Stochastic Analysis of Interplay Among Drug Mode of Action, Nutrient Availability, and Antibiotic Resistance

Chimezie Izuazu, Cameron Browne

Department of Mathematics, University of Louisiana at Lafayette (chimezie.izuazu1@louisiana.edu)

Motivation

- Compared with the Pre-COVID-19 era, antibiotic treatment has increased in this Post-COVID-19 era.
- Antibiotic treatment creates a beneficial environment for the evolution of antibiotic-resistant bacterial strains [Peter Czuppon et al., 2023 [1]].
- Optimal treatment to mitigate the issue of antibiotic resistance?.

Introduction

Mathematical models, particularly Markov chains, have gained considerable attention for understanding the evolution of AMR. Unlike most existing models that assume standing genetic variation or an external source of resistant bacteria, we propose a pharmacodynamics-based continuous-time Markov chain (CTMC) considering the emergence of a bacterial strain via random or drug-induced mutations. The proposed model is tractable as a generalized birth–death process with immigration (GBDP-I).

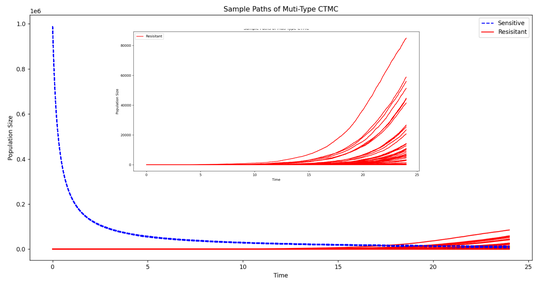


Figure 1:Treatment-resistance-induced bacteria rescue

Notations: Let w_t and m_t denote wild-type (susceptible) and mutant (resistant) bacteria counts, respectively, $\lambda_i(.)$ and $\mu_i(.)$ denote the per capita birth and death rates, respectively ($i \in \{w, m\}$); $\epsilon(t, m_t, c) := \epsilon_0(t, c) + \epsilon_h(t, c)m_t$, where $\epsilon_0(.)$ and $\epsilon_h(.)$ denote the *de novo* mutation and horizontal gene transfer (HGT) rates, respectively.

Proposed Model: PD-Based CTMC

$$
\begin{aligned}
w_{t+h} &\to w_t + 1 : \left[\lambda_w(t, N_t, c)\left(1 - \epsilon(t, m_t, c)\right)\right] w_t h + o(h) \\
w_{t+h} &\to w_t - 1 : \left[\mu_w(t, N_t, c)\right] w_t h + o(h) \\
m_{t+h} &\to m_t + 1 : \left[\lambda_w(t, N_t, c)\,\epsilon(t, m_t, c)\right] w_t h + \left[\lambda_m(t, N_t, c)\right] m_t h + o(h) \\
m_{t+h} &\to m_t - 1 : \left[\mu_m(t, N_t, c)\right] m_t h + o(h).
\end{aligned}
$$

Survival Probability

Survival probability of the resistant strain under biocidal and biostatic treatments:

$$P_s(T; c) = 1 - \left[\frac{I_T}{1 + I_T}\right]^{n_0} e^{-\left[\int_{t_0}^{T} \frac{\epsilon_0 \alpha_w (K - w(\tau;c)) w(\tau;c)}{K\left(1 + I_T - I_\tau\right)} d\tau\right]},$$

$$P_s^*(T; c) = 1 - \left[\frac{I_T^*}{1 + I_T^*}\right]^{n_0} e^{-\left[\int_{t_0}^{T} \frac{\epsilon_0 \alpha_w \left(K(1 - \frac{E^*}{\alpha_w}) - w^*(\tau;c)\right) w^*(\tau;c)}{K\left(1 + I_T^* - I_\tau^*\right)} d\tau\right]}.$$

High mutation shifts dynamics from nonmontonic (Figure 2) to monotonic (Figure 3).

Tractability: GBDP-I

$$
\begin{aligned}
m_{t+h} &\to m_t + 1 : \lambda_w(t, c)\,\epsilon(t, m_t, c)\, w(t)h + \lambda_m(t, c)\, m_t \\
m_{t+h} &\to m_t - 1 : \mu_m(t, c)\, m_t h.
\end{aligned}
$$

Solving the resulting Chapman–Kolmogrov equation using the method of characteristics, we obtain:

Probability generating function

$$G^{m_0, t_0}(t, z) = \left[1 + \frac{1}{\frac{e^{\rho(t)}}{z-1} - \int_{t_0}^{t} \lambda_h(\tau) e^{\rho(\tau)} d\tau}\right]^{n_0} e^{\int_{t_0}^{t} \left[\frac{\epsilon_0(\tau)\lambda_w(\tau) w(\tau)}{\frac{e^{\rho(t)}}{z-1} - \int_{\tau}^{t} \lambda_h(\vartheta) e^{\rho(\vartheta)} d\vartheta}\right] d\tau}.$$

For $T \geq t_0$, the transition probability $P_n^{0,t_0}(t)$ of GBDP-I is given by

$$P_n^{n_0, t_0}(t) = \left[\frac{I_T}{1 + I_T}\right]^{n_0} e^{-\left[\int_{t_0}^{t} \frac{\epsilon_0(\tau)\lambda_w(\tau) w(\tau)}{e^{\rho(t) - \rho(\tau))} + \int_{\tau}^{t} \lambda_h(\vartheta) e^{\rho(\vartheta)} d\vartheta} d\tau\right]} \times \frac{B_n(\bar{h})}{n!},$$

where B_n's are the complete Bell polynomials [2], and $I_t = \int_{t_0}^{T} \mu_m(t) \exp \int_0^t (\mu_m(\tau) - \lambda_h(\tau)) d\tau dt$.

Effects of Drug Mode, Nutrient Availability, and Mutation Rate

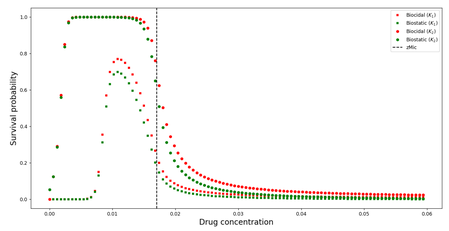
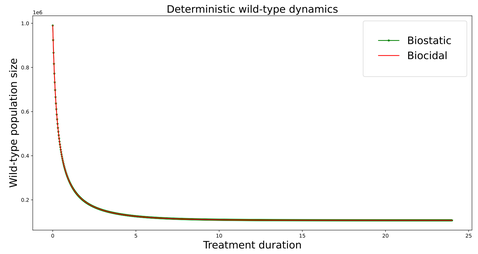


Figure 2:On antibiotic resistance with low HGT



Results and Conclusion

1. Besides *de novo* mutation, HGT is a major driver of resistant bacteria survival.
2. A biocidal drug is more suited for the "hit hard, hit early" strategy, whereas administering a biostatic drug at low doses suppresses resistance.
3. Yes to Fernanda Pinheiro's [3] question "if the abundance of the antibiotic target depends on growth condition, does the same happen to antibiotic susceptibility?"
4. Competition between sensitive and resistant cells dominates the bacterial dynamics under limited resources
5. Aggressive treatment under nutrient-rich environment accelerates bacteria evolution toward resistance.
6. Transformative changes in the human diet or the use of probiotics can reduce nutrient availability to resistant bacteria while increasing antibiotic susceptibility.

Additional Work

1. Validated simulations analytically
2. Considered linear and nonlinear dose-dependent mutations
3. Incorporating pharmacokinetics

References

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