Review of

Multileveled Selection on Plasmid Replication

Paulsson 2002
Outline

1. A model of plasmid replication

2. Intracellular competition

3. Intercellular competition

4. Multi-level selection conflicts

5. Discussion
Introduction

• Plasmids: self-replicating gene clusters (procaryotes)

• Plasmids that replicate fast inside their cell have a better chance of fixing in the descendant cells

• BUT: cells grow slower as the plasmid grow faster

• An interesting case of “group selection”
1. A model of plasmid replication

- Maximal exploitation scenario: plasmid population determined by carrying capacity of cell env.

- In nature: auto-regulating plasmid replication

- Kinetics of replication control: interplay of plasmid encoded activators (cis/trans) and inhibitors (trans)

- Regulation acts in two ways: (1) limits replication; and reduces variance in average copy number $m \Rightarrow$ lower losses at cell div.
• Single-rate equation:

\[ \frac{dy}{dt} = y^* (r(y) - \mu) \]

• \( y \) is plasmid concentration, \( \mu \) represents dilution due to cell growth, and \( r(y) \) is the replication frequency function, modeled as

\[ r(y) = \frac{k}{1 - (K_y)^i} \]

• \( k \) is the maximum replication rate, \( K \) is a compounded constant accounting for: (1) rate of inhibitor synthesis, (2) inhibitor half-life and (3) interactions b/w inhibitors and activators

• \( i \): Hill coefficient of inhibition
• Replication control checks random fluctuations

• Aside from limiting replication below carrying capacity, replication control reduces variance in copy number $m$

\[ \text{Var}(m) = \langle m \rangle / i \]

• Thus, sharper negative feedback (greater $i$) suppresses random fluctuations around $\langle m \rangle$

• How does this favor plasmids? By increasing segregational stability
  (i.e. when cells divide, fewer daughter cells will be plasmid-free)
2. Intracellular (individual) selection

- Replication control is subject to intracellular selection.
- Replication control allows plasmids to communicate its presence to other copies.
- Some mutations are public (trans); others are private (cis).
- Since they affect all copies in the same way, trans mutations are neutral for intracellular selection.
- Cis mutations, by contrast, play an important role.
• Plasmids with replication systems that are very similar are unable to coexist

• Main cause: mutual susceptibility to inhibitors and activators

• Replication frequency function $r()$ for incompatible plasmids $Y1$ and $Y2$:

$$R1 = k1(C1 (K1y1 + K2y2))^{-i}$$

$$R2 = k2(C2 (K1y1 + K2y2))^{-i}$$

(Newly introduced constant $C$ depends on the inhibitor's cis-target sites)
• Two assumptions have been made here
  • Clear cut b/w cis and trans mutations
  • No frequency-dependent intracellular selection (A stringent assumption)

• Incompatibility and genetic drift:

• If two organisms exploit the same niche, then the carrying capacity acts over the total population. This leads to genetic drift and the fixation of one or the other population
Figure 1.—(A) Stationary copy number distributions calculated from master equations (Appendix). Parameter $i$ determines the sensitivity of negative feedback and thus the significance of intrinsic copy number fluctuations. The numbers represent approximate $\langle L \rangle$ when $L = 2^{(L/2)^{m}}$. (B) Simplistic burdens (solid line) and losses (dotted lines) as functions of average copy number $\langle m \rangle$. The sum (dashed lines) of burdens and losses has a minimum at $\langle m \rangle_{opt}$. When $\langle m \rangle < \langle m \rangle_{opt}$ selection for lower burdens is weak, while when $\langle m \rangle > \langle m \rangle_{opt}$ selection for lower loss rates is weak. The approximation $\langle L \rangle_{\mu} \approx \langle L \rangle_{\mu_0}$ is used so that the net growth rate is $\mu_0(1 - (10^{-4}\langle m \rangle + 2b^{(\infty)}))$. 
3. Intercellular (group) selection

- To reproduce, plasmids must maximize the net growth rate of container cells
- Simplified model: consider two homoplasmid cells X1 and X2, containing plasmids Y1 and Y2
- Plasmids are essential to their cells; no heteroplasmid cell remains so for long: one of the two plasmids fixates
• X1 and X2 densities are modeled as

\[
\frac{dx_1}{dt} = [\mu_1 - \langle L \rangle_1 \mu_1 - \omega_2 - \Delta \gamma x_2 - \rho(x_1, x_2)]x_1 + \omega_1 x_2
\]

\[
\frac{dx_2}{dt} = [\mu_2 - \langle L \rangle_2 \mu_2 - \omega_1 + \Delta \gamma x_1 - \rho(x_1, x_2)]x_2 + \omega_2 x_1,
\]

• Accounts for growth, losses and horizontal transfer (conjugation: the sharing of genetic material b/w bacteria)

• Allows us to understand the plasmid burden on a given cell
Figure 2.—(A) An intracellular fitness landscape (Equation 7) for two replication control sensitivities. (B) An intercellular fitness landscape for \( Y_2 \) plasmids when \( Y_1 \) is optimal, \( Q_{cis1} / Q_{trans1} = \langle m \rangle_{opt} \), using \( \langle L \rangle = 2 \times 0.6^{(m)} \) and \( 1 - \mu / \mu_0 = 10^{-4} \langle m \rangle \) so that \( \langle m \rangle_{opt} \approx 18.\)
• Do copy fluctuations have a significant impact on the average host growth rate?

• Yes, but only if the growth rate of the cell quickly and non-linearly responds to plasmid fluctuations

• An increase in m (number of plasmid copies) burdens the cell but also reduces the plasmid loss rate
4. Selection conflicts

- Faster replication favors a plasmid compared to its cell mates but burdens its home cell.
- Can we compare the strength of selection at these two levels?
- When does selfishness, as expressed by high replication rate, promote an increase in copy numbers?
Assuming low mutation, conjugation, and plasmid losses as well as small differences in cell growth rates, selfish plasmids are favored when

\[
\frac{\Delta \langle I \rangle - \Delta \mu/\mu}{\Delta \ln r} < \frac{m_T}{n_T} + \frac{\Gamma_0}{\mu}.
\]

Conforms with Leigh's (1983) analysis of group selection. Requirements for group sel.:

- Each new group is founded by members from other groups
- The number of groups should be high compared to number of individuals per group (nt >> mt)
- Low transfer b/w groups (low conjugation)
Main conclusion:

- **Intracelluar** selection dominates when the populations are small and the selection coefficients are large.
- **Intercellular** selection dominates with large populations and small selection coefficients.
• Mechanisms for conflict suppression

• *Trans* suppression of replication

• Discriminatory conjugation: effective horizontal transfer without mixing closely related plasmids (conjugation mixing incompatible plasmids promotes selfishness) - e.g. through cell surface exclusion

• Site-specific recombination to resolve over-replication of plasmid multimers. (Multimerization causes high burden on host and high plasmid loss rate)
5. Discussion

- There are various definitions of group selection:
  - group selection as “natural selection on groups”; strict analogy to individual/gene selection
  - group selection as the partitioning of within- and between-group selection; looser analogy
- What kind of “group selection” are we seeing here?