Advanced Bayesian Phylogenetics: Recombination

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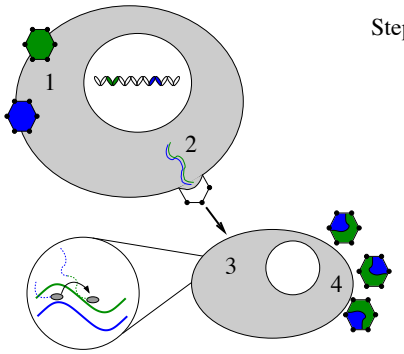
Genomic Reassortment in HIV

Dual infection can lead to inter-subtype recombination:



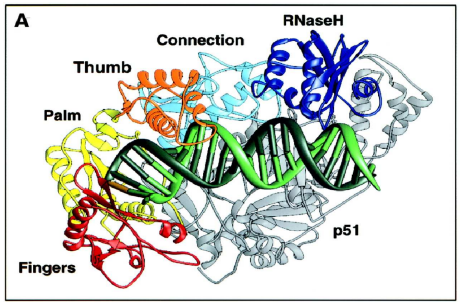
Steps in HIV Sex:

1. Co–infection of host cell by two different HIV subtypes
2. Co–packing of two different HIV RNAs into a single viron
3. Strand jumping during reverse transcription in newly infected host
4. Release of recombinant virus

- Originally believed **rare**
- Now suspected as **major** contributor to genetic diversity
- Clinical implications of intra-host recombination

Mechanisms and Hot-Spots?

Reverse Transcriptase



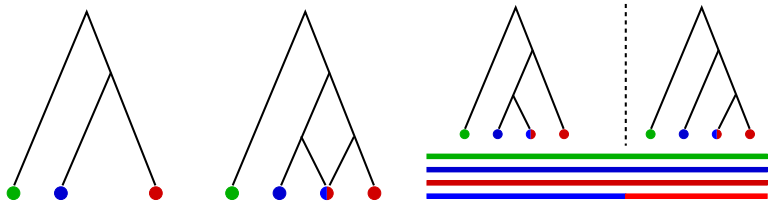
- Probability of strand-slippage/jumping may be function of genomic 1° or 2° structure

Clinical Relevance of Hot-Spots

- *In vivo* evidence
- *In vitro* recomb. rates $50\times$ greater in *env* than *gag*
- Development of multiple drug resistance (Kitchen *et al.*, 2006)
- Drug choice

Phylogenetic Recombination Detection

Recombination $\Rightarrow$ genomic break-points with **incongruent** topologies:

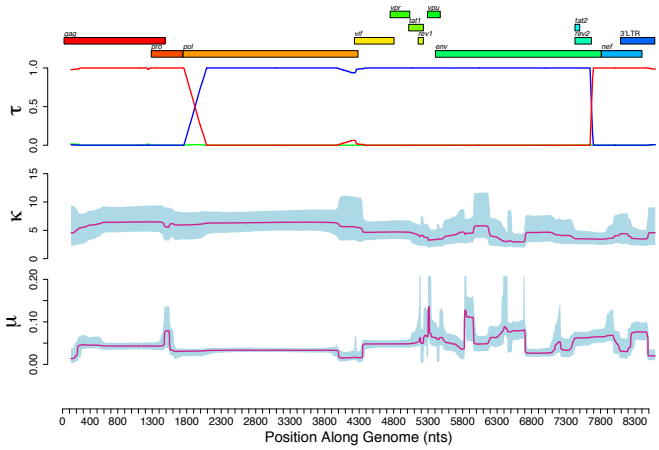


Map break-point locations:

- Hidden Markov models (Husmeier *et al.*, 2003, 2005)
- Multiple change-point models (Suchard, Minin *et al.*, 2002, 2003, 2005)

Dual Multiple Change-Point Process

KAL153
(AB recombinant)

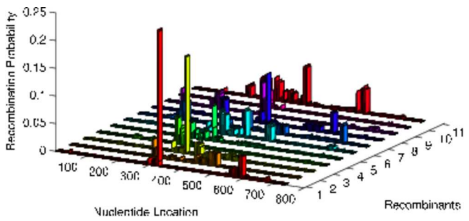


- Separate break-points and rate change-points
- Uncertainty on **number** and **locations** of break-points
- Variable dimensional model $\Rightarrow$ reversible jump MCMC

Putative A/G Inter-Subtype Recombinants

Data:

- 42 **unrelated** (hopefully) recombinants from LANL
- Of **African** origins
- Same subtypes to maximize power



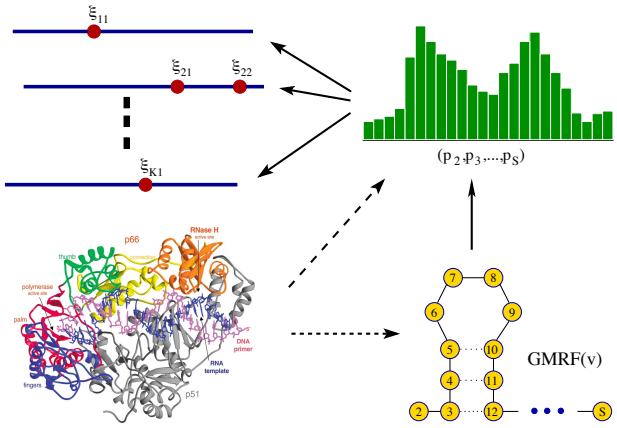
Subset of **independent** analyses

How to **pool** information?

- Sparse "observations" (# break-points $<<$ seq. length)
- Neighboring sites should have similar probabilities

Joint Analysis via Gaussian Markov Random Fields

A GMRF to smooth and estimate **population-level** recombination log-odds (probabilities):



Normally distributed vector

$$\mathbf{x} \sim \mathcal{N}(\boldsymbol{\nu}, \mathbf{Q}^{-1})$$

is a GMRF wrt graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ when $\mathbf{Q} > 0$ and $Q_{ij} \neq 0$ iff $(i, j) \in \mathcal{E}$

- $\mathbf{Q}$ can be huge, but very sparse
- Fast numerical methods available, make the approach feasible (Rue *et al.*, 2001, 2004)

GMRF as an Improper Prior

Field (population-level log-odds) $\boldsymbol{\gamma}$:

$$\boldsymbol{\gamma}|\omega \sim \mathcal{N}(\prime, \tilde{\mathbf{Q}}^{-1}), \text{ where } \tilde{\mathbf{Q}}^{-1} = \mathbf{Q} + \epsilon\mathbf{I}$$

Impropriety: 1^{st}-order random-walk field defined on **differences**. Baseline $\propto 1$. Normally, not a **problem** (Sun, 1999).

- Think of break-points as "success counts" $\mathbf{C} = (C_1, \ldots, C_S)$ in binomial trials
- What if $C_s = 0$ or $C_s = 42$ for all s?

Prior: Random-walk precision $\omega \sim \Gamma(\cdot, \cdot)$. Express prior belief via $p_i/p_j \leq 7$-fold (Bernardinelli, 1995; Moumen, 2001)

Non-linearly Constrained GMRFs

The number of break-points $M \sim$ approximately Poisson(δ) with $\delta = \sum_{s=1}^{S} p_s$ (le Cam, 1960) for each recombinant.

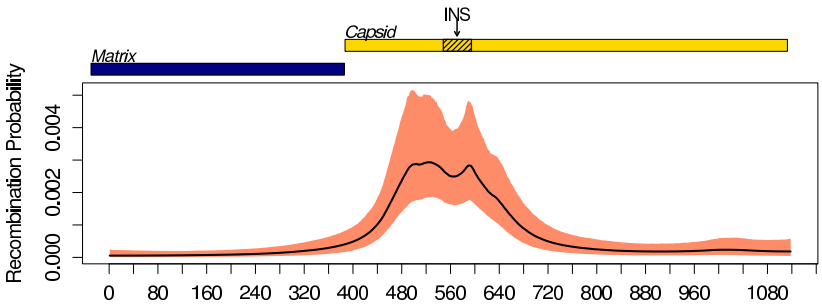
Aim: $\Pr(M > 0) \approx 1 - e^{\delta} = c = 0.5$.

Problem: Sum-of-$\mathbf{p}$ constraint is **non-linear** in the field (γ):

$$\sum_{s=1}^{S} \frac{e^{\gamma_s}}{1 + e^{\gamma_s}} = -\ln(1 - c) \tag{1}$$

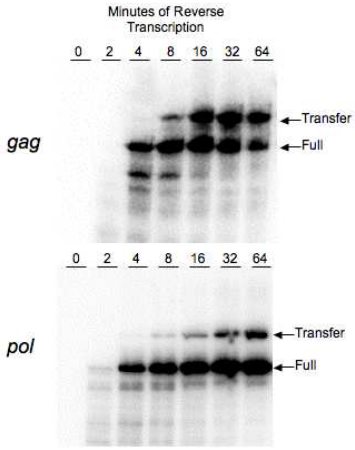
Solution: Linearize constraint via Taylor expansion about arbitrary point $\mathbf{v}$, then constraint $\Rightarrow$ "re-centering" proposal $\gamma^{\star}$ from unconstrained GMRF. How to choose $\mathbf{v}$?

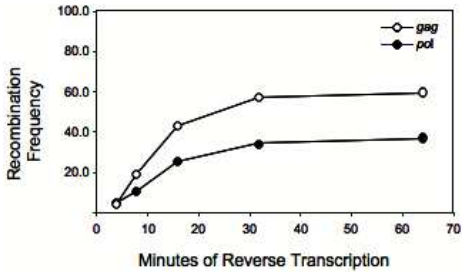
Hot-Spot in *gag* Gene



- Spatial association with an **instability element** (INS). INSs are motifs involved in post-transcriptional regulation of gene expression
- *In vivo* confirmation of hot-spot in the works

Preliminary *in vitro* Strand Transfer Assay





- Results **support** *gag* hot-spot. First *de novo* elucidation of HIV recombination mechanism with computational methods?