Mapping single-cell responses to population dynamics in beta-lactam treatment

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Beta-lactam treated single bacterial cell response and antibiotic-sensitive population dynamics have been studied, but separately. Here, we show that the varying degrees of bacterial filamentation cause two salient population dynamic features: a transient increase of total biomass and a linear correlation between growth and killing rates. Using time-lapse microscopy, we found that the probability of lysis increases with the extent of filamentation. This dependence is characterized by a critical length that is unique to bacterial strain, antibiotic dose, and growth conditions. Our mathematical models may explain where the dependence is emerged from and how it gives rise to the population dynamics. By mapping single-cell lysis probabilities to population biomass dynamics, our study provides a quantitative constraint on the molecular mechanisms underlying the bacterial responses to β-lactams. and allows single-cell trait predictions in both dose- and time-dependent manners.

***Keywords* — bacterial filamentation, population dynamics, beta-lactam, antibiotics, mapping, lysis probability.**

I. Purpose

BETA-LACTAM killing kinetics to antibiotic-sensitive bacteria has been widely studied at both single-cell and population levels, but separately. Single-cell responses have shown continuous growth in length without division [1-2], and population biomass measurements have shown transient increase and delayed decay [3-4]. However, single-cell filamentation has not been quantitated in a way to link with population dynamics [5]. Despite the apparent connections between the two, it remains unclear how the latter emerges from the collective response of single cells.

II. Results

To investigate to what extent a cell can elongate in a certain antibiotic condition, we measured long-axis cell length over time using time-lapse microscopy. By collecting the final, longest length, we found that the lysis probability increases with the extent of filamentation. We showed that the lysis probability distributions over final length were well-fitted to a log-logistic distribution, which is represented by two parameters: the critical length and hill-coefficient. We found that the critical length was inversely correlated to antibiotic dose and unique to bacterial strain and growth environment; the hill-coefficient was the slope of linear correlation between maximum growth and killing rates of the population. We reasoned that the larger rates of damage accumulation in higher doses make a cell reach faster to a thresholding number of cell wall damages in a cell. This is represented by a gamma distribution which is defined by the total number of damages and damage accumulation rate. As the mean of the gamma distribution is equal to the critical length of log-logistic distribution, the damage accumulation model explains why the higher dose of beta-lactam led shorter critical length if all else is equal.

Using mathematical models and the log-logistic-fitted single-cell lysis probabilities, we were able to recapitulate population biomass dynamics from both collective and averaging single-cell responses. Our model clearly explains the time- and dose-dependent killing kinetics of beta-lactams from a boundary condition. Our model successfully predicted the elongated individual length distributions in lower dose antibiotics, where the population level measurement is indistinguishable from that of the non-treated population.

III. Conclusion

Our work reveals a robust dependence of the lysis probability on the cell length during beta-lactam treatment and two coarse-grained parameters that characterize the probability. Our measurements and mathematical modeling serve the quantitative basis for interpreting well-established population biomass dynamics from the parameters of lysis probability. Having only two parameters, we can represent both single- and population-level responses in beta-lactam exposure. On the other hand, they imply the fundamental constraint of the possible molecular mechanisms that underlie single-cell responses.

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