# Growth bistability from obligatory interactions between antibiotics and antibiotic resistance

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***Short Abstract* — Bacterial cells expressing antibiotic resistance can grow at antibiotic concentrations that would otherwise inhibit the growth of wild type cells. When the resistance-expressing cells are exposed to antibiotics, the degree of resistance expression is expected to change via global growth-mediated effects, resulting in a positive feedback between the growth-inhibiting effect of the antibiotics and the cells' ability to resist the antibiotics. Consistent with this positive feedback effect, *E. coli* cells expressing antibiotic resistance are found to exhibit an abrupt transition from rapid growth to non-growth at a threshold antibiotic concentration. Below the threshold, the population consisted of a mixture of growing and non-growing cells. Quantitative modeling of known interactions between the antibiotics and the expression of antibiotic resistance can quantitatively account for various experimental observations.**

***Keywords* — drug-host interactions, growth transition, bistable growth, growth-mediated positive feedback.**

## EXTENDED ABSTRACT

It has been shown for a variety of antibiotics that bacterial cells exposed to sublethal antibiotic levels exhibit dramatic change in global gene expression [1-2]. If one of these genes confers antibiotic resistance to the cells, antibiotic action and its resistance may form a feedback, leading to an unexpected drug-host interaction.

We tested this possibility for a translation-inhibiting drug chloramphenicol (Cm) using *E. coli* cells constitutively expressing Chloramphenicol acetyltransferase III (CAT) that deactivates Cm. We first grew these cells in batch culture at various concentrations of Cm. They grew at moderately reduced rates in medium with increasing Cm concentrations, and abruptly stopped growing when the Cm concentration exceeded a threshold value. When the growth of individual cells is tracked by time-lapse microscopy in microfluidic devices near the threshold Cm concentration, we observed that the population consisted of a mixture of growing and non-growing cells. Thus, the system exhibited two hallmarks of positive feedback; sharp transition and bistability [3], without the need of any specific regulation. Very similar results are obtained for cells expressing tetracycline resistance grown in medium containing varying amounts of tetracycline, indicating that this phenomenon is not drug-specific.

Next we analyzed the feedback system mathematically using the known effects of Cm on constitutive gene expression and cell growth [2][4], and the known biochemical interaction between Cm and CAT [5]. The analysis quantitatively explains the experimental data with a single fitting parameter. The model makes quantitative, parameter-free predictions on the effect of the degree of constitutive CAT expression on the threshold Cm concentration. The predictions are validated quantitatively by varying the basal CAT expression level.

The results of this study is of relevance to understanding the very rapid evolution of antibiotic resistance – the abrupt change in cell growth at the threshold antibiotic concentration depicts an abrupt fitness plateau which can drastically speed up the evolution of antibiotic resistance [6-7].

## REFERENCES

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