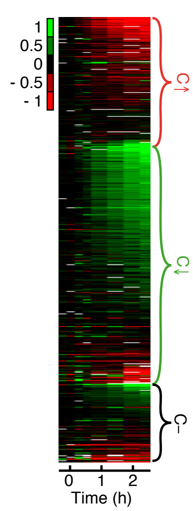
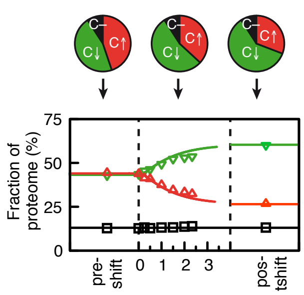
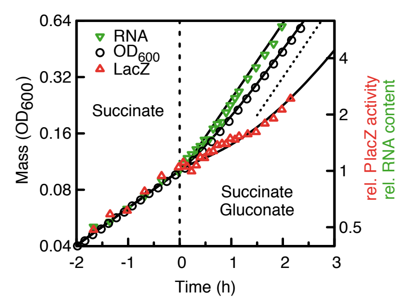
Growth transition kinetics

[Erickson et al, Nature (2017)]

proteome-wide response to nutrient up-shift







upshift kinetics:

- rapid increase in ribosome synthesis
- rapid reduction of C-protein synthesis
- slow recovery of growth rate due to slow dilution of pre-existing C-proteins

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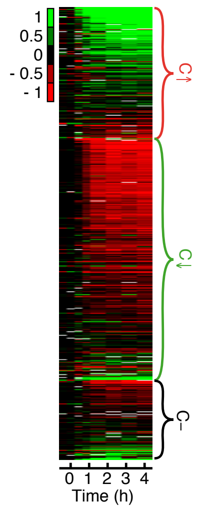
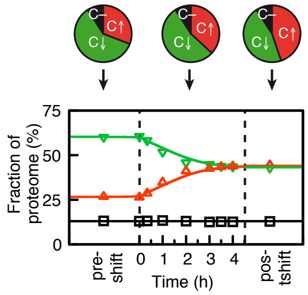
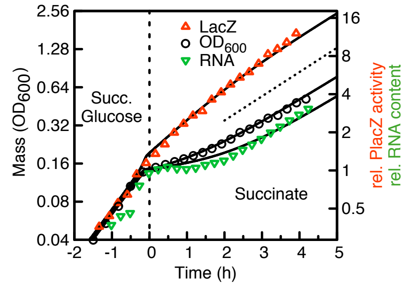
Growth transition kinetics

[Erickson et al, Nature (2017)]

proteome-wide response to nutrient down-shift



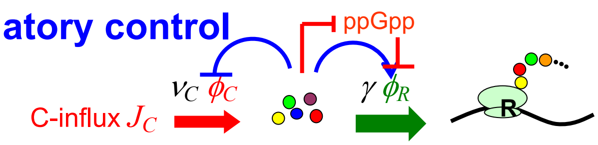




downshift kinetics:
- rapid increase in C-protein synthesis
- rapid reduction of ribosome synthesis

Strategy of regulatory control

coarse-grained metabolism



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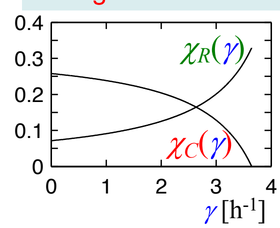


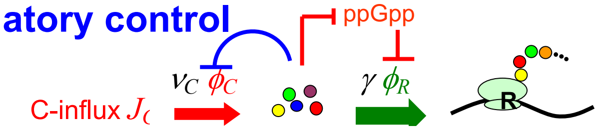
Molecular implementation?

- ribosome synthesis controlled by ppGpp (of conc $g(t)$)
- ppGpp synthesized by RelA in response to ~~uncharged tRNA~~ translational speed

➔ Hypothesis: $\boxed{\gamma(K) \dashv g(t)} \dashv \chi_R(t)$

Strategy of regulatory control

coarse-grained metabolism

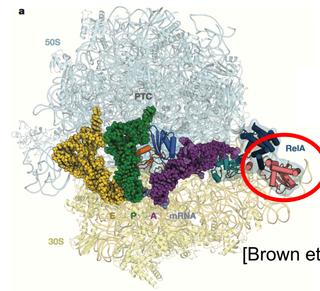


Model of RelA regulation:

$$\frac{dg}{dt} = \alpha \cdot \tau_{charge} - \beta \cdot g$$

$$\tau_{charge} + \tau_{translocate} = 1/\gamma$$

➔ $\boxed{g \propto \tau_{charge} \propto \gamma_{\max}/\gamma - 1}$



[Brown et al, Nature 2016]

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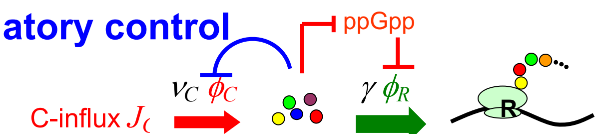
Strategy of regulatory control

coarse-grained metabolism



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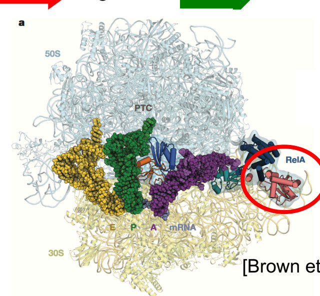

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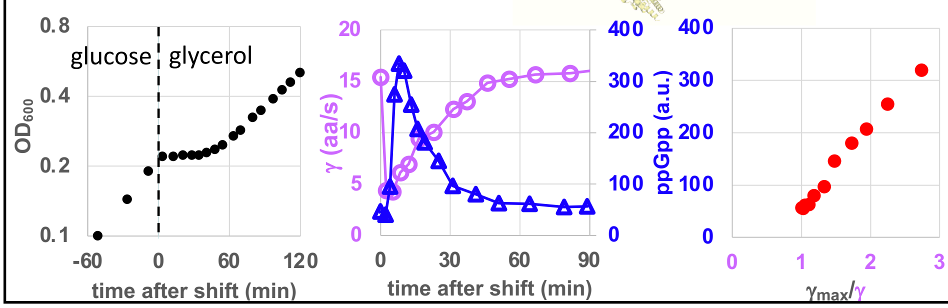

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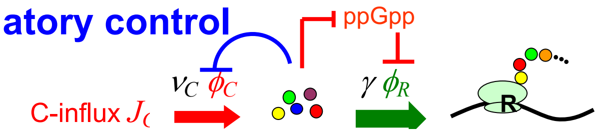
Strategy of regulatory control

coarse-grained metabolism



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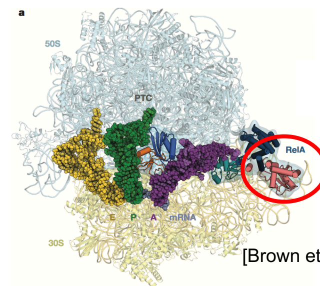
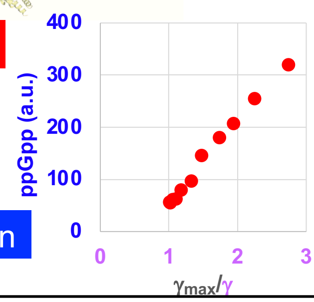


[Brown et al, Nature 2016]

➔ an "activity-based" mode of regulation

[cf: supply-driven or product-inhibited mode of regulation]

➔ curse of concentration-based regulation



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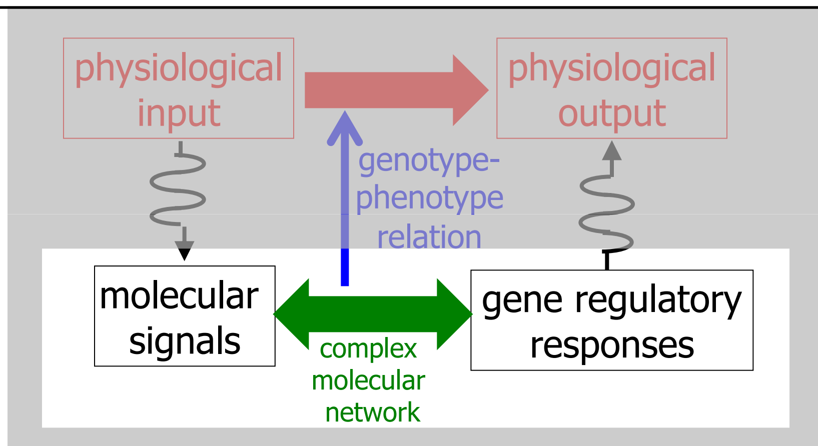

Tenet of classical molecular biology:
molecular knowledge ➔ biological function

Problem with the bottom-up approach:
quantitative, predictive understanding of the system requires many inaccessible *in vivo* parameters

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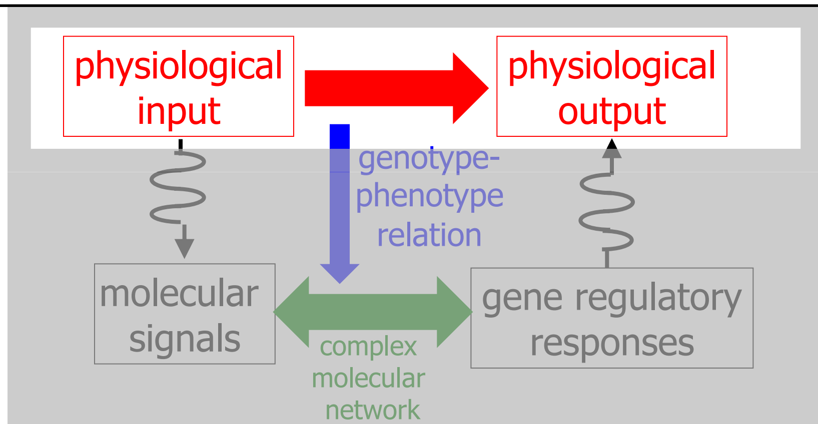

Top-down solution:

tame complexity by <u>quantitative</u> phenomenology (‘laws’)
= simple relations between physiological inputs/outputs

- ➔ quantitative predictions on physiological responses
- ➔ useful guide for synthetic biology
- ➔ insight on the “purpose” of regulatory mechanisms
- ➔ guide for regulatory strategies & molecular implementations

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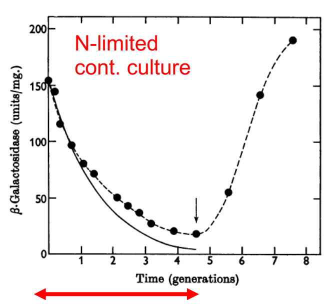
Catabolite repression

➔ “catabolites” formed rapidly from glucose would accumulate and repress the formation of enzymes whose activity would augment the already large intracellular pools of these compounds [B. Magasanik, 1961]

➔ qualitative effect of N-, S-, P- limitations known already in the early 60s

[Mandelstam, Magasanik, …]



➔ **Molecular Physiology**

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Proc. Natl. Acad. Sci. USA
Vol. 73, No. 10, pp. 3476–3479, October 1976
Biochemistry

Catabolite modulator factor: A possible mediator of catabolite repression in bacteria

(physiological repression and derepression/β-galactosidase/adenosine 3′:5′-cyclic monophosphate)

AGNES ULLMANN, FRANCOISE TILLIER, AND JACQUES MONOD*

ABSTRACT Water soluble extracts of *Escherichia coli* cells have been found to exert an extremely strong repressive effect upon the expression of catabolite sensitive operons. The compound responsible for this activity has been partially purified and proves to be of low molecular weight and heat stable. The effect of this compound, hereafter designated as catabolite modulator factor, is only partially antagonized by adenosine 3′:5′-cyclic monophosphate. The possible role of catabolite modulator factor in the physiological regulation of catabolite repression is discussed.

Citing Articles

Author(s): KOLB, A; BUSBY, S; BUC, H; GARGES, S; ADHYA, S
Title: TRANSCRIPTIONAL REGULATION BY CAMP AND ITS RECEPTOR PROTEIN
Source: ANNUAL REVIEW OF BIOCHEMISTRY, 62: 749-795 1993

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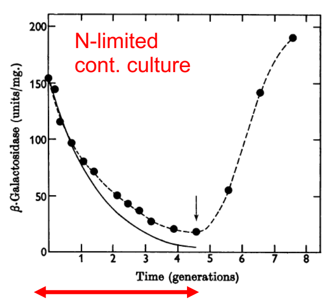
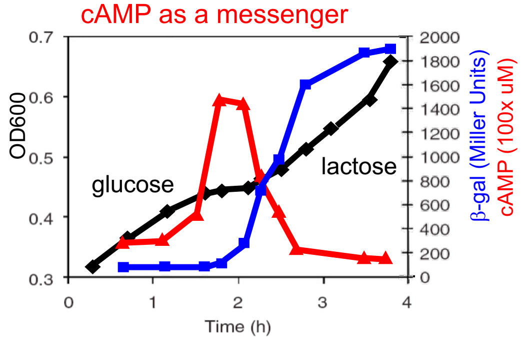


Molecular Physiology

cAMP as a messenger



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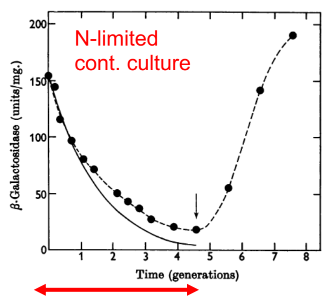
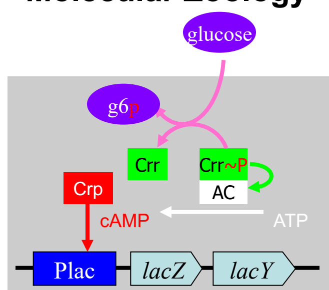


Molecular Physiology

Molecular Zoology



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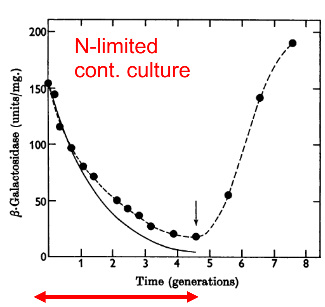
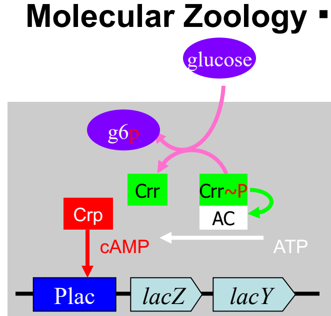
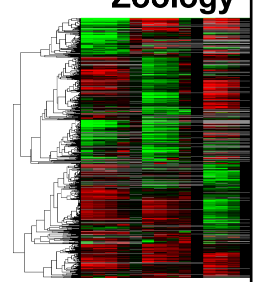


Molecular Physiology

Molecular Zoology

Systems Zoology





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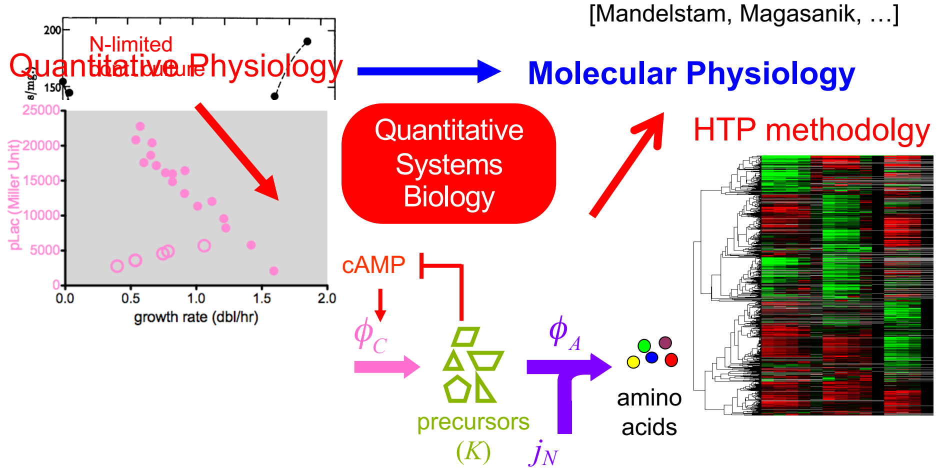

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