Evolution Dynamics of Human Papillomavirus

Joint Graduate Seminar
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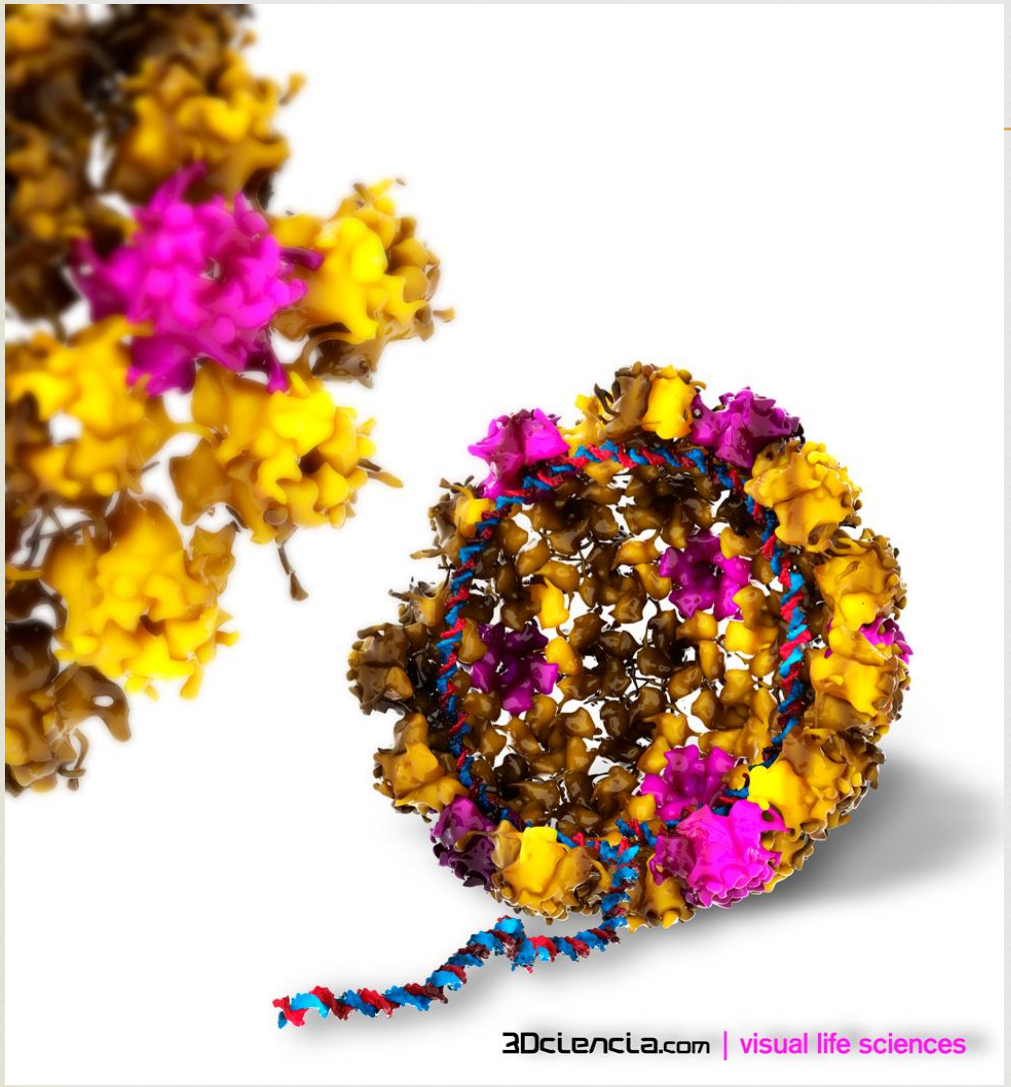
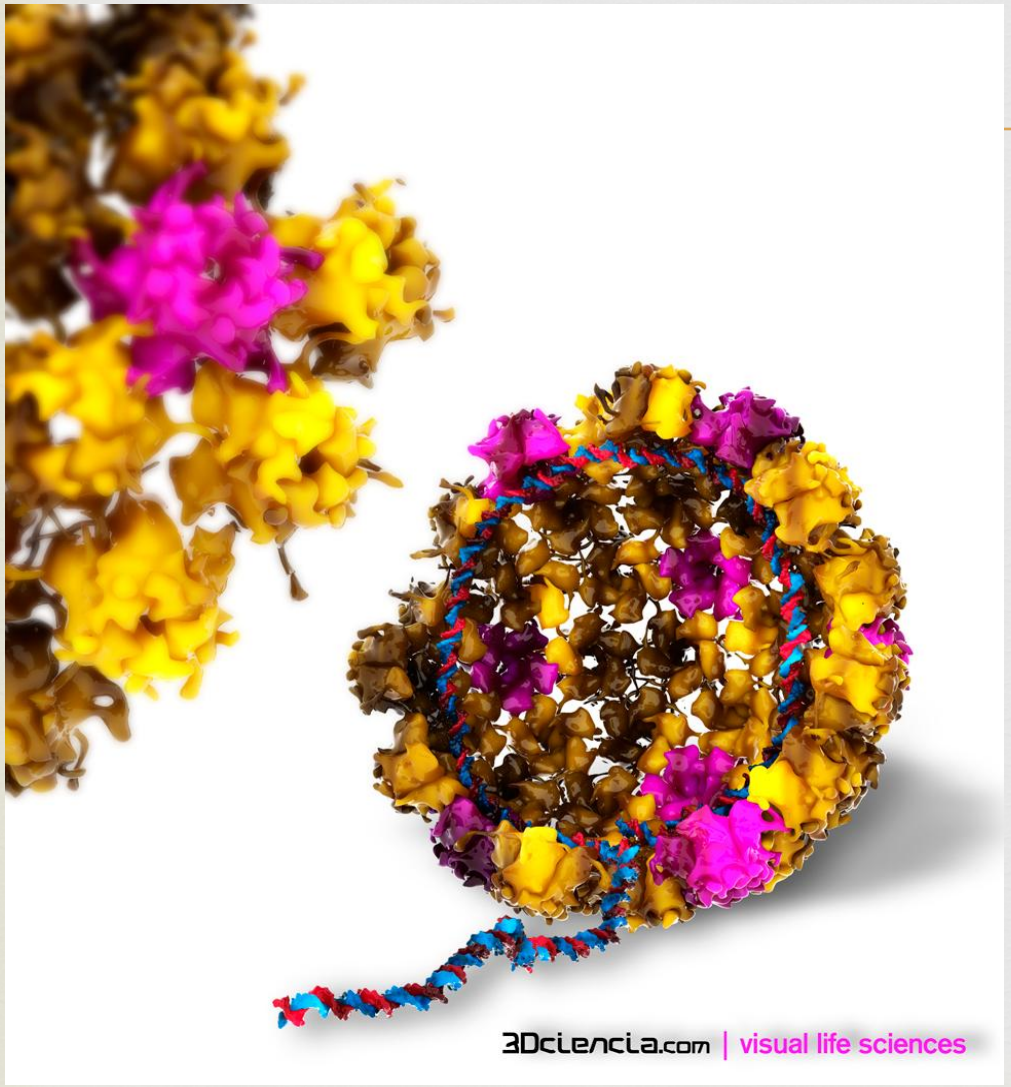
Introduction

Human Papillomavirus (HPV)



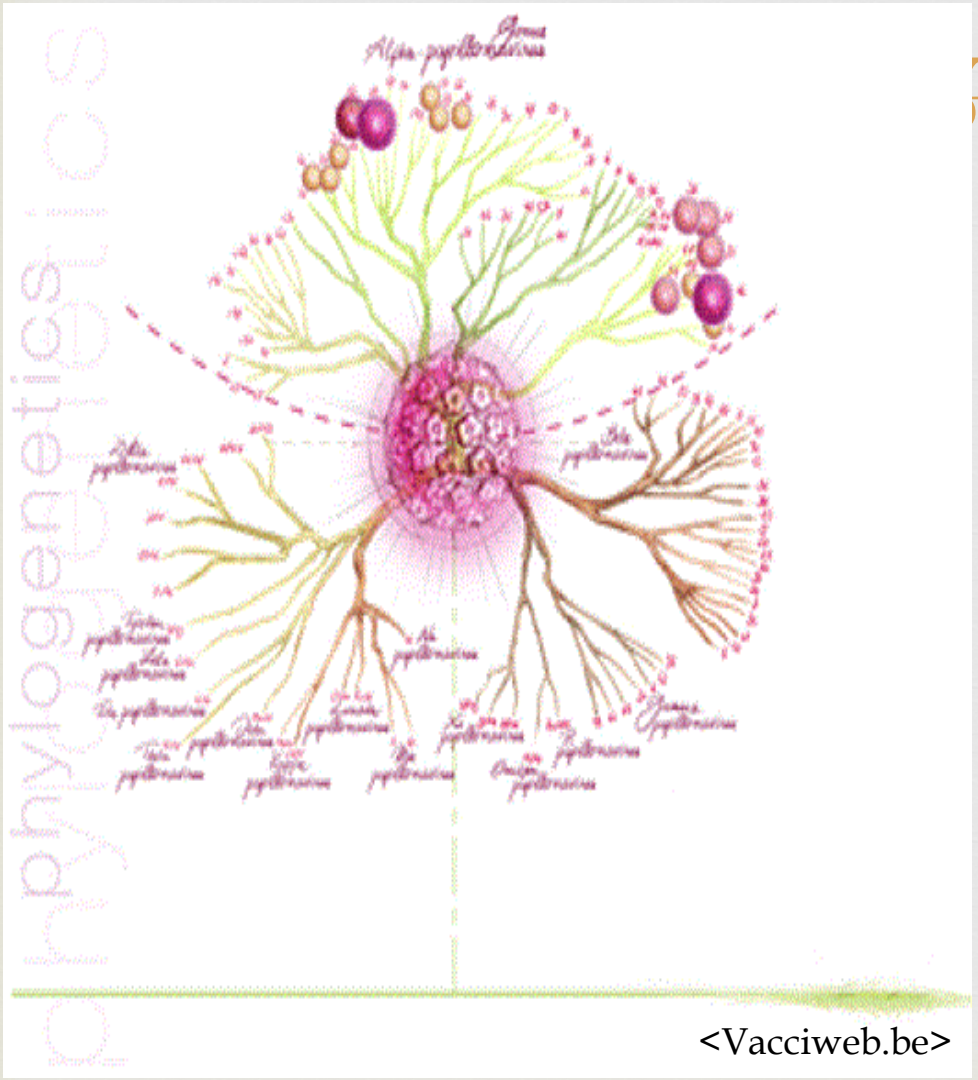
- *Papillomaviridae* family
- 50 nm in diameter
- non-enveloped
- ~8 kb of double-stranded, circular DNA
- 8 protein-coding genes
  - 6 early genes: E1, E2, E4, E5, E6 and E7
  - 2 late genes: L1 and L2
- a noncoding, regulatory long control region (LCR)

Human Papillomavirus (HPV)



- Sexually transmitted
- Infect keratinocytes
- 90% infections are naturally cleared within 2 years
- Primary causative agent of cervical cancer

Human Papillomavirus (HPV)



<Vacciweb.be>

- More than 100 types
- High-risk (HR) and low-risk (LR) HPV
- 15 HR types
  (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82)
- HPV 16 and 18 are most prevalent

Evolutionary Dynamics

- **Evolutionary dynamics** is the study of the mathematical principles according to which life has evolved and continues to evolve. This is mostly achieved through the mathematical discipline of population genetics.

Evolutionary Dynamics

- Mechanisms of population genetics
  - Genetic drift
  - Gene flow
  - Mutation
  - Natural selection
    - Host-linked evolution

Host-linked Evolution

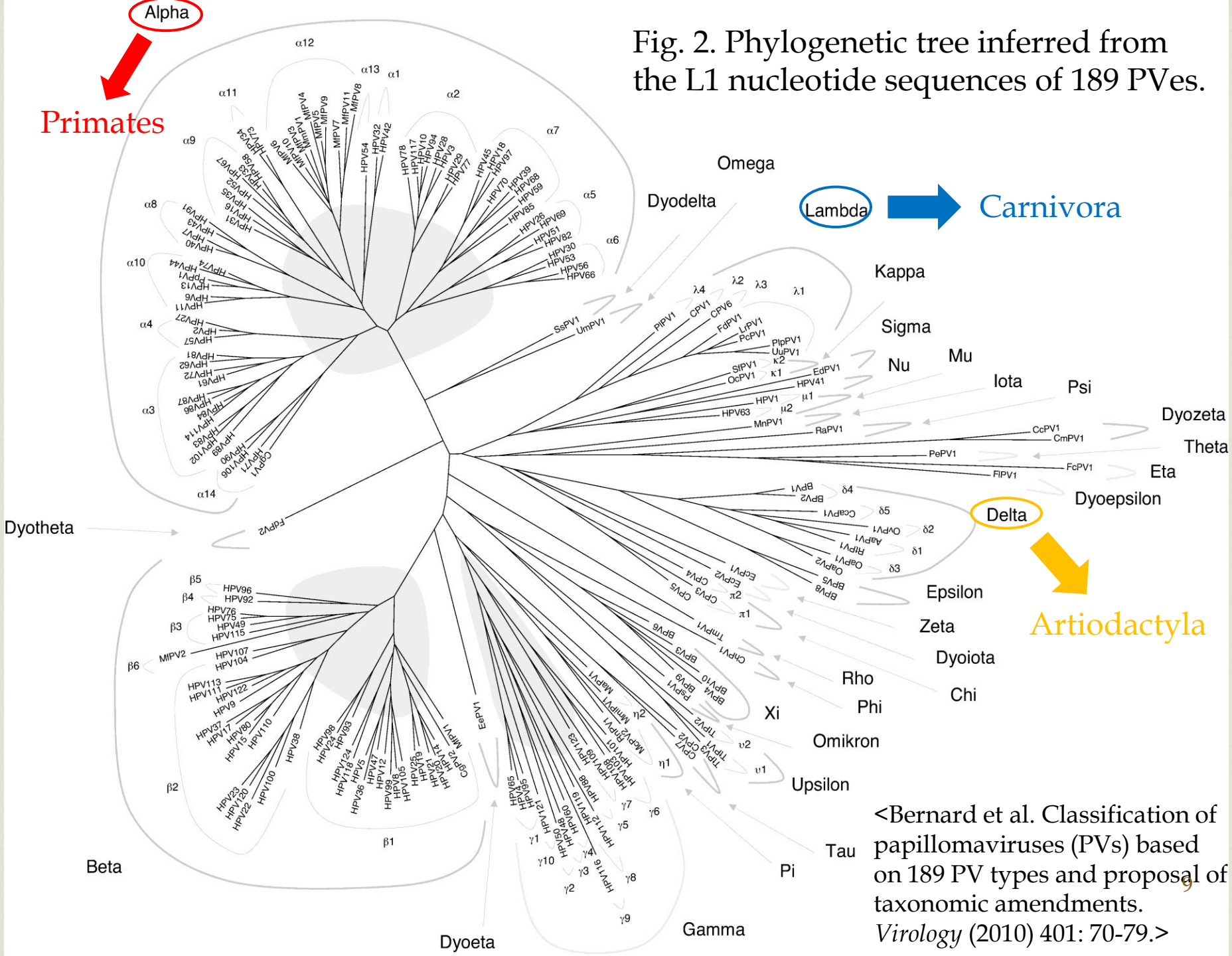


Fig. 2. Phylogenetic tree inferred from the L1 nucleotide sequences of 189 PVes.

<Bernard et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* (2010) 401: 70-79.>

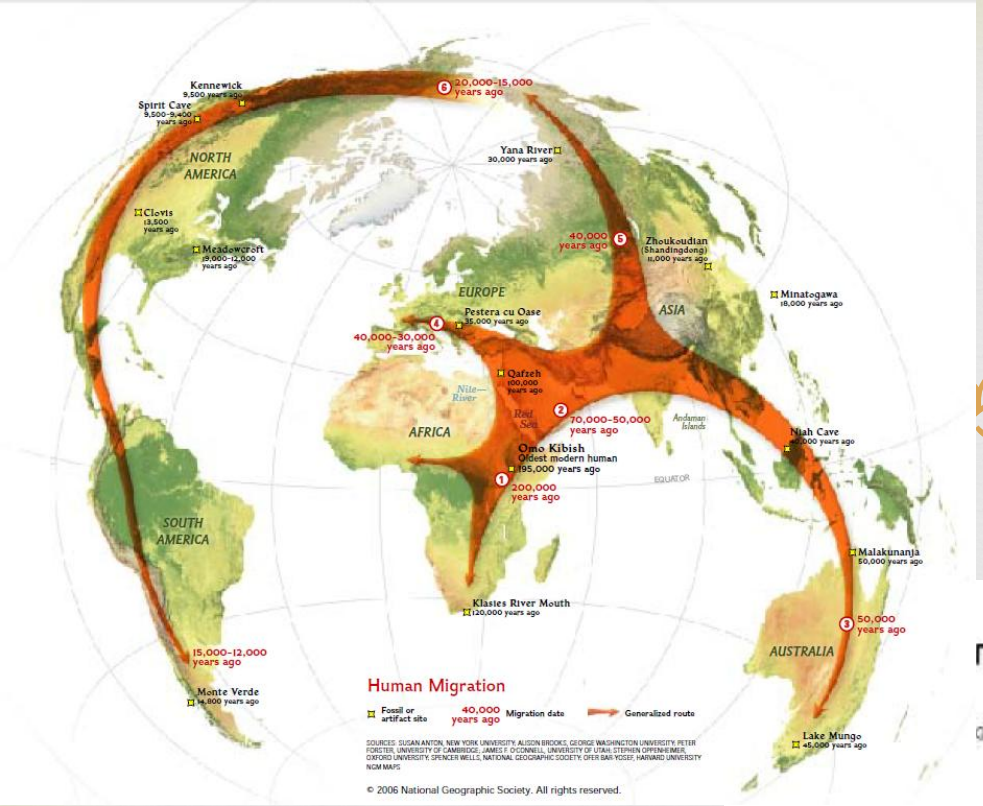
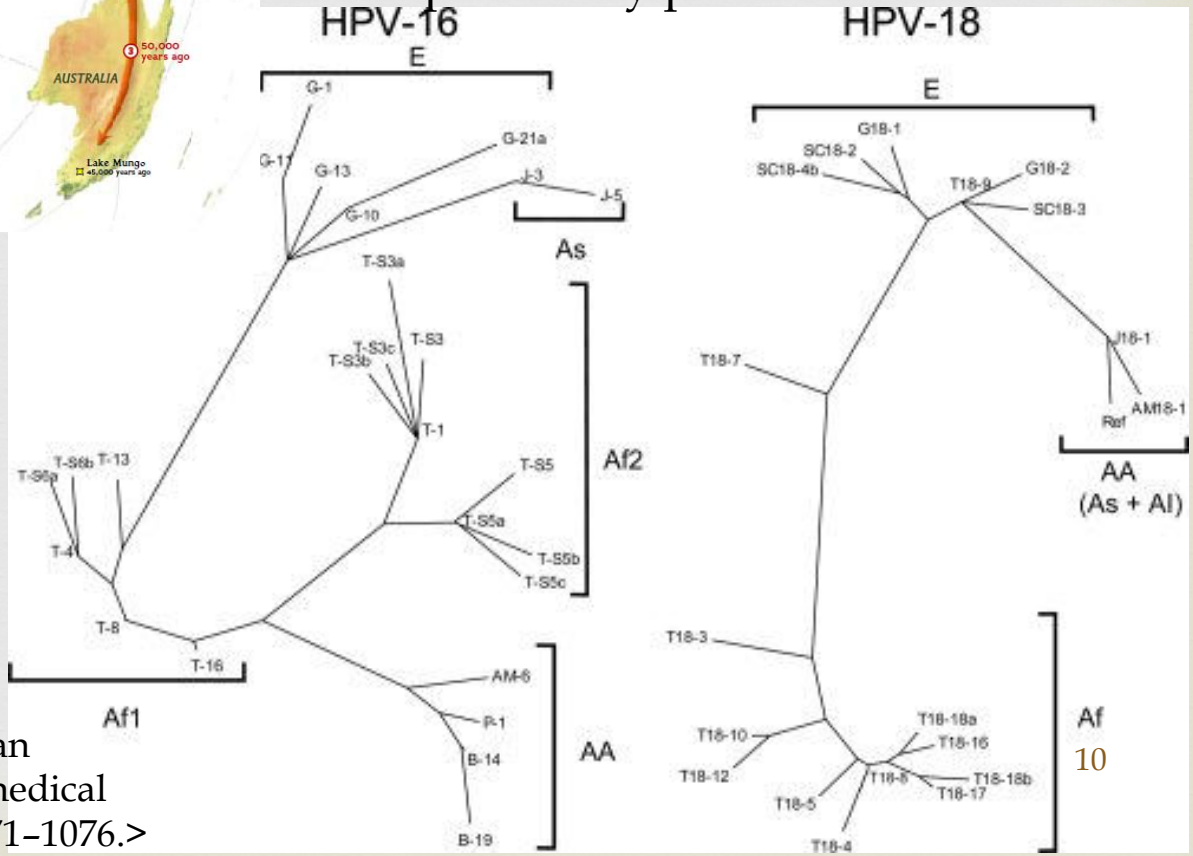


Fig.2. Phylogenetic trees of HPV-16 and 18 variants based on a reanalysis of previously published databases.



<Bernard et al. Genome variation of human papillomavirus types: Phylogenetic and medical implications. *Int. J. Cancer*: (2006) 118: 1071–1076.>

Evolutionary Ecology of Human Papillomavirus: Trade-offs, Coexistence, and Origins of High-Risk and Low-Risk Types

Orlando P A et al. J Infect Dis. 2011;infdis.jir717

The Journal of Infectious Diseases

3 Questions

- What evolutionary selection pressures and viral adaptations/strategies result in the observed HR and LR HPV types?
- How does variation in human sexual activity contribute to the evolution and persistence of HR and LR types in populations?
- What will the ecological and evolutionary consequences be of an HPV vaccine?

Hypothesis

- HPV faces an evolutionary tradeoff between persistence and per-contact transmission probability.
- LR HPVs use the high virion production strategy.
- HR HPVs use the low virion production strategy.
- Sexual behaviors in a host population determine the success of each strategy.

Methods

- A susceptible-infectious-resistant model
- Includes the sexual behaviors of the host population

The Model

- Let the humans be celibate or in relationship
  - 3 celibate pools of individuals:
    - Susceptible (S)
    - Infected (I)
    - Resistant (R)
  - 6 combinations of relationships:
    - SS, SI, SR, II, IR, and RR
- Assume the total sexually active human population size remains constant

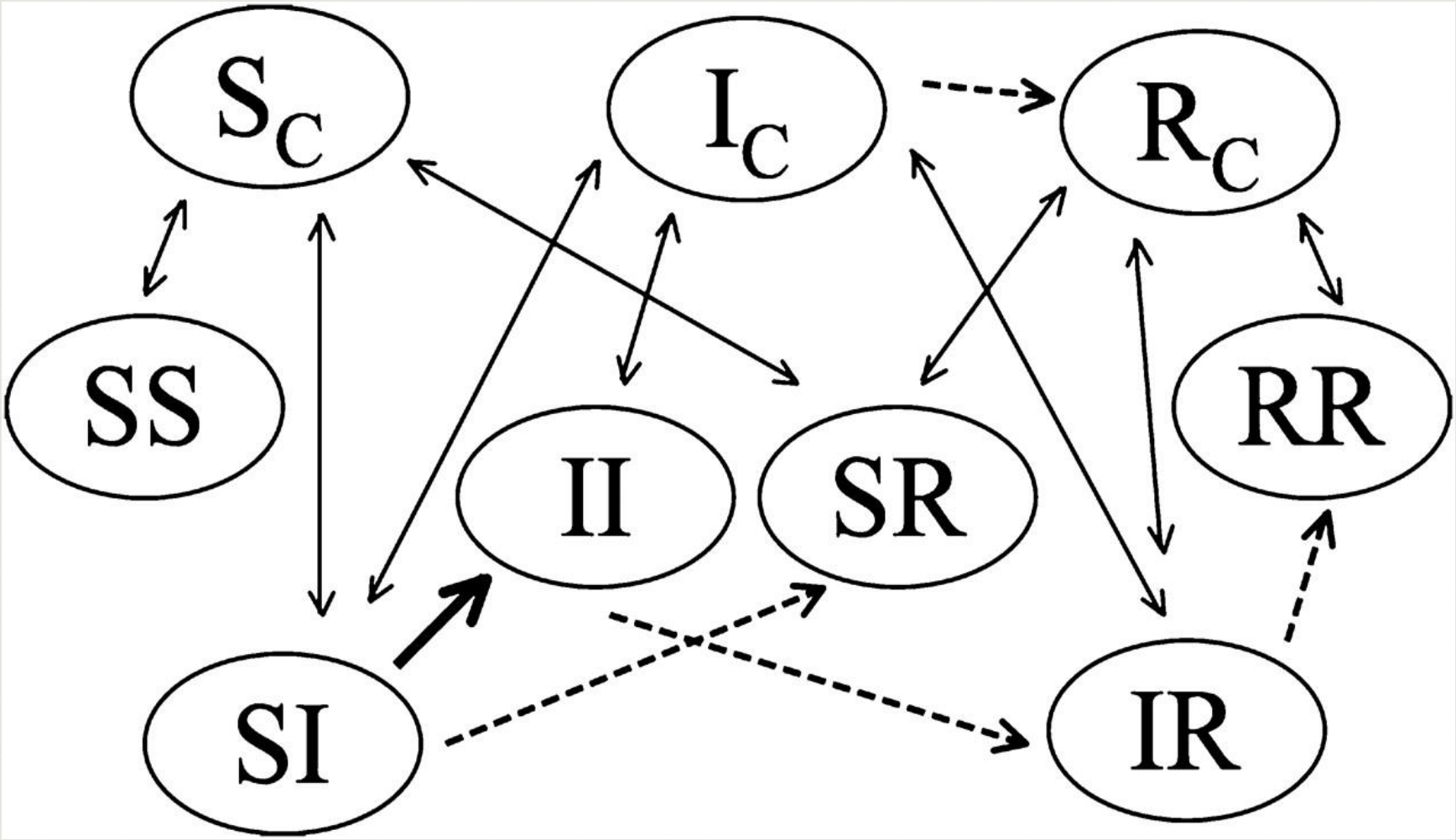


Fig.3. The social dynamics for how individuals transition from being celibate to being in sexual relationships (thin solid arrows) and the transmission dynamics of HPV as it spreads by infecting susceptible (thick solid arrow) and decreases as infected individuals become resistant (dotted arrows).

The Model

- Consider 2 scenarios
  - Population with a single sexual culture
  - Population with 2 different sexual subcultures
    - Subculture 1: relatively low rate of relationship turnover
    - Subculture 2: relatively high rate of relationship turnover
    - A mixing of subcultures by having celibates switch between Subculture 1 and 2
    - Assume the sexual relationships are exclusively in each subculture

Dynamics of HPV Prevalence

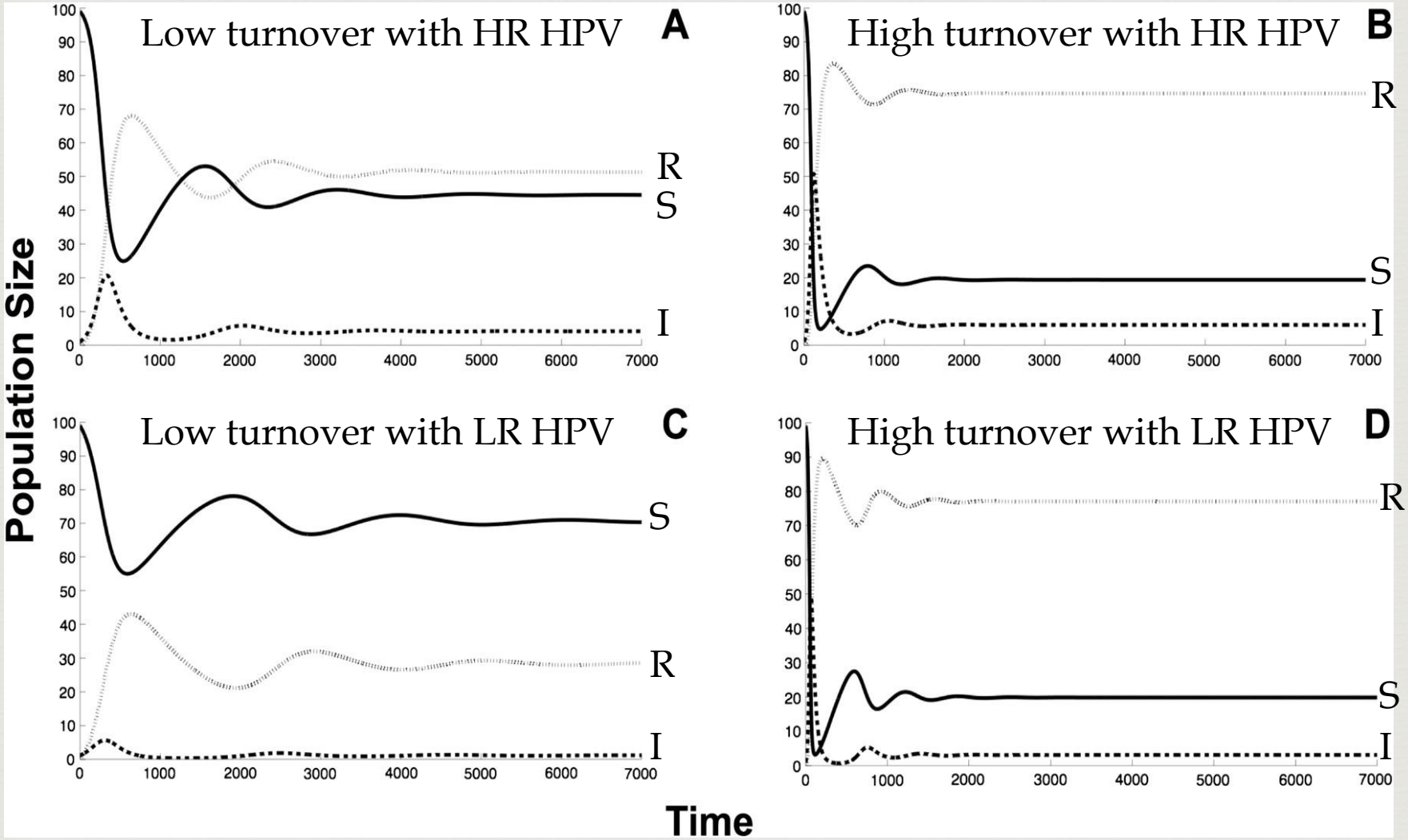
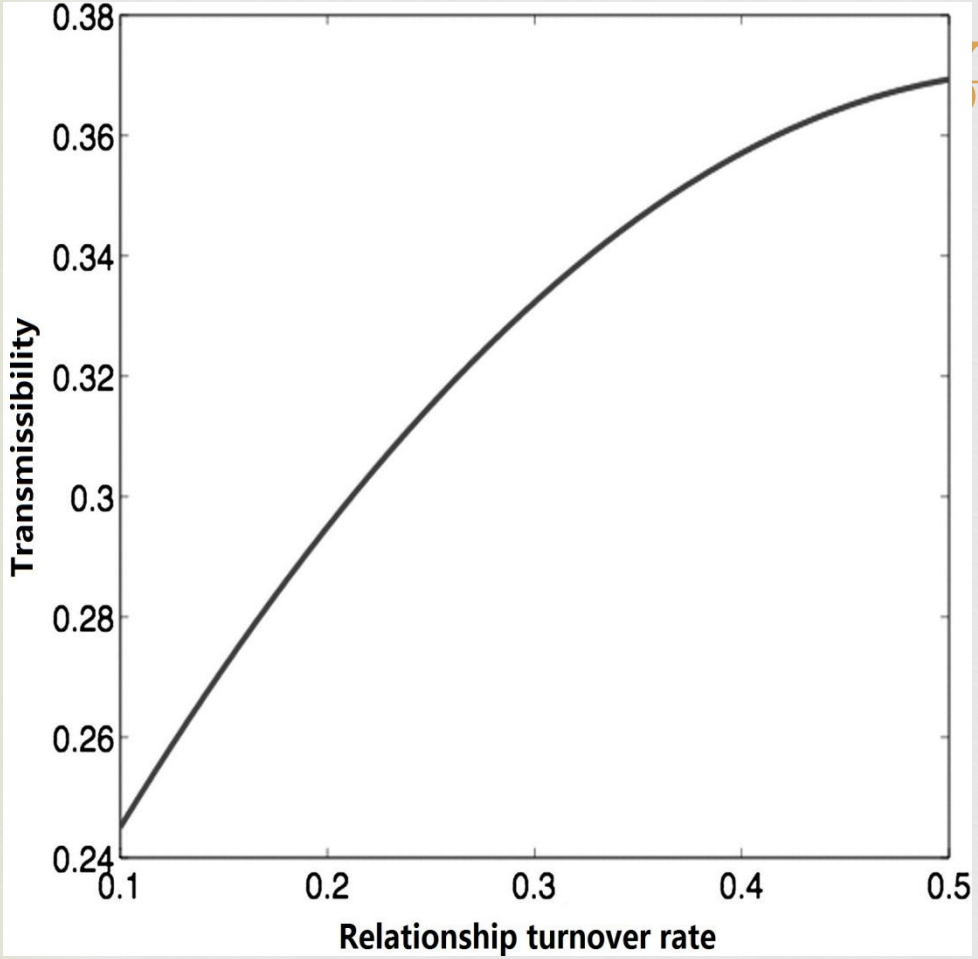


Fig.4. Infection dynamics of HPV

HPV Evolutionary Dynamics in Sexual Subcultures



- A high turnover rate selects for a high transmissibility, low persistence HPV – LR types
- A low turnover rate selects for an HPV strain with low transmission rate but high persistence – HR types

Fig.5. The Evolutionarily Stable Strategy (ESS) of HPV

Evolutionarily Stable Strategy

- **Evolutionarily Stable Strategy (ESS)** is a strategy which, if adopted by all individuals of a population, cannot be invaded by a mutant strategy through the operation of natural selection.

HPV Evolutionary Dynamics With 2 Sexual Subcultures

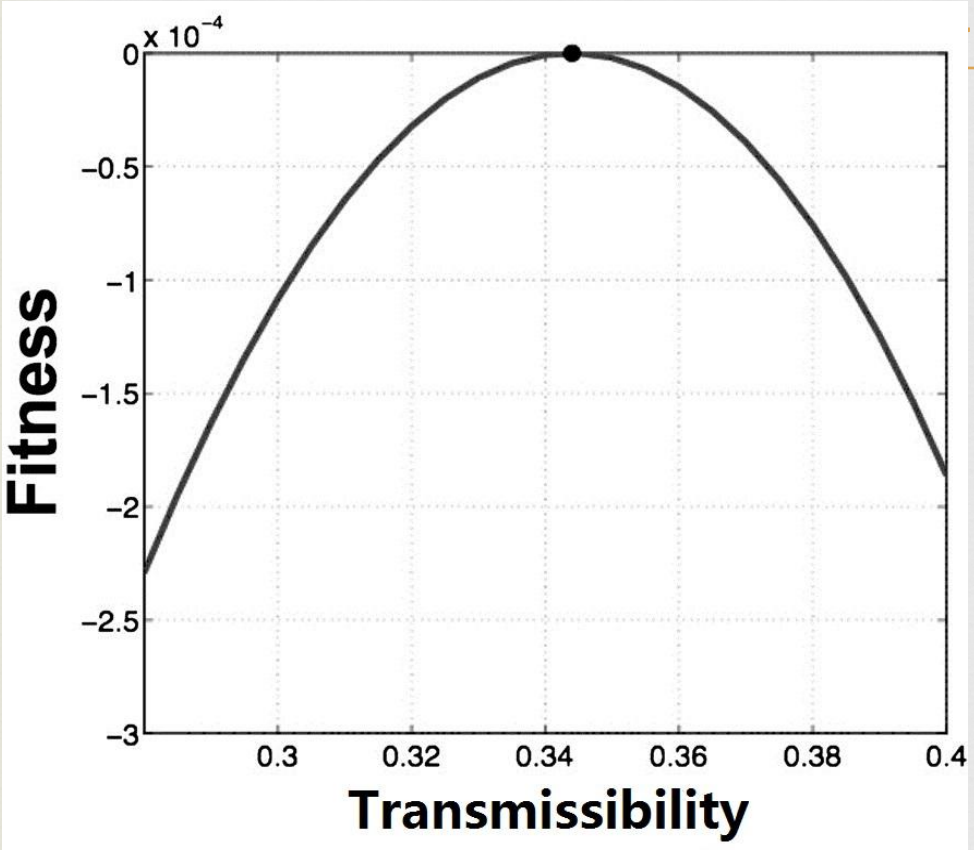
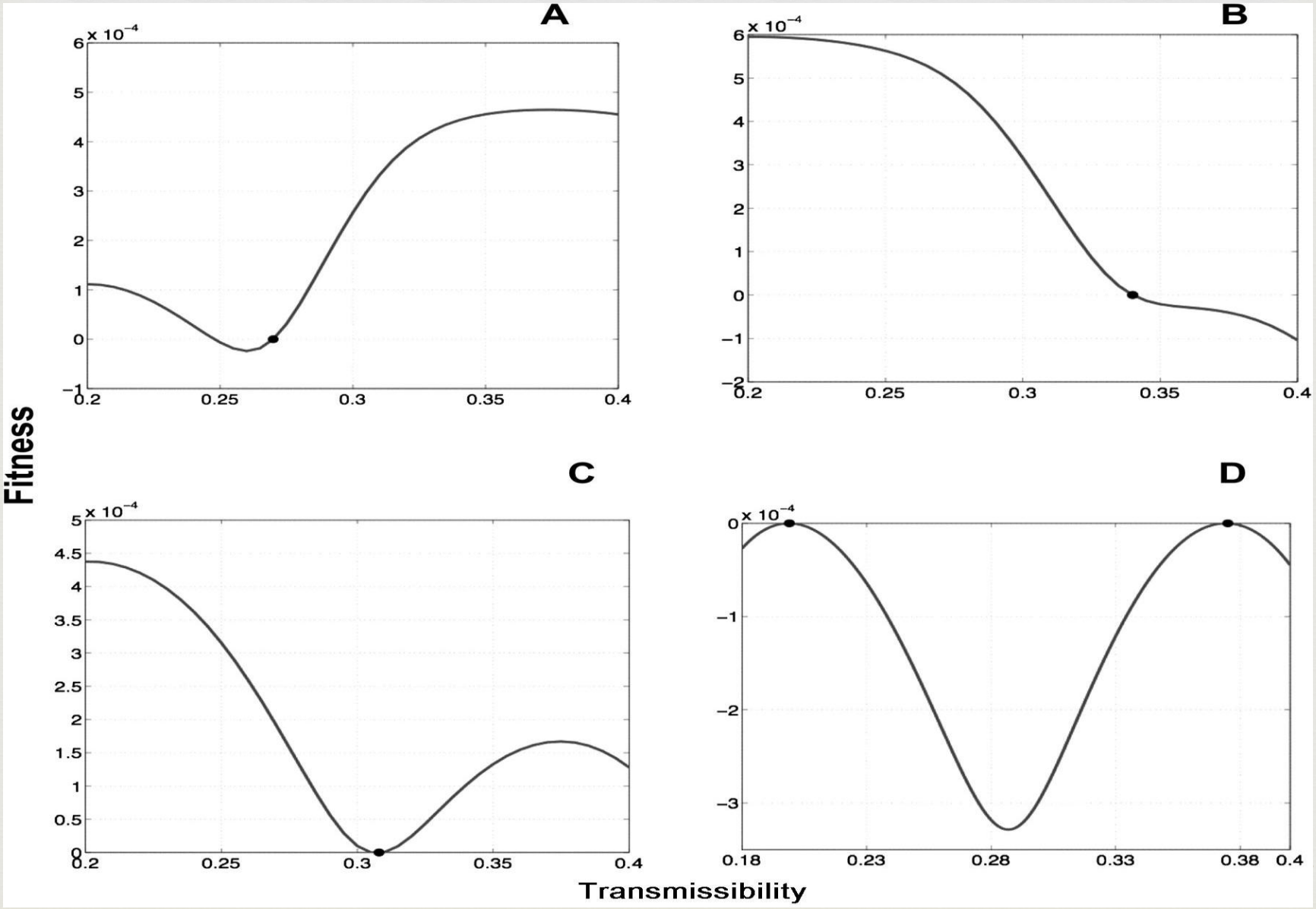


Fig.6. Adaptive landscapes for a HPV strain facing 2 subcultures with a high rate of switching of human individuals from one subculture to the other.

- High switching rate leads to an intermediate phenotype with moderate proliferation and persistence.
- This would likely be manifest as an HPV type with intermediate cancer risk.

Fig.7. Adaptive landscapes depicting a situation in which the rate of switching by humans among subcultures is relatively low.



Discussion

- A slow turnover of sexual partners favors HR HPVs, whereas high frequency of partner turnover selects for LR types.
- When both sexual behaviors exist as subcultures in a population, disruptive selection can result in the co-evolution and ecological coexistence of both HR and LR HPV types.

Evolutionary strategy of HR HPV

- Fewer virion production
- Longer persistence
- Reduced per-sex transmission probability
- Clinically, these infections are inconspicuous, such as the flat lesions of HPV 16 and 18.

Evolutionary strategy of LR HPV

- Large numbers of virion production
- Higher transmission probabilities per sexual contact
- More-rapid elimination
- Clinically, this infection manifests as genital warts (types 6 and 11), which act as virus factories.

2 Assumptions

- All HPV phenotypes compete for susceptible individuals.
- HPV evolves and responds to natural selection.

The Impact of HPV Vaccine

- *Gardasil*® and *Cervarix*® both target HPV 16 and 18.
- Ecologically, they should reduce the prevalence of these types by reducing the resource pool available to them.
- Evolutionarily, the eradication of these types will leave an open niche, causing other types to evolve and fill this HR niche.

Conclusion

- Elimination of HR HPV through vaccines may alter the evolutionary trajectory of the remaining types and promote evolution of new HR HPV types.

The End.

Thank you!