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Sociobiological control of plasmid copy number

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Abstract

Background:
All known mechanisms and genes responsible for the regulation of plasmid replication lie with the plasmid rather than the chromosome. It is possible therefore that there can be copy-up mutants. Copy-up mutants will have within host selective advantage. This would eventually result into instability of bacteria-plasmid association. In spite of this possibility low copy number plasmids appear to exist stably in host populations. We examined this paradox using a computer simulation model.

Model:
Our multilevel selection model assumes a wild type with tightly regulated replication to ensure low copy number. A mutant with slightly relaxed replication regulation can act as a "cheater" or "selfish" plasmid and can enjoy a greater within-host-fitness. However the host of a cheater plasmid has to pay a greater cost. As a result, in host level competition, host cell with low copy number plasmid has a greater fitness. Furthermore, another mutant that has lost the genes required for conjugation was introduced in the model. The non-conjugal mutant was assumed to undergo conjugal transfer in the presence of another conjugal plasmid in the host cell.

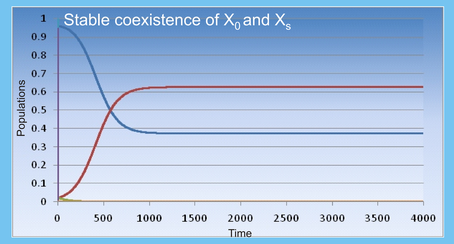
Results:
The simulatons showed that if the cost of carrying a plasmid was low, the copy-up mutant could drive the wild type to extinction or very low frequencies. Consequently, another mutant with a higher copy number could invade the first invader. This process could result into an increasing copy number. However above a certain copy number within-host selection was overcompensated by host level selection leading to a rock-paper-scissor (RPS) like situation. The RPS situation allowed the coexistence of high and low copy number plasmids. The non-conjugal "hypercheaters" could further arrest the copy numbers to a substantially lower level.

Conclusions:
These sociobiological interactions might explain the stability of copy numbers better than molecular mechanisms of replication regulation alone.

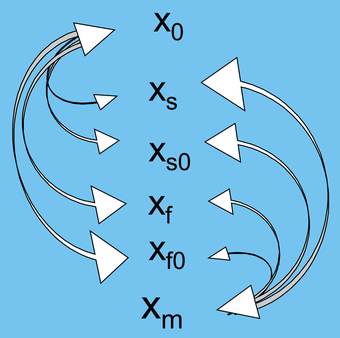
Model assumptions

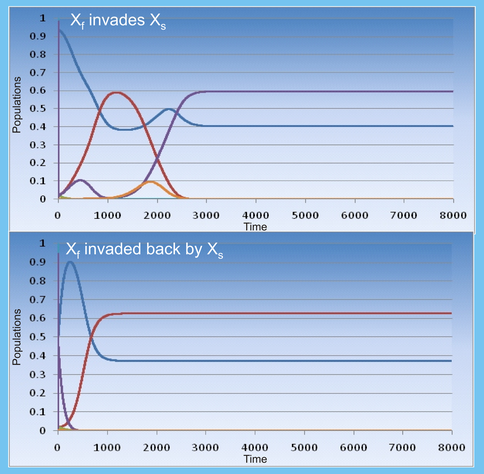
- Host free of plasmid and those with four types of plasmids namely low copy number, slow replicating wild type (X_s), mutant lacking *tra* gene complex *i. e.* Non-conjugal (X_{s0}) , copy-up faster replicating mutant (X_f) and copy-up non-conjugal mutant (X_{f0}) compete with each other in a host population.
- Cost of carrying a plasmid is directly proportional to the copy number or intra-host plasmid fitness. The cost affects intrinsic growth rates of host populations (Host level selection).
- There is a cost of carrying conjugation mechanism which the non-conjugal plasmids do not pay. Non-conjugal plasmids hitch hike on the conjugation machinery of others.
- Constant rate of spontaneous curing.
- No incompatibility assumed. Hosts can carry multiple plasmids at a time.

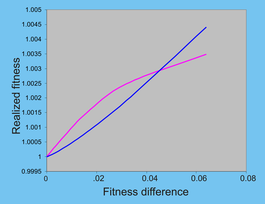
Results:
1. In the absence of other plasmids, plasmid free host and wild type plasmid carrying host attain equilibrium quickly (below).
2. Plasmid with a slightly higher intra-host fitness (IHF) invades the wild type (right).
3.This mutant can be invaded by another with higher intra-host fitness.
4. Plasmid with very high IHF can be invaded back by the wild type (lower right)



Model dynamics





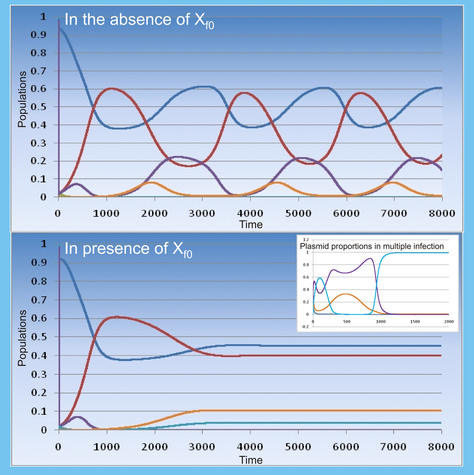


The dynamics of the 2 fitness components is different. The realized fitness by IHF gives a saturation curve, whereas the benefits of host level fitness increase exponentially.

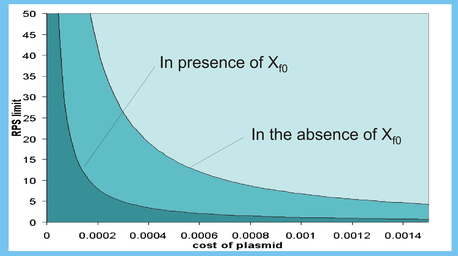
5. The saturating benefits of IHF and exponential benefits of between host fitness results in a rock-paper-scissor (RPS) like situation on a continuous scale. This can lead to coexistance of 3 or more plasmids with different copy numbers within a host population.

An additional twist to the story

If copy-up mutants are 'selfish' or 'cheater' plasmids, non-conjugal variants are 'hypercheaters' as they exploit the conjugation machinery of the others.
Non-conjugal plasmids substantially reduce the benefit of copy-up mutants and stabilize low copy number in the population



Zone of RPS like relationship in the presence and absence of hypercheaters: Hypercheaters reduce the range considerably



Discussion:

Molecular mechanisms of plasmid replication regulation fail to explain the evolutionary stability of low copy number plasmids. Our model predicts that the low copy numbers are maintained by sociobiological interactions. It allows the coexistence of low, intermediate and high copy number plasmids as well as conjugal and non-conjugal plasmids in the same population. This is perhaps the first example of a RPS game on a continuous scale and first theoretical explanation of coexistence of different types of plasmids.

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