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On conjugative plasmids

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In this thesis several mathematical models are formulated to analyse the population dynamics of plasmids. Furthermore it is investigated how selection affects the characteristics of the population dynamics of plasmids. In the Introduction (*Chapter 1*) a survey is given of the principal properties of plasmids. In the Chapters 2, 3, 4 and 5 the fate of a mutant plasmid in a plasmid population is investigated. A mutant will in most cases be incompatible to the corresponding wild-type plasmid, because a plasmid and its mutant mostly use the same mechanism to regulate their replication and partitioning.

First the question is answered whether one, two or three incompatible plasmids, which exclude each other completely, can coexist. In *Chapter 2* this is done for plasmids in a bacterial population kept in a chemostat and in *Chapter 3* for the case that the bacterial population is periodically transferred to fresh medium. It appears that under both growth conditions two plasmids may be able to coexist if one of them has a higher transfer rate, whereas bacteria bearing the other plasmid possess a higher growth rate. In a chemostat the concentrations of both plasmids will converge to stable equilibria concentrations. In a periodically transferred bacterial population the frequency of plasmids may oscillate, both when one plasmid type is present and when two plasmid types are competing. Three plasmids are able to coexist under neither growth conditions.

Occasionally plasmid mutants with a different transfer rate will arise. It is assumed that as the transfer rate of the plasmid mutant is the higher, the more negative the effect of the plasmid on the growth rate of its bearer will be. In that case selection will ultimately lead to the establishment of a plasmid with an optimal transfer rate, or to a situation in which two plasmids, one with a high transfer rate and the other non-conjugative, will coexist. The first situation will occur if the relation between the transfer rate and the bacterial growth rate is convex, and the second

if this relation is concave (see fig. 2, p. 30).

Plasmids often exclude other incompatible plasmids from their hosts by changing some of the bacterial membrane properties. This change has probably a negative effect on the bacterium. Since survival and growth of the bacterial host are of great importance for the survival and spread of the plasmid, a property disadvantageous for the bacterial host tends also to be detrimental to the plasmid. So it can be asked why plasmids exclude other incompatible plasmids. This question is dealt with in *Chapter 4*. It appears that exclusion is advantageous for a plasmid if its transfer rate is high and its copy number low. For plasmids with a high copy number exclusion does not seem to be profitable since the entering plasmid will probably disappear out of the majority of the descendants of the invaded bacterium by incompatibility segregation.

Many plasmids regulate their ability to induce transfer. Plasmids have only an efficient transfer in newly infected hosts. After several generations in a bacterial cell line, the ability to transfer becomes repressed. In *Chapter 5* the dynamics of transfer regulation is modelled, both in a chemostat and in a bacterial population with serial transfer. It appears that competition between a transfer regulating plasmid and its mutants in a chemostat will lead to a situation of neutrality for a non-regulating plasmid, provided that the ability to regulate transfer has no costs. In the case where bacteria, bearing non-regulating plasmids, have a slightly higher growth rate than bacteria bearing derepressed regulating plasmids (i.e. if regulation has some costs), the non-regulating plasmid will eventually win. In a serially transferred bacterial population optimal regulation dynamics exist. A regulating plasmid with optimal regulation is able to compete successfully with a non-regulating plasmid, even if regulation has some costs. How great the costs of regulation may become without regulation becoming disadvantageous, depends on several factors. One of these is the extent of the environmental differences the plasmid has to cope with during its stay at each growth site. More particularly, how

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much the bacterial concentration differs between the start and the end of each growth period. A greater difference leads to a higher advantage for transfer regulation.

The dynamics of competition between compatible plasmids differs from those of incompatible plasmids. Compatible plasmids often do not exclude each other and from the moment they are combined in a bacterium they stay together in that bacterial cell line. In *Chapter 6* the competition between compatible plasmids is analysed. It appears that it is possible for at least three compatible plasmids to coexist; this probably also holds for higher numbers. Two (or three) plasmids can coexist, although one of them is superior to the other, i.e. when it has a higher transfer rate and its bacterial host has a higher growth rate. Sometimes it depends on the initial plasmid concentrations which equilibrium concentration will be reached. When a bacterial population carrying a plasmid is invaded by a second compatible plasmid, which is slightly superior to the resident plasmid, it may occur that the less fit plasmid, which was present first, remains predominant. The competition between two (or three) compatible plasmids can be considered as an example of the possibility of stable coexistence of two (or three) species in the same niche.

In *Chapter 7* some unanswered questions about plasmid dynamics are discussed:

- How are the population dynamics of competing incompatible plasmids affected by incomplete surface exclusion?
- Is the structure of the plasmid genome arbitrary or influenced by selection?
- Why do plasmids carry so often genes coding for properties which are only once in a while favourable for bacteria?
- How are the (theoretical) conditions for plasmid spread in nature affected by the ability of a plasmid to regulate its transfer rate?