Systematic discovery of drug interaction mechanisms

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Abstract

- To uncover the causes of drug interactions
- We found that drug interactions highly robust to genetic perturbation
- Small molecule adjuvants targeting these functions synthetically reshape drug interactions in predictable ways.

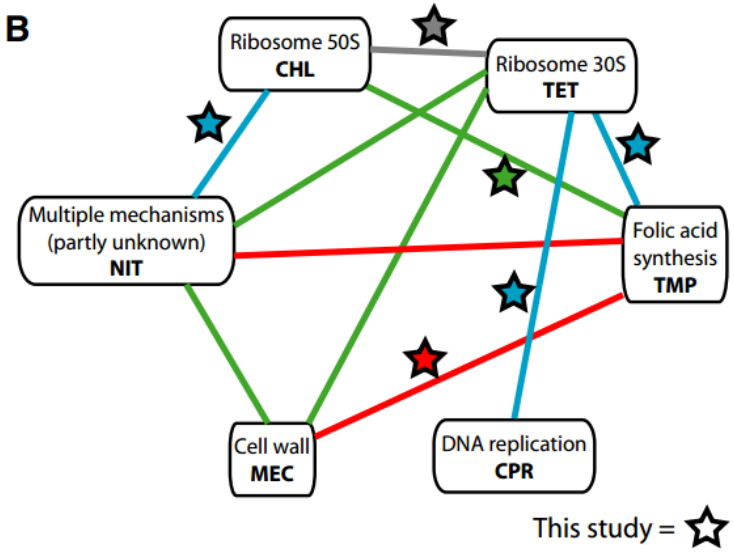
Materials

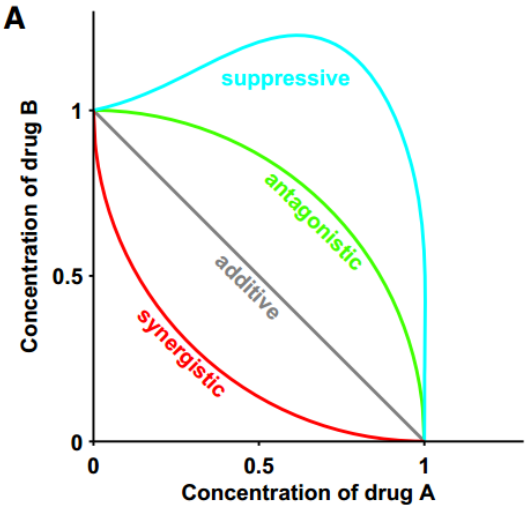
- Escherichia coli strains with kanamycin resistance marker
- Low-copy-number plasmid (pUA66）
- Antibiotics from Sigma-Aldrich
- Adjuvants

Materials

Table 1. Antibiotics used in this study.

Abbreviation	Drug	Mode of action (known target)	Concentration
CHL	Chloramphenicol	Protein synthesis (50S ribosome subunit)	1 μg/ml
CPR	Ciprofloxacin	DNA replication (gyrase)	4 ng/ml
MEC	Mecillinam	Cell wall (Penicillin Binding Protein)	38 ng/ml
NIT	Nitrofurantoin	Multiple mechanisms	2 μg/ml
TET	Tetracycline	Protein synthesis (30S ribosome subunit)	150 ng/ml
TMP	Trimethoprim	Folic acid synthesis (DHFR)	80 ng/ml





Methods

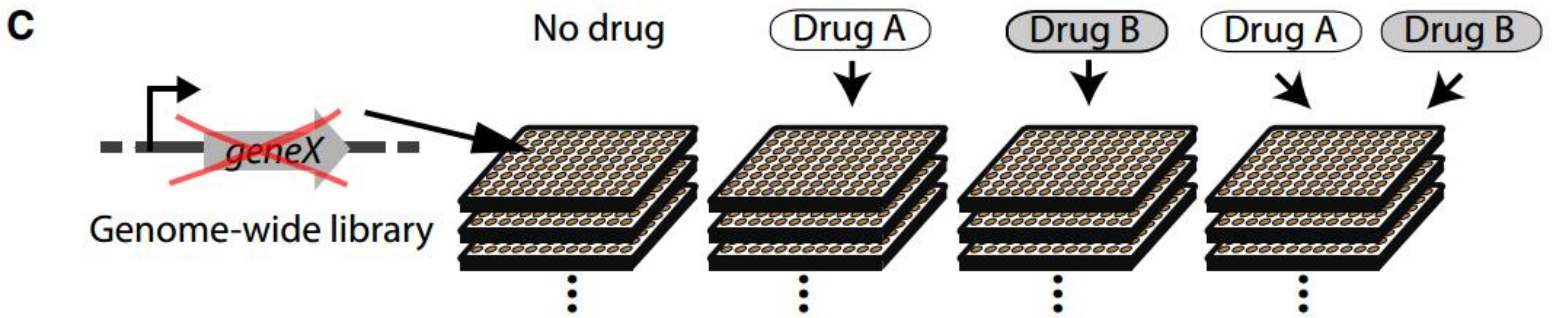


Plate containing 200μl medium.PRE: plates were shaken on a magnetic shaker at 900 rpm for 20 s. Cultures were inoculated using a replicator transferring ~0.2 μl from aovernight culture kept at -80° C with 15% glycerol.The plates were incubated in an automated incubator (Liconic Storex) kept at 30° C, > 95% humidity, and shaken at 720 rpm,for ~20h.

Methods

- Growth rate measurements
- Two-drug response surfaces
- Expected growth rate in drug combinations
- Gene ontology enrichment analysis

Methods-Growth rate measurements

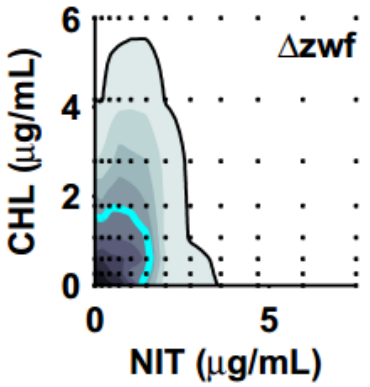
- The growth rate in exponential phase was quantified from the OD increase over time by a linear fit of log(OD) in the range 0.022 < OD < 0.22

For the representation of two-dimensional response surfaces, we used the optical density 12 h after inoculation instead of the growth rate because this quantity was slightly more reproducible and yielded smoother response surfaces; this representation does not affect any of the conclusions on drug interaction changes

Methods-Two-drug response surfaces

$$c = c_{max} \frac{x^3 + ax}{1 + a}$$

- c_{max} was the highest concentration used,
- x was linearly spaced from 0 to 1 with 8, 12, or 24 stepsdepending on the experiment,
- a = 1/3



Methods-Expected growth rate in drug combinations

$$r^i(a) = \frac{g^i(a)}{g^i(0)}$$

$g^i(a)$ denote the growth rate of mutant i in the presence of drug A

$g^i(0)$ denote the growth rate of mutant i in the absence of drug A

$$r^{\mathrm{WT}}(a^i_{\mathrm{eff}}) = r^i(a)$$

a^i_{eff} —— effective concentration

$$\alpha^i = a^i_{\mathrm{eff}}/a$$

$$\beta^i = b^i_{\mathrm{eff}}/b$$

$$\gamma^i = g^i(0)/g^{\mathrm{WT}}$$

$$I^{\mathrm{WT}}(a,b) = \frac{r^{\mathrm{WT}}(a,b)}{r^{\mathrm{WT}}(a)r^{\mathrm{WT}}(b)}$$

$$g^i(a,b) = g^i(0) \cdot r^i(a) \cdot r^i(b) \cdot I^{\mathrm{WT}}(a^i_{\mathrm{eff}}, b^i_{\mathrm{eff}})$$

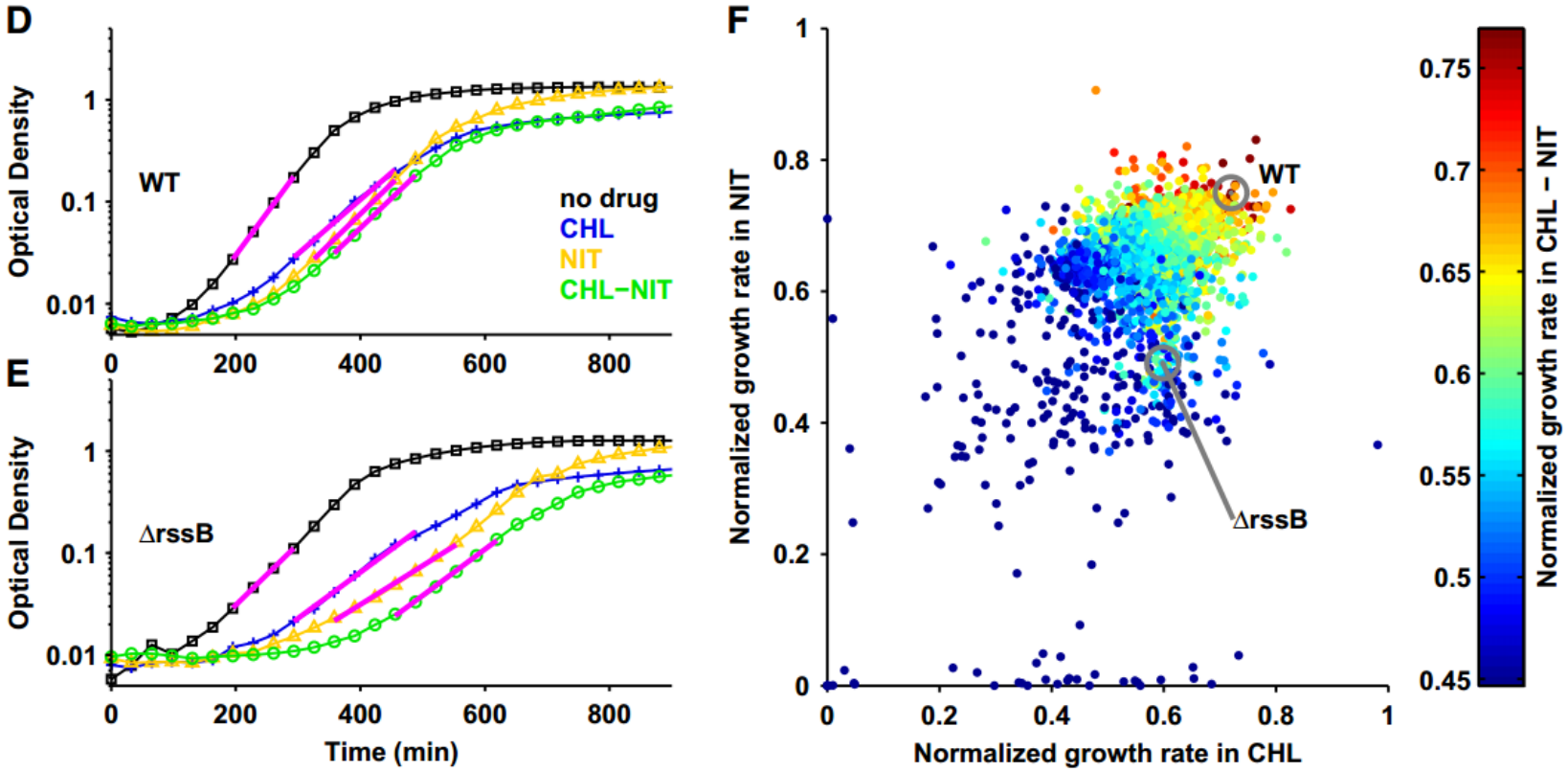
this equation formalizes the assumption that the interaction coefficient is a universal invariant and, for all mutants, is the same as in the WT at the effective drug concentrations.

Methods-Gene ontology enrichment analysis

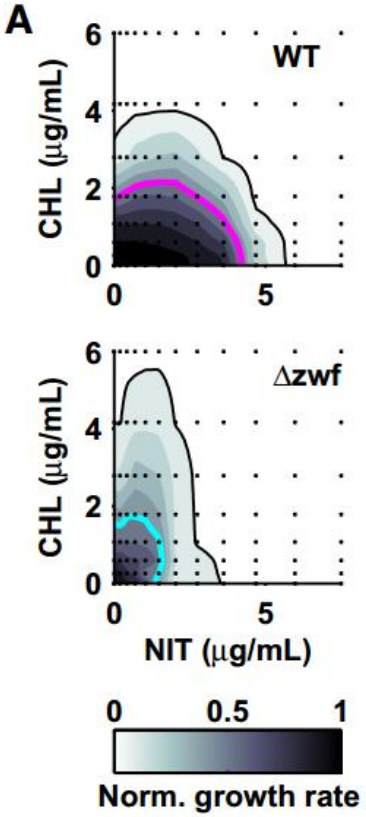
- 分子生物学上的功能
- 生物学途径
- 在细胞中的组件作用

Results & Discussion

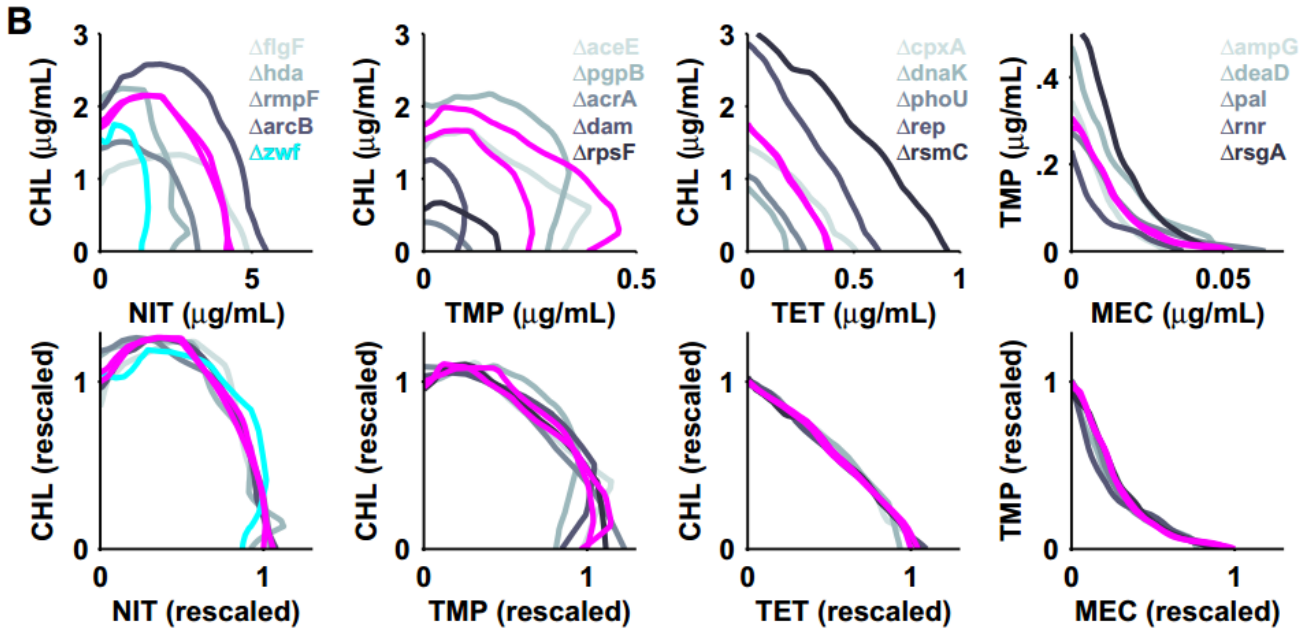
drug interactions highly robust to genetic perturbation



Results & Discussion

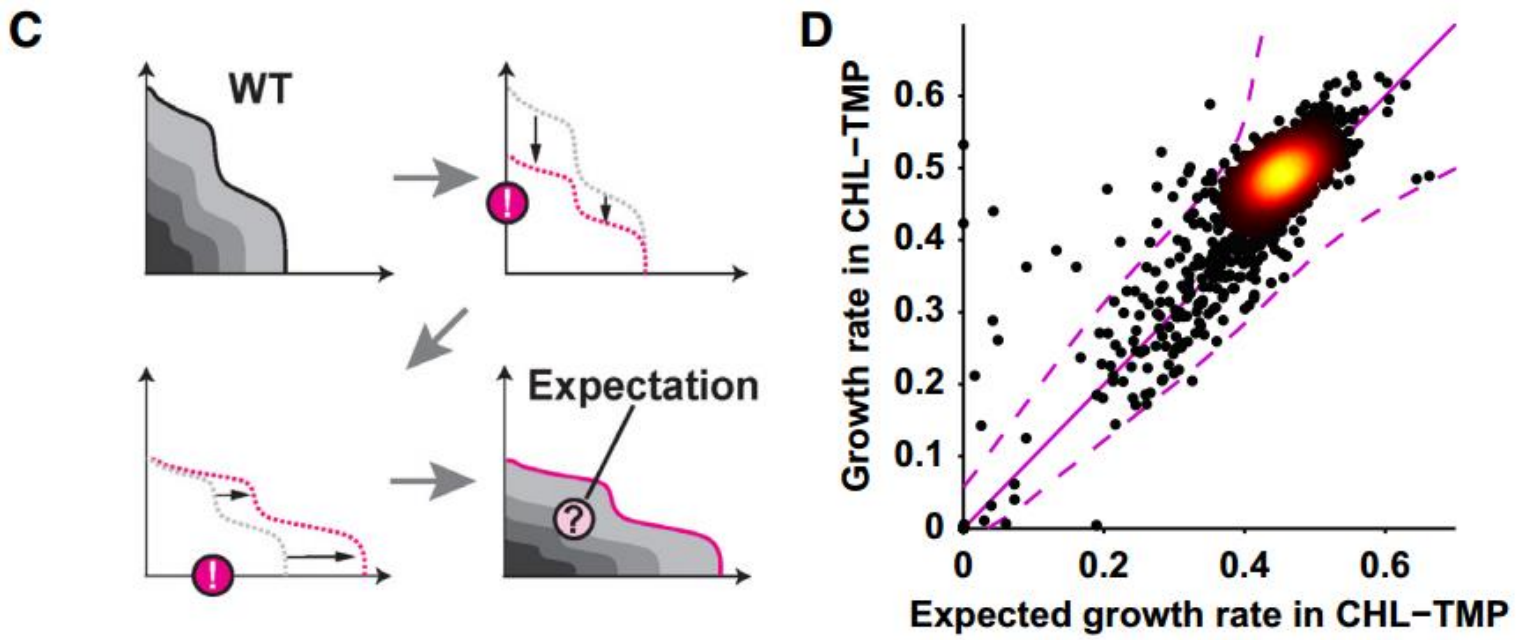


drug interactions affect by rare genetic perturbation



drug interactions highly robust to the most of genetic perturbation

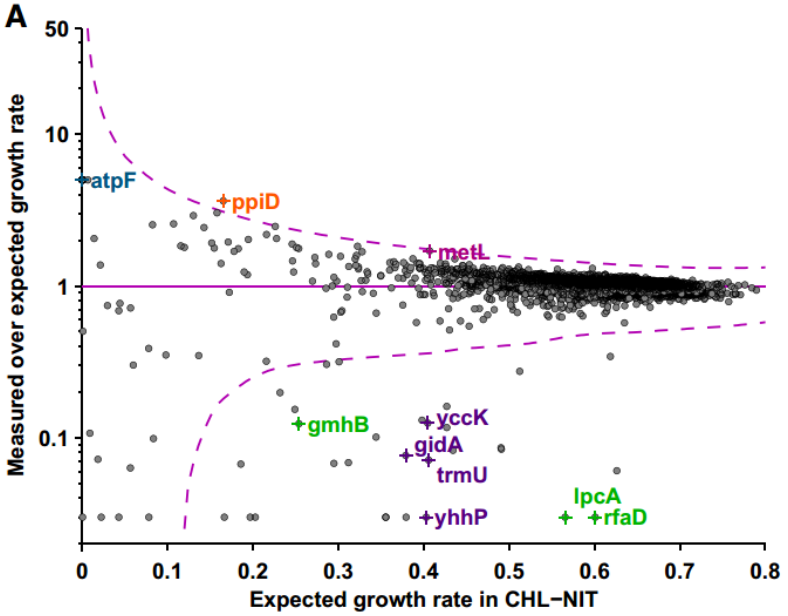
Results & Discussion



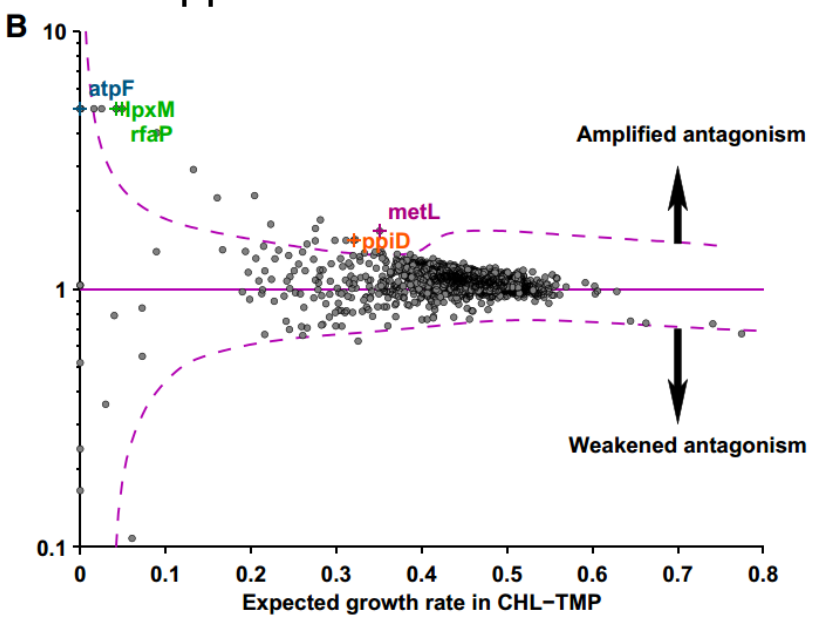
faithfully followed robustness

Results & Discussion

chloramphenicol–nitrofurantoin suppression was weakened or entirely removed in most mutants affecting this interaction

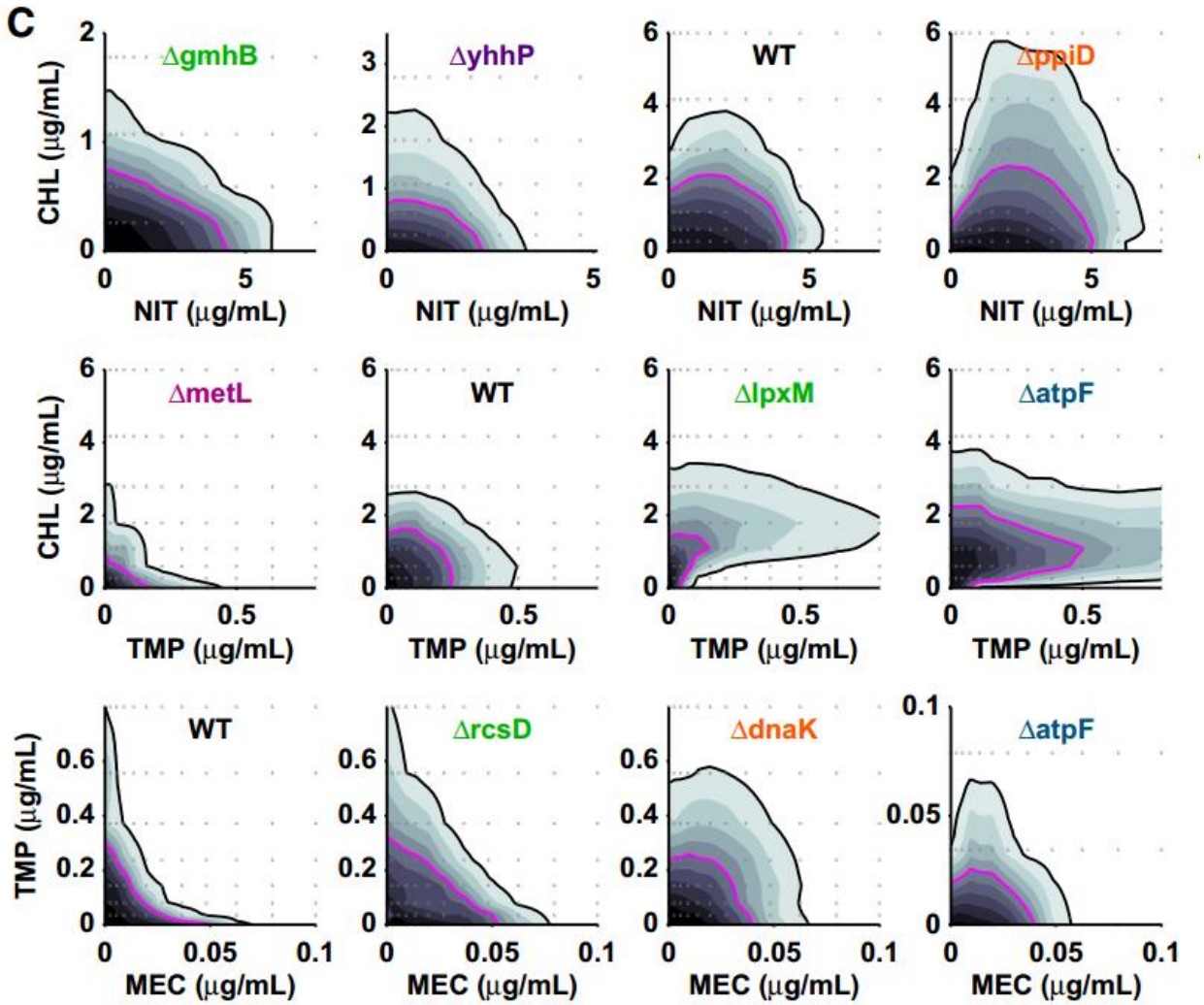


chloramphenicol–trimethoprim antagonism was often amplified to suppression



Results & Discussion

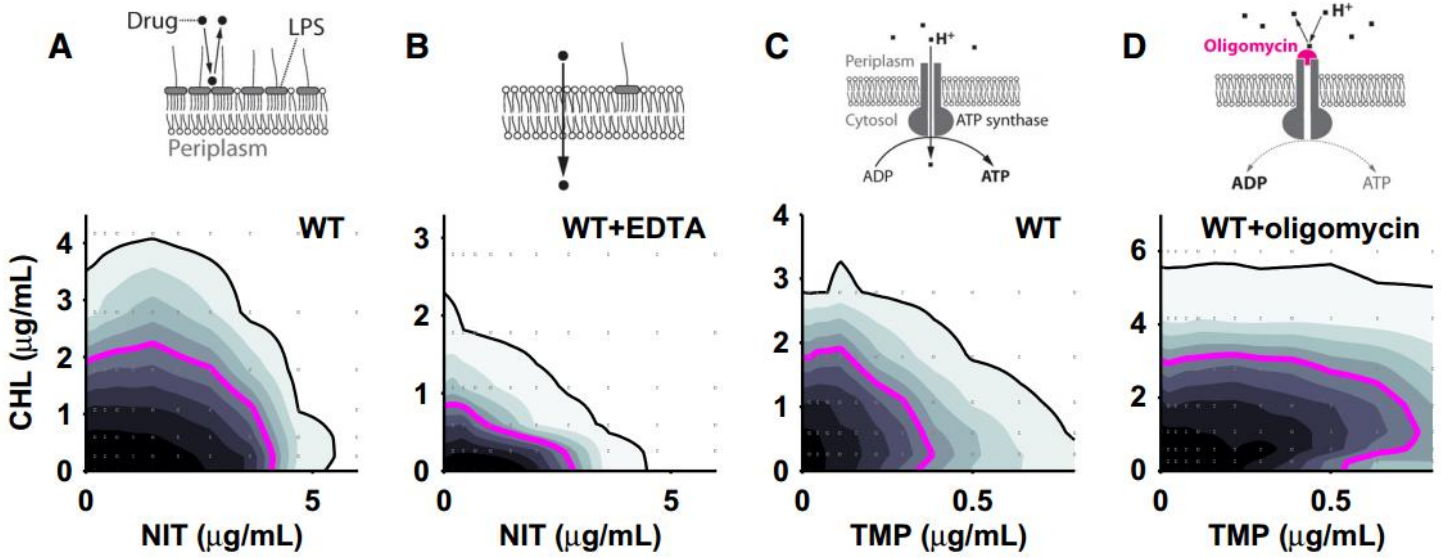
difference between WT and mutant strains on drug interactiuon



Results & Discussion

Polysaccharide synthesis

ATP synthesis



suppressive→additive

antagonistic→suppressive

个人总结

- 结论
- 作者得出一个普遍规律：大多数药物的互做对基因扰动是稳定的。少数基因突变会改变药物互做反应。在多糖合成和ATP合成中可以通过影响非靶标途径，改变药物互作机制。

个人总结

- 创新点
- 作者用系统的方法，从药物分子在生物学上的功能出发，研究了结合了其生物学途径、在细胞中的组件作用，最终发现规律。这种以小见大，是他们的一种新思路。

个人总结

- 启发
- 1.作者做研究的全局性值得我们学习，因小见大，不被微观研究局限；
- 2.作者欲将他发现的规律，像物理规律一般，能有普适性。我们在研究中，也不要仅停留在表象，要有一颗深入研究的心，找到事物本质联系。

个人总结

- 改进
- 作者研究了药物互做机制，如何从拮抗转化到抑制，其实可以进一步研究，看能不能找到一些佐剂，再转化到加成或者协作。
- 作者没有明确讲述所使用的基因突变的类型，不同位置的突变可能对药物互做的影响不同，没有做分类说明，这个可以进行分类，排除突变造成的差异影响对药物互作影响的判断。

- Thank you