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Rule-based modelling of conjugative plasmid transfer and incompatibility

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Abstract

COSMIC-rules, an individual-based model for bacterial adaptation and evolution, has been used to study virtual transmission of plasmids within bacterial populations, in an environment varying between supportive and inhibitory. The simulations demonstrate spread of antibiotic resistance (R) plasmids, both compatible and incompatible, by the bacterial gene transfer process of conjugation. This paper describes the behaviour of virtual plasmids, their modes of exchange within bacterial populations and the impact of antibiotics, together with the rules governing plasmid transfer. Three case studies are examined: transfer of an R plasmid within an antibiotic–susceptible population, transfer of two incompatible R plasmids and transfer of two compatible R plasmids. R plasmid transfer confers antibiotic resistance on recipients. For incompatible plasmids, one or other plasmid could be maintained in bacterial cells and only that portion of the population acquiring the appropriate plasmid-encoded resistance survives exposure to the antibiotics. By contrast, the compatible plasmids transfer and mix freely within the bacterial population that survives in its entirety in the presence of the antibiotics. These studies are intended to inform models for examining adaptive evolution in bacteria. They provide proof of principle in simple systems as a platform for predicting the behaviour of bacterial populations in more complex situations, for example in response to changing environments or in multi-species bacterial assemblages.

Keywords: Plasmid; Bacteria; Antibiotic; Incompatibility; Horizontal gene transfer; Individual-based model

1. Introduction

Horizontal gene transfer is a crucial driving force in bacterial adaptation and evolution. The three naturally occurring bacterial gene transfer processes, conjugation, transduction and transformation, all contribute to the spread of genes within bacterial populations (Ochman et al., 2000; Frost et al., 2005; Sørensen et al., 2005). Such genetic interplay can lead to the acquisition of new traits, that may in turn confer selection benefits on their hosts for survival in changing environments (Waters, 1999; Barkay and Smets, 2005).

Conjugation has evolved as a process for gene transfer mediated by certain plasmids and transposable elements. Plasmids are extrachromosomal elements that specify mechanisms controlling their own replication and maintenance, and are ubiquitous in bacteria. They can be either conjugative, encoding mechanisms for self-transfer by conjugation, or non-conjugative and hence incapable of initiating conjugation for self-transmission. In addition, plasmids are assigned to incompatibility

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(Inc) groups, depending on their ability to co-exist in the same cell line (Novick, 1987; Actis et al., 1998). Incompatible plasmids belong to the same incompatibility group. They have related replication control mechanisms and fail to co-exist. By contrast, compatible plasmids are from different incompatibility groups. Such plasmids replicate independently of each other, having different control mechanisms and will co-exist in the same cell. Many naturally occurring plasmids are mosaics comprising multiple replicons that have complex incompatability patterns (Osborn et al., 2000), but for the purposes of this study each model plasmid is deemed to have a single incompatability determinant.

Plasmids carry genes for a wide range of functions, including resistance to antimicrobial agents, metabolism of novel carbon sources and virulence. Antibiotic resistance (R) plasmids have a central role in the dissemination of antibiotic resistance and are largely responsible for the rapid emergence of multiple antibiotic resistant bacteria, especially in the hospital environment (Hawkey and Munday, 2004). Generally plasmid-encoded genes are dispensable to their hosts under most conditions; antibiotic resistance being strictly required only when the bacteria are challenged by a specific antibiotic(s). However, the continued presence of antibiotic resistance in the bacterial population would be advantageous against the possibility of future antibiotic exposure. Thus, although maintaining plasmids incurs fitness costs, both genetic and energetic, such genetic elements confer selective advantages on their hosts, particularly in promoting responses to changes in the local environment (Dahlberg and Chao, 2003). Conjugative plasmid transfer thus promotes the spread of beneficial genes within bacterial populations and is a source of variation for adaptive evolution. However, such transfer is limited by various barriers, including incompatibility with resident plasmids. Failure of incompatible plasmids to co-exist can restrict their spread, particularly where the density of a specific plasmid is high within local populations.

The purpose of this study is to develop and validate an individual-based model (IbM), COSMIC-rules (see Gregory et al., 2006, 2007), to simulate plasmid transfer events and incompatibility in bacterial populations. The IbM is used here to develop biologically-realistic simulations of plasmid transfer with predictive potential, for example in examining the spread of antibiotic resistance in clinically-important bacteria. Having validated such simulations using a limited number of parameters, more realistic models reflecting the complexity of natural bacterial populations in their habitats and with predictive value can be addressed. The overall objective is to develop and expand, by using larger-scale Grid technology, the capacity of COSMIC-rules to embrace modelling of complex bacterial genetic systems. In this way the role of horizontal gene transfer in effecting genetic innovations and influencing the behaviour of bacterial populations in changing environments could be explored.

COSMIC-rules models three levels: the genome, the bacterial cell and the environment (for details see Gregory et al., 2007). The genome comprises genes or sets of genes, each represented by a discrete bit string. The environment consists of a multiplicity of substances, including nutrients and antimicrobial agents, into which the bacterial populations are placed. Each bacterial cell is an individual and for individuals to interact there must be compatible pairing of gene types; valid pairings create a successful outcome. In this virtual world each bacterial cell may be subject to mutations and/or genome rearrangements mediated by mobile genetic elements. Such mechanisms contribute to bacterial variation and allow adaptation to a changing environment. COSMIC-rules can create changes in the local environment, e.g. by introducing bacteriocidal antibiotics, in turn generating isolated ecologies where R plasmid-free (antibiotic–susceptible) and R plasmid-containing (antibiotic–resistant) cells can compete for limited resources. The simulations described here use virtual conjugative R plasmids from the same and different incompatibility groups. Spread of the R plasmids is highlighted through displaying infected bacteria as coloured cells and through an environment exposed to antibiotics that provide selection pressures to monitor plasmid dissemination and maintenance.

2. Cell Interactions and R Plasmid Transfer by Conjugation

The genetic makeup (genome) of individual organisms dictates the susceptibility or resistance to substances in the environment. Fig. 1 provides the basic bacterial genome structure and environmental interactions applicable to the conjugative plasmid transfer events described here. Individual bacteria have their own genome that encodes all the functions required for growth and metabolism. The genome comprises the chromosome and any extrachromosomal elements, e.g. plasmids, residing in the cell. The chromosome of donor and recipient cells is isogenic, with two ‘susceptibility’ gene sets that can encode sensitivity to antibiotics A and B, respectively. The donor cell additionally carries a conjugative R plasmid, e.g. α or β, with genes for replication, conjugation and antibiotic resistance. The recipient is plasmid-free or could harbour a com-