molecular systems biology

Published online: August 3, 2016

# Negative frequency-dependent interactions can underlie phenotypic heterogeneity in a clonal microbial population

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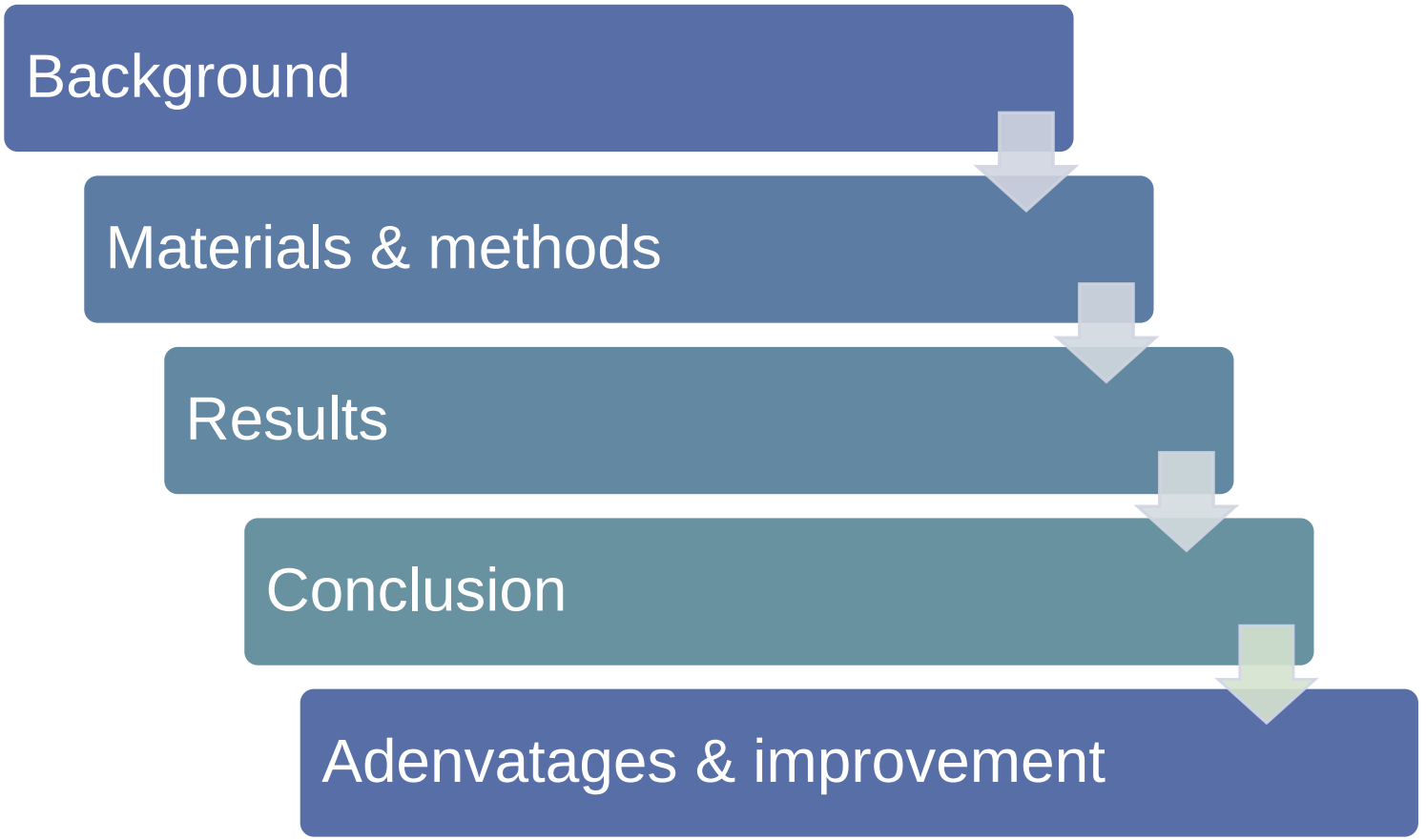
2016/12/14

# Workflow


Background
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Adenvatages & improvement

# Noun explanation

- Evolutionarily stable strategy（ESS）
- Frequency-dependent selection
- Negative interactions
- Evolutionarily stable mixed strategies
- Clonal microbial population-------CMP

# Background

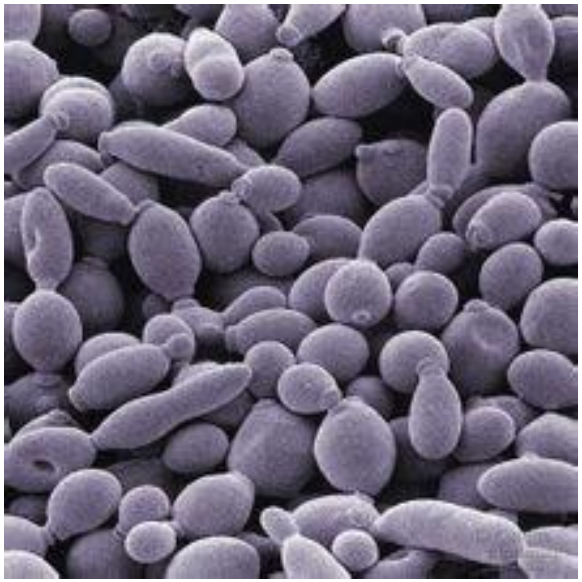
- Stochastic gene expression is ubiquitous in CMP----the coexistence of distinct phenotypes among genetically identical cells

- Heterogeneity in CMP is thought to be a bet-hedging response to environmental uncertainty

- Evolutionary game theory predicts that **phenotypic heterogeneity may also be a response to negative frequency-dependent interactions** that favor rare phenotypes over common ones

- There is a lack of experimental evidence for such interactions as a driving force of phenotypic heterogeneity in CMP

# Materials



- Saccharomyces cerevisiae

  wild-type mixed strategist,
  GAL-OFF specialist,
  GAL-ON specialist

derived from the diploid W303 strain of S. cerevisiae

# Methods

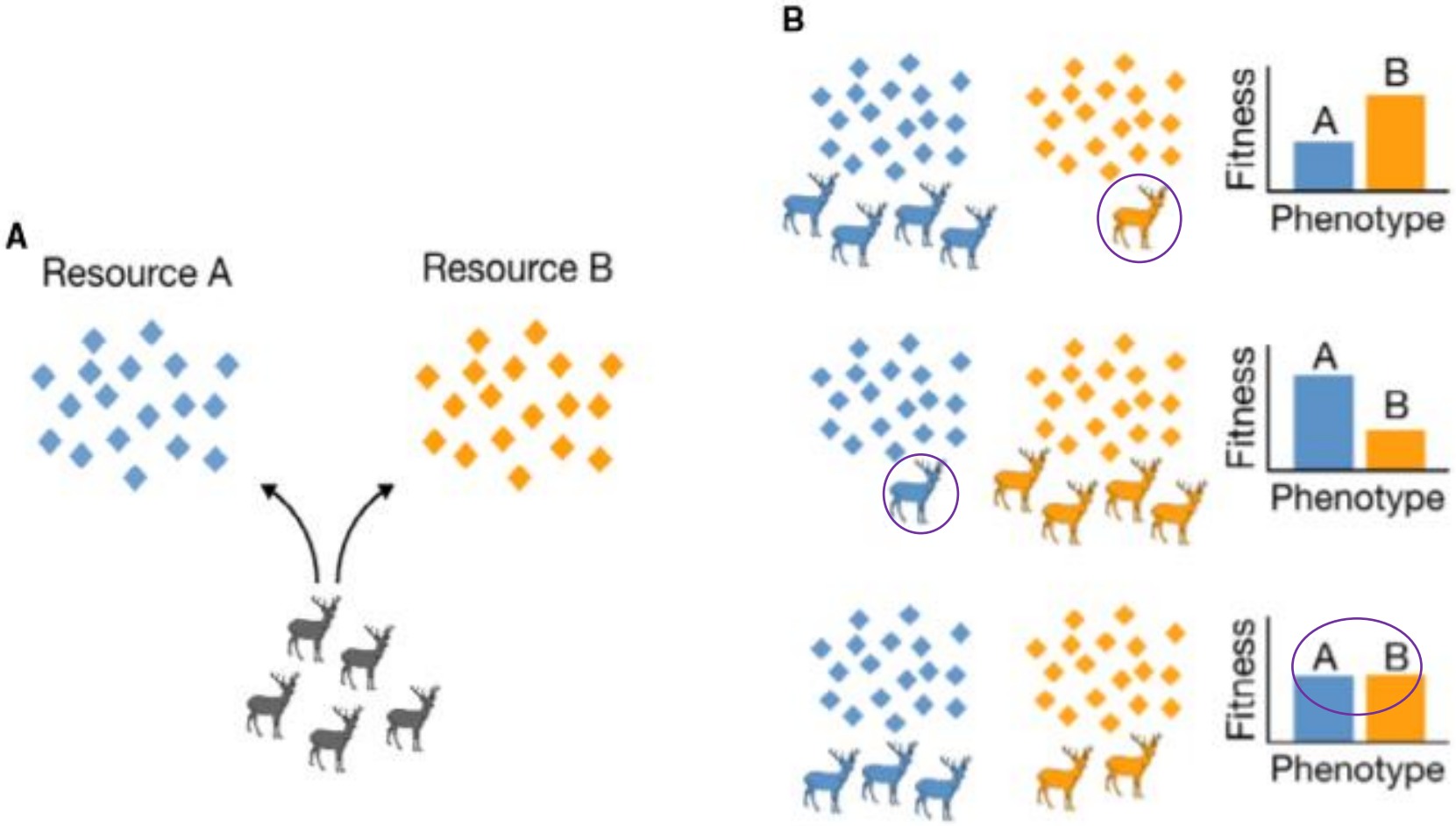
- 流式细胞术（flow cytometry,FCM）是利用流式细胞仪进行的一种单细胞定量分析和分选技术。流式细胞术是单克隆抗体及免疫细胞化学技术、激光和电子计算机科学等高度发展及综合利用的高技术产物。最大的优点是对混合细胞群体中亚群细胞的计数。

- 影印培养法（replica plating）是使在一系列培养皿的相同位置上能出现相同菌落的一种接种培养方法。

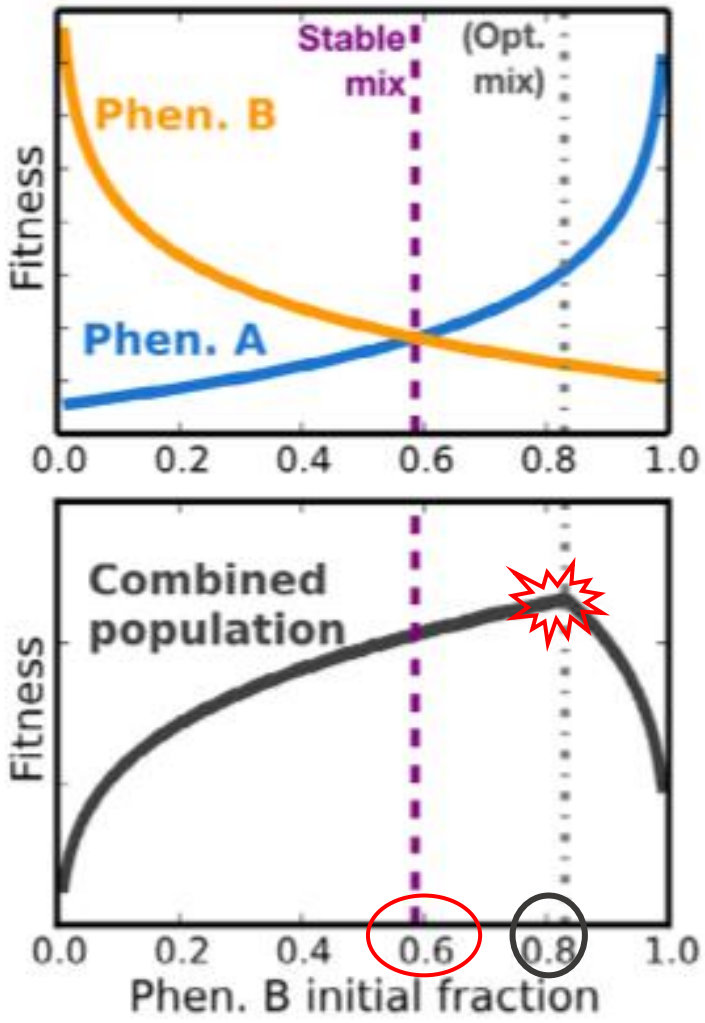
- Relative fitness for each strain was calculated as follows:

$$W_{rel} = \ln\left[\frac{OD_f * f_f}{OD_i * f_i}\right] / \ln\left[\frac{OD_f * (1 - f_f)}{OD_i * (1 - f_i)}\right]$$

Figure 1. Negative frequency-dependent interactions exist in a simple foraging game with multiple resources.



C


Stable mix
(Opt. mix)
Phen. B
Phen. A
Fitness
0.0
0.2
0.4
0.6
0.8
1.0
Combined population
Fitness
0.0
0.2
0.4
0.6
0.8
1.0
Phen. B initial fraction

D

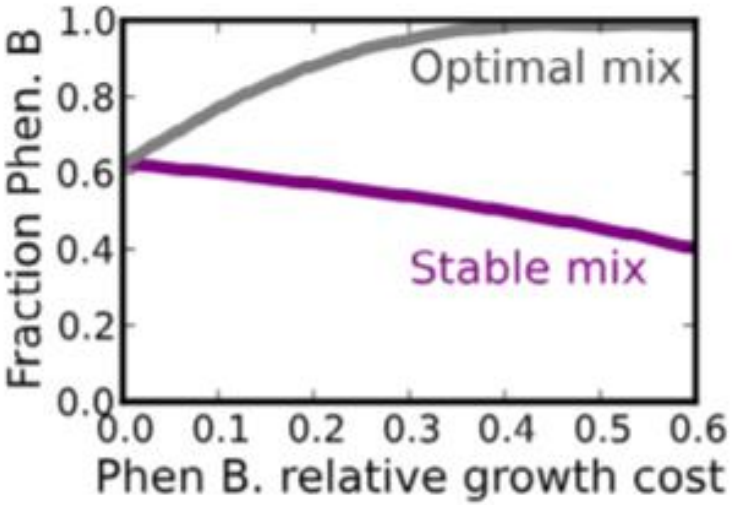
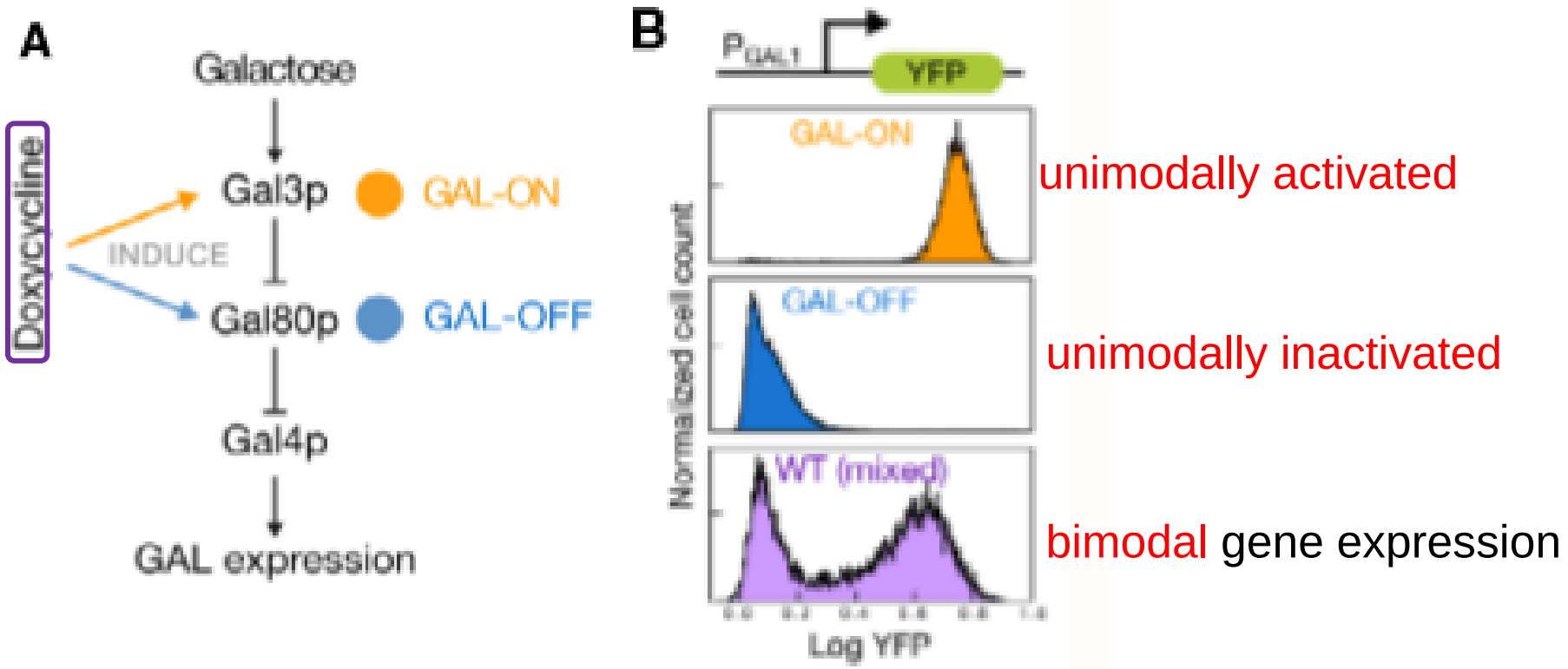
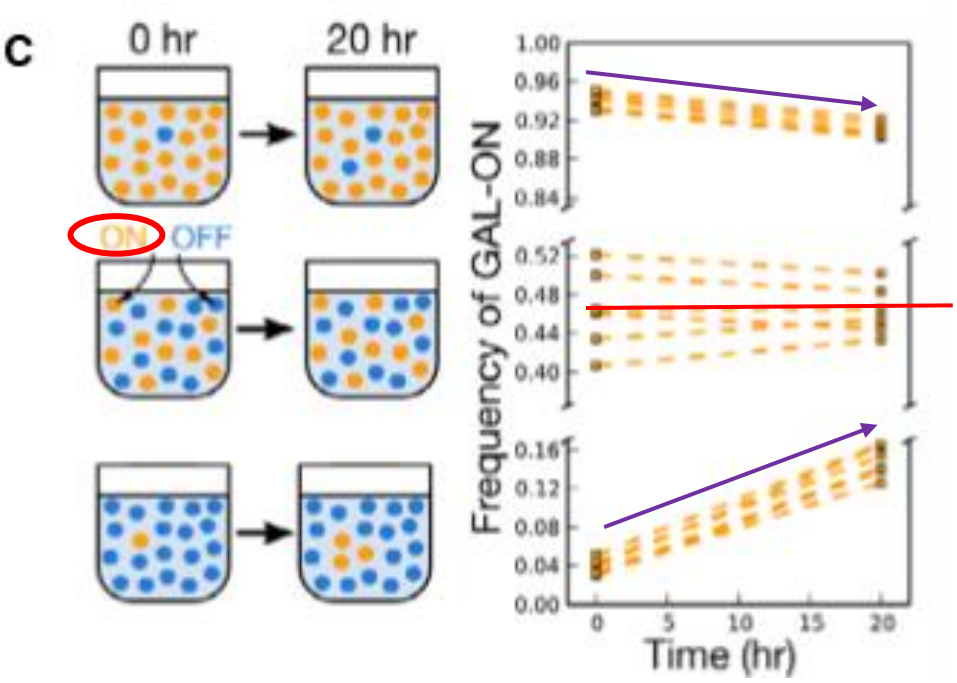

Optimal mix
Stable mix
Fraction Phen. B
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Phen B. relative growth cost

**Figure 2. Yeast GAL network ON and OFF phenotypes are mutually invasible in mixed glucose and galactose.**

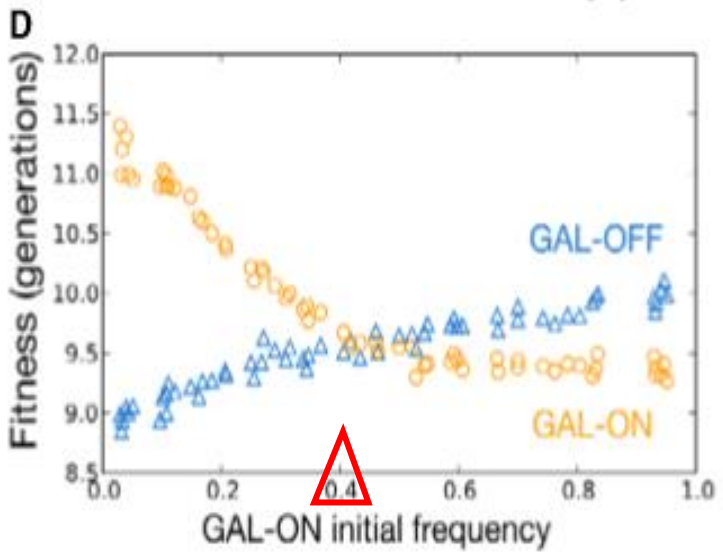


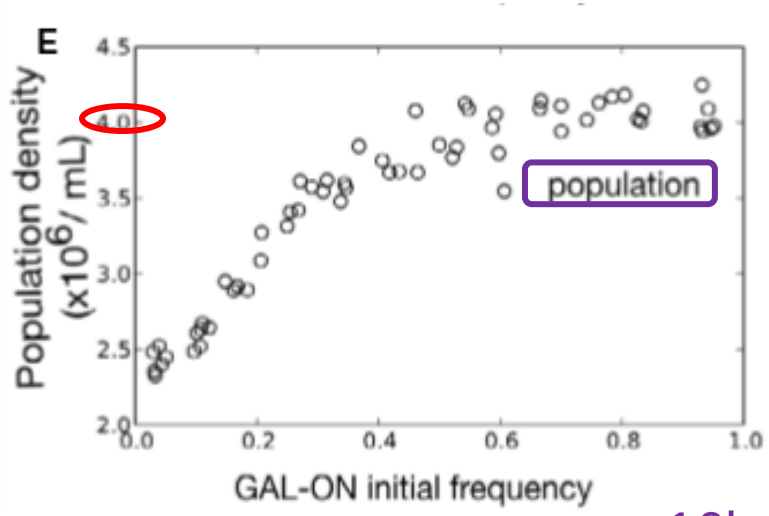

mixed sugar environment (0.03% (w/v) glucose, 0.05% (w/v) galactose, 1 lg/ml doxycycline), 10h

带有RFP标签的GAL-OFF以及带有GFP标签的GAL-ON菌株的【6个重复对】在60个不同的初始频率下，20h



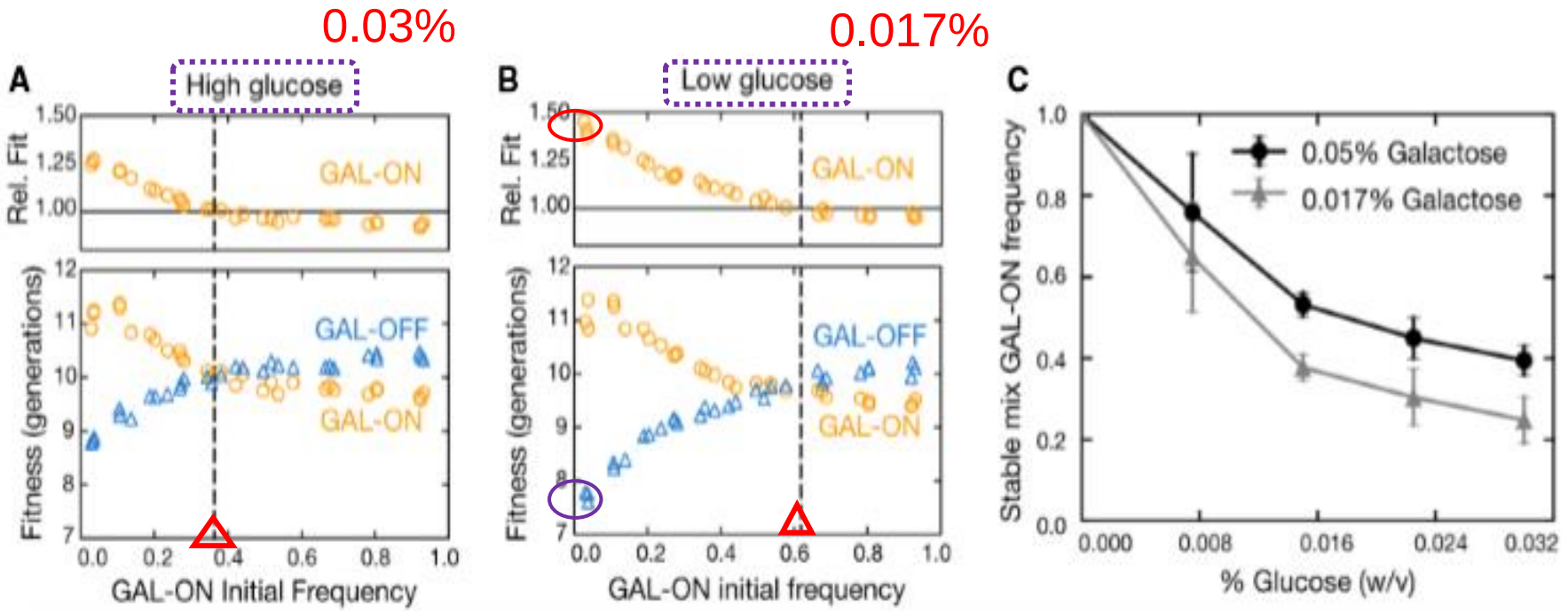

虚线： (0h-20h)整体频率变化的方向




16h

**Figure 3. Altering sugar concentration adjusts phenotypic fitness and equilibrium fractions accordingly.**




30 different populations ; 0.05% galactose

we replicated the **initial competition** of our two pure strategists in **eight** different concentrations of glucose and galactose.

**Figure 4. Wild-type mixed strategist invades both pure strategists and is uninvasible by either.**

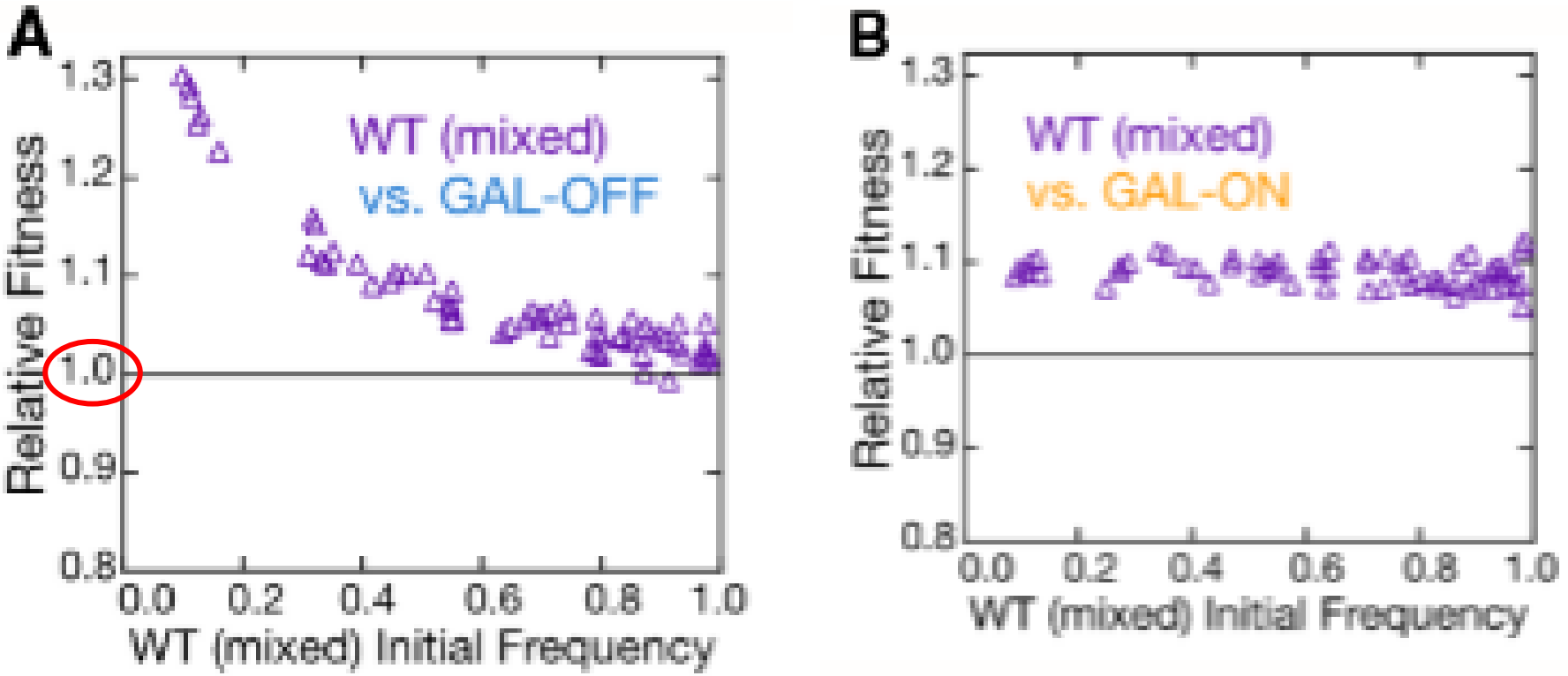
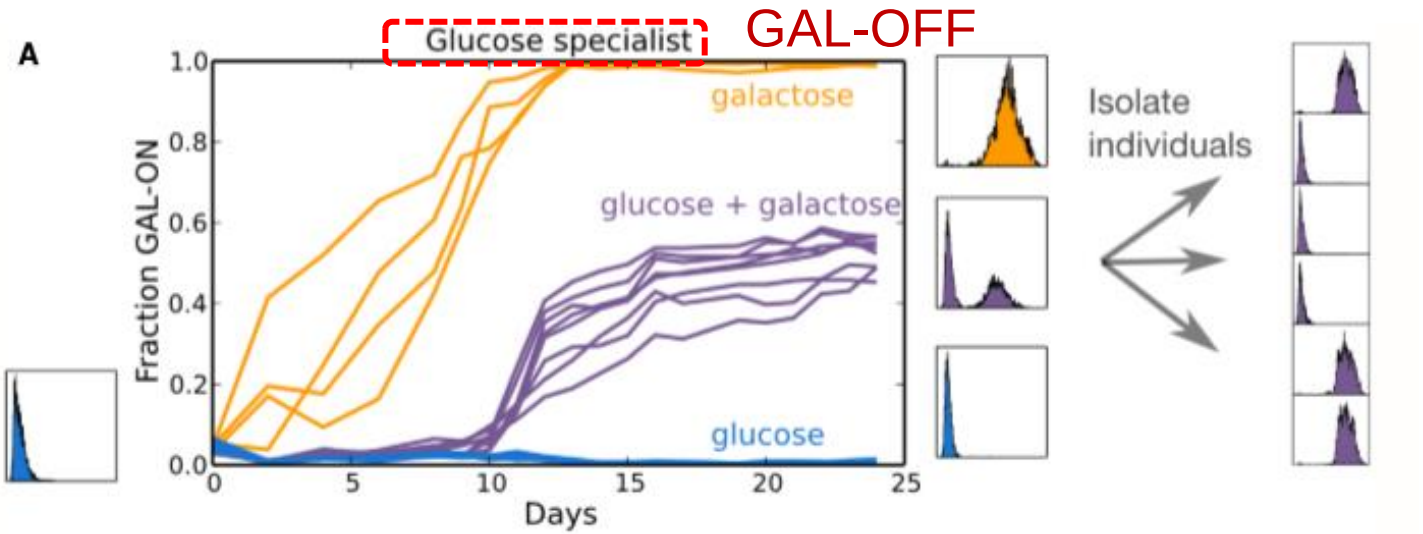
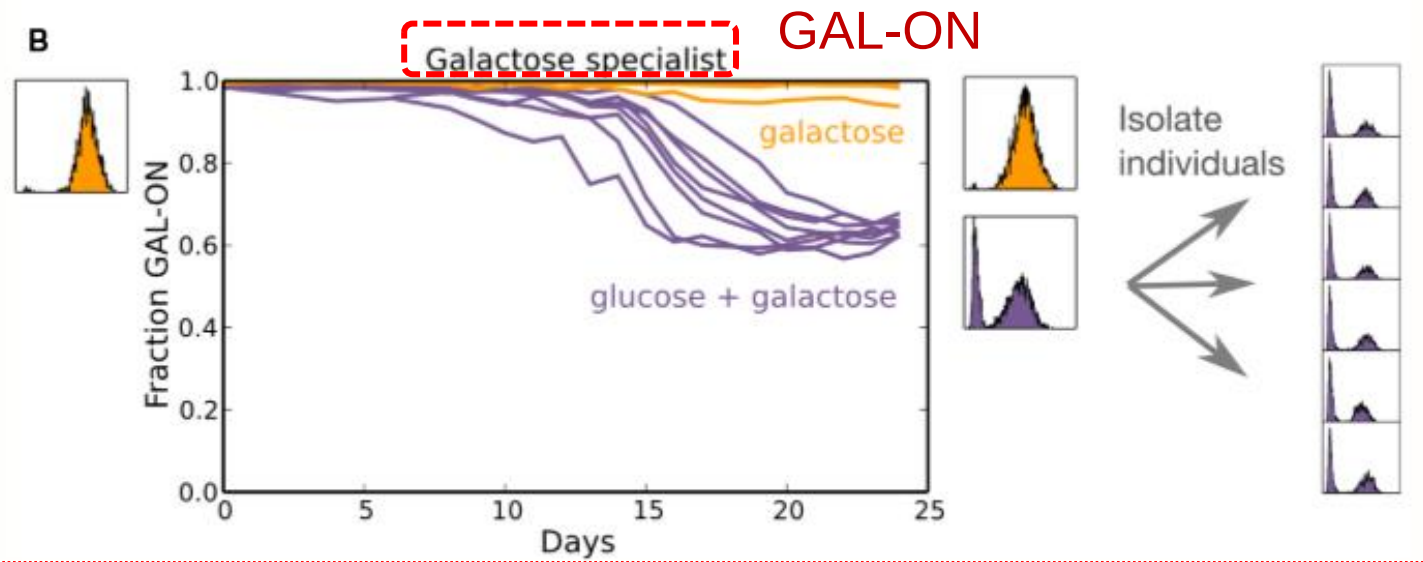


Figure 5. Frequency dependence from a mixed resource environment drives the evolution of both phenotypic and genetic heterogeneity.




各8个重复




0.1% glucose , 0.1% galactose , 0.03% glucose&0.05% galactose

# Conclusion

- 微生物群体中表型多样性可能作为负频率依赖互作的结果，称为“进化稳定混合策略”（最初用于描述动物冲突中的鹰-鸽模型）

- 表型多样性是生物用来应对负频率互作的一个稳定混合策略。多资源觅食游戏中的互作可以驱动同基因的微生物群体中的表型多样性，但还有待观察负频率依赖到底到什么程度才是同基因的群体中广泛的表型多样性存在的原因。

- 由负频率依赖引起的进化稳定混合策略，在资源消耗过程中，对于群体增长不是最佳的策略。

- 野生型混合策略(W303菌株)不能被任意一个纯策略侵入。

## 优点：

- 这是第一个实验证据关于在多资源觅食游戏中的互作可以驱动同基因的微生物群体中的表型多样性。
- 巧妙地实验设计，在研究的很透彻地酵母GAL网络进行实验
- 在多个层面上，进行了分析验证，表型多样性是一个响应负频率互作的稳定混合策略。

## 可改进处：

- 此工作都是在实验室中完成。虽然在实验室里，表型间可以相互入侵，但不能说，这些条件就是W303野生型GAL网络的实际进化
- 使用纯策略的菌株不是各自野生型表型的完美近似
- 不能排除在酵母GAL网络中，两面下注策略可能对于观察到的表型多样性是一个共贡献者
- 还有待观察负频率依赖到底到什么程度才是同基因的群体中广泛的表型多样性存在的原因

# Thank You