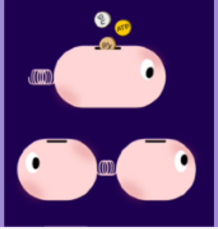
Economic Principles in Cell Biology

Paris, July 10-14, 2023



Metabolic diversity

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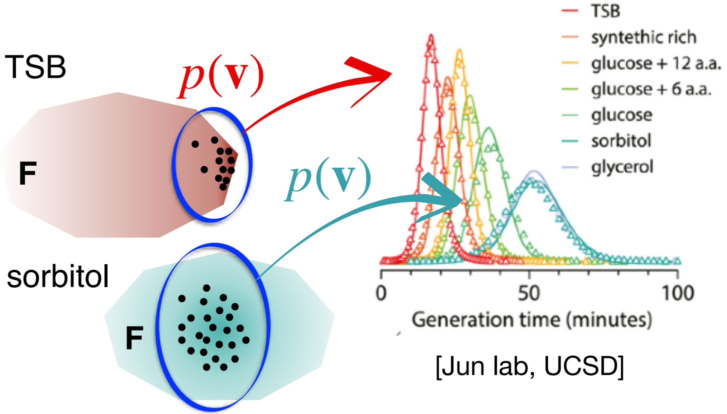
- Part 1: (Optimal) Probability densities on the flux polytope
- Part 2: Inference of single-cell quantities

- Constraint-based models are mostly calibrated for *population averages*
- But cells within a population differ in both `observable' (e.g. growth rate) and `internal' properties (e.g. metabolic phenotype, like fermentative vs respiratory)
- In some cases, diversity is a plus (see e.g. bacterial persistence)
- **Question:** can we capture single-cell properties within the frame of CBMs?

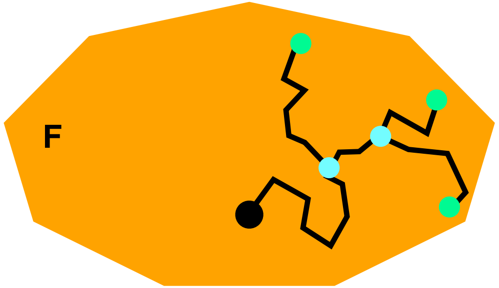
For instance



[Jun lab, UCSD]

- **Feasible space (F)**: defined by mass balance conditions (**Sv**=**0**) and ranges of variability for each v_i ; dim(**F**)=$\mathcal{O}(10^2)$
- **Basic idea:** empirical distributions represent marginals of an unknown high-dimensional distribution $p(\mathbf{v})$ on **F**
- Two ways to understand $p(\mathbf{v})$:
  - **Dynamics**: $p(\mathbf{v},t) \to p(\mathbf{v})$
  - **Statics (variational)**: "$p(\mathbf{v})$ is optimal"

A minimal model of population dynamics in F



- Same feasible space **F** for all cells
- $n(\mathbf{v},t)$ = nr of cells with flux vector **v** at time t
- Time evolution of n due to (i) replication (rate $\lambda(\mathbf{v})$), (ii) **diffusion** in **F** (small random changes in the flux vector), and (iii) **advection** (cells adjusting **v** to maximize $\lambda(\mathbf{v})$)
  - *The dynamics is sensitive to the growth-rate landscape*
- Finite carrying capacity
- Steady state: balance of diffusion and advection

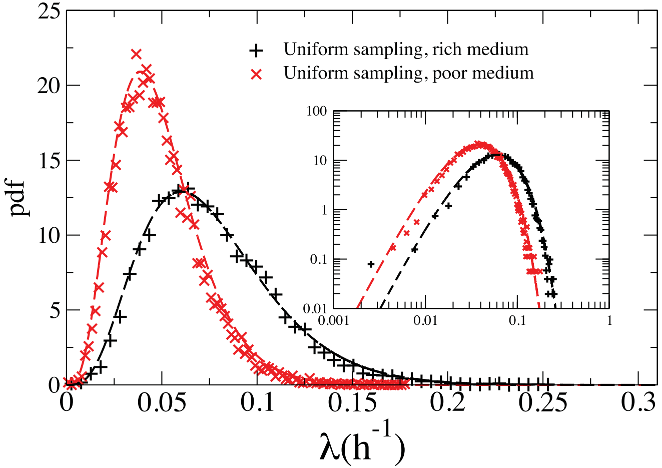
1d case (simple) : $$J_{\text{diff}} = -D\frac{\partial n}{\partial v} \quad , \quad J_{\text{adv}} = \chi n \frac{\partial \lambda}{\partial v}$$

[De Martino et al 2016]

$$J_{\text{diff}} + J_{\text{adv}} = 0 \quad \rightarrow \quad \frac{\partial n}{\partial v} = \beta n \frac{\partial \lambda}{\partial v} \quad \rightarrow \quad n(v) \sim e^{\beta \lambda(v)}$$

$$\beta = \chi / D$$

- *The dynamics is sensitive to the growth-rate landscape*



$$q(\lambda) \propto \lambda^{b}(\lambda_{\max} - \lambda)^{a} \quad , \quad a \gg b \quad , \quad a \gg 1$$

- Small random changes to v are overwhelmingly more likely to reduce the growth rate than increase it

"FBA" (max λ)

$\chi \gg D$

$$n(v) \sim e^{\beta \lambda(v)}$$

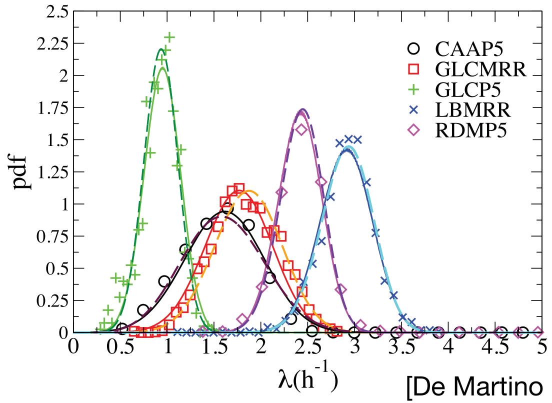
$$\beta = \chi / D$$

$D \gg \chi$

Uniformly distrib. over F

Comparisons

- Compare marginals of $p(\mathbf{v})$ for the growth rate with data (fitting parameter: β)



[De Martino et al 2016]

Table 1. Inferred maximum growth rates, level of optimization and rate of metabolic change for the experimental data [19, 20] fitted with the stationary distributions retrieved by the MaxEnt framework of section 3 and from the dynamical model of section 4. Growth rates are measured in h^{-1}, while σ and $\beta\lambda_{max}$ are adimensional.

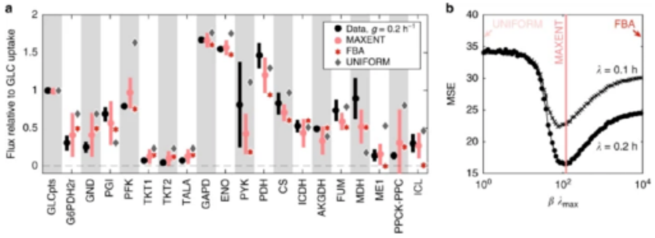
Data set	MaxEnt		Dynamical	
	λ_{max} (h^{-1})	$\beta\lambda_{max}$ (adim.)	λ_{max} (h^{-1})	σ (adim.)
[19] rich medium	5.9	220	7.2	10^{-5}
[19] poor medium	3.2	220	3.8	10^{-5}
[20] GLCP5	3.5	220	4.3	10^{-5}
[20] GLCMRR	7	220	8	10^{-5}
[20] CAAP5	8.6	190	9	1.2×10^{-5}
[20] RDMP5	5.5	300	6.4	5×10^{-6}
[20] LBMRR	6.6	300	7.7	5×10^{-6}

$$p(\mathbf{v}) = \frac{e^{\beta\lambda(\mathbf{v})}}{Z(\beta)}$$

(data: Kennard et al 2016)

[De Martino et al 2018]

Fig. 2



a Comparison of measured fluxes (black, mean, error bars defined as SD over 12 experiments, technical replicates; normalized to glucose uptake) with predictions of FBA (red stars) and of the maximum entropy model (pink, error bars defined as SD with simulation sample size 10^5). Also shown are mean fluxes predicted by uniform sampling, i.e., using $\beta = 0$ in Eq. (7) (gray stars; mean, for clarity, large SDs are not displayed). Data for **a** are a collection of 12 experiments at average growth rate $\bar{\lambda} = 0.2\ h^{-1}$. Wild-type *E. coli* was grown in glucose-limited medium in aerobic

- Compare marginals of $p(\mathbf{v})$ vs MS fluxes
  - Assume $p(\boldsymbol{v})$ with empirical β
  - Sample $p(\boldsymbol{v})$ (e.g. MC)
  - Compute marginals
  - Compare vs experiments

Variational route to *n*(v)~exp[βλ(v)]

- Mean growth rate <*λ*> ~ population fitness
- **An `energy-entropy' tradeoff:** distributions *p*(**v**) with large <*λ*> have small entropy and v.v.

$$\max_{p(\mathbf{v})} H[p] \quad \text{s.t.} \quad \langle \lambda \rangle \quad \rightarrow \quad p(\mathbf{v}) = \frac{e^{\beta\lambda(\mathbf{v})}}{Z(\beta)}$$

Entropy of *p* :

$$H[p] = -\int_F p(\mathbf{v}) \ln p(\mathbf{v})\, d^N v$$

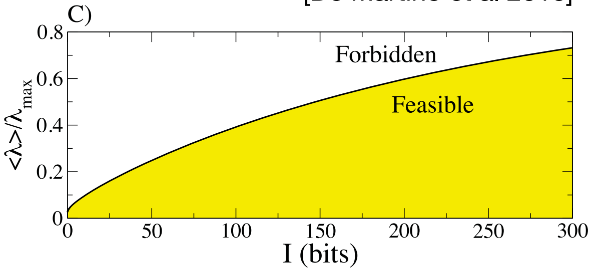
- ***Lesson (2016):** at the metabolic level (CBMs), cells within a population appear to have maximal growth-rate heterogeneity for the population's fitness (!)*
- ***To go more in depth:** some more theory + inference...*

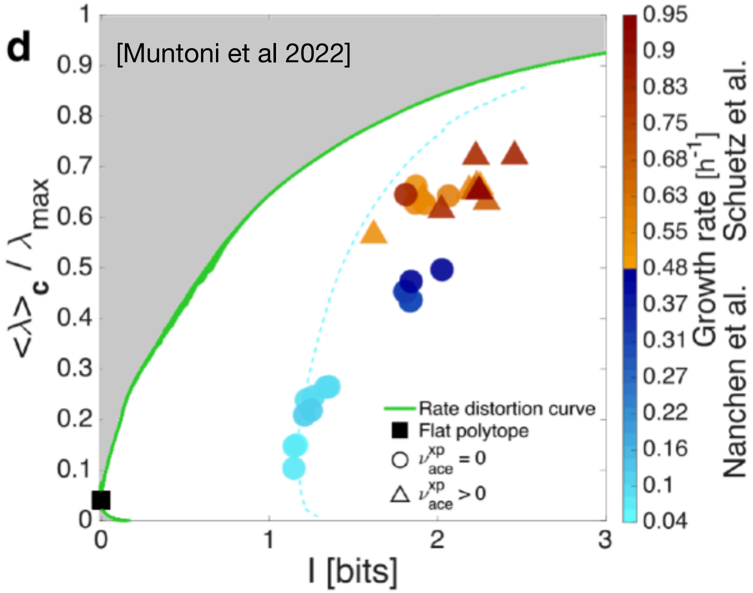
- **Relationship between <*λ*> and *H***

$$H(0) - H(\beta) \equiv I \ln 2 = \beta\langle\lambda\rangle - \int_0^\beta \langle\lambda\rangle\, d\beta'$$

- **Re-phrasing:** what is the minimum number of bits (*I*) to be encoded in *p*(***v***) in order to achieve a given “fitness” (mean growth rate)?

[De Martino et al 2016]

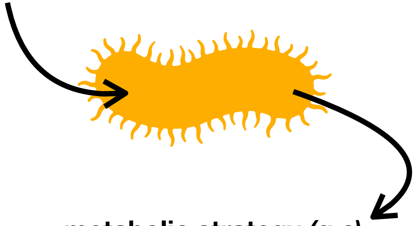



d
[Muntoni et al 2022]
$<\lambda>_c / \lambda_{max}$
I [bits]
Rate distortion curve
Flat polytope
$\nu^{xp}_{ace} = 0$
$\nu^{xp}_{ace} > 0$
Growth rate [h^{-1}]
Schuetz et al.
Nanchen et al.
0.95
0.9
0.83
0.75
0.68
0.63
0.55
0.48
0.37
0.31
0.27
0.22
0.16
0.1
0.04

Best metabolic strategy in a fluctuating medium

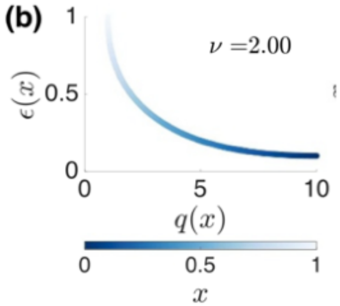
[Muntoni et al 2023]

Stress level *s*



metabolic strategy *(q,ε)*

q-ε trade-off



- *q(x)* = specific intake
- ε(x) = specific proteome cost

$$\lambda(x,s) = \frac{\phi}{w + sq(x) + \epsilon(x)}$$

- What if *s* fluctuates?
- *P(s)* (distrib of stress levels)
- Fast fluctuations: maximize <λ> (avg over *s*)

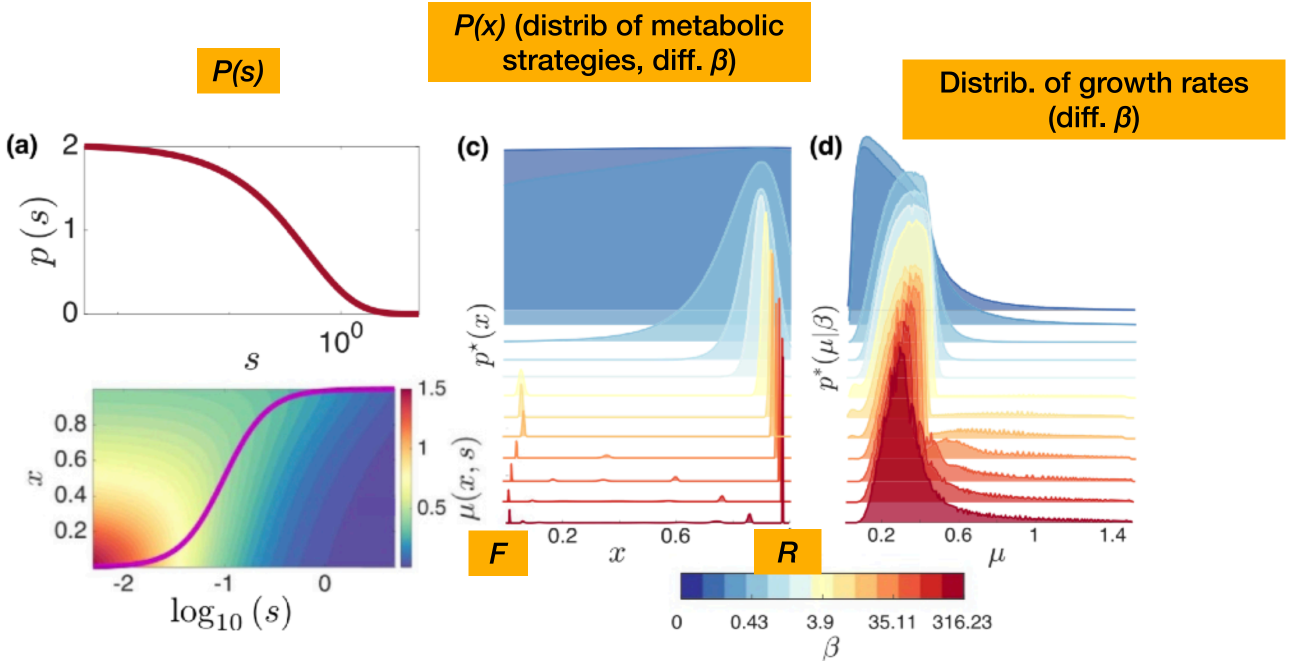
$$\langle\lambda\rangle = \int ds\, P(s) \int dx\, P(x\,|\,s)\lambda(x,s)$$

- Optimize over conditional response *P(x|s)* ...
- ... subject to mutual information of *x* and *s*

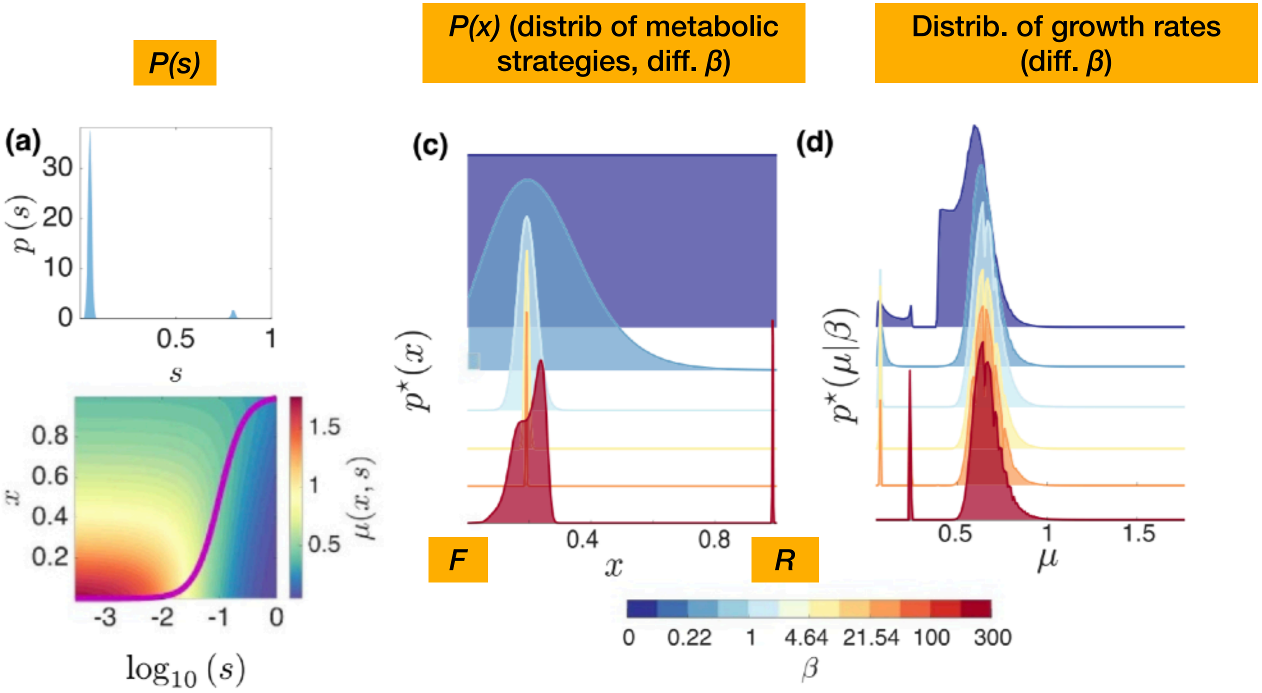
$$I(x;s) = \int ds\, P(s) \int dx\, P(x\,|\,s) \log_2 \frac{P(x\,|\,s)}{P(x)}$$

- Solution:

$$P(x\,|\,s) = \frac{P(x)}{Z(s,\beta)} e^{\beta\lambda(x,s)}$$



E.g. exponential *P(s)*



E.g. bimodal *P(s)*

Summary

- Metabolic diversity from dynamics
- Beyond bulk properties: probability densities on the flux polytope (with some simplifying assumptions)
- Bacterial populations close to maximizing diversity at given fitness
- Diversity as optimal response (e.g. in fluctuating media)
- **This half:** distributions that are "optimal" (in some sense)
- **Next half:** learning distributions from data (and see how far they are from optima)

POLITECNICO DI TORINO

MARIE CURIE ACTIONS

Italian Institute for Genomic Medicine IIGM

joint work with ***D De Martino (BFI Bilbao), AP Muntoni (IIGM)****,*
A Braunstein, A Pagnani, T Gueudrè, M Miotto, F Capuani
&
many more