Constrained-allocation FBA: modeling the interplay of regulation and metabolism in bacteria at genome scale

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Joint work with

- M Mori (Sapienza)
- E Marinari (Sapienza)
- T Hwa (UCSD)

See also Matteo's POSTER

MARIE CURIE ACTIONS

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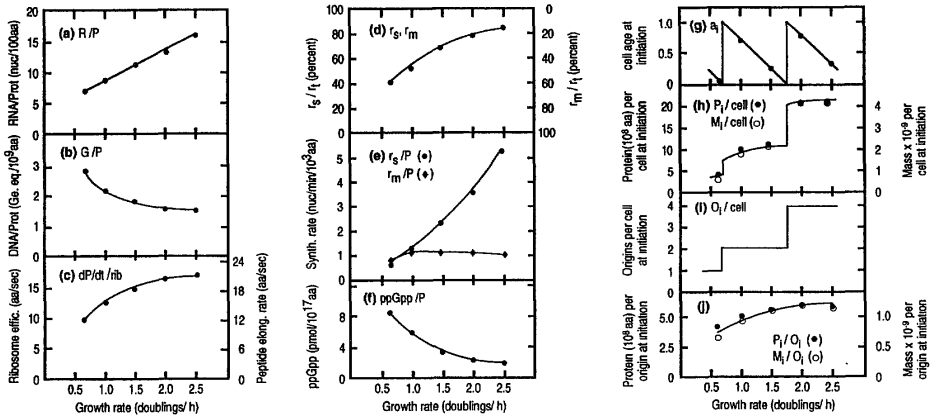
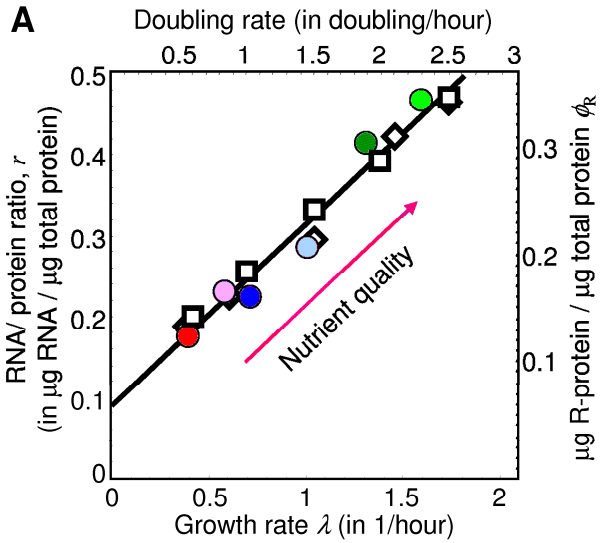
Center for Life Nano Science

Bacterial growth laws

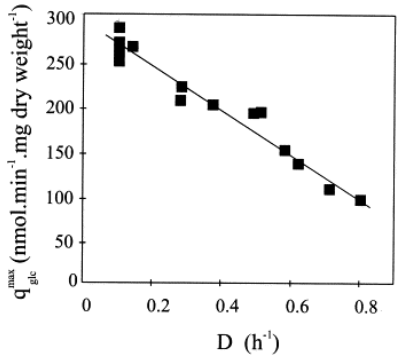
- Quantitative empirical relationships linking cellular composition to growth rate [Schaechter *et al.*, Bremer & Dennis, etc.]



[Bremer & Dennis 1996]



[Scott *et al.* Science 2010]



[Teixeira & Neijssel, J Biotech 1997]

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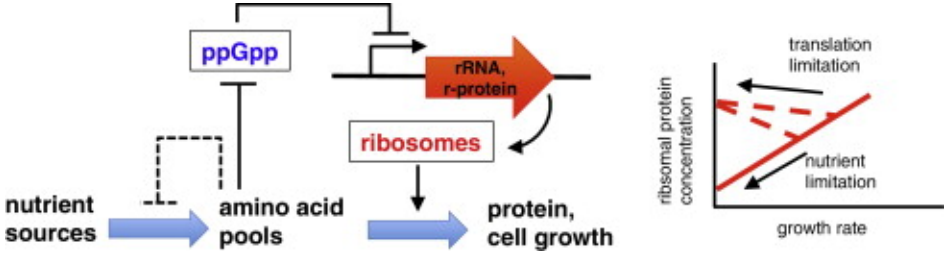
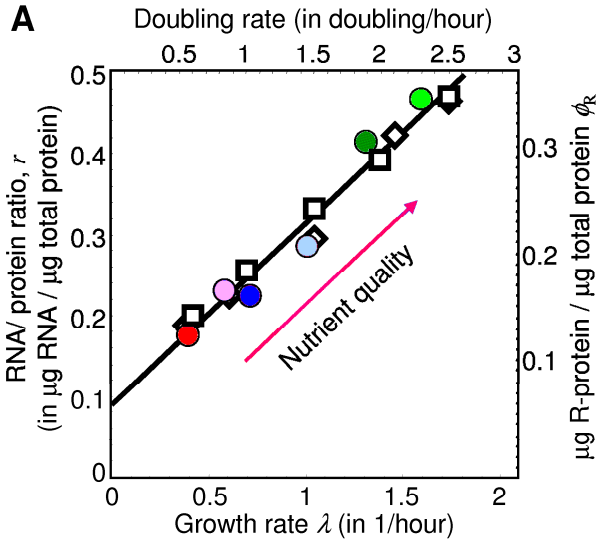


[Klumpp & Hwa, Curr Op Biotech 2014]



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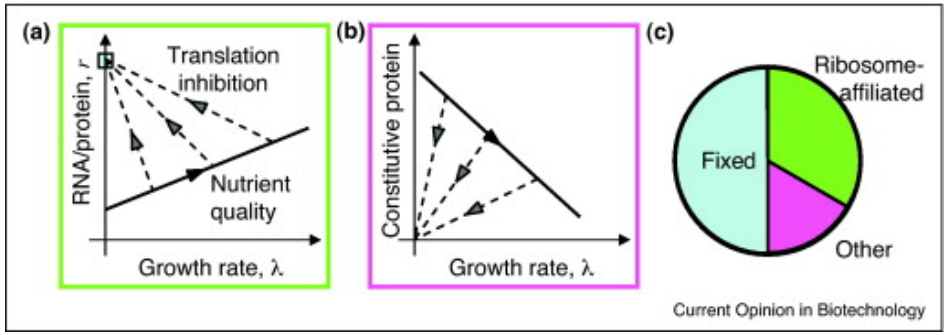

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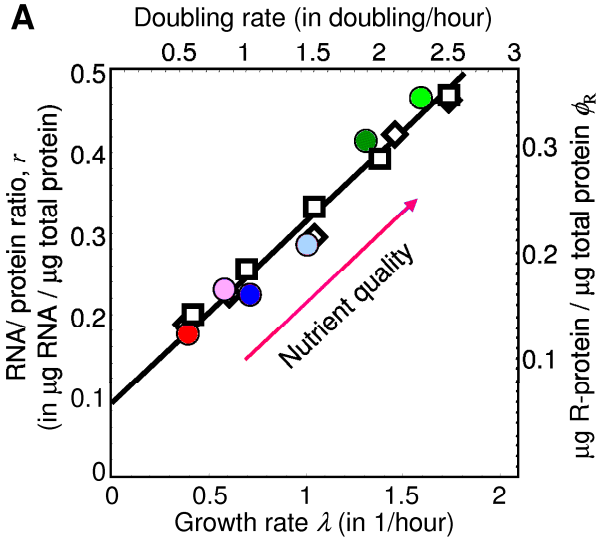
Bacterial growth laws

- Quantitative empirical relationships linking cellular composition to growth rate [Schaechter *et al.*, Bremer & Dennis, etc.]
- Probed at higher and higher resolution
- Proteome organization is actively regulated



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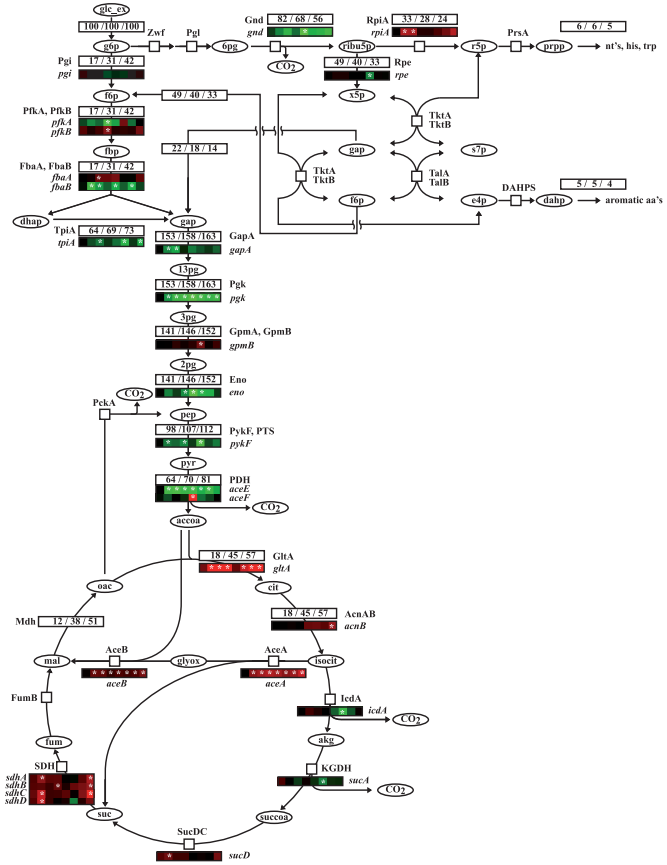

[Lemuth *et al.* AEM 2008]

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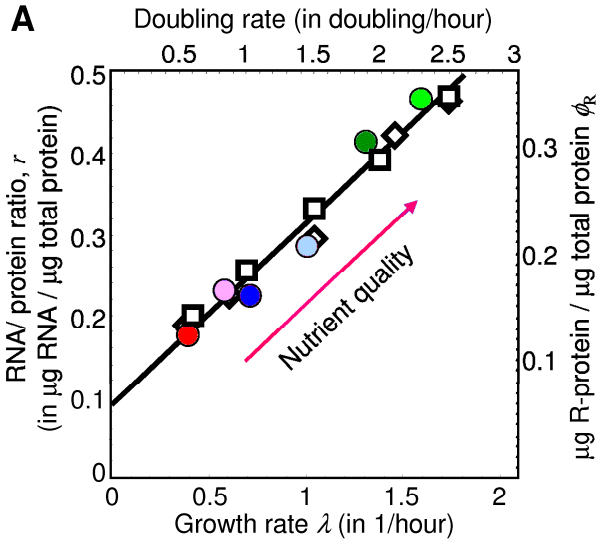

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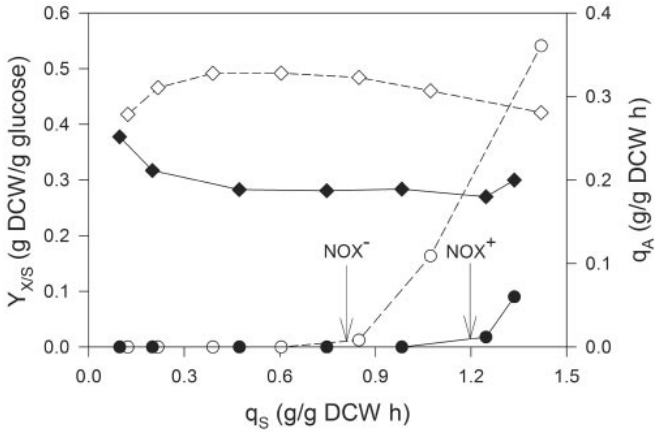
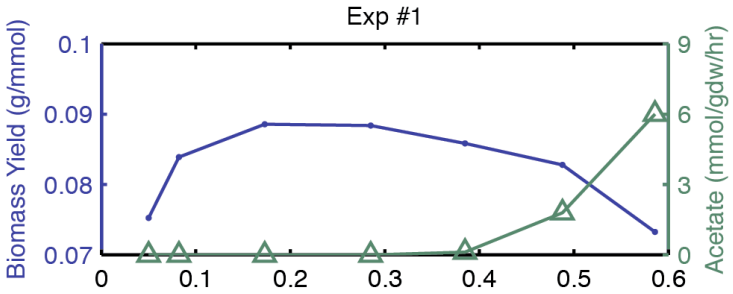


[Vemuri *et al.* AEM 2006]



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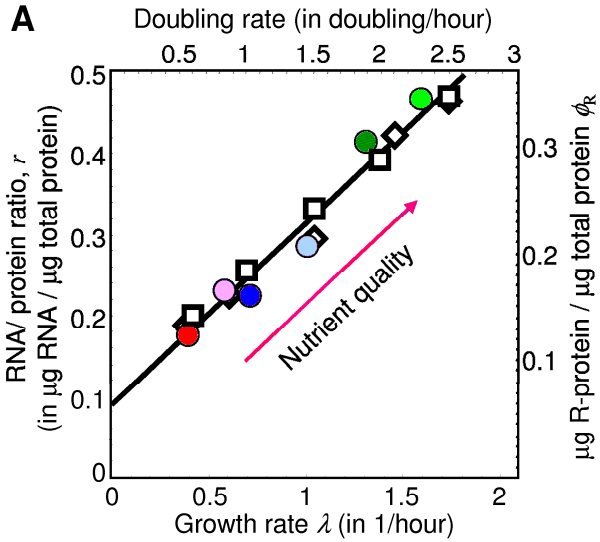

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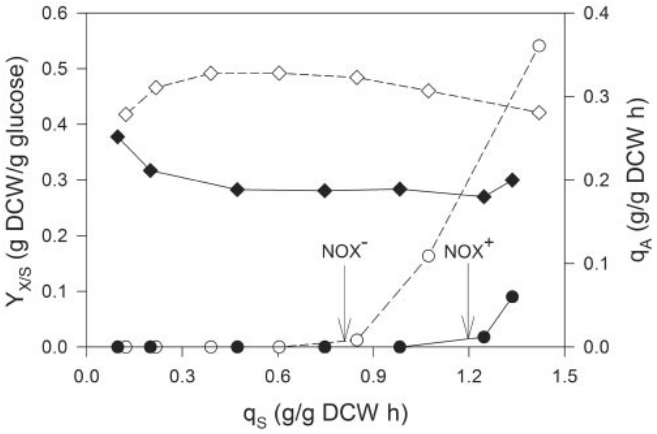
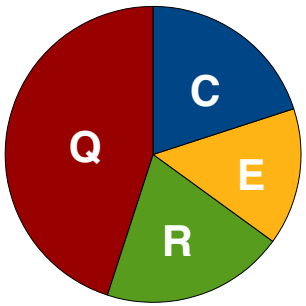


[Vemuri *et al.* AEM 2006]

- "Phenomenological" models, e.g. [Tadmor & Tlusty, PLoS CB 2008] [Klumpp & Hwa, PNAS 2008] [Molenaar *et al.* MSB 2009]
- **Here**: genome-scale [ME-model, O'Brien *et al.* MSB 2013]

Proteome sectors



C = catabolic

E = enzymes

R = ribosomal

Q = housekeeping

ϕ_X = prot. fraction of sector X

$$\boxed{\phi_C + \phi_E + \phi_R + \phi_Q = 1} \quad \rightarrow \quad \phi_C + \phi_E + \phi_R = \underbrace{1 - \phi_Q}_{\lambda\text{-indep.}}$$

- **R-sector** : linear dep. on λ $\rightarrow$ $\phi_R = \phi_{R,0} + w_R \lambda$
  $w_R \simeq 0.169$ h [Scott *et al.* Science 10]
- **C-sector** : glc sensing, transport & processing $\rightarrow$ $\phi_C = \phi_{C,0} + w_{\text{glc}} u_{\text{glc}}$

$$u_{\text{glc}} = \frac{1}{M_{\text{DW}}} \times \underbrace{(M_C/\mu_C)}_{\phi_C M_{\text{prot}}/\mu_C} \times \underbrace{k_{\text{cat}} \frac{[\text{glc}]}{[\text{glc}] + K_M}}_{k_{\text{cat}}} = \frac{\phi_C}{w_{\text{glc}}} \quad , \quad \boxed{w_{\text{glc}} = \frac{M_{\text{DW}}}{M_{\text{prot}}} \frac{\mu_C}{k_{\text{cat}}}}$$

- **E-sector** : prop. to metabolic fluxes $\rightarrow$ $\phi_E = \phi_{E,0} + \sum_i w_i |v_i|$

$$\xrightarrow{\text{MM kinetics}} \boxed{w_i = \frac{M_{\text{DW}}}{M_{\text{prot}}} \frac{\mu_i}{k_{\text{cat},i}}}$$

CAFBA: setup

$$\max_{\mathbf{v}} \lambda \quad \text{s.t.} \quad \mathbf{Sv} = \mathbf{0}$$

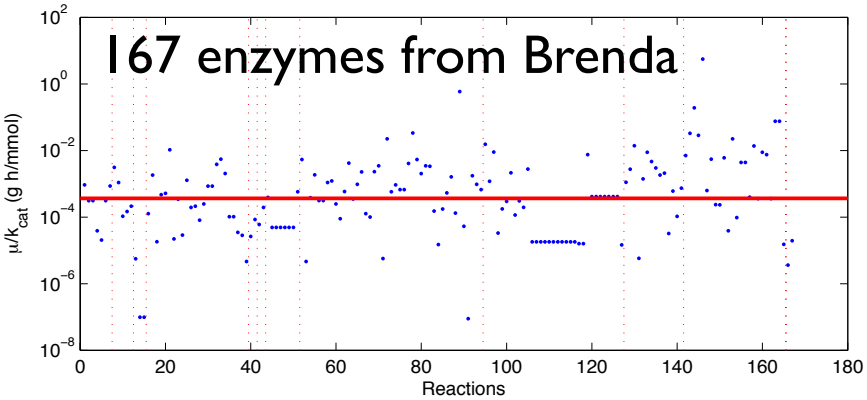
$$\underline{v}_j \leq v_j \leq \overline{v}_j \quad \forall \text{ reaction } j$$

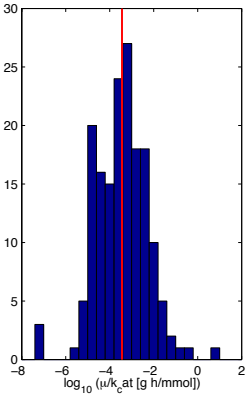
$$w_{\text{glc}} u_{\text{glc}} + \sum_i w_i |v_i| + w_R \lambda = \text{const.} \simeq 0.484$$ [Scott *et al.* Science 10]

- λ-indep. biomass composition : LP POSTER
- **Control parameters** : w_{glc}, $\{w_i\}$, w_R $\rightarrow$ **Here** : C-limitation (w_{glc}) [R-/E-lim.: POSTER]
- Reminder : $w_{\text{glc}} \propto \frac{1}{k_{\text{cat}}} = \frac{1}{k_{\text{cat}}} \left(1 + \frac{K_M}{[\text{glc}]}\right)$, i.e. optimal $\lambda \nearrow$ as $w_{\text{glc}} \searrow$
- w_R from [Scott *et al.* Science 10] , i.e. $w_R \simeq 0.169$ h
- $\{w_i\}$'s : focus on two "limiting" cases

CAFBA: setup

$$w_i \propto \frac{\mu_i}{k_{\text{cat},i}}$$



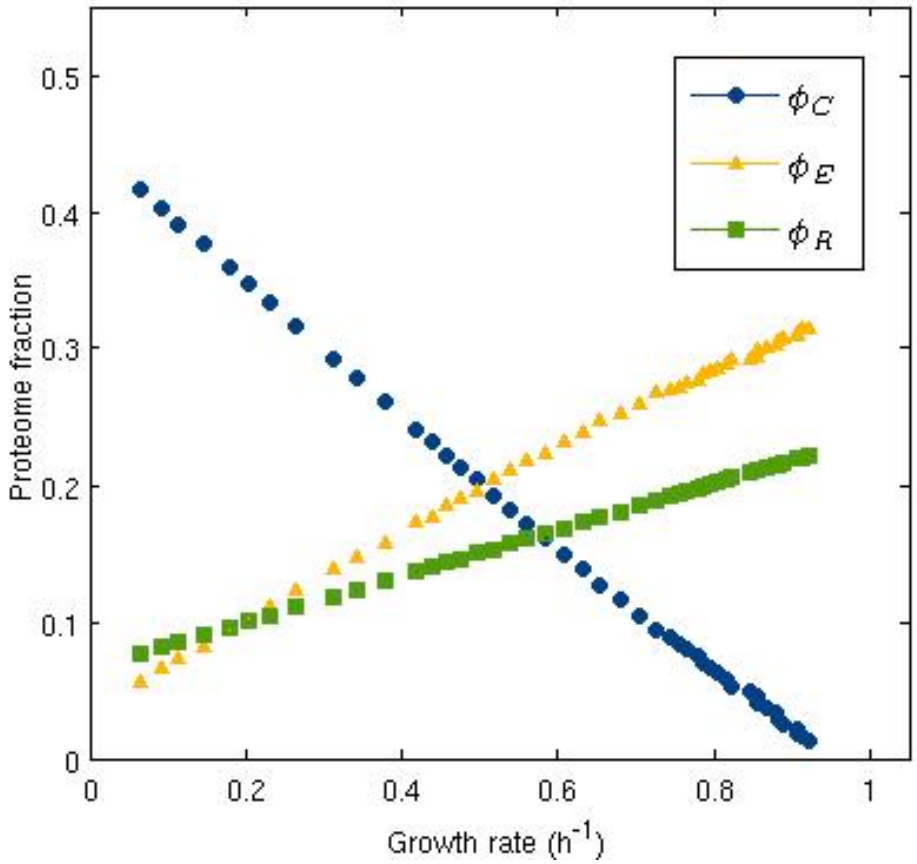


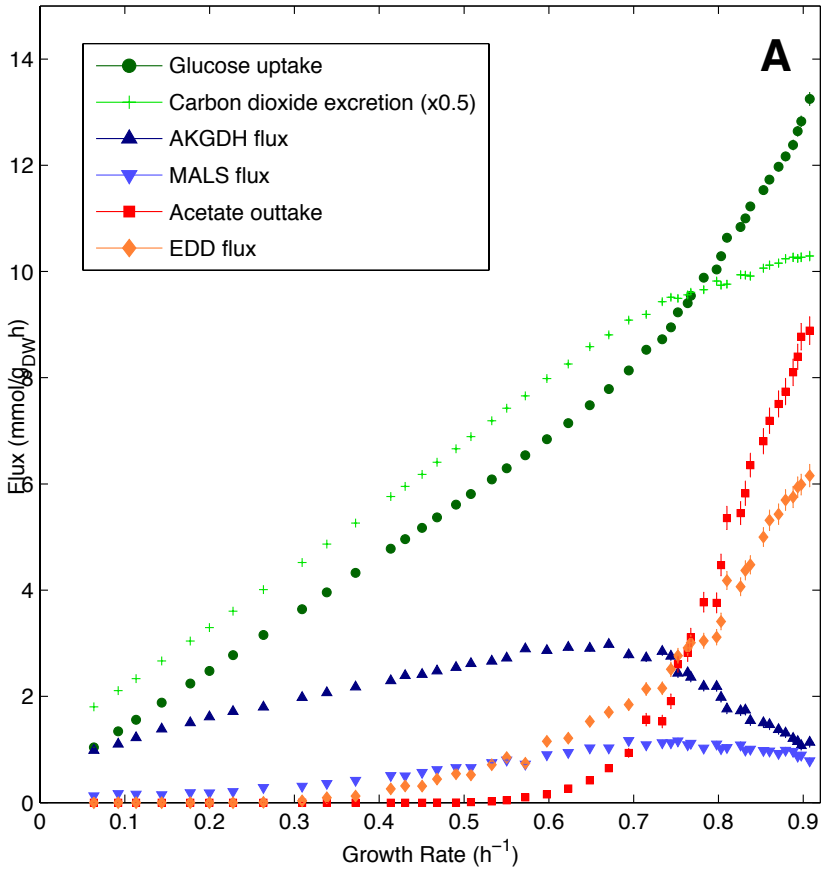
1. $w_i = w_E$ for each i, with w_E such that $\lambda \leq 0.9/\text{h}$

2. $\{w_i\}$ i.i.d. sampled from $p(w) \sim 1/w$ with $\underbrace{\text{given } \langle w \rangle}_{\langle \lambda \rangle \leq 0.9/\text{h}}$ and $\delta = \log_{10} \frac{w_{\max}}{w_{\min}} = 1$

[δ-dependence : POSTER]

"Disorder-averaged" case





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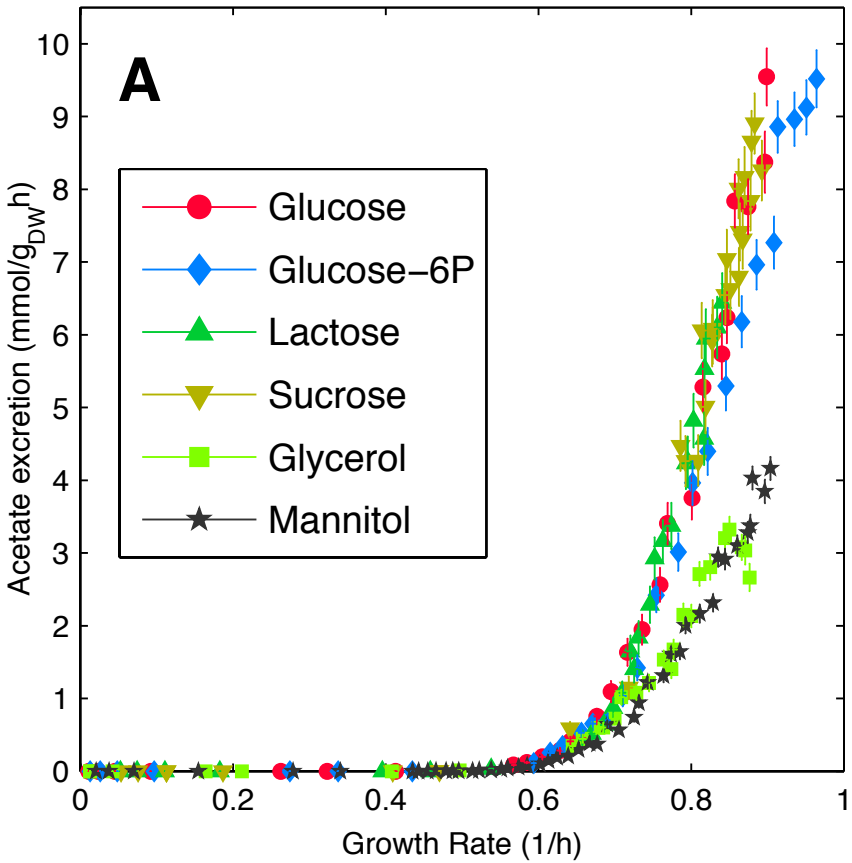
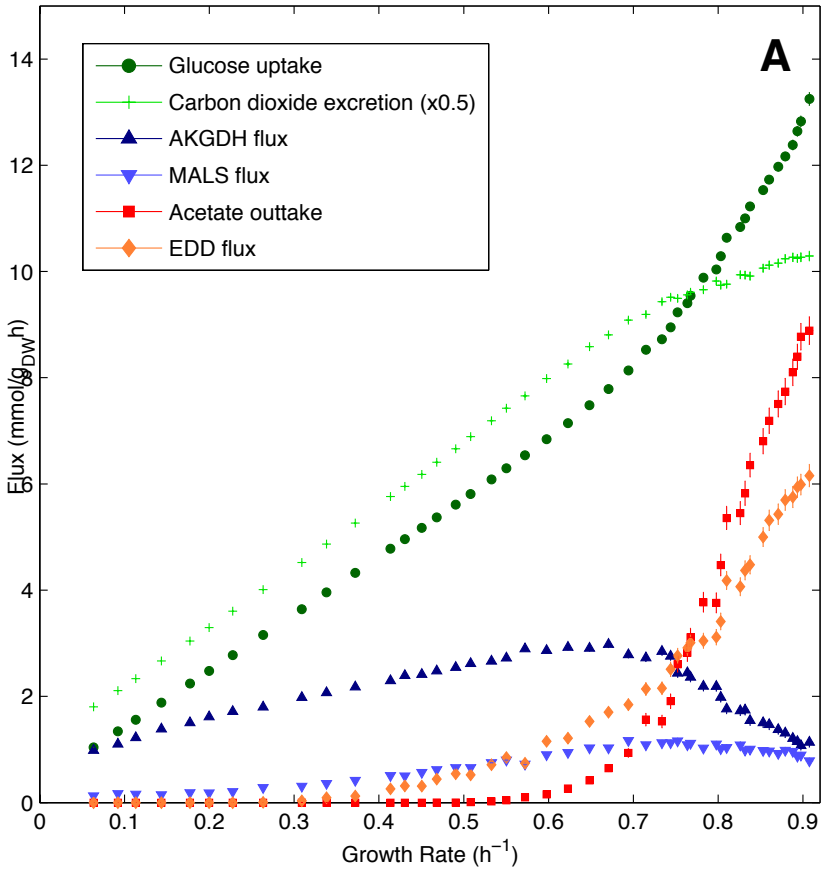




The trade-off behind CAFBA solutions

$$\overbrace{w_{\text{glc}}u_{\text{glc}} + \sum_i w_i|v_i|}^{\phi_C+\phi_E} + \underbrace{w_R\lambda}_{\phi_R} = \text{const.}$$

- $\max \lambda \;\leftrightarrow\; \max \phi_R \;\leftrightarrow\; \min\,[\phi_C + \phi_E]$
- **Question:** can we understand CAFBA solutions as a ϕ_C/ϕ_E trade-off?
- Limiting problems (* = CAFBA value)

  1 minimize ϕ_E at given λ : $\min \sum_i w_i|v_i|$ s.t. $\mathbf{Sv} = \mathbf{0}$ & $\lambda = \lambda^\star$

  a maximize λ with $\phi_E \leq \phi_E^\star$: $\max \lambda$ s.t. $\mathbf{Sv} = \mathbf{0}$ & $\sum_i w_i|v_i| \leq \phi_E^\star$ $\rightarrow$ **"crowding"**

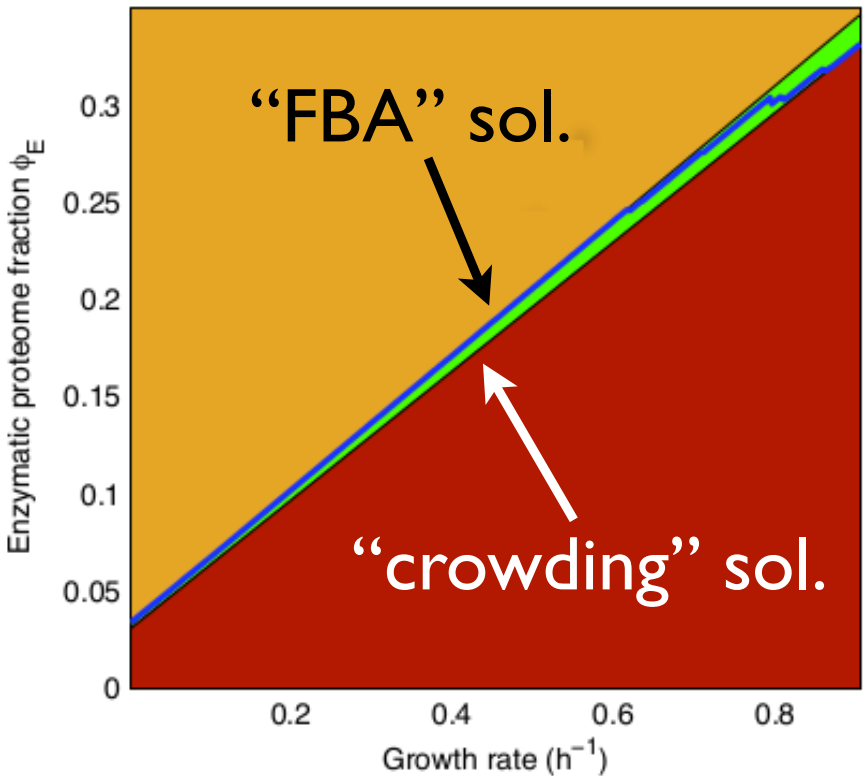
  2 minimize ϕ_C at given λ : $\min u_{\text{glc}}$ s.t. $\mathbf{Sv} = \mathbf{0}$ & $\lambda = \lambda^\star$

  b maximize λ with $\phi_C \leq \phi_C^\star$: $\max \lambda$ s.t. $\mathbf{Sv} = \mathbf{0}$ & $w_{\text{glc}}u_{\text{glc}} \leq \phi_C^\star$ $\rightarrow$ **FBA**

The trade-off behind CAFBA solutions

$$\phi_E^{\text{crowd}} \leq \phi_E^{\star} \leq \phi_E^{\text{FBA}}$$

$$\phi_C^{\text{FBA}} \leq \phi_C^{\star} \leq \phi_C^{\text{crowd}}$$



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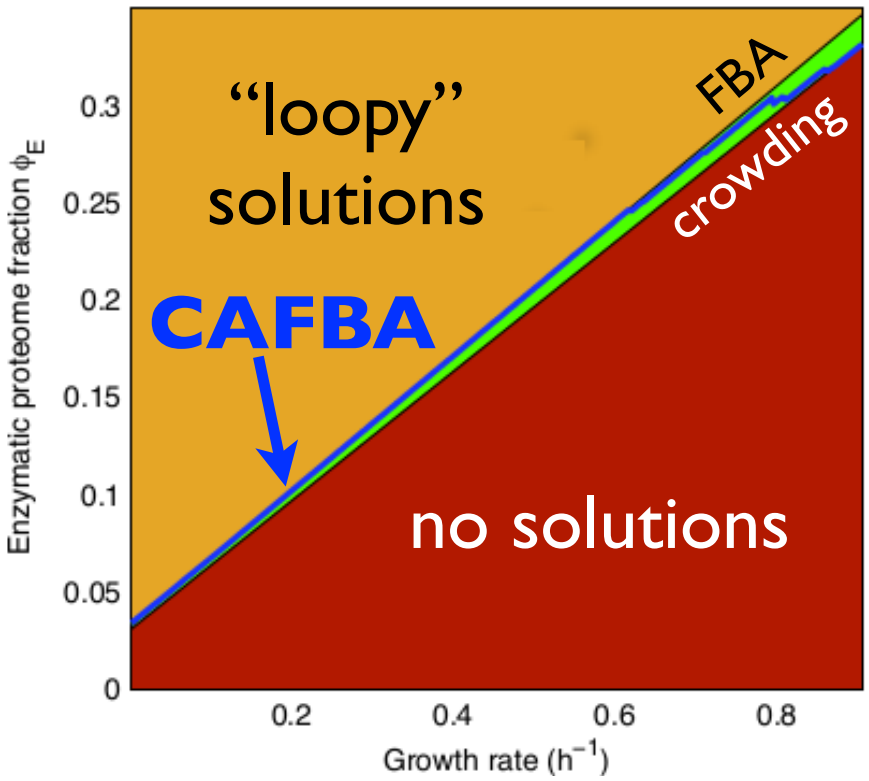
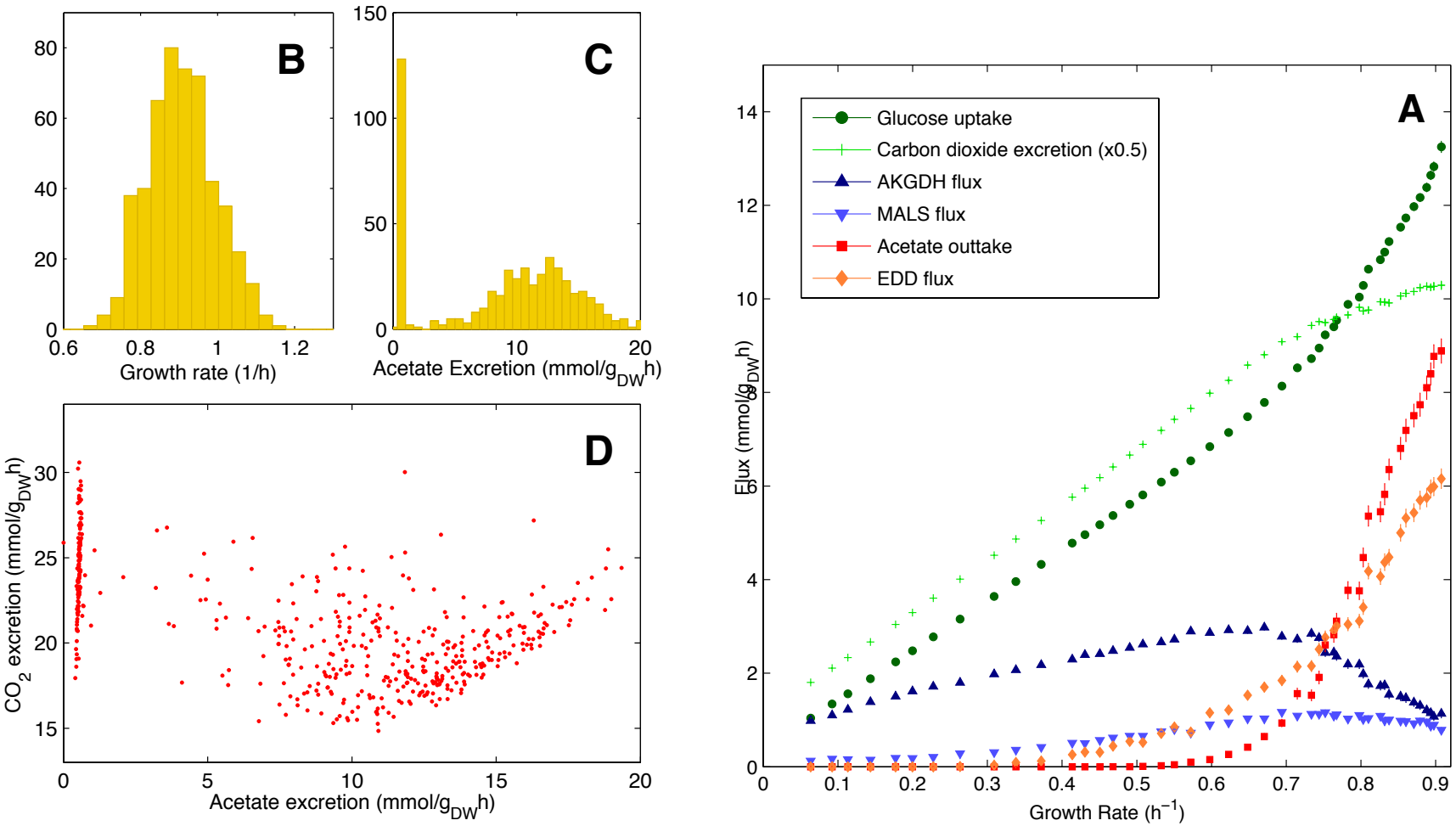
$$\phi_E^{\text{crowd}} \leq \phi_E^{\star} \leq \phi_E^{\text{FBA}}$$

$$\phi_C^{\text{FBA}} \leq \phi_C^{\star} \leq \phi_C^{\text{crowd}}$$

- CAFBA "interpolates" between the "FBA" scenario (lower λ) and the "molecular crowding" scenario of [Beg et al PNAS 07] (higher λ)
- Averaging over $w_i \propto \mu_i / k_{\text{cat},i}$ smooths out the crossover



“Cell-to-cell” fluctuations



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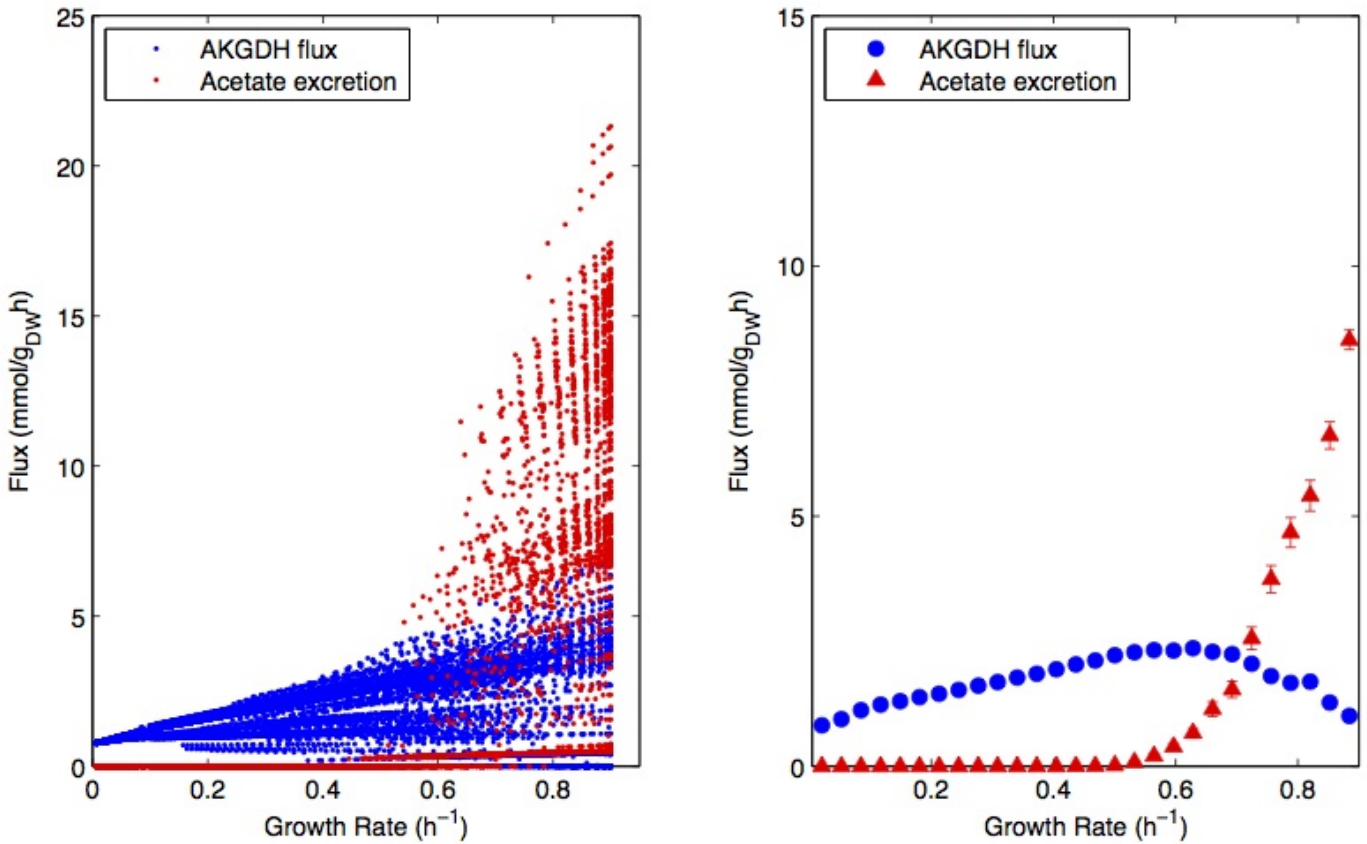
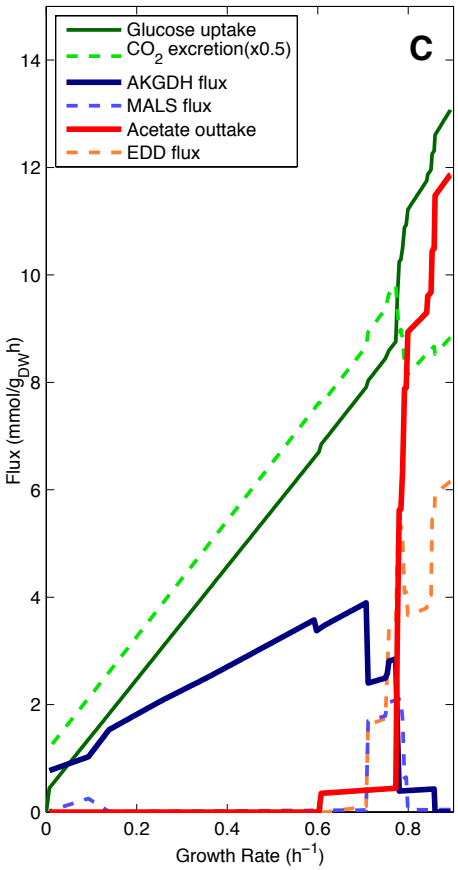
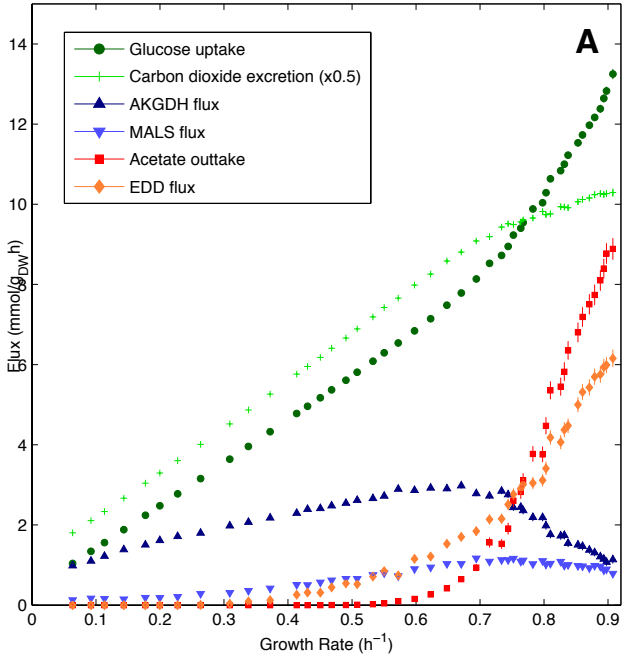


Homogeneous versus random w_i's



$w_i = w_E \quad \forall i$



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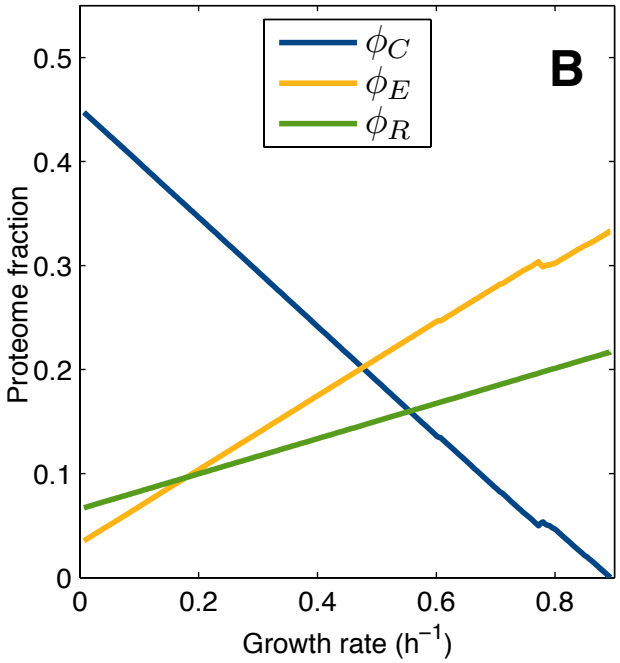

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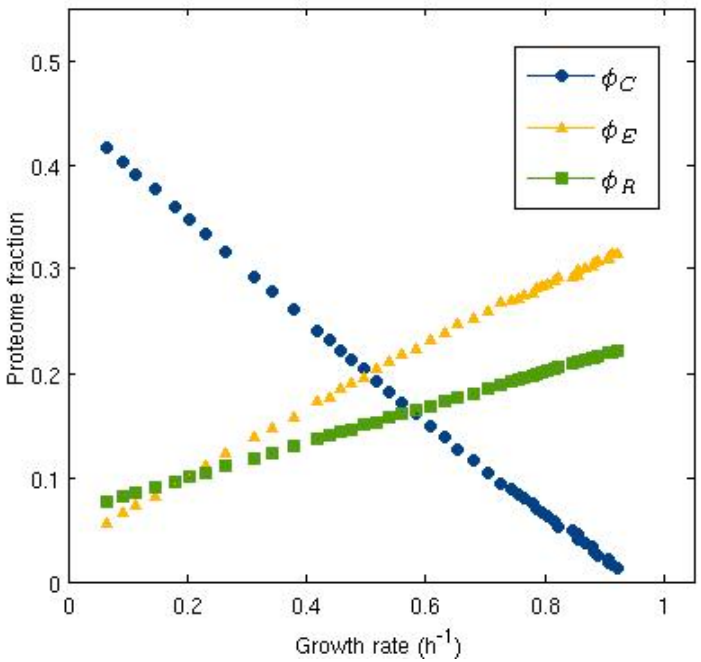

"Disorder-averaged"

ME-model for E. coli

Molecular Systems Biology 9; Article number 693; doi:10.1038/msb.2013.52
Citation: *Molecular Systems Biology* 9:693
www.molecularsystemsbiology.com

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Genome-scale models of metabolism and gene expression extend and refine growth phenotype prediction

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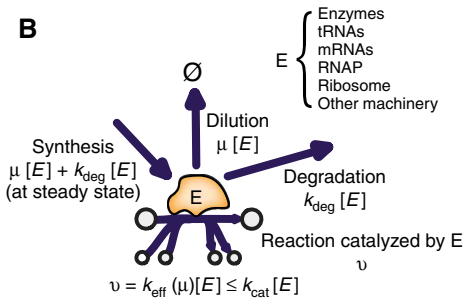
Growth rate-dependent demand functions

1. Cell wall demand (μ)
2. DNA demand (μ)
3. ATP demand (μ)



- Genome-scale model integrating metabolism, gene expression and proteomic data
- Key ingredients
  - empirically-derived, λ-dependent demand functions
  - prescriptions for flux-enzyme level relationships
  - 3 different solution regimes (SNL, Janusian, Batch)
- Control parameter: glc intake (vs cost of in-taking glc in CAFBA)

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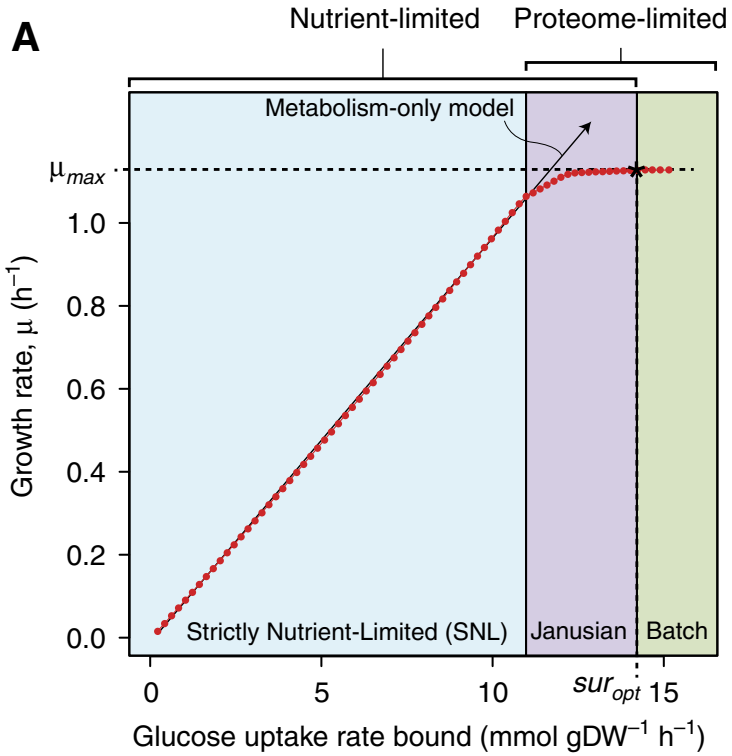

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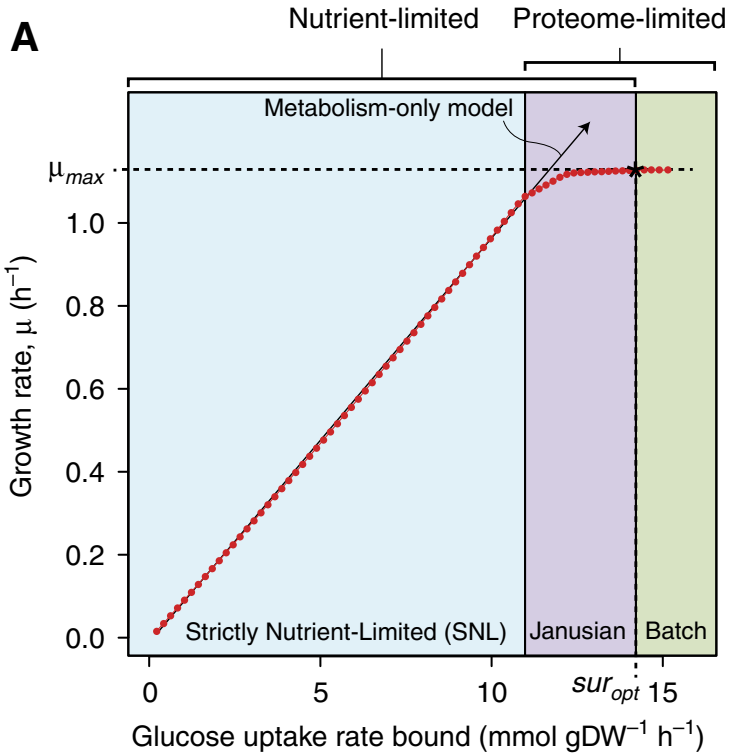
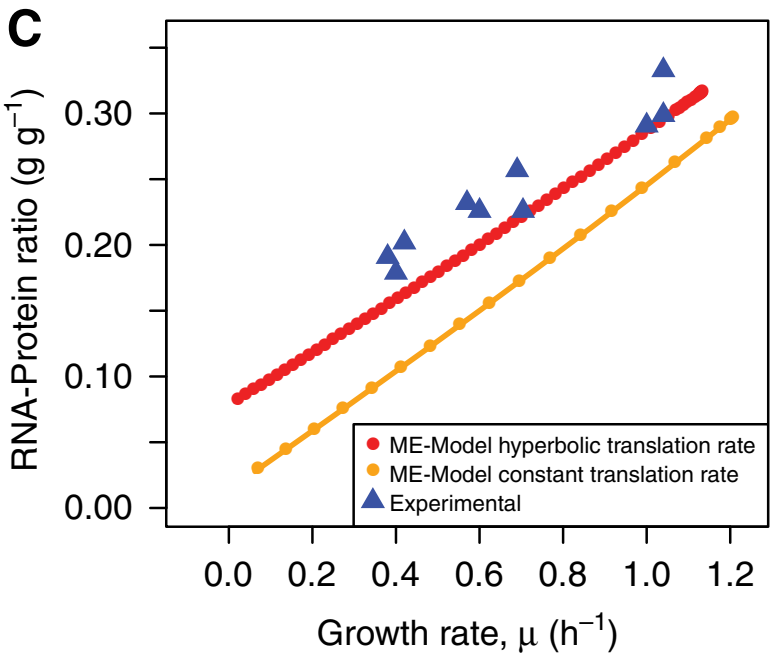
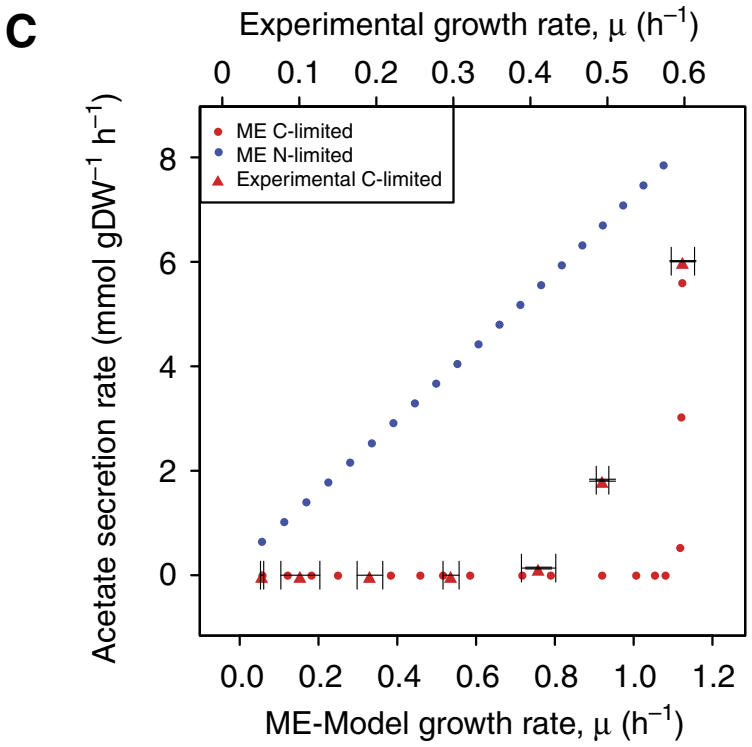
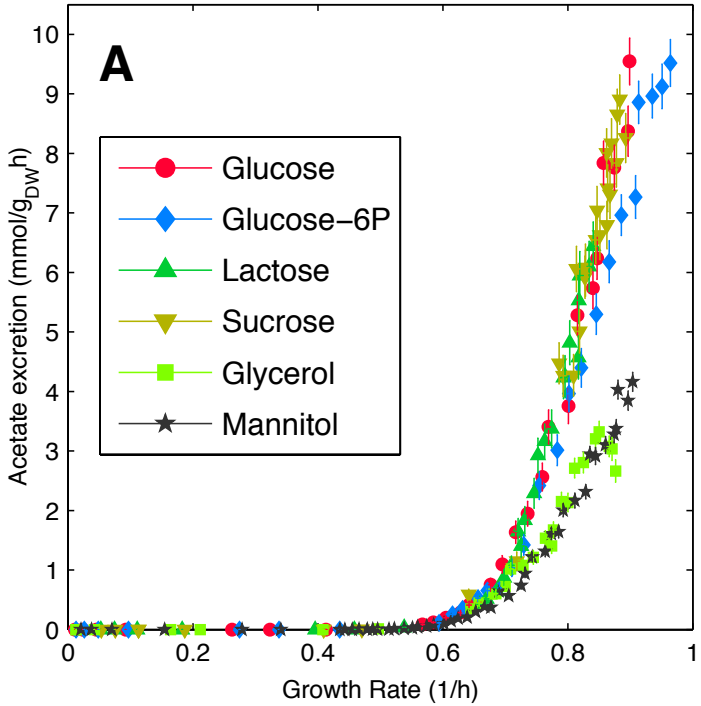




Acetate excretion

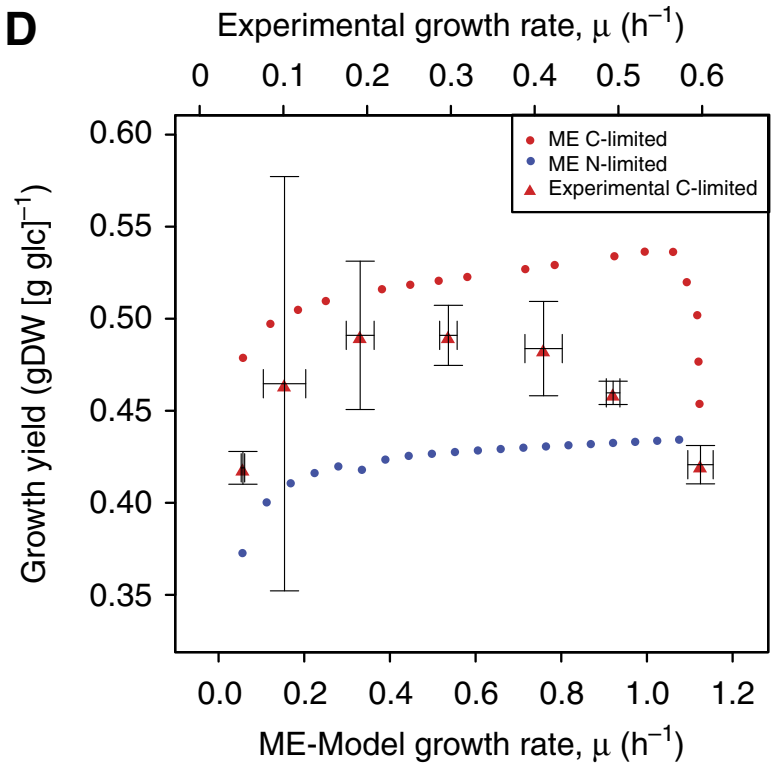


ME-Model



CAFBA

Growth yield



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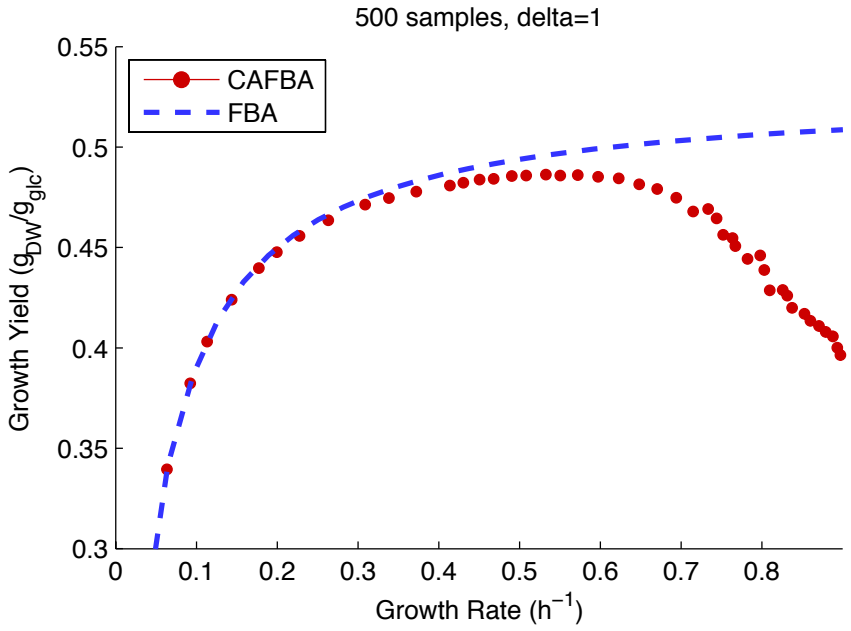
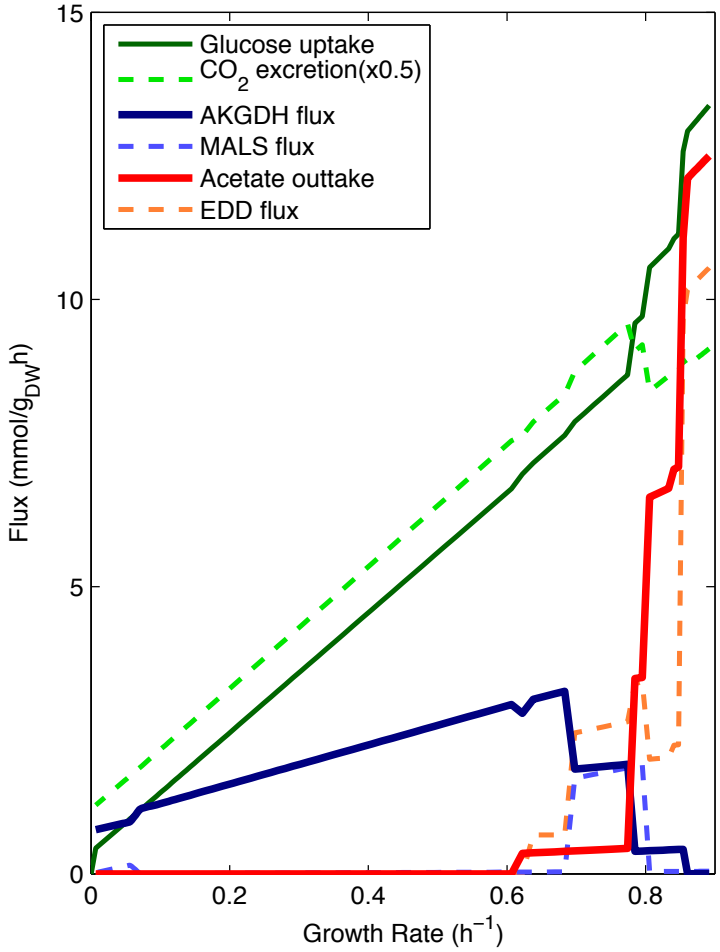


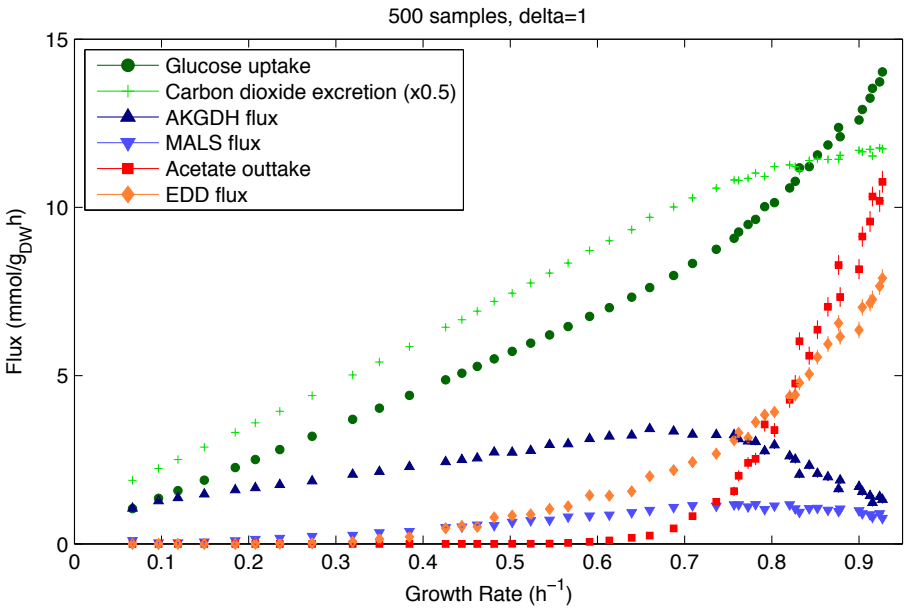
CAFBA

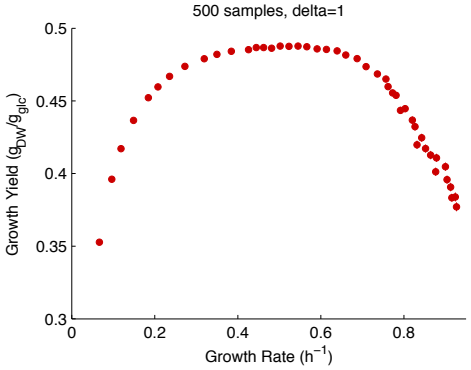
Outlook

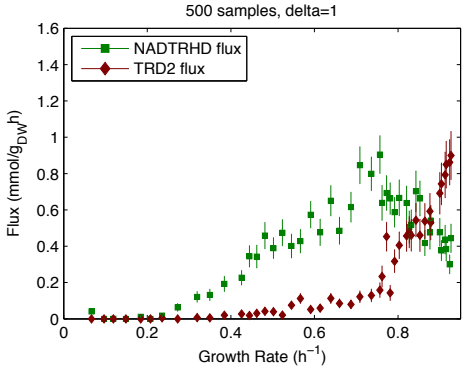
- Empirical observation: growth-rate dependent effects on gene expression suggesting a trade-off between different proteome sectors
- Minimal (3-sectors) phenomenological models explain observations
- CAFBA aims at incorporating the constraints that regulation imposes on metabolism in genome-scale models
- Effectively uses a 4-sector partition of the proteome
- Many empirical λ-dep. features are reproduced correctly, more study is under way
- Pros: LP, robust against noise in protein costs, no fine tuning, theoretical insight
- **Note** : "disorder-averaging" of protein costs gives qualitatively correct predictions
- **Extension with λ-dependent biomass**

Outlook


Glucose uptake
CO2 excretion(x0.5)
AKGDH flux
MALS flux
Acetate outtake
EDD flux
Flux (mmol/gDWh)
Growth Rate (h−1)


500 samples, delta=1
Glucose uptake
Carbon dioxide excretion (x0.5)
AKGDH flux
MALS flux
Acetate outtake
EDD flux
Flux (mmol/gDWh)
Growth Rate (h−1)


500 samples, delta=1
Growth Yield (gDW/glc)
Growth Rate (h−1)


500 samples, delta=1
NADTRHD flux
TRD2 flux
Flux (mmol/gDWh)
Growth Rate (h−1)