Localised Sex, Contingency and Mutator Genes

Bacterial Genetics as a Metaphor for Computing Systems

Outline

- Living Systems as metaphors
- Evolutionary mechanisms
- Mutation
- Sex and Localized sex
- Contingent gene expression
- Applications

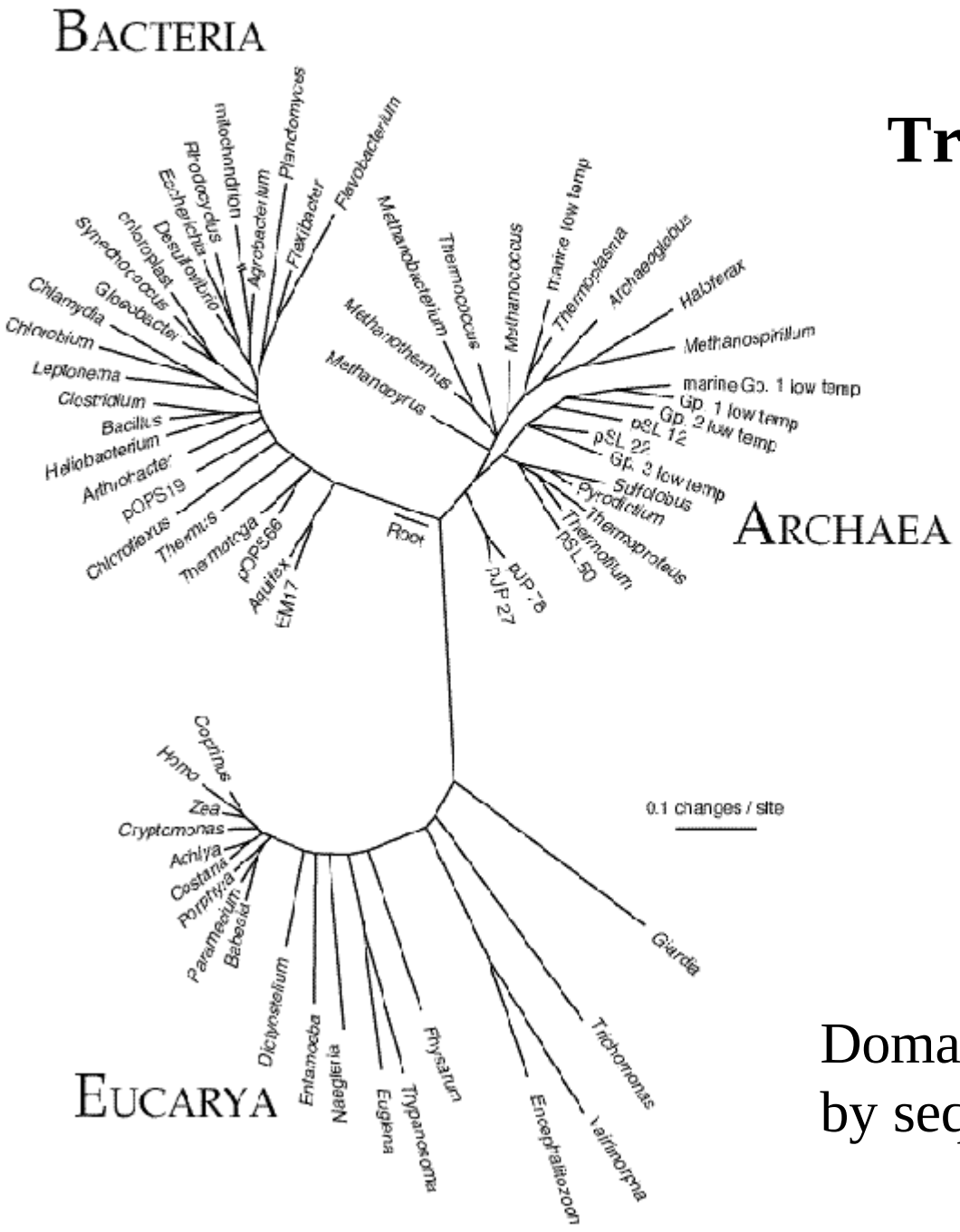
Genetic Programming

- Genetically breeding population of programs using principles of Darwinian natural selection and biologically-inspired operations
- Fitness evaluation, Darwinian selection
- Genetic operations
  - Mutation
  - Crossover (sexual recombination)
  - Reproduction
  - Architecture-Alteration (deletion/duplication)

Adaptation and Optimization

- Natural adaptation normally sub-optimal
- High wastage in natural systems
- Apparently optimal behaviour for an individual can lead to resource depletion and extinction of the group (density dependence of fitness)
- Local selection – sensitivity of selection to local environment and resources

Tree of Life

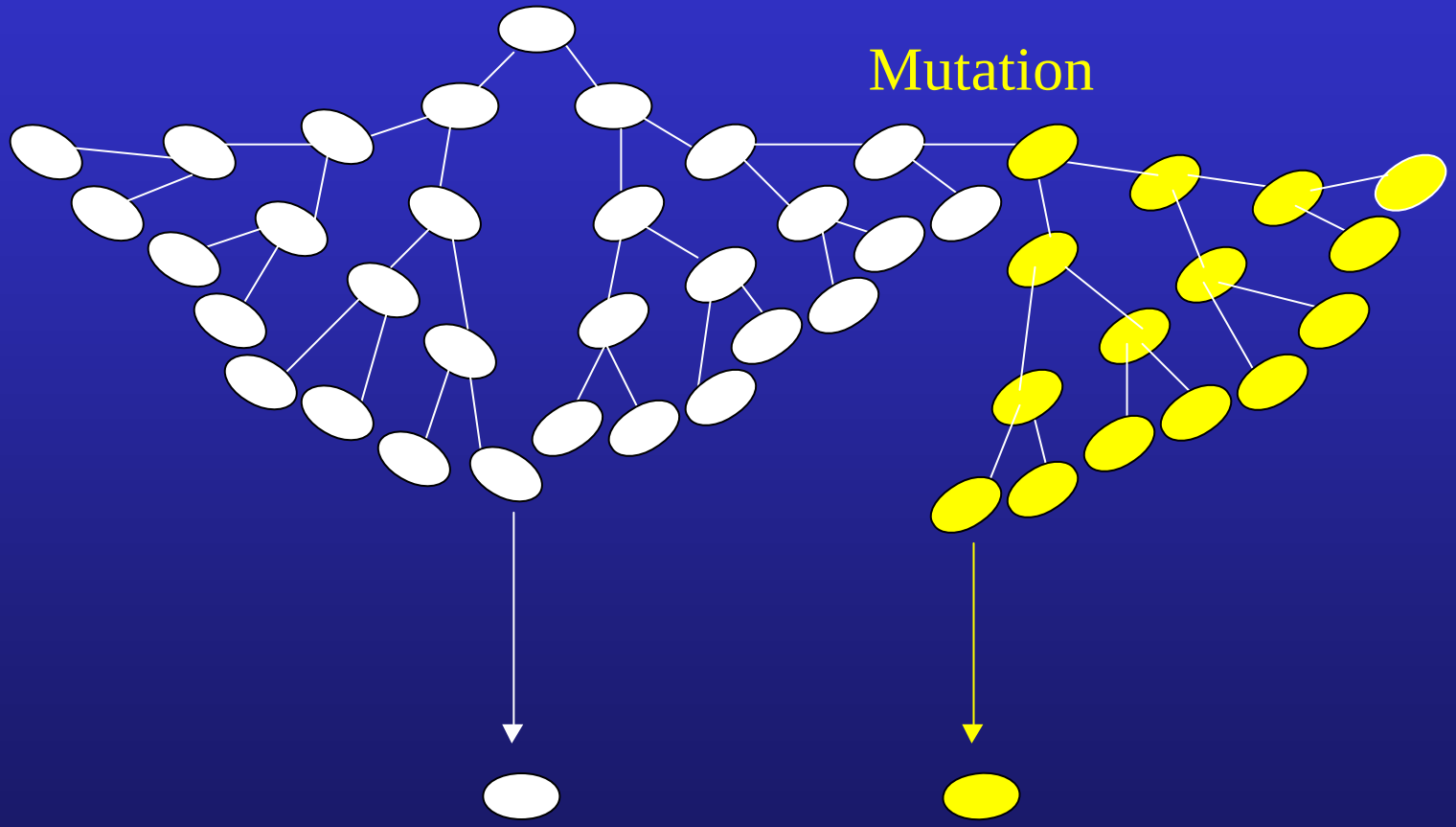


Domains arranged
by sequence distance

Evolution – why bacteria as models/metaphors

- Single point of all life on Earth
- 3 primary domains
  - *Archaea* – slowly evolving
  - *Bacteria* - intermediate
  - *Eukarya* – rapidly evolving (fast clocks)
- Most diversity in *Bacteria* and *Archaea*. *(*Animals, plants minor components in terms of sequence space.)
- Flexible adaptive genetic systems
- Bacterial and archael endosymbionts of eukarya

Consequences of Asexual Reproduction

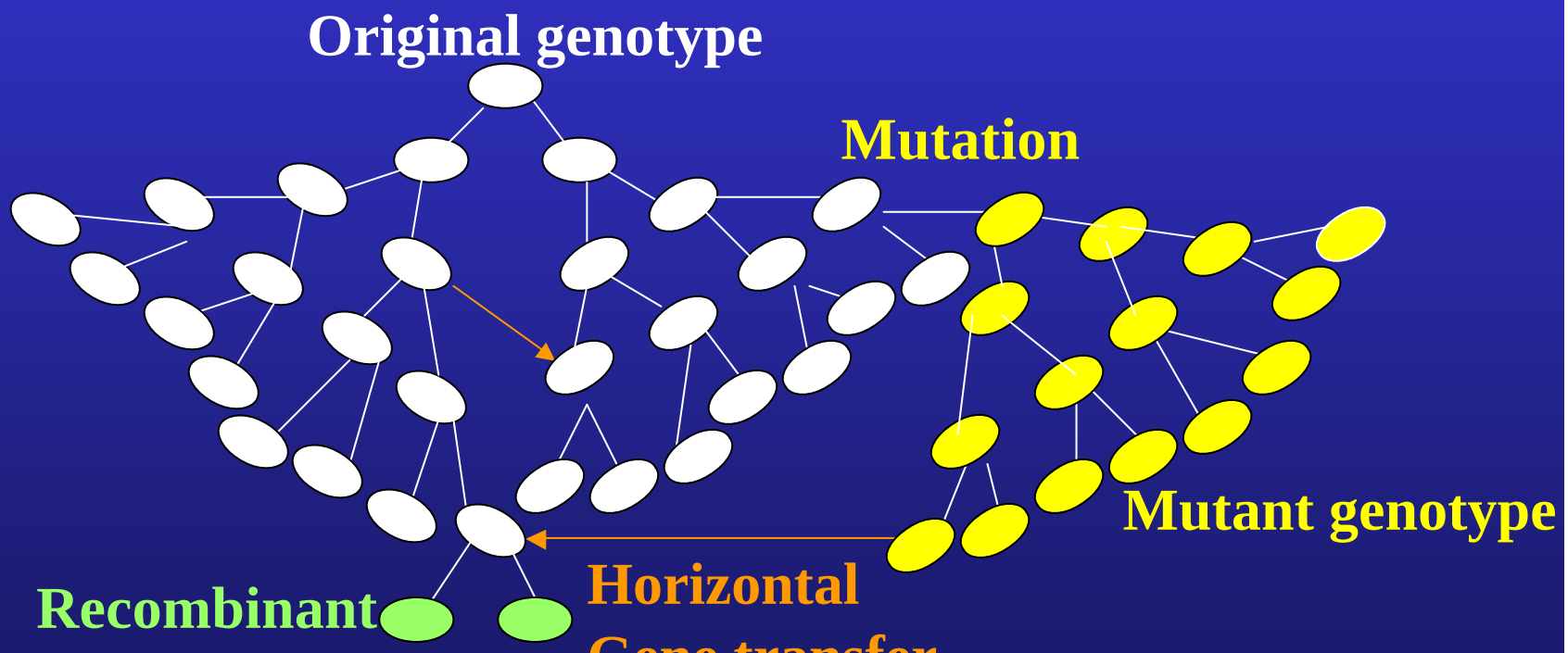


Clonal Population: highly structured with low diversity, bottlenecking, back mutations

Mutation and mutator genes

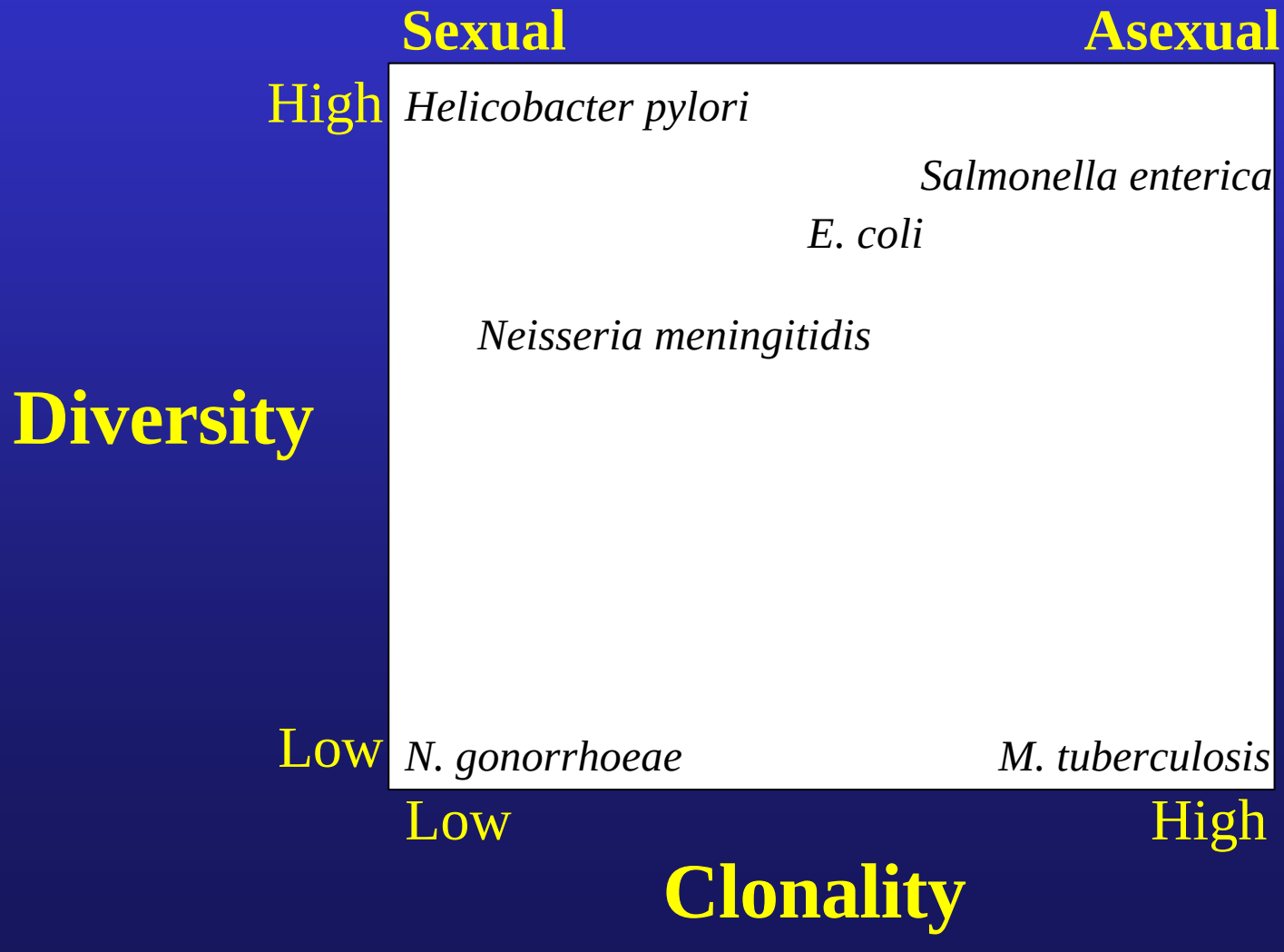
- In asexual reproduction, novelty introduced mainly by **mutation**
- Background mutation rates ~1 x 10^{-7} per cell per generation but many silent mutations
- high rates of mutation allow population to track environmental changes quickly, but at a cost
- **strong mutators -** genes that raise mutation rates in nearby genes
- harmful mutations tolerated if environmental conditions favour mutants.
- Can gain genetic novelty in less costly ways than mutation
  - **Recombination/sex**.
  - **Contingent gene systems (focus variation)**
- Simulations suggest recombination generates diversity more often than even strong mutators.

Horizontal Genetic Exchange

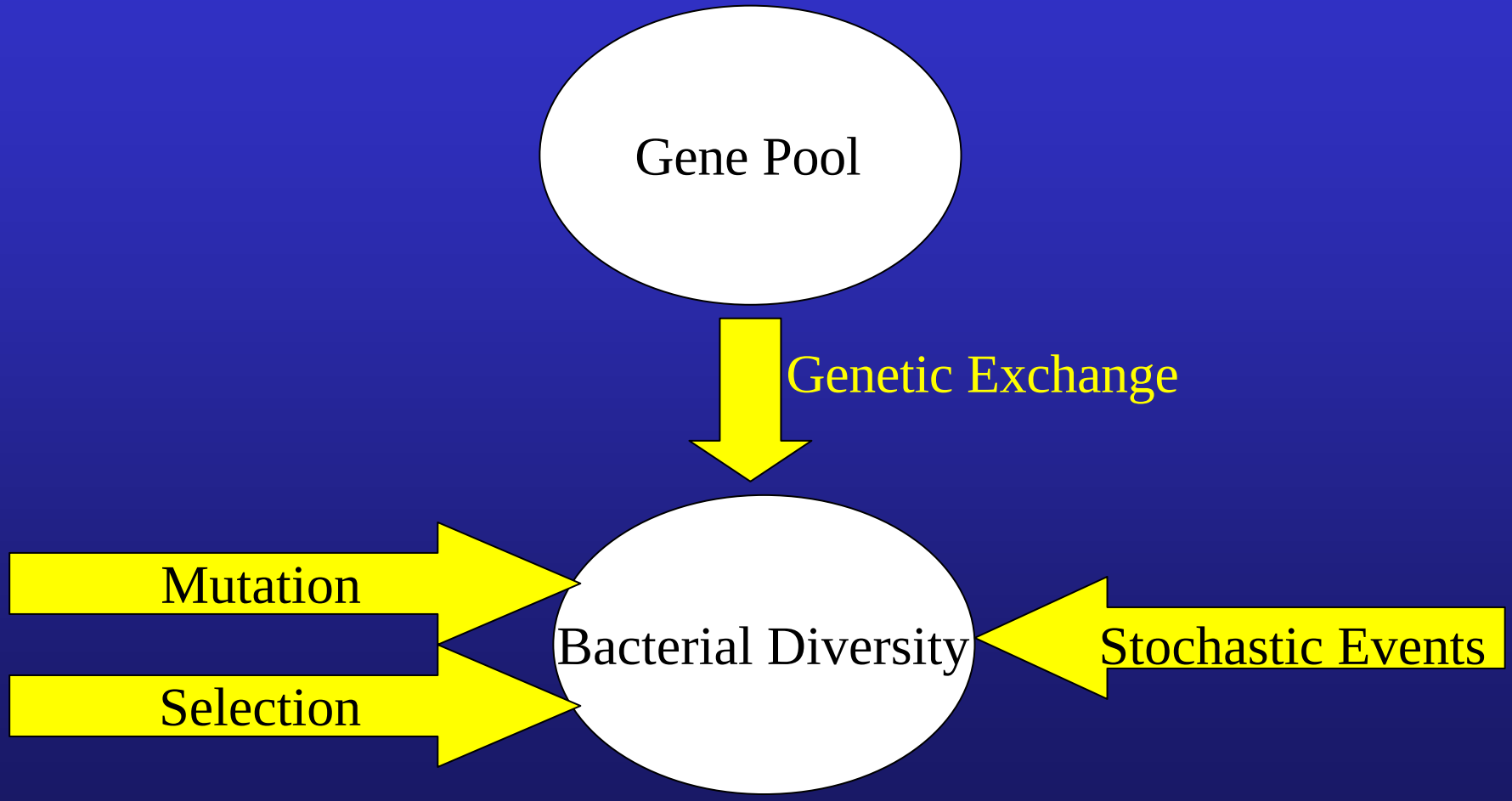


Changes population structure: generates genetic diversity
(new mosaic genes, reassortment of genes, sharing of genes)

Sex and Bacteria - Diversity and Population Structures



Structured diversity in Bacterial Populations



Adaptative strategies for environmental change

- Conventional gene regulation – expression of genes switched on and off in response to an environmental stimulus. Individual-based but population responds co-ordinately.
- Contingent Gene expression – series of genes are switched ON/OFF or UP/DOWN-regulated randomly. Population-based, but individuals have phenotype (expressed characteristics) for any eventuality. Suitable phenotype selected.

Variation - Contingeny

- **Phase Variation -** quantitative changes in transcription or translation
  - On-Off
  - Volume
- **Antigenic Variation -** qualitative changes in a single gene or multiple phase variation in related genes
  - Antigenic / structural changes
  - Functional changes
- Stochastic genetic switching followed by selection

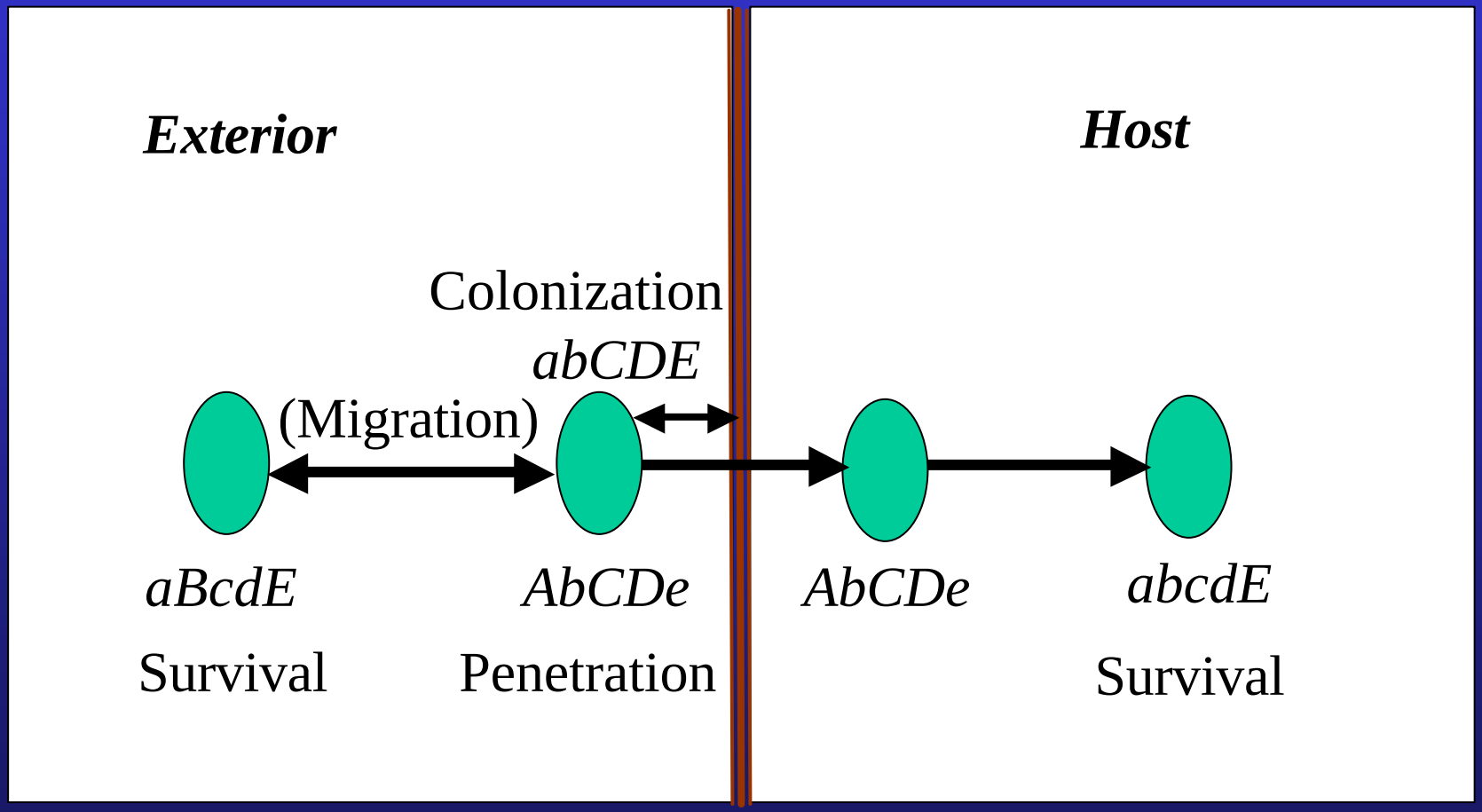
A Combinatorial Strategy for Adaptation to Contingencies

- Consider a hypothetical bacterial pathogen with 2000 genes, 7 of which are controlled by reversible binary switches *e.g.* A <-> a operating at 10^{-3} per bacterium per generation.
- If each gene switches independently = 128 phenotypic possibilities.
- Suppose a pathogen requires phenotypes:

  a,b,c,D,e,f,g - for **colonisation** of its host

  A,b,c,d,e,F,G - for i**nvasion** and **survival** in host
- Switching to favoured (invasion) phenotype = 1 in 10^{12} cells.

Contingency in pathogen colonization/invasion

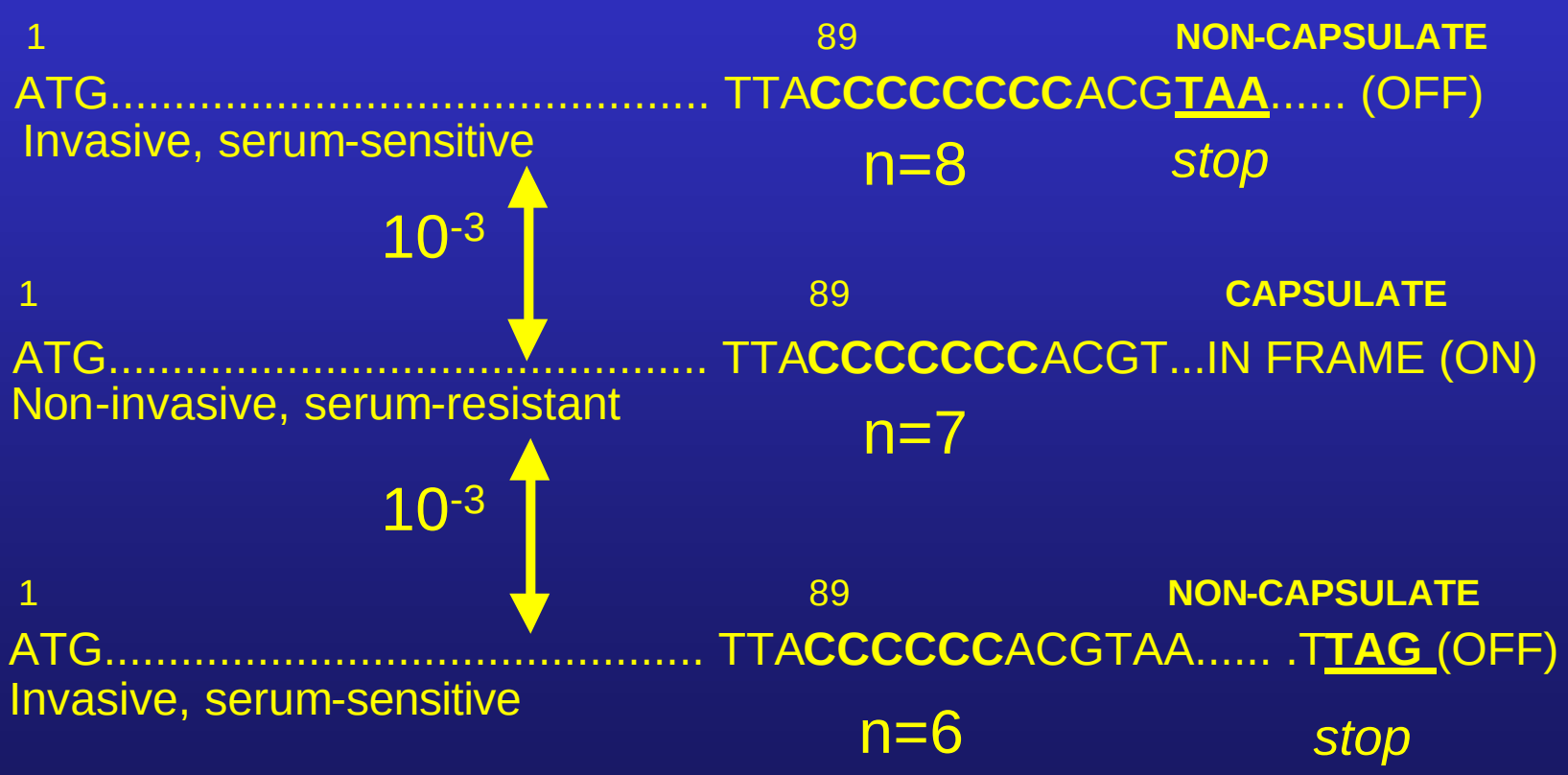


Epithelial/Endothelial barrier

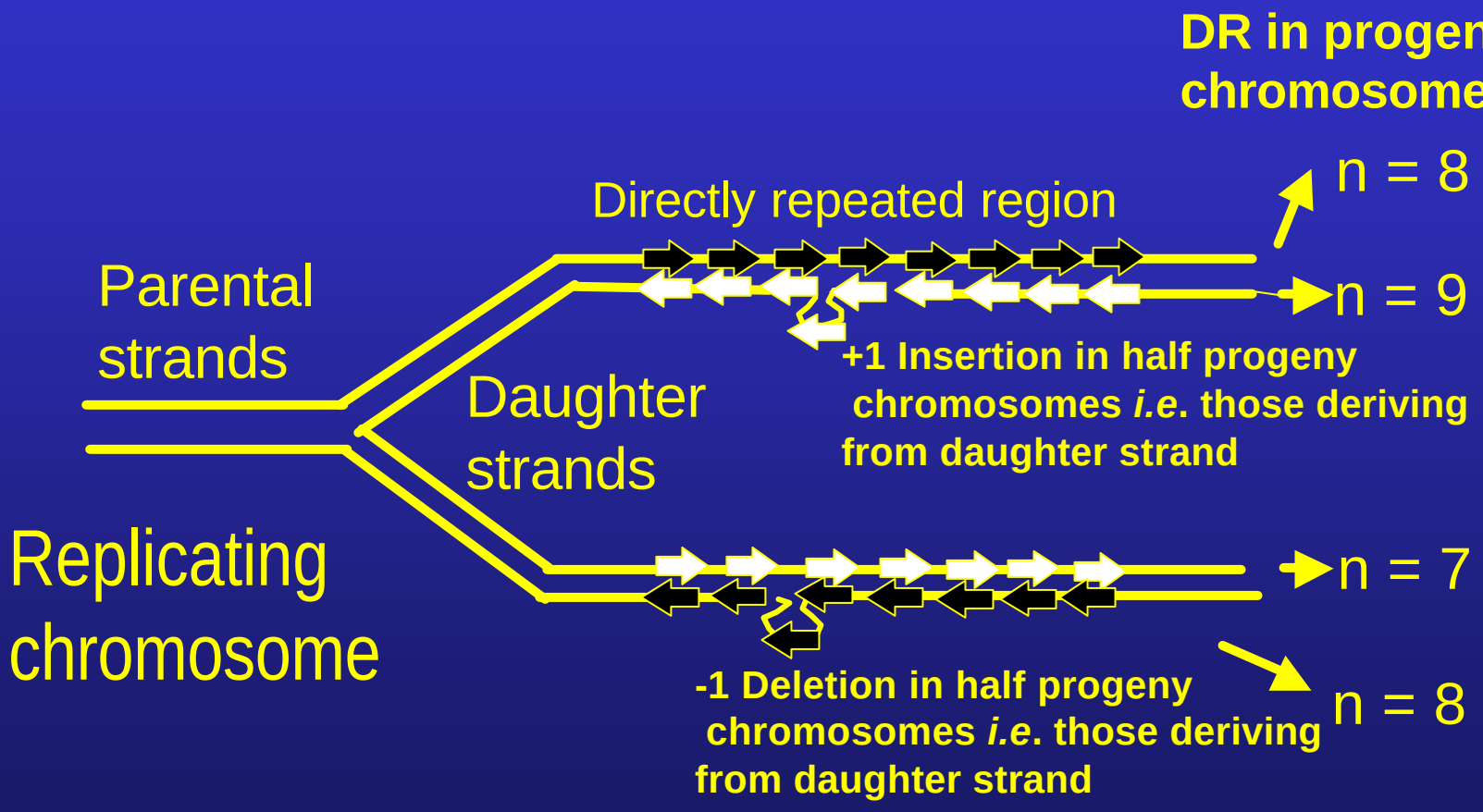
Gene Expression from Contingency Loci

- **Hypermutable loci** typically encoding surface molecules (***e.g.* adhesins, invasins**) in pathogens
- Focus change differentially in genome
- **Large repertoire of phenotypes explored,** but minimises deleterious effects on fitness
- Often controlled by **reversible binary genetic switches (On-Off, qualitative or quantitative)**
  - Slipped stand mispairing
  - Duplication, deletion or inversion
  - Site-specific recombination or hot-spots for generalized recombination
- Switching rates higher than spontaneous mutation ~ 10^{-3} per cell/generation *cf.* 10^{-7}- 10^{-8}

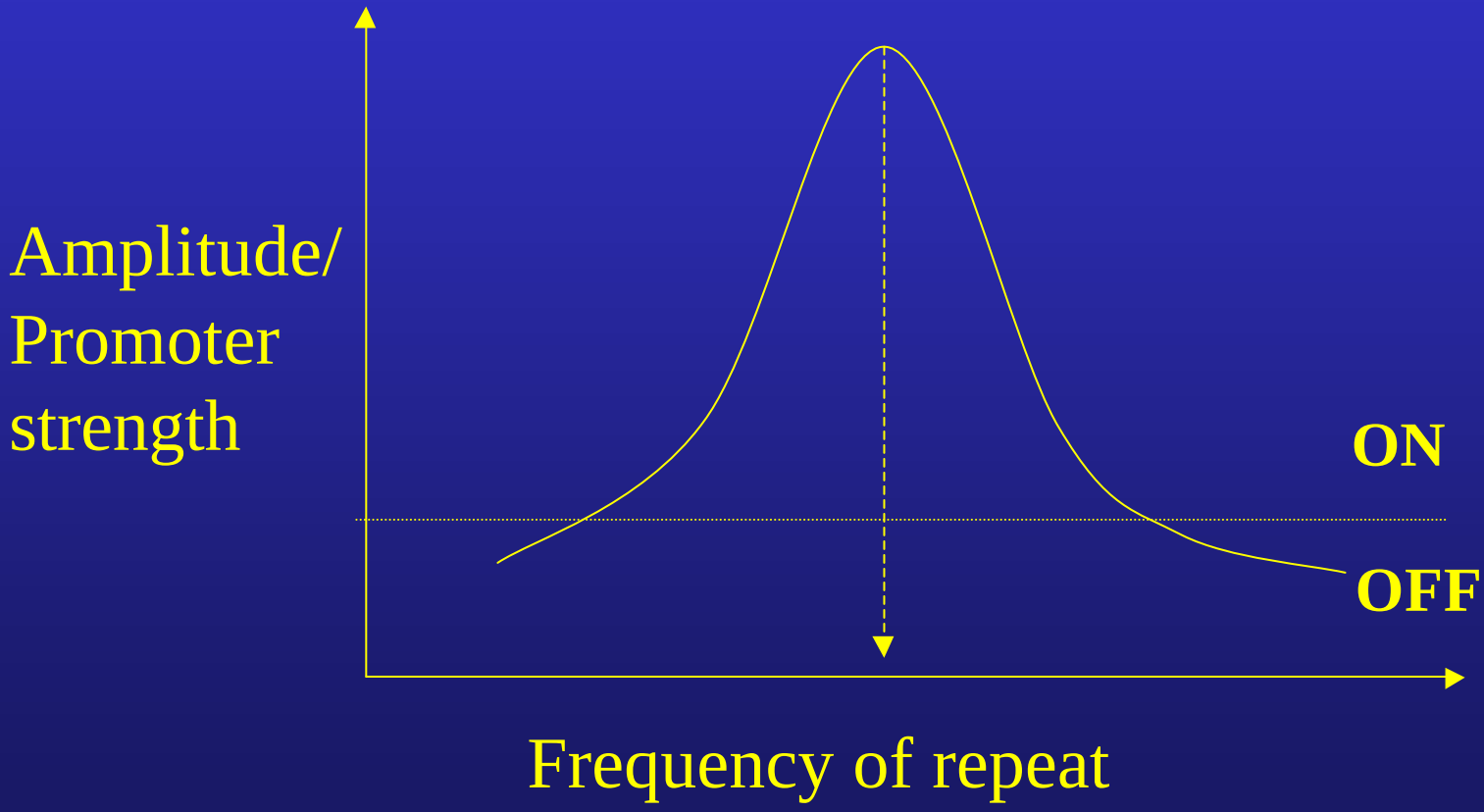
Capsule Phase Variation by translational frame-shifting in the *Neisseria meningitidis siaD* gene



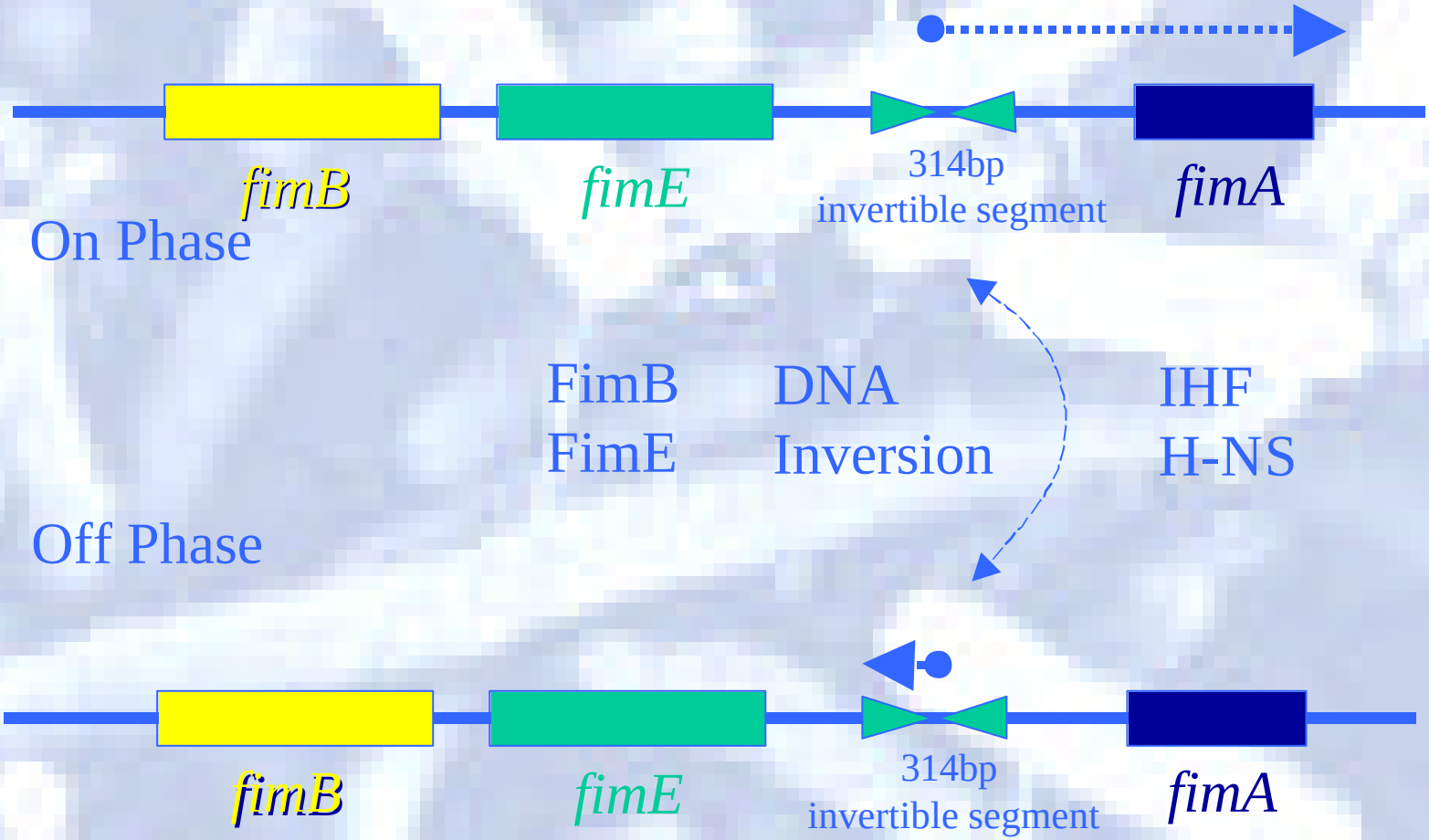
Slipped-Strand Mispairing

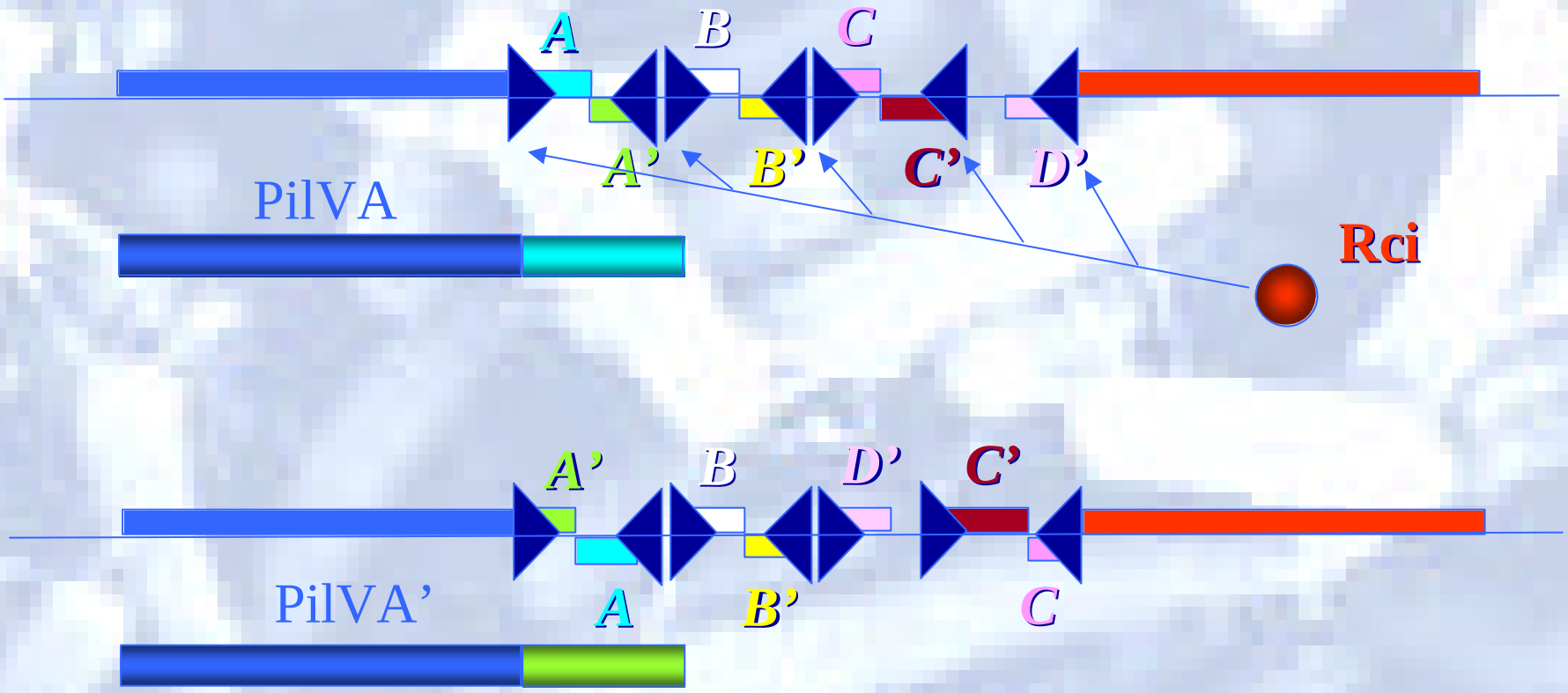


Contingency – Slipped Stand Mispairing



Invertible control of Type 1 fimbrial production in *E. coli*

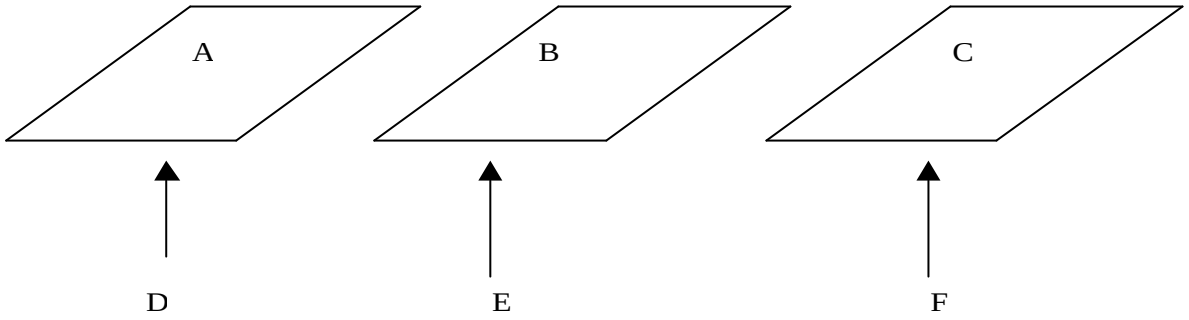


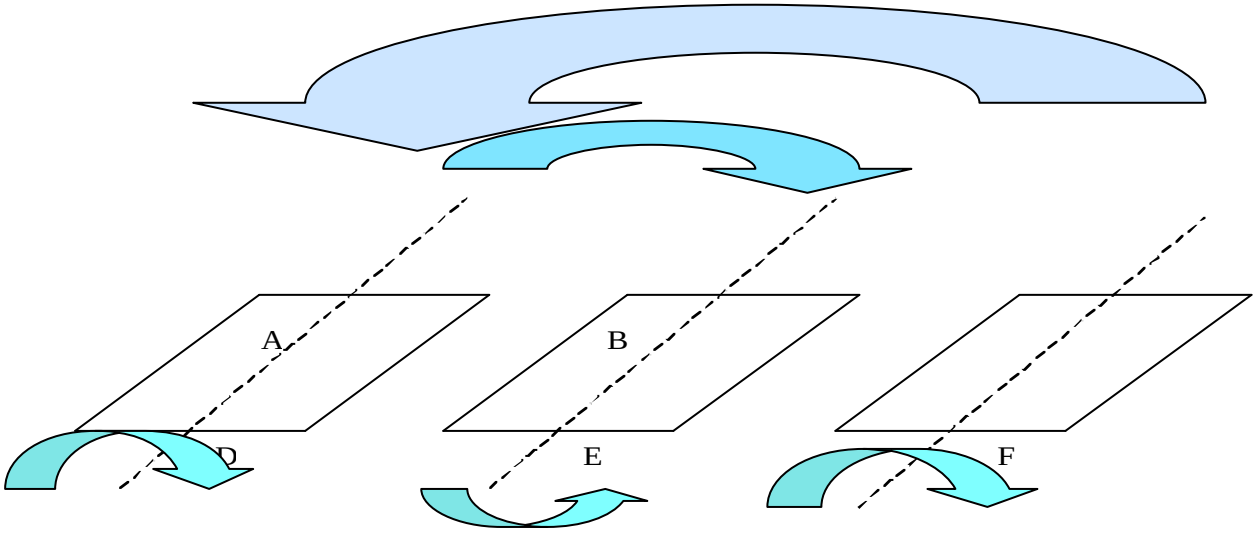


The ColIb Shufflon

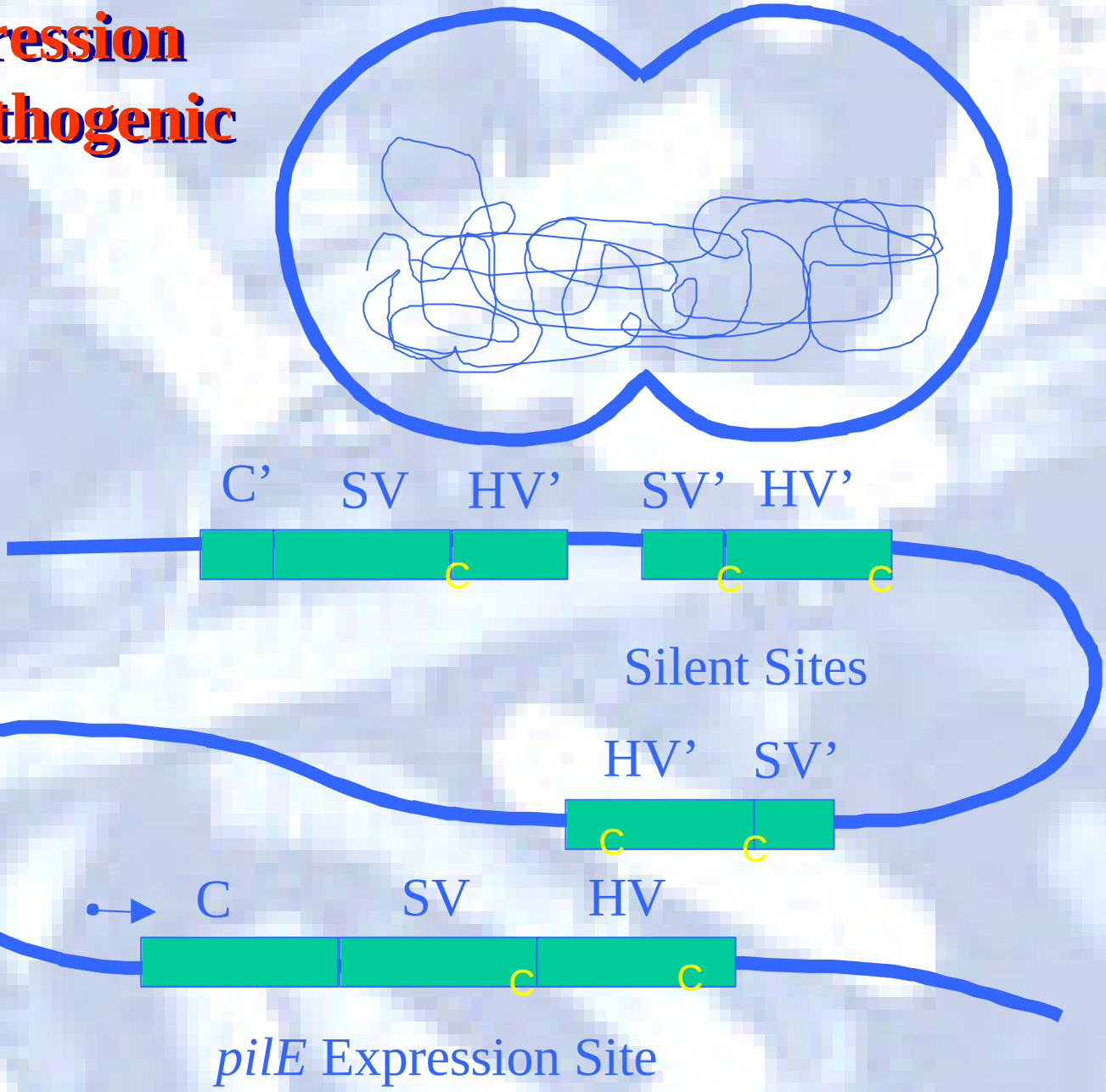
PilVB, PilVB' etc……..

Shufflon





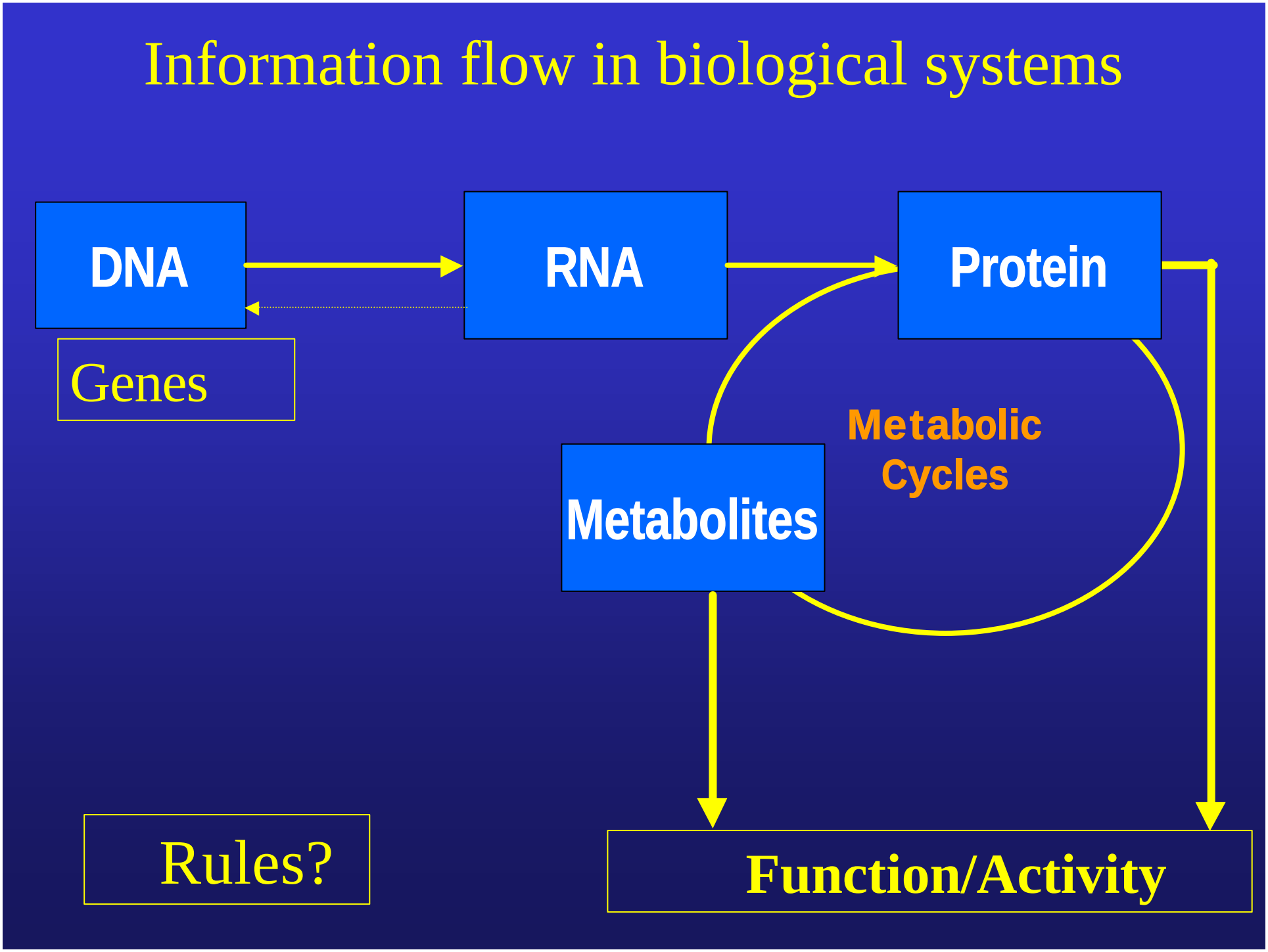
Silent and Expression Pillin loci in pathogenic Neisseria



Virtual bacteria - COSMIC

- With Ray Paton, Costas Vlachos, Richard Gregory, Henry Wu
- Developing virtual bacteria (represented by agents) able to interact and evolve in response to changing environments.
- Inform novel computing architectures
- Inform modelling of complex biological processes

Information flow in biological systems



Potential Biological Applications for Rule –based Models

- Evolutionary modelling
- Minimal genomes and their expression
- Modelling microbial processes and ecology *e.g.*
  - Epidemiology of infectious diseases
  - Antibiotic resistance
  - Biogeochemical cycles