The Population Genetics of Antibiotic Resistance

Biol 509
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Overview of the Talk

Background
Modelling Antibiotic Resistance
Summary
Questions

Why Does This Matter?

Resistance presents a huge healthcare burden:
  • Increased morbidity and mortality
  • Significant economic costs

Resistance is increasing
  • Multidrug resistance problematic

What Causes Drug Resistance?

Simple model:
  • Initial population has varying drug susceptibility
  • Selection occurs during treatment
  • Final population comprised of resistant bacteria

Sources:
- [HealthyDebate.ca](http://healthydebate.ca/2011/11/topic/cost-of-care/health-care-spending)
- [Wikimedia](http://upload.wikimedia.org/wikipedia/commons/7/7b/MRSA7820.jpg)
How Do Bacteria Acquire Resistance?

- Conjugation
- Transformation
- Transduction
- Mutation

Resistance Mechanisms and Fitness Cost

Three main mechanisms:
- Preventing antibiotic binding
- Antibiotic modification or degradation
- Prevent antibiotic entry into the cell

Resistance usually has a fitness cost!
- Lower growth rate
- Higher death rates
- Decreased transmissibility and invasiveness

Why do resistant bacteria persist?

Compensatory Mutations

The effects of deleterious mutations can be compensated by secondary site mutations

Persistence of resistance mutations:
- Tradeoff between:
  - Fitness costs
  - Compensation

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Modelling Bacterial Fitness

Parameters:
- Cost of resistance mutations
- Cost of compensatory mutations
- Antimicrobial activity

Scenarios
- Fitness during drug treatment
- Fitness after drug treatment

Two locus model:
- $R =$ resistance
- $C =$ compensatory

Four Genotypes:
- ++
- +R
- C+
- RC

Parameters:
- $\mu_R, \mu_C$: mutation rates at resistance locus
- $\nu_C, \nu_R$: mutation rates at compensatory locus
Modelling Bacterial Fitness

Parameters:
• \( \mu_R; \mu_S \): mutation rates at resistance locus
• \( \nu_c; \nu_S \): mutation rates at compensatory locus
• \( d \): death rate
• \( w_{ij}, A \): growth rate

Types of Compensatory Mutations

Three main scenarios:
1. Fitness advantage only in absence of drug treatment
2. Fitness advantage only in presence of drug treatment
3. Fitness advantage in absence and presence of drug treatment

Determines likelihood of reversion to wildtype

Scenario A
Compensatory mutation confers advantage only in absence of drugs
Compensatory mutations arise following therapy
Reversion to wildtype unlikely

Scenario B
Compensatory mutation confers advantage only in presence of drugs
Compensatory mutations during therapy
Reversion to wildtype probable
Scenario C

Compensatory mutation confers advantage in both presence and absence of drugs
Compensatory mutations during both presence and absence of drugs
Reversion to wildtype unlikely

Examples From Literature

Each scenario has been observed
Scenario A (advantage only in presence of drugs)
  • Common
  • ie: vancomycin-resistant *enterococci*
Scenario B (advantage only in absence of drugs)
  • Rare
  • ie: *Salmonella enterica*
Scenario C (advantage during both presence and absence of drugs)
  • Most common
  • ie: HIV

Source: hDp://web.uconn.edu/mcbstaff/graf/Student%20presentations/Salmonellatyphi/Salmonellatyphi.html
hDp://en.wikipedia.org/wiki/VancomycinResistant_Enterococcus
hDp://www.aidsmeds.com/articles/hiv_life_cycle_9635.shtml

Model Limitations

Assumes that R & C mutations are deleterious in absence of drugs
Ignores several key factors
  • Horizontal gene transfer
  • Migration
  • Cross-resistance
  • Environmental Factors
    • Mutational supply
    • Drug dosage

Only two loci are modelled
Assumes infinite population
  • Ignores bottlenecks
Other Considerations

Drug design
• Antibiotic targets with high resistance costs
• Likelihood of compensatory mutations

Other approaches
• Mutation and conjugation inhibition
• Replacement with susceptible bacteria?

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Summary
Antibiotic resistance poses considerable healthcare challenges
Resistance usually comes with a cost
Secondary mutation mutations compensate for fitness costs

Modelling
• Demonstrates why reversion to wildtype is rare
• Better understanding of resistance may lead to better healthcare interventions
References


