Canadian Association of Physicists

Association canadienne des physiciens et physiciennes

Contribution ID: **491** Type: **Oral Competition (Undergraduate Student) / Compétition orale (Étudiant(e) du 1er cycle)**

(U*) Quantitatively Analysing Evolutionary Effects in the Transition From Non-Genetic to Genetic Drug Resistance

Wednesday 9 June 2021 16:00 (5 minutes)

Antimicrobial drug resistance is a growing health threat that is predicted to kill 10 million people per year globally by 2050 unless preventative measures are put in place. The first step in implementing these measures is to gain a better understanding of the fundamental processes involved in antimicrobial drug resistance through quantitative approaches from fields such as biophysics, molecular biology, computational biology, bioinformatics, and synthetic biology. With this in mind, this study aimed to quantitatively analyse evolutionary effects by studying the interplay between non-genetic antimicrobial resistance due to gene expression noise and resistance due to genetic mutation. This was done using numerical simulations of deterministic mathematical models along with the corresponding stochastic simulations to investigate cellular and population dynamics in various drug conditions. The results of these simulations were quantitatively analyzed to determine the establishment and fixation times of genetic mutations within the cell population for varying levels of relative fitness between non-genetically drug-resistant and genetically drug-resistant subpopulations to investigate the evolutionary interplay between these processes. Counterintuitively, we found that gene expression noise can prolong the establishment and fixation of genetic mutations for populations exposed to cidal and static drugs.

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Session Classification: W3-4 Molecular and Cellular Biophysics (DPMB) / Biophysique moléculaire et biophysique cellulaire (DPMB)

Track Classification: Physics in Medicine and Biology / Physique en médecine et en biologie (DPMB-DPMB)