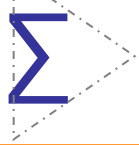




Quantitative proteomic analysis reveals a simple strategy of global resource allocation in bacteria

细菌中全局资源分配的简单策略

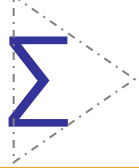
报告人：沈威



abstract

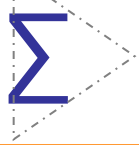


- 研究者通过质谱分析的方法来对蛋白质进行定量的研究，材料是大肠杆菌
- 在不同的限制条件下，研究者发现蛋白质组可以分为若干个模块（**sector**），每个模块的质量丰度与生长速率呈现出正线性或负线性的关系
- 与生长速率相关的蛋白大约占了整个蛋白组的**50%**，它们相互之间的关系可以用一个简单的模型来描述，这个模型仅包含两个有效参数



background

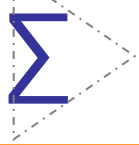
- 生物学中研究的最为广泛的问题之一就是细胞在环境胁迫的作用下如何对基因表达进行调控
- 在这个问题上，被广泛接受的一个观点是：在给定的限制因素上，细菌通过增加对应酶的量来弥补某一受限制的通路，可以比喻为“供需平衡”的关系
- 定性被广泛明确地描述在概念模型，但是，在资源配置上对量的理解很浅，即使是在单个细胞内



background



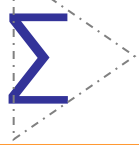
- 在分子水平上，一个细胞对外加限制条件的应答是代谢物、转录因子、启动子以及其他因子之间复杂相互作用的结果，这些因子的协同作用产生可以观测到的基因表达现象
- 因此单个基因在特定调控下的行为能否被概括为外界环境变化下全局的基因表达依然是一个问题



Question



- 在应对外界限制条件时，细胞会在量上对其合成物调整多少来调节受限通路？
- 在供给营养物的条件下，细胞是否会调整对应短缺营养物的基因操纵子？
- 或者基因表达是否会在更高的层次上被整合？
- 从分析的观点上，细胞的基因表达在“组学实验”所产生的数以万计的量的数据上，是通过统计来进行总括，那么能否用简单有效的定量方法来进行分析？

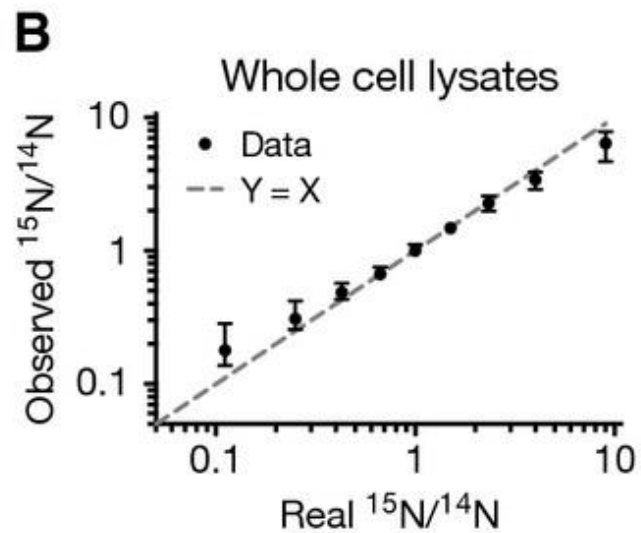
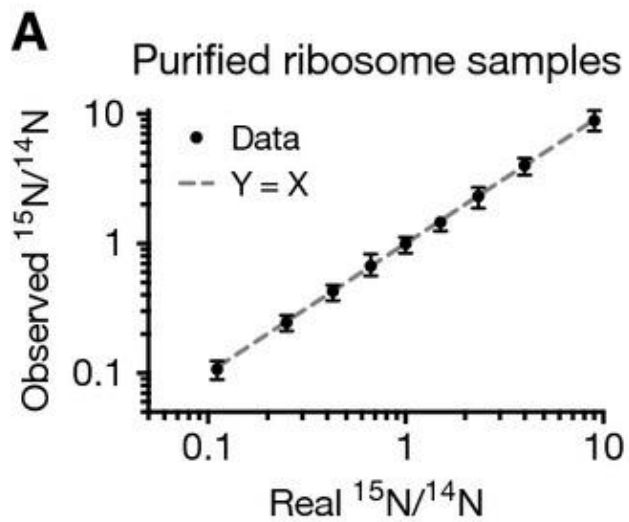
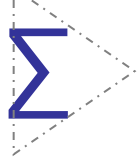


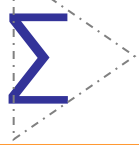
Solution



- In characterizing the state of a gas, useful quantitative measures are macroscopic quantities such as pressure and temperature, not the statistical clustering of the trajectories of molecules in the gas. **In systems biology, might similar measures exist to provide meaningful quantitative characterization of cellular responses?**
- Method: Quantitative proteomic mass spectrometry
- Material: E. coli cells







Distribution of observed ^{14}N to ^{15}N protein ratios

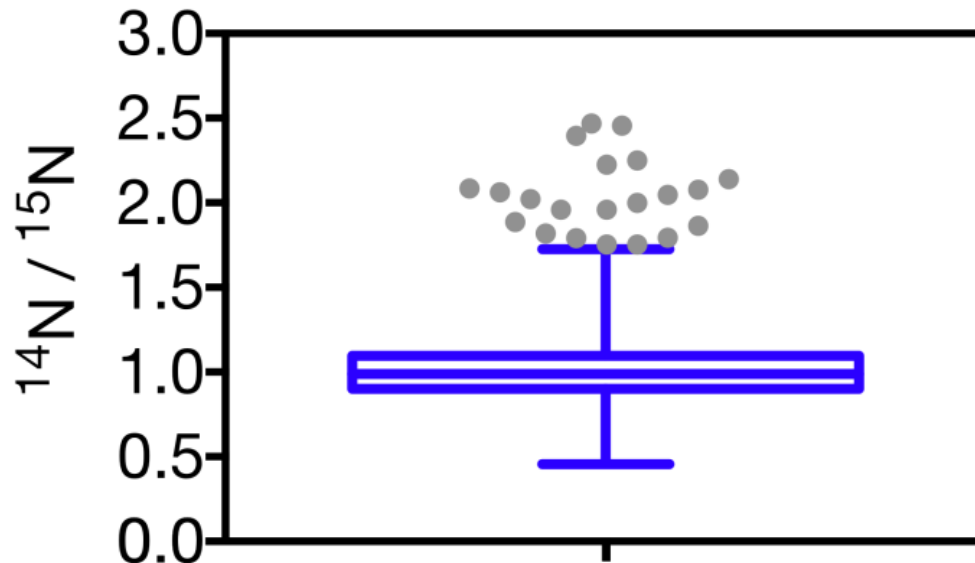
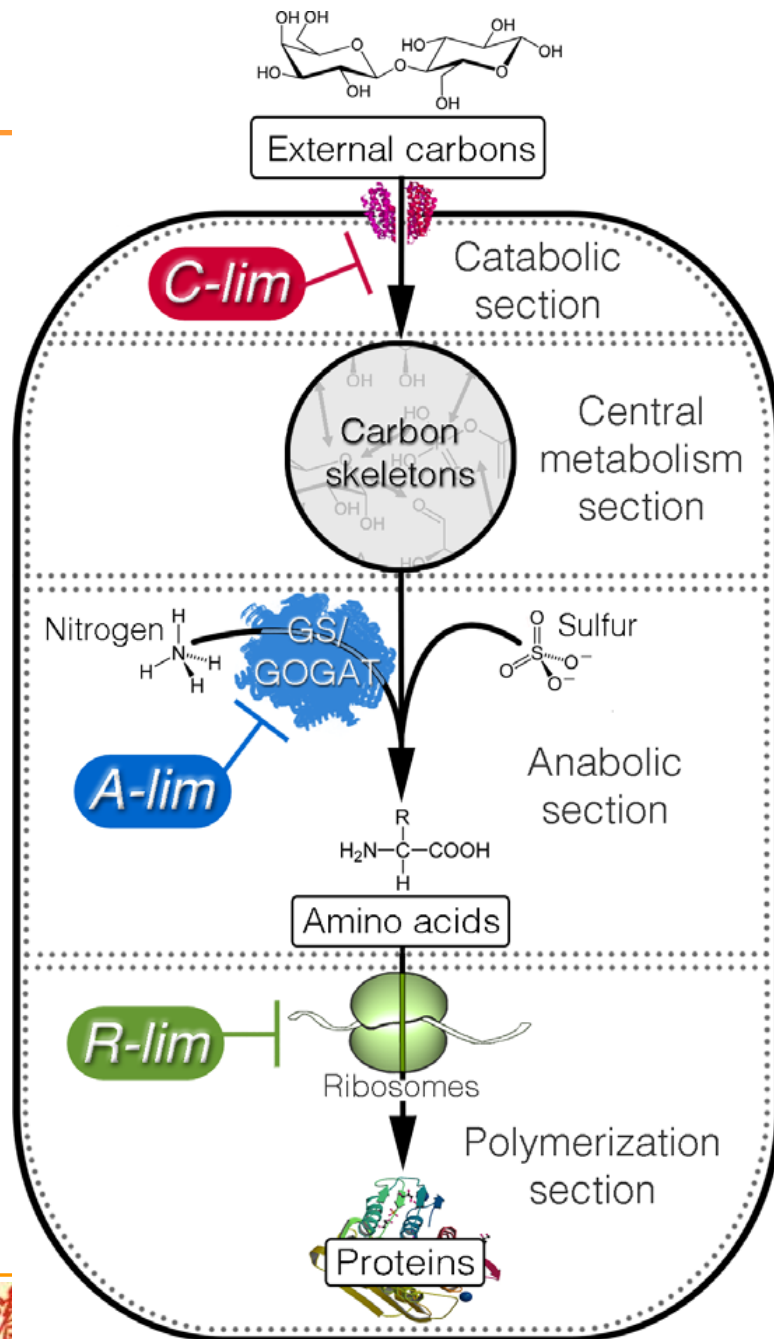
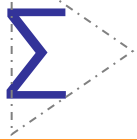
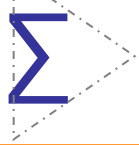


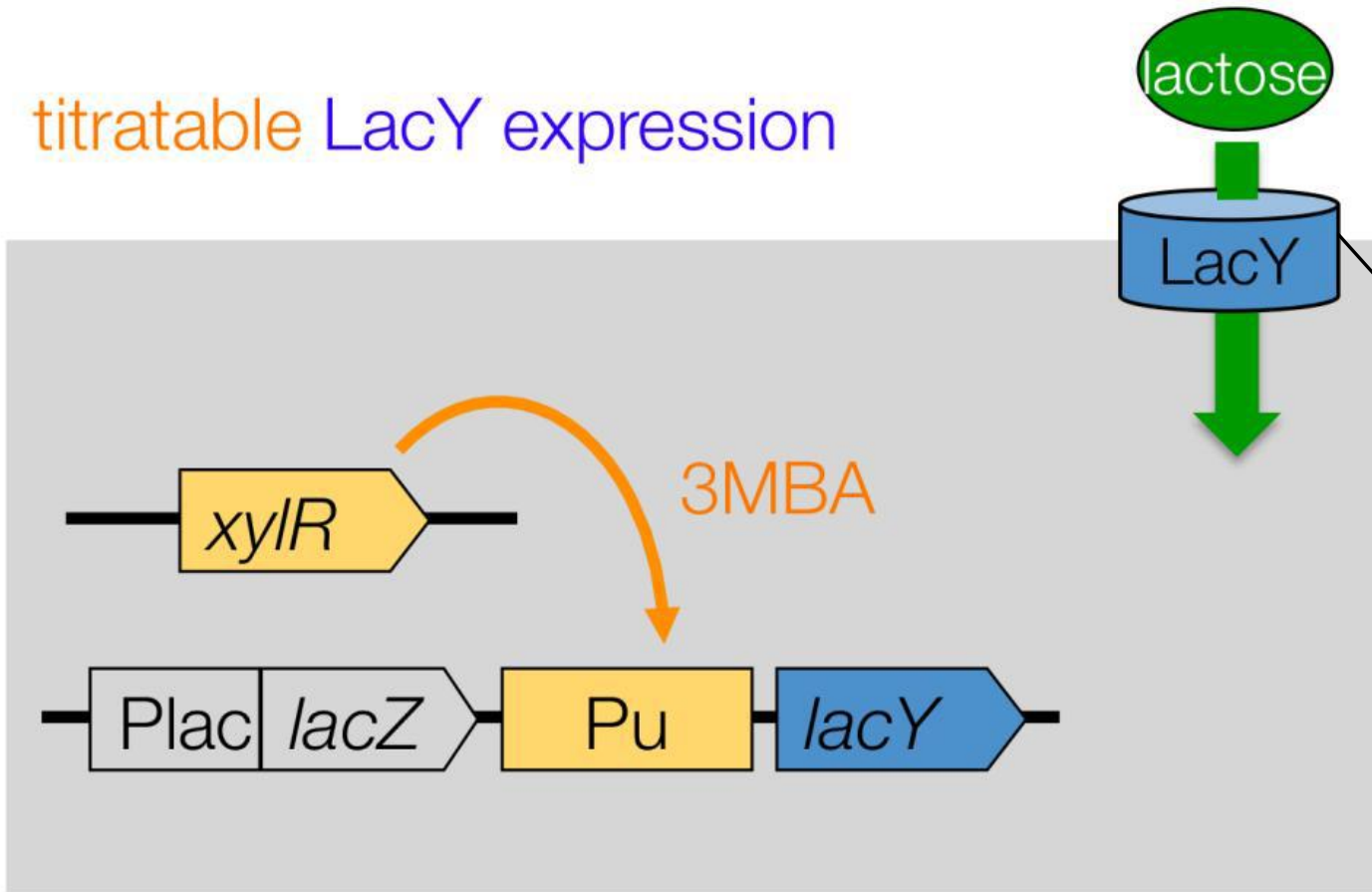
Figure S3. The overall precision of the method of quantifying relative protein expression levels with mass spectrometry.



A coarse-grained metabolic flow diagram for protein production by *E. coli* growing in minimal medium



titratable LacY expression



乳糖通透酶

Figure S1. C-limitation by titrating lactose uptake.

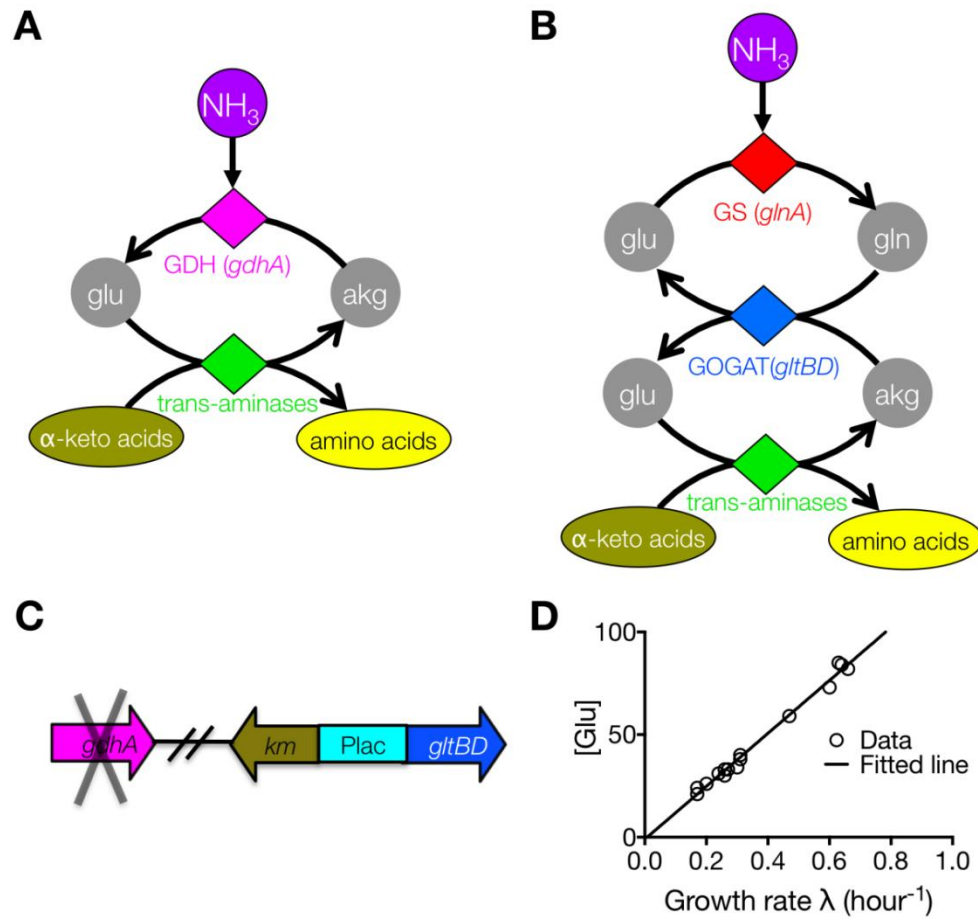
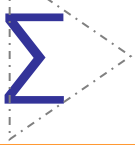
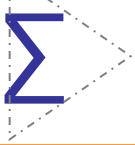
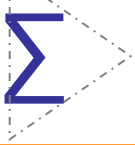


Figure S2. A-limitation by titrating ammonia assimilation

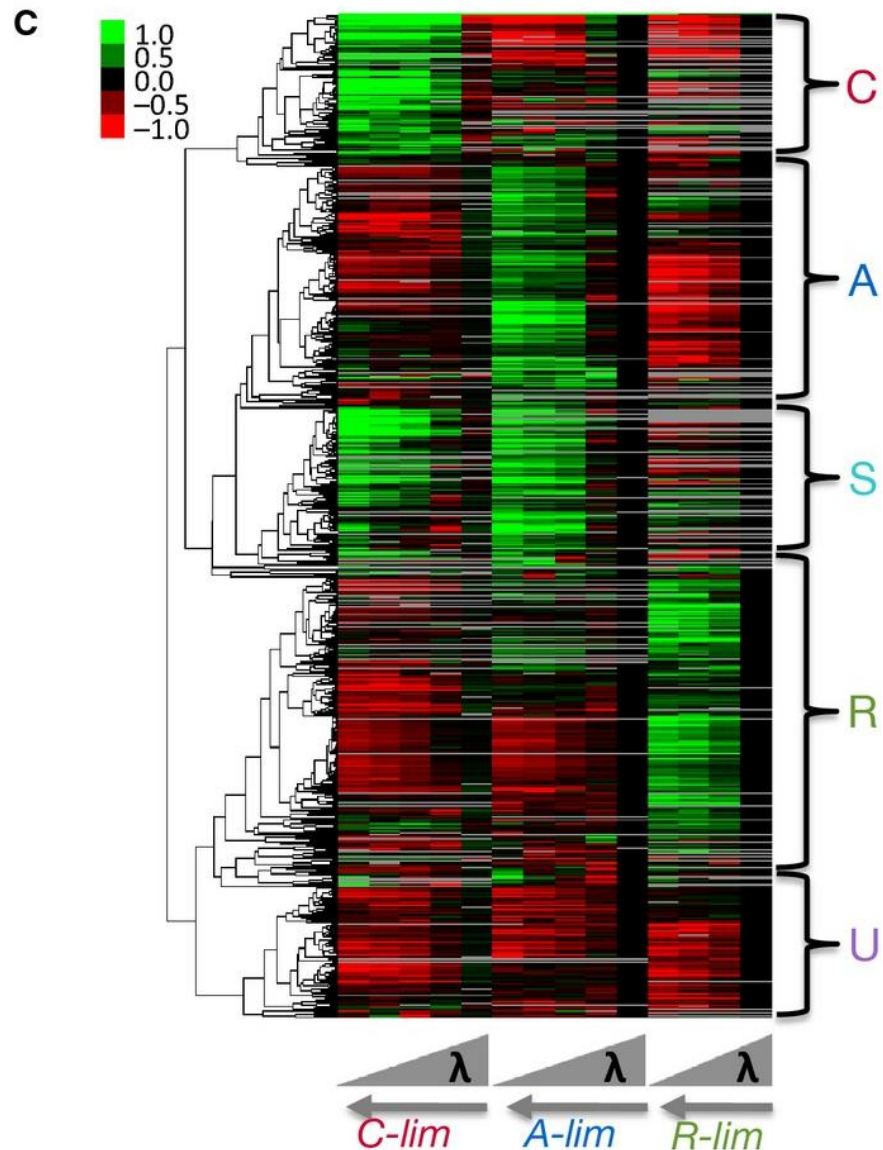


Growth limitations	Medium	Strains, inducers/antibiotic amounts, and doubling times					
C-limitation	Lactose minimal medium	Titrateable LacY NQ381 (<i>attB::P_{Lac-O1}-xylR, lacY::km-Pu-lacY</i>)					WT NCM3722
		3MB A (uM)	0	25	50	500	
		Dbl (min)	92	72	62	48	40
A-limitation	Glucose minimal medium	Titrateable GOGAT NQ393 (<i>attB::Sp-lacIQ-tetR, ΔlacY, ΔgdhA, P_{Lac-O1}-gltBD</i>)					WT NCM3722
		IPTG (uM)	30	40	50	100	
		Dbl (min)	91	69	58	47	43
R-limitation	Glucose minimal medium	WT NCM3722 (wild type)					
		Chloramphenicol (uM)	8	4	2	0	
		Dbl (min)	147	102	65	42	



Clustering analysis of protein expression trends

Coverage: ~80%



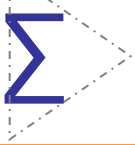
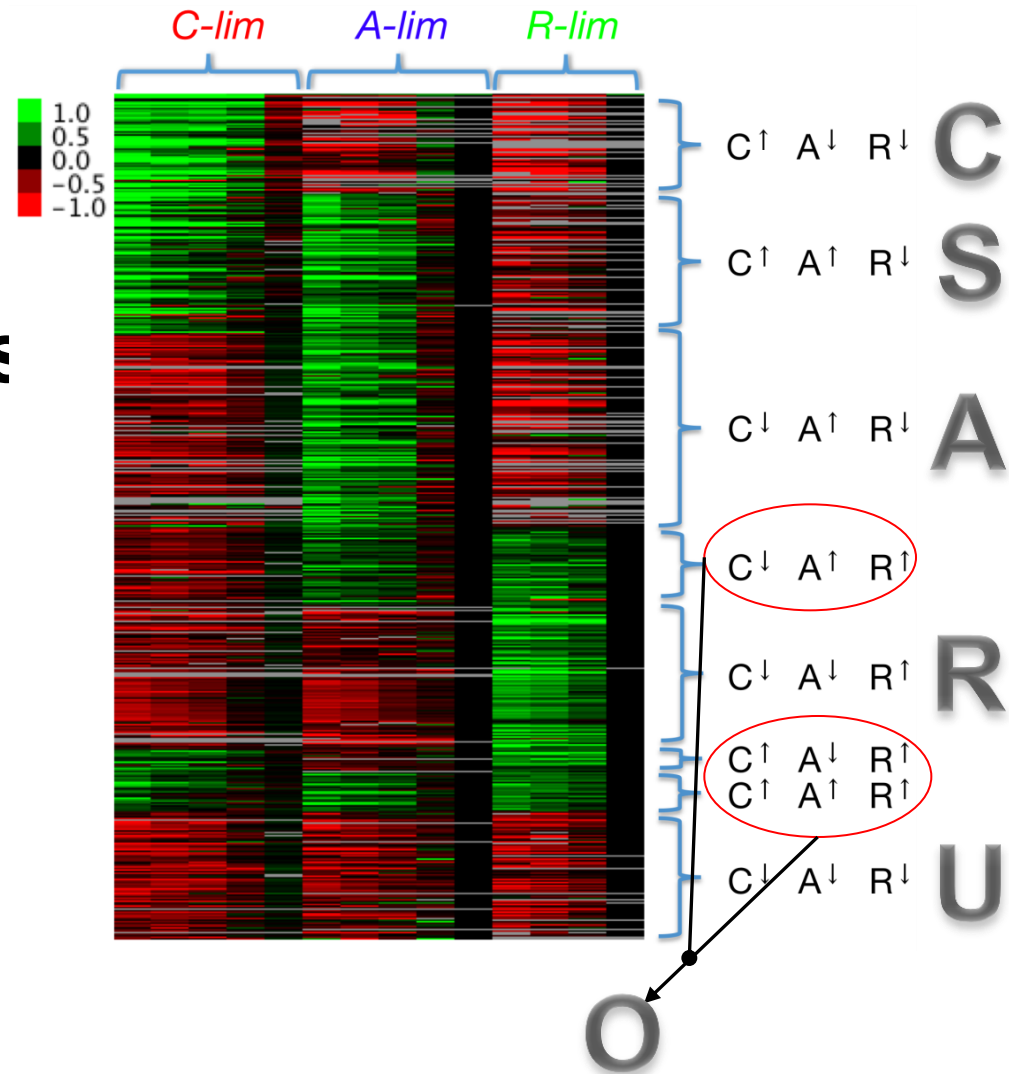
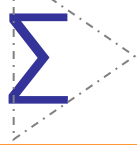
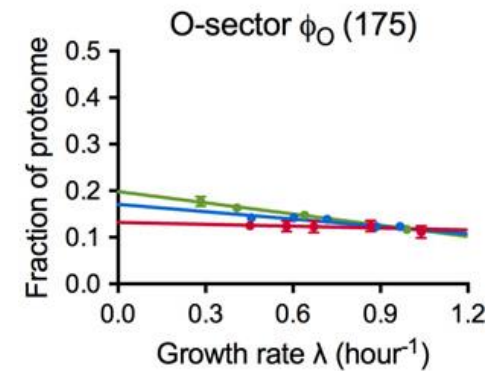
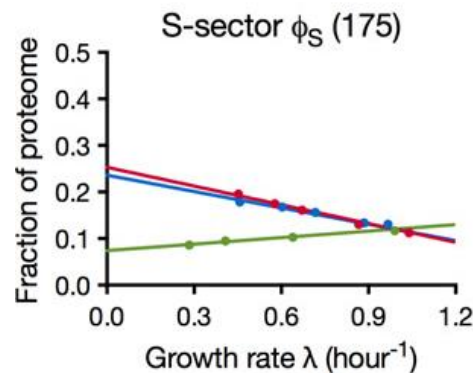
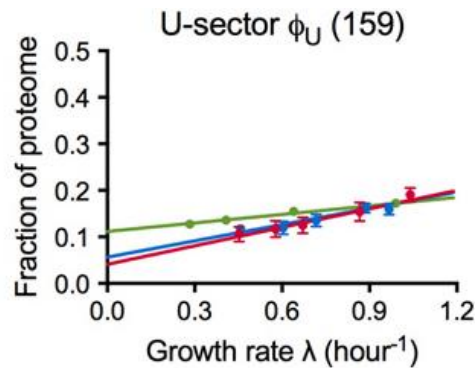
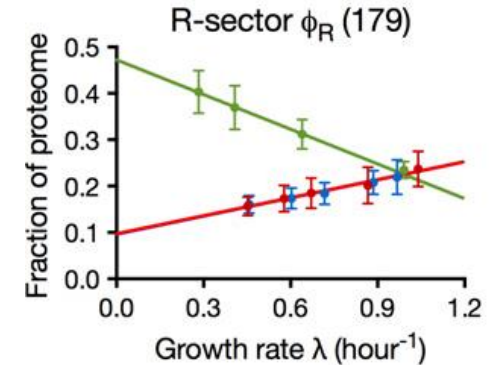
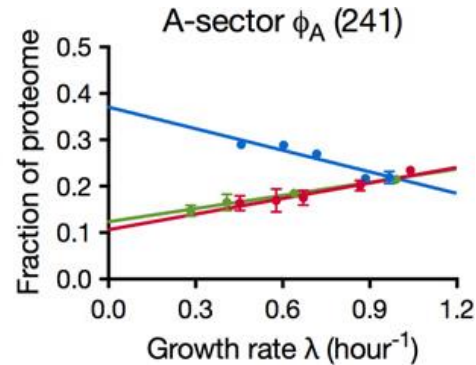
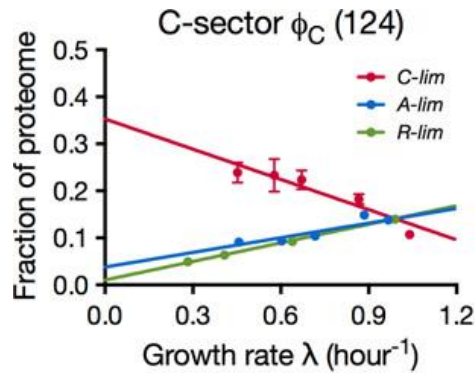


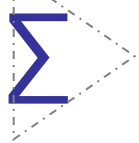
Figure S8.
Grouping proteins
into 8 groups.



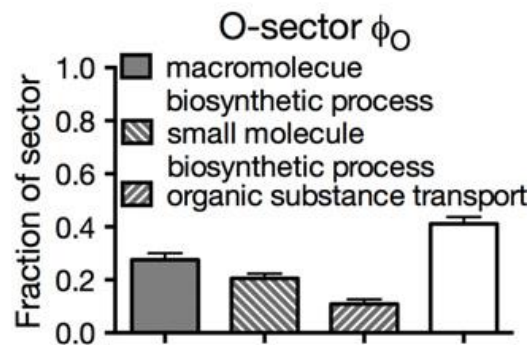
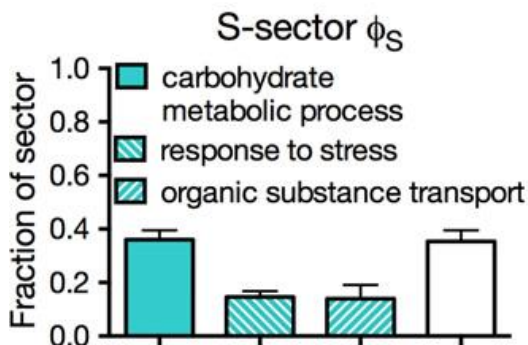
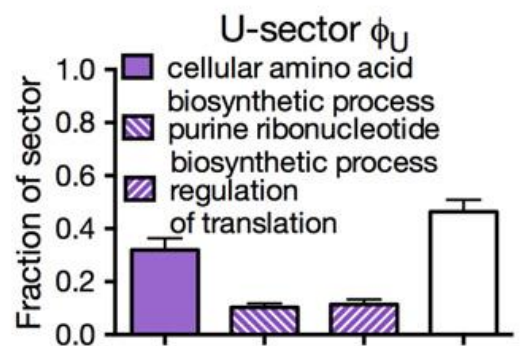
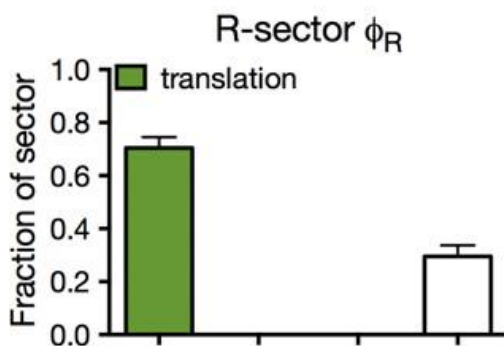
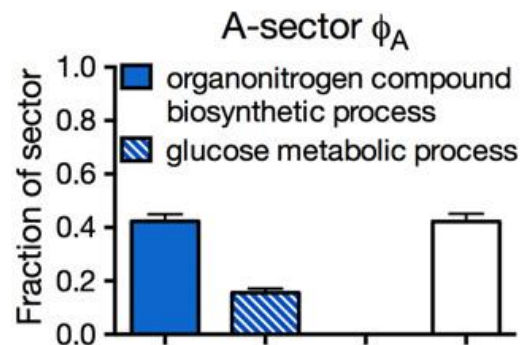
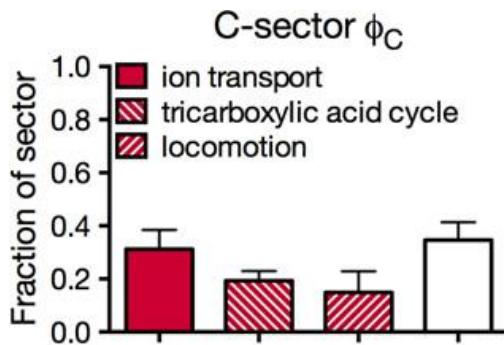


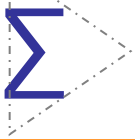
The coarse-grained proteome sectors



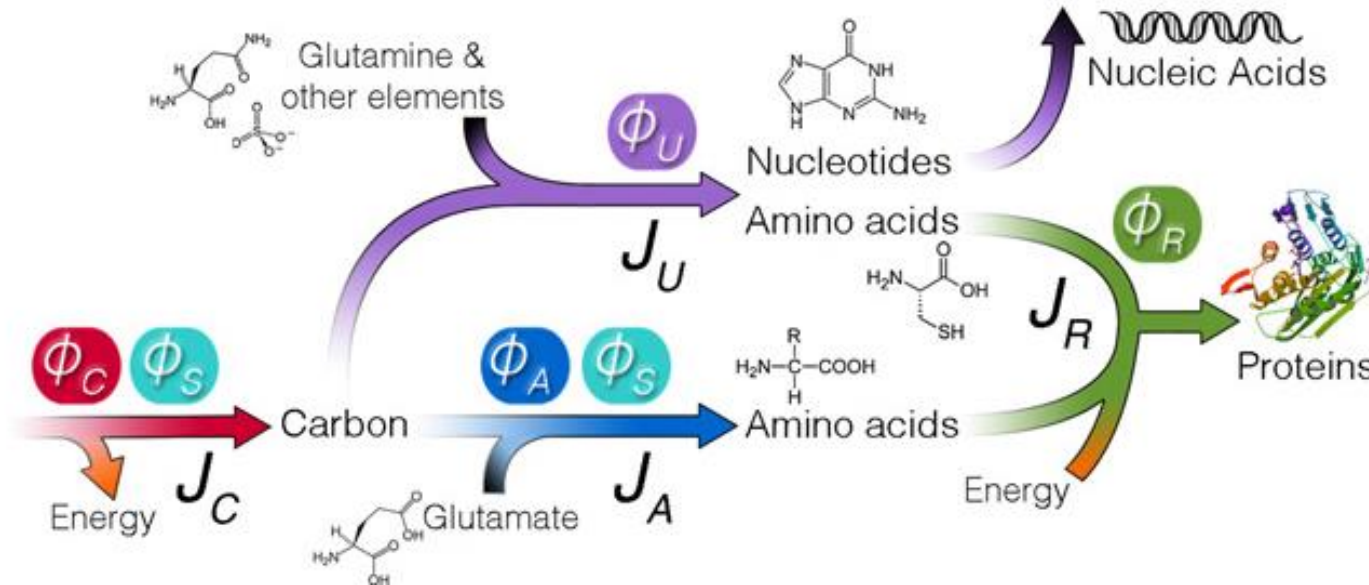


Abundance-based GO analysis





Flux matching

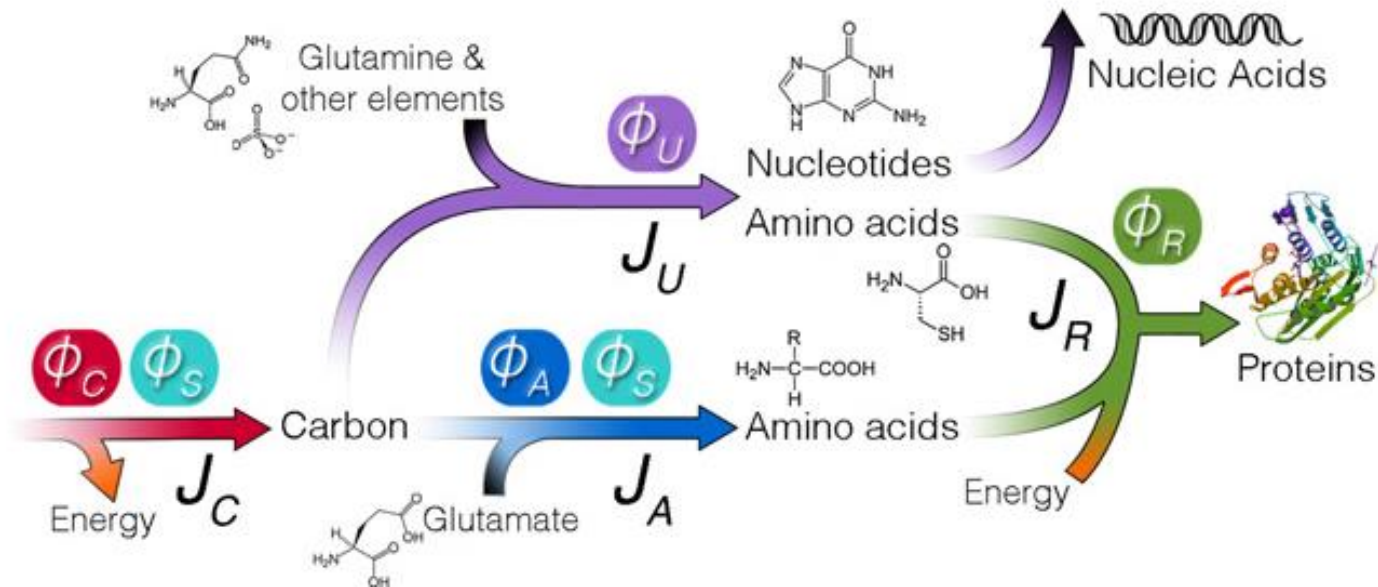
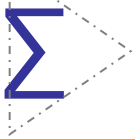


$$\phi_{\sigma}(\lambda) = \phi_{\sigma,0} + \Delta\phi_{\sigma}(\lambda).$$

Proteome sector

Basal level

Growth rate-dependent component

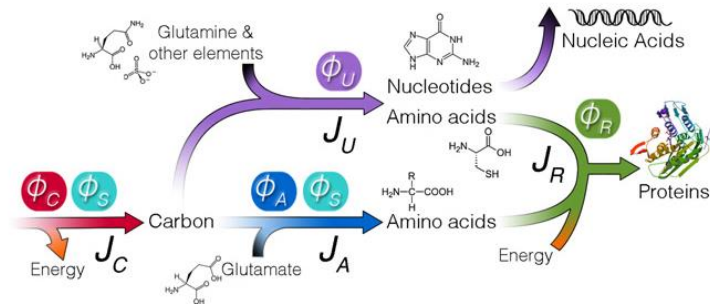
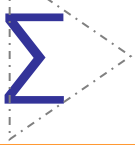


$$J_{\sigma} = k_{\sigma} \cdot \Delta\phi_{\sigma}$$

Corresponding proteome fraction

Flux by a sector

coefficient



$$J_R = k_R \cdot \Delta\phi_R$$

Corresponding proteome fraction

Flux by a sector

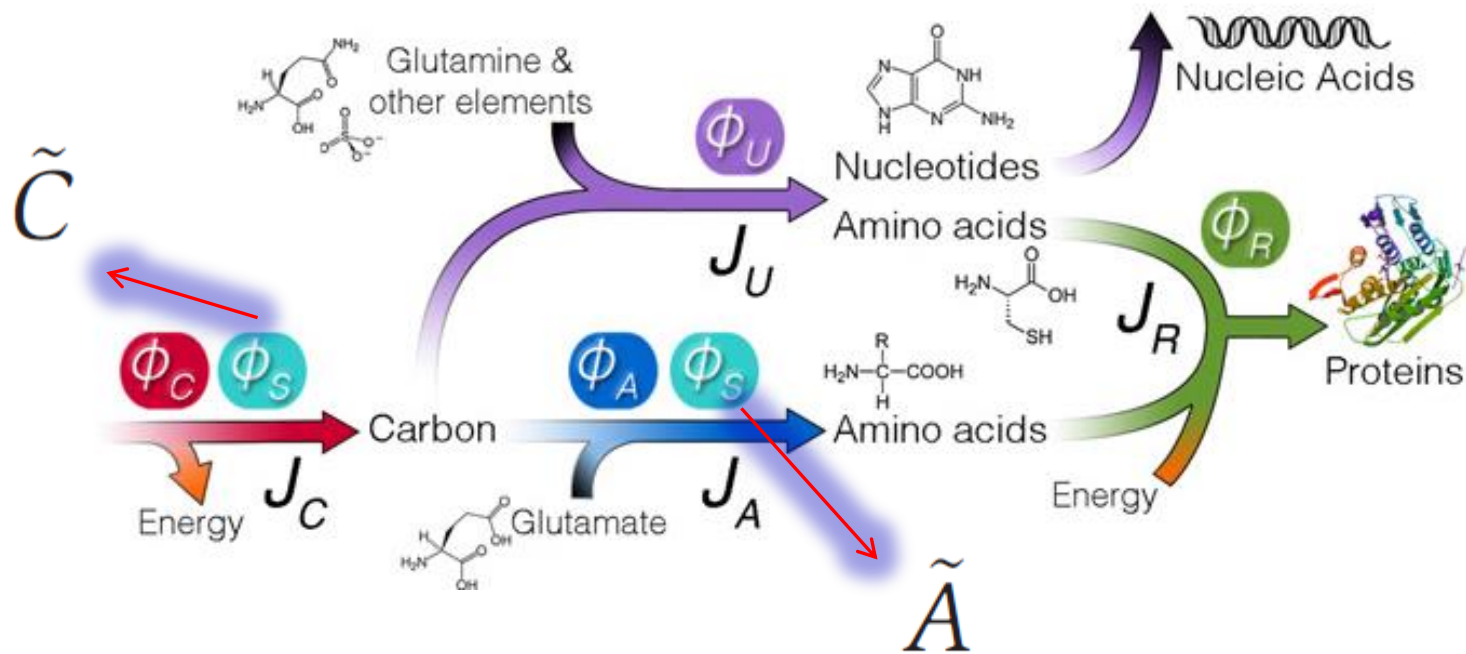
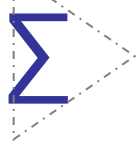
coefficient

$$C_R \cdot J_R = \lambda$$

Stoichiometric coefficient

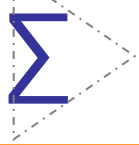
$$\Delta\phi_R(\lambda) = \lambda / v_R$$

$$v_R = k_R C_R$$



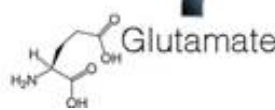
$$\phi_{\tilde{C}}(\lambda) = \phi_{\tilde{C},0} + \lambda/v_C$$

$$\phi_{\tilde{A}}(\lambda) = \phi_{\tilde{A},0} + \lambda/v_A$$



fraction of ~ C- and ~A-
sector proteins that are in
common

Energy J_C



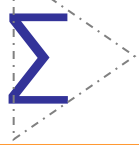
Glutamate J_A

Ener $\Delta\phi_O(\lambda) = 0$

$$\Delta\phi_C(\lambda) = (1 - f) \cdot \lambda/v_C,$$

$$\Delta\phi_A(\lambda) = (1 - f) \cdot \lambda/v_A,$$

$$\Delta\phi_S(\lambda) = f \cdot [\lambda/v_C + \lambda/v_A]$$



Constraint of finite proteome resources



约束条件: $\sum_{\sigma} \phi_{\sigma}(\lambda) = 1$



$$\sum_{\sigma} \Delta \phi_{\sigma}(\lambda) = \phi_{\max}$$

$$f_{\max} \circ 1 - \dot{a}_s f_{s,0}$$

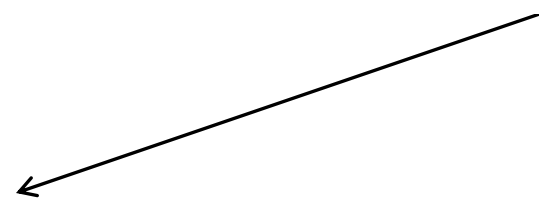


Constraint of finite proteome resources

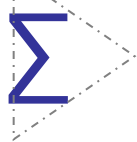


Under R-lim: $\Delta\phi_R(\lambda) = \phi_{\max} - \lambda/\kappa_R$

$$\kappa_R^{-1} \equiv v_C^{-1} + v_A^{-1} + v_U^{-1}$$

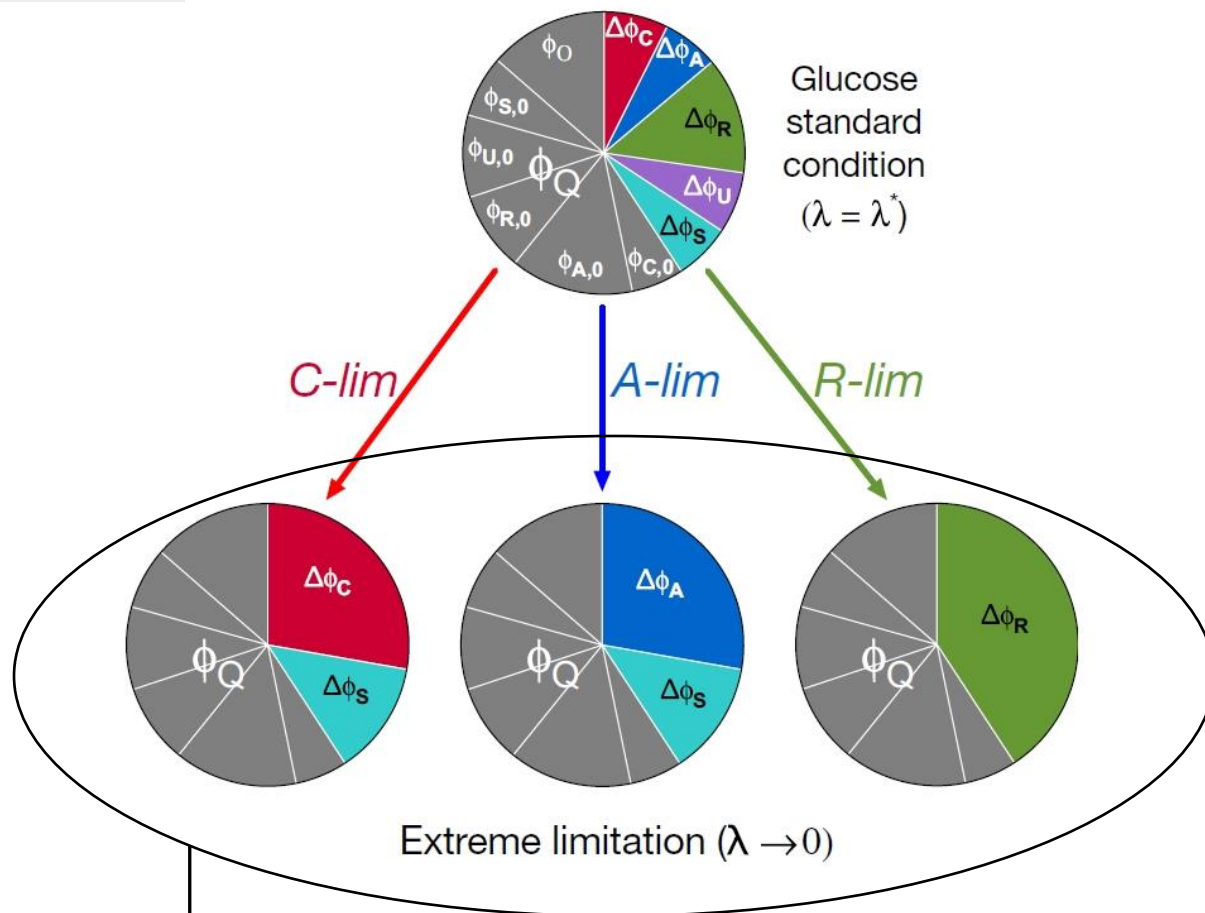


- under R-limitation only v_R is reduced, all other sectors still follow the general responses



Sector ^o	<i>C-lim</i> ^o	<i>A-lim</i> ^o	<i>R-lim</i> ^o
C ^o	$\phi_C(\lambda) = \phi_{C,0} + (1-f) \cdot (\phi_{\max} - \lambda / \kappa_C)$ [S8a] ^o $\kappa_C^{-1} = \nu_A^{-1} + \nu_R^{-1} + \nu_U^{-1}$ [S8b] ^o	$\phi_C(\lambda) = \phi_{C,0} + (1-f) \cdot \lambda / \nu_C$ [S3] ^o	$\phi_C(\lambda) = \phi_{C,0} + (1-f) \cdot \lambda / \nu_C$ [S3] ^o
A ^o	$\phi_A(\lambda) = \phi_{A,0} + (1-f) \cdot \lambda / \nu_A$ [S4] ^o	$\phi_A(\lambda) = \phi_{A,0} + (1-f) \cdot (\phi_{\max} - \lambda / \kappa_A)$ [S9a] ^o $\kappa_A^{-1} = \nu_C^{-1} + \nu_R^{-1} + \nu_U^{-1}$ [S9b] ^o	$\phi_A(\lambda) = \phi_{A,0} + (1-f) \cdot \lambda / \nu_A$ [S4] ^o
R ^o	$\phi_R(\lambda) = \phi_{R,0} + \lambda / \nu_R$ [S1] ^o	$\phi_R(\lambda) = \phi_{R,0} + \lambda / \nu_R$ [S1] ^o	$\phi_R(\lambda) = \phi_{R,0} + \phi_{\max} - \lambda / \kappa_R$ [S7a] ^o $\kappa_R^{-1} = \nu_C^{-1} + \nu_A^{-1} + \nu_U^{-1}$ [S7b] ^o
U ^o	$\phi_U(\lambda) = \phi_{U,0} + \lambda / \nu_U$ [S2] ^o	$\phi_U(\lambda) = \phi_{U,0} + \lambda / \nu_U$ [S2] ^o	$\phi_U(\lambda) = \phi_{U,0} + \lambda / \nu_U$ [S2] ^o
S ^o	$\phi_S(\lambda) = \phi_{S,0} + f \cdot (\phi_{\max} - \lambda / \kappa_S)$ [S10a] ^o $\kappa_S^{-1} = \nu_R^{-1} + \nu_U^{-1}$ [S10b] ^o	$\phi_S(\lambda) = \phi_{S,0} + f \cdot (\phi_{\max} - \lambda / \kappa_S)$ [S10a] ^o $\kappa_S^{-1} = \nu_R^{-1} + \nu_U^{-1}$ [S10b] ^o	$\phi_S(\lambda) = \phi_{S,0} + f \cdot \lambda \cdot (1 / \nu_C + 1 / \nu_A)$ [S5] ^o
O ^o	$\phi_O(\lambda) = \phi_{O,0}$ [S6] ^o	$\phi_O(\lambda) = \phi_{O,0}$ [S6] ^o	$\phi_O(\lambda) = \phi_{O,0}$ [S6] ^o

$${}^2\varphi_C = 0.07 \quad {}^2\varphi_A = 0.06 \quad {}^2\varphi_U = 0.07 \quad {}^2\varphi_R = 0.13 \quad {}^2\varphi_S = 0.06$$



$$\varphi_{\max} = 1 - \varphi_Q \quad f \approx 0.32$$

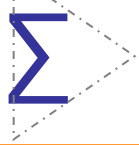
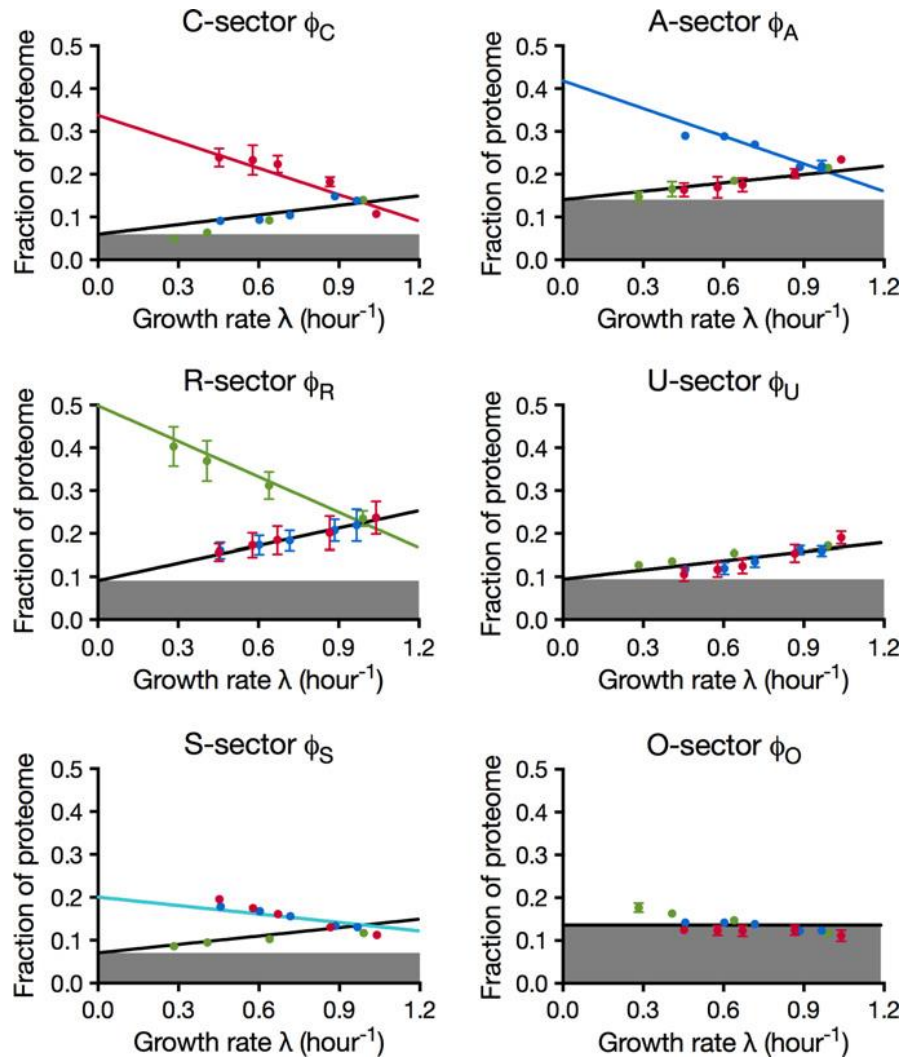
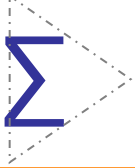
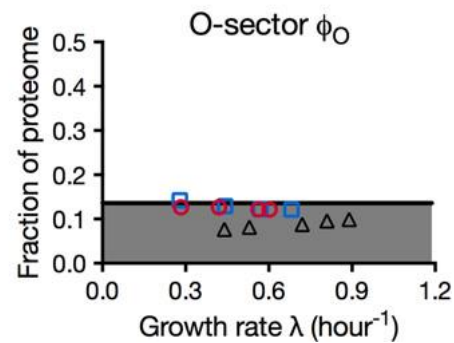
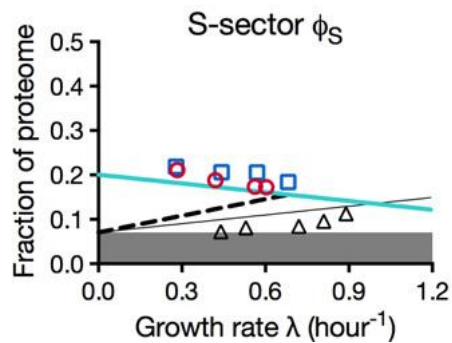
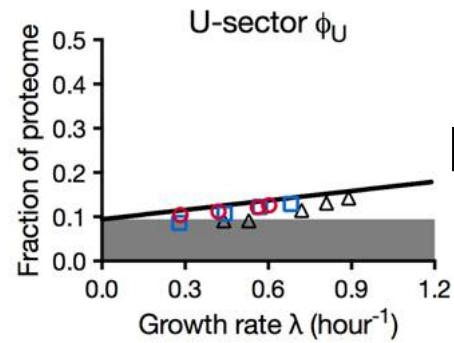
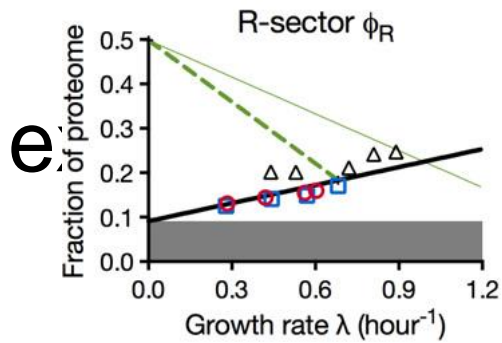
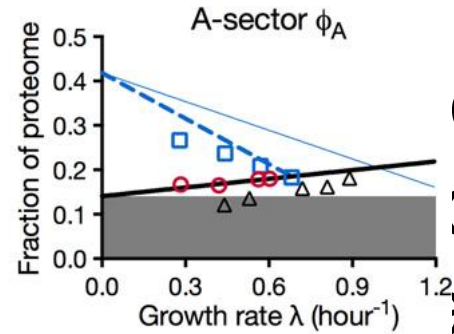
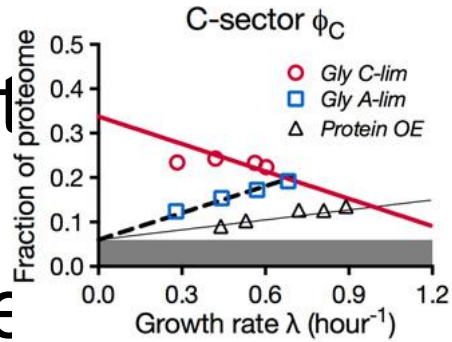


Figure 5. Performance of the proteome-based flux model.





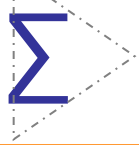
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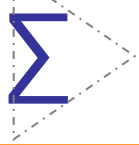
ϕ_{\max} ↓



Discussion



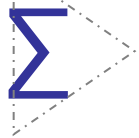
- 阐明全局基因表达调控所遵循的规律是系统生物学的一个主要目标。然而基因调控网络的错综复杂使得难以从由下而上的分析来实现这个目标。
- 细胞内数以万计的蛋白质、mRNA以及代谢产物的定量方法现在变得可能。这些技术启示细胞内各种各样的合成物的量可以构建为生长条件的函数，或者可以构建成为细胞配置资源的一个框架。



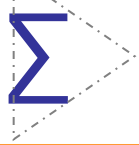
Discussion



- **Coarse-grain**的处理手段为我们提供了一个研究细胞蛋白水平上资源配置的有效方法。
- 在其他生长条件的限制下，预测会有其他新的**Sector**出现



请批评指正



- 概括：本文的主要创新点在于从宏观的角度出发，根据数据的特点利用模块化的方法来进行模型构建。
- 启发：从实验方法上，要紧跟实验技术的发展；从数据分析上，要有灵活的思路来理解数据所想要表达的内在含义。
- 改进：蛋白组数据可以结合转录组数据进行再一步的分析