Literature Report

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Article

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Stress-response balance drives the evolution of a network module and its host genome

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Subject Categories Quantitative Biology & Dynamical Systems; Synthetic Biology & Biotechnology; Evolution

- **Background**
- **Biological Problems**
- **Materials & Methods**
- **Results**
- **Comments**

Background

Keywords drug resistance; experimental evolution; positive feedback; synthetic gene circuit; tradeoff

耐药性（drug resistance）又称抗药性，系指微生物、寄生虫以及肿瘤细胞对于化疗药物作用的耐受性，耐药性一旦产生，药物的化疗作用就明显下降。当长期应用抗生素时，占多数的敏感菌株不断被杀灭，耐药菌株就大量繁殖，代替敏感菌株，而使细菌对该种药物的耐药率不断升高。

Background

- 合成生物学（synthetic biology）是基于生命系统的工程技术，旨在设计、构建自然界不存在的生命或使已存在生命具有新功能。可为系统生物学的定量分析提供模式生物。
- 生物砖（biobrick）是标准化的基因元件，是具有可连接性末端（前后缀）的基因元件。
- 基因回路（genetic circurt）与电子科学中的电路相似，在合成生物学中，不同功能的生物砖联接后，能像电路一样运行。

Biological Problems

- Stress response genes and their regulators form networks that underlie drug resistance. They can quickly emerge in the genomes of infectious microbes and cancer cells, protecting them from treatment.
- Yet, the evolution of stress resistance networks is not well understood.
- How mutations alter stress response networks to improve fitness under such circumstances, how quickly, especially in phenotypically heterogeneous populations.

?

Materials & Methods

Material:

Haploid *Saccharomyces cerevisiae* strain YPH500

Methods:

- Using a two-component synthetic gene circuit integrated into the budding yeast genome to model experimentally the adaptation of a stress response module and its host genome in three different scenarios.
- Developing two computational models to predict specific aspects of evolutionary dynamics in six different environmental conditions.

Results

- Gene regulatory networks that control the expression of stress-protective genes.
- Cells can survive because they respond to stress.
- However, stress-protective gene expression can be costly or toxic in the absence of stress, or even in the presence of stress when the expression level exceeds the requirement for survival.
- Overall, the costs and benefits of survival mechanisms create a tradeoff between maximizing growth while also ensuring survival during stress.

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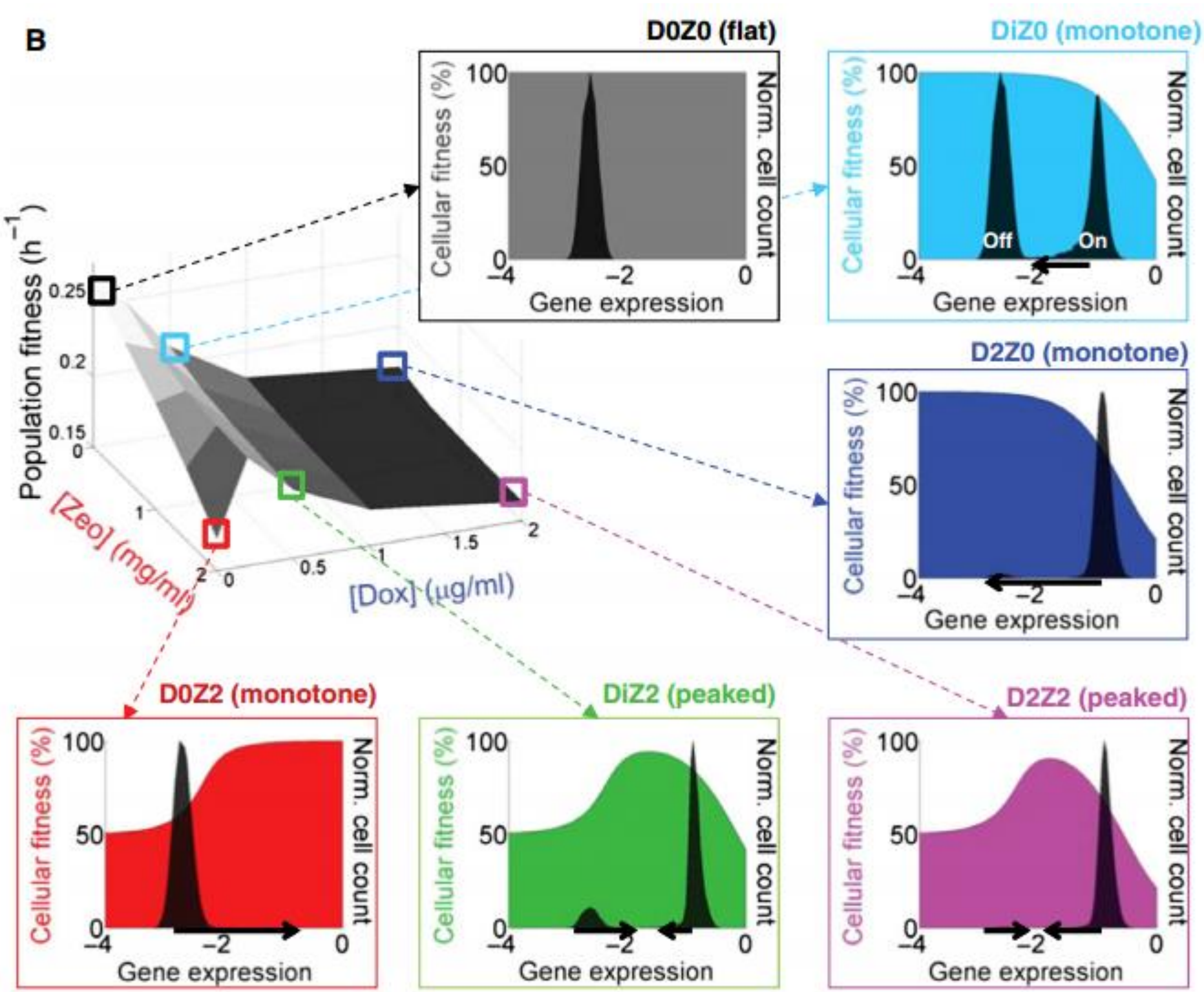

- Gene expression is measured as $\log_{10}$(fluorescence).
- DxZy denotes the environment.(the x and y indicate lg/ml doxycycline and mg/ml zeocin concentrations, respectively.)
- Cellular fitness (cell division rate) is a function of gene expression.

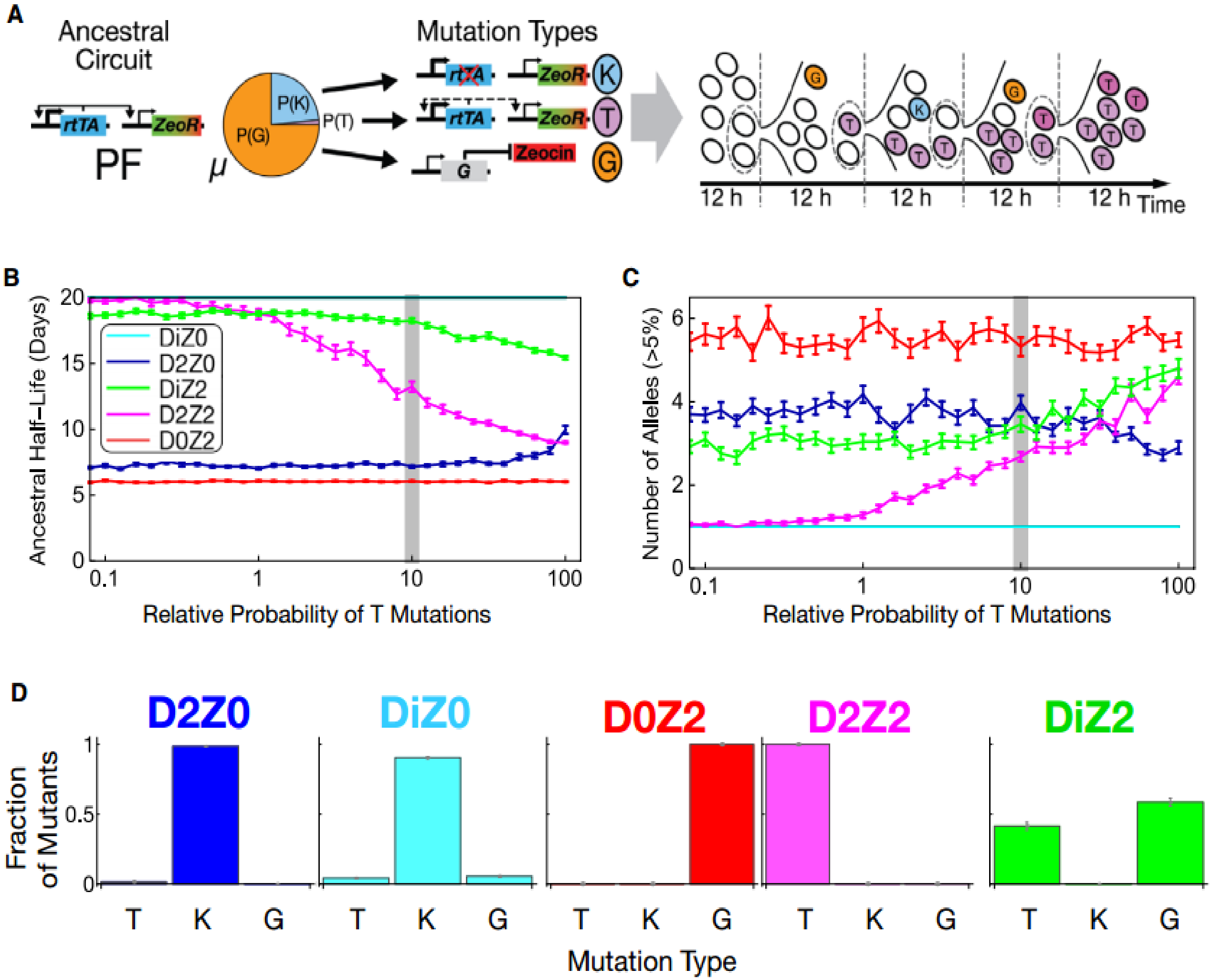

Figure 2. Simulation framework predicts evolutionary dynamics.

A

- Simulating the initial steps of evolution.

B

- The speed at which mutants.

C

- Number of established mutations.

D

- Population fractions of T-, K-, and G-type mutations at day 20.

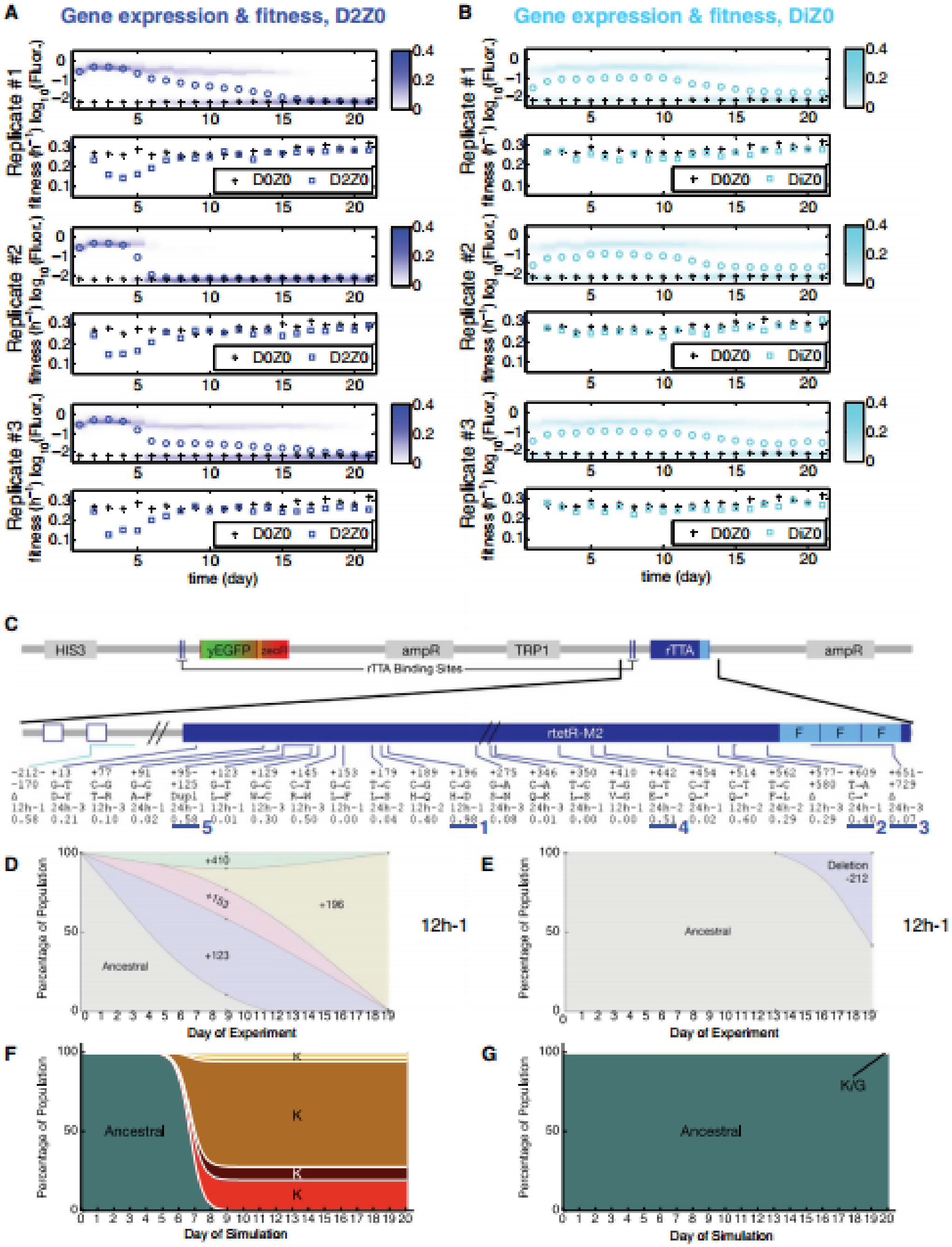

Figure 3. Evolutionary dynamics of PF cells in D2Z0 and DiZ0, corresponding to scenario (i): futile response to harmless signal.

Scenario (i): reproducible circuit failure from gratuitous circuit response

A

- Time-dependent changes in the fluorescence distributions.
- Both the fluorescence and fitness were significantly different in populations evolving in D2Z0 compared at Days 4 and 21 (t-test).

B

- Pairwise comparisons with the same days in D0Z0 showed no significant fitness differences.

C

- Intra-rtTA mutations observed in conditions D2Z0 (blue lines) and DiZ0 (light blue lines) mapped along the rtTA activator.

D, E

- Time-dependent allele frequencies for mutations observed in conditions D2Z0 (D), and DiZ0 (E).

F, G

- Time-dependent allele frequencies from simulations using mutation parameter values.

$\log_{10}$[(fluorescence with doxycycline)/(fluorescence without doxycycline)]

$\log_{10}$[(fitness with zeocin)/(fitness without zeocin)]

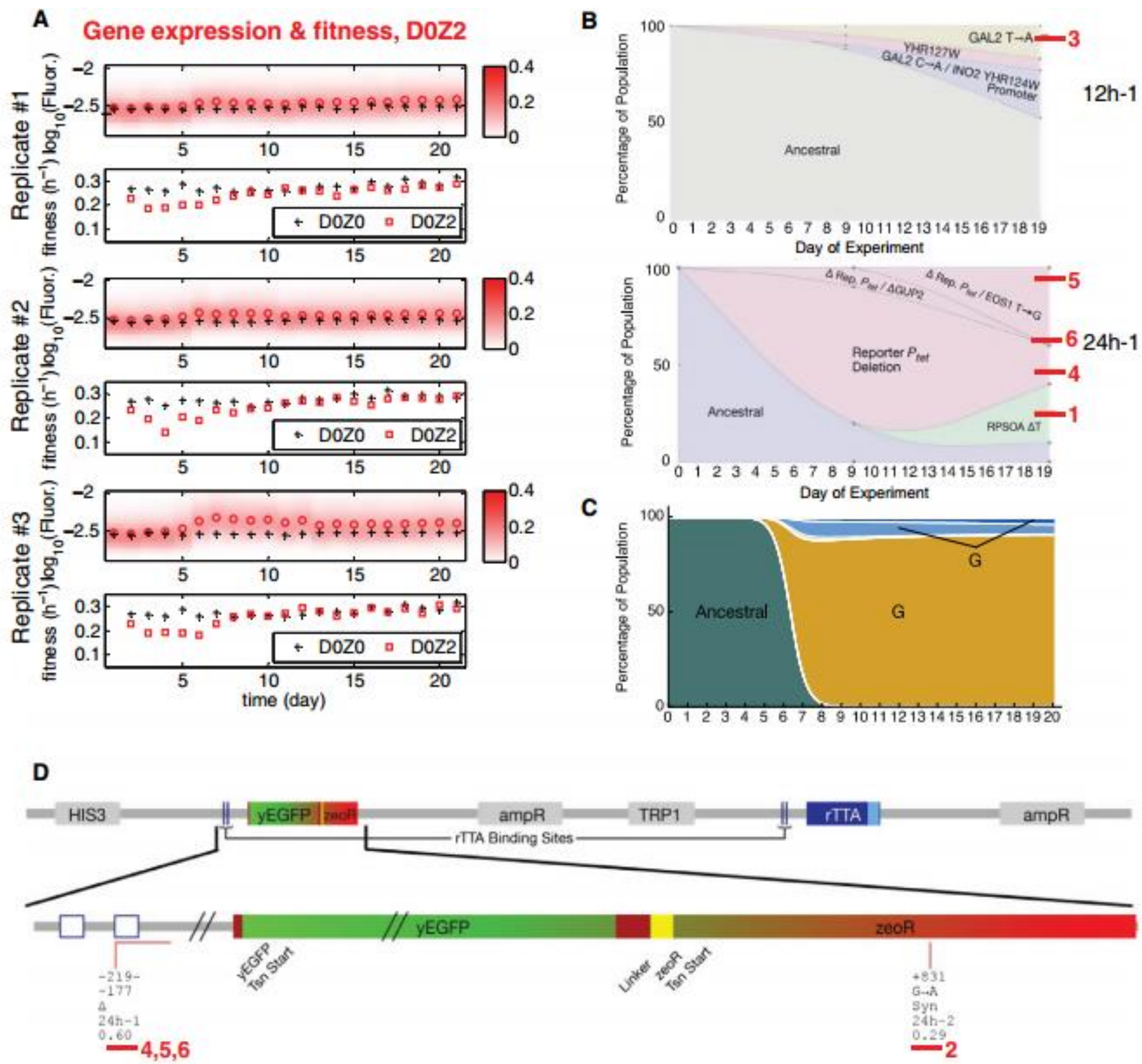

Figure 4. Evolutionary dynamics of PF cells in D0Z2, corresponding to scenario (ii): lack of response when needed.

Scenario (ii): gaining gene expression for an initially unresponsive gene circuit

A

- Time-dependent changes in the fluorescence distributions
- Both the fluorescence and fitness were significantly different in populations evolving in D0Z2 when compared at days 4 and 21.

B

- Time-dependent allele frequencies for mutations observed in condition D0Z2.

C

- Time-dependent allele frequencies from simulations using mutation parameter values.

D

- Extra-rtTA, but intra-circuit mutations observed in condition D0Z2 (red lines) mapped along *yEGFP::zeoR*.

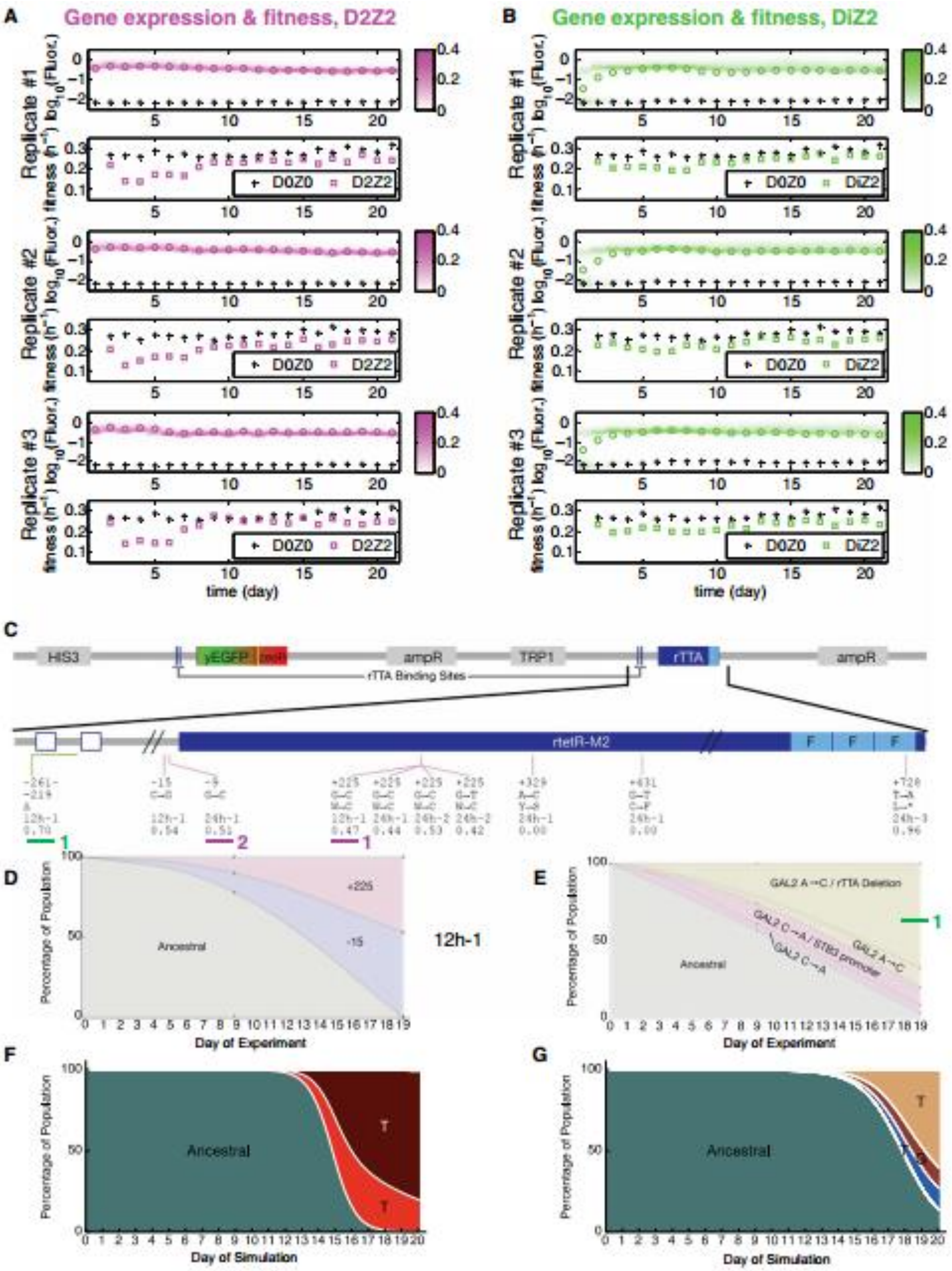

Figure 5. Evolutionary dynamics of PF cells in D2Z2 and DiZ2, corresponding to scenario (iii): suboptimal response.

Scenario (iii): optimization of gene expression under opposing evolutionary pressures

A

- Time-dependent fluorescence distributions.
- Both the fluorescence and fitness were significantly different in populations evolving in D2Z2 when compared at days 4 and 21.

C

- Intra-circuit mutations observed in conditions D2Z2 (magenta lines) and DiZ2 (green lines) mapped along the rtTA activator.

D, E

- Time-dependent allele frequencies for mutations observed in conditions D2Z2 (D) and DiZ2 (E).

F, G

- Time-dependent allele frequencies from simulations using mutation parameter values.

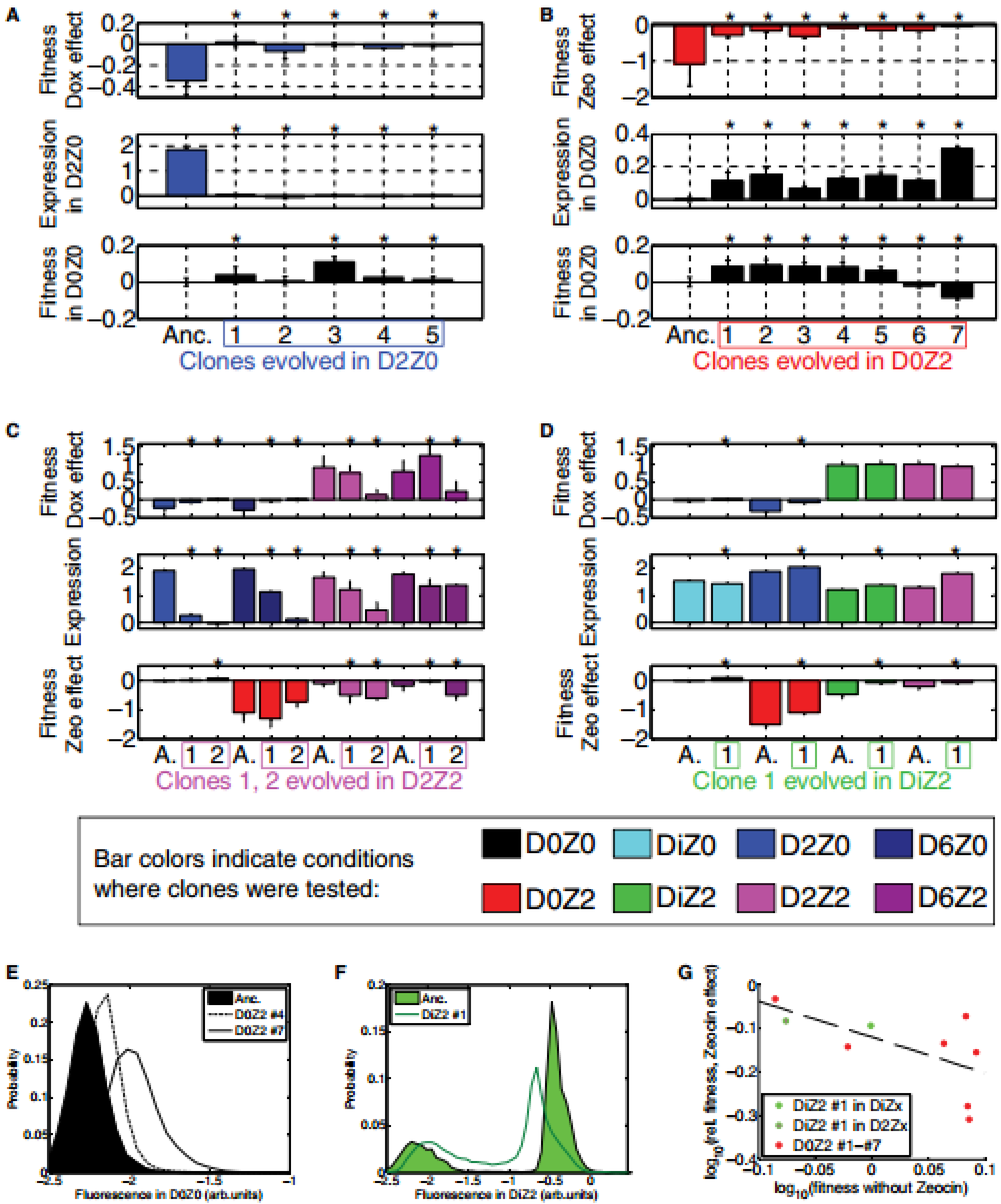

Figure 6. Gene expression and fitness characteristics of clonal isolates from various evolved populations.

A
- Phenotype of clones evolved in inducer doxycycline alone (D2Z0, "futile response"). The first bar ("Anc.") corresponds to the ancestral PF cells.

B
- Phenotype of clones evolved in antibiotic zeocin alone (D0Z2, "lack of response when needed").

C
- Phenotypes of two clones evolved in doxycycline and antibiotic zeocin (D2Z2, "suboptimal response").

D
- Phenotype of the single clone isolated from intermediate doxycycline and antibiotic zeocin (DiZ2, "suboptimal response").

E
- Gene expression histograms measured in D0Z0 for Clones #4 and #7 (evolved in D0Z2) compared to the PF ancestor.

G
- Tradeoff between *yEGFP::zeoR* expression and zeocin resistance for clones evolved in D0Z2 (red) and DiZ2 (green).

Comments

- 创新点：
  - 将合成生物学中的基因回路与实验相结合，把系统的问题定量化处理，巧妙地解决胁迫响应模块的适应性演化问题。
- 启发：
  - 面对某个难解的生物学问题或者自己的课题推进不动时，不要被禁锢在一种思想方法上，要懂得用多学科交叉的方法去考虑，也许会有不一样的体会。
- 问题：
  - 合成的基因回路能否完全反应真实的情况，未可知。
  - 预测模型是基于已知的适应性和表达的信息，因此会造成一定的偏差，使得模型具有局限性。
  - 模拟进化实验进行验证时，预测和实验的结果只是在短期的数据上得到支持，能否进一步推广到多个物种的长期进化，从而得到一个普遍性的规律，有待研究。

Thanks for your attention!