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Modelling the influence of bacteriophage activity and horizontal gene transfer on the spread of bacterial resistance

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The global spread of Antibiotic Resistance Genes (ARGs) or Metal Resistance Genes (MRGs) represents an increasing health concern, and has been mainly attributed to antibiotics abuse and misuse. Dissemination of ARGs and MRGs is largely associated to plasmids, extra-chromosomal genetic elements. Plasmid-carried resistance is transferred to new host cells through Horizontal Gene Transfer (HGT) mechanisms, which play a crucial role in the ecological success of plasmids in bacterial communities. HGT occurs through three main mechanisms, namely conjugation, transformation and transduction, the latter referring to the case where foreign DNA is acquired by the receiver bacterium through infection by bacteriophages.

We develop here a mathematical model for the spread of resistance in biofilm communities by conjugation, natural transformation and generalised transduction. Generalized transduction results from the replication error of a random piece of bacterial DNA by the bacteriophage. This leads to the formation of a transducing phage, which can carry any bacterial gene, including resistance genes. Upon further infection, the transducing phage will release this piece of DNA into the infected bacterium, leading to eventual incision into the chromosome or recircularisation, in case of plasmid DNA.

The model is applied to the dissemination of an MRG plasmid in a growing biofilm. This plasmid carries the *merA gene*, conferring Hg resistance and the ability to reduce cationic Hg into its less toxic elemental form. This detoxification ability allows plasmid carrying bacteria to detoxify their local environment, therefore benefiting sensitive bacteria in their surroundings.

We include in the model the presence of lytic phages, in levels typically associated with water environments, and transducing phages. Their production is considered as a deterministic process resulting from infection by lytic phages of bacterial cells carrying the plasmid. Numerical studies focus on the impact of phage predation on bacterial communities and plasmid spread. We then investigate the relative influence of HGT and VGT (Vertical Gene Transfer) on plasmid dissemination, with a focus on generalised transduction.