Purity Dependant Markov Models for Microsatellite Mutation

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Overview

1. Microsatellites

2. Existing Models

3. Purity-dependant Model

4. Applications

Microsatellites

- Repeats of a short motif, e.g. AT repeated 6 times:

$$\boxed{A}\boxed{T}\boxed{A}\boxed{T}\boxed{A}\boxed{T}\boxed{A}\boxed{T}\boxed{A}\boxed{T}\boxed{A}\boxed{T}$$

Microsatellites

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- Think of microsatellites as repeat units:

$$\boxed{AT}\;\boxed{AT}\;\boxed{AT}\;\boxed{AT}\;\boxed{AT}\;\boxed{AT}$$

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- Think of microsatellites as repeat units:

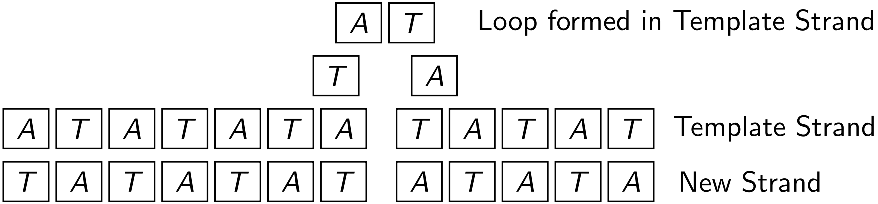
$$\boxed{AT}\quad\boxed{AT}\quad\boxed{AT}\quad\boxed{AT}\quad\boxed{AT}\quad\boxed{AT}$$

- Highly polymorphic.
- Abundant in eukaryote genomes.
- Often selectively neutral.

Slipped-strand mispairing

Contraction

During replication, a loop may form in the template strand leading to a decrease in the number of repeats in the new strand.



A T Loop formed in Template Strand

T A

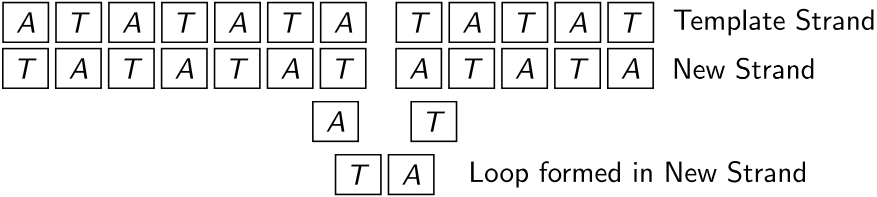
A T A T A T A T A T A T Template Strand

T A T A T A T A T A T A New Strand

Slipped-strand mispairing

Expansion

Alternatively, a loop may form in the new strand, leading to an increase in repeat number relative to the template.



A T A T A T A T A T A T Template Strand

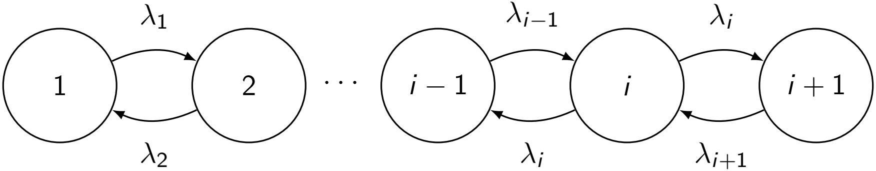
T A T A T A T A T A T A New Strand

A T

T A Loop formed in New Strand

Models for repeat number

- e.g. a symmetric random walk:



- The main factors accounted for are:
  - Length dependence of mutation rate.
  - Bias towards contraction or expansion.
  - Size of the mutation events.

General one-phase slippage model

- [Wu and Drummond, 2011] proposed a class of models which captures many of the models in the literature as subclasses.
- This model allows for:
  1. Quadratic functions of repeat number for mutation rate.
  2. Length dependent mutational bias.
  3. Geometrically distributed slippage event sizes.

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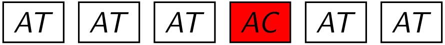
For the one-phase models (slippage events of size 1 only) model is given by

$$q_{ij} = \begin{cases} \alpha(u_0, u_1, u_2, i)\beta(b_0, b_1, i) & \text{if } i - j = -1 \\ \alpha(u_0, u_1, u_2, i)(1 - \beta(b_0, b_1, i)) & \text{if } i - j = 1 \\ -\sum_{k \neq i} q_{ik} & \text{if } i = j. \end{cases}$$

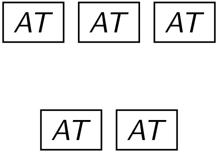
Point mutation

- Microsatellites also susceptible to point mutations.



AT AT AT AC AT AT

- How to deal with this?

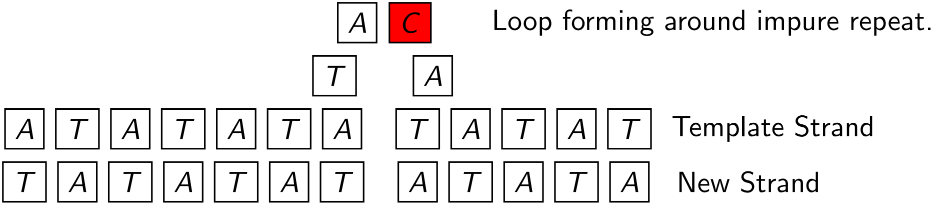


AT AT AT

AT AT

Point mutation

- These models lose useful information, and may invalidate IID assumption.



A C Loop forming around impure repeat.

T A

A T A T A T A T A T A T Template Strand

T A T A T A T A T A T A New Strand

Kruglyak's proportional slippage model

- [Kruglyak, 1998] proposed a model which included point mutation.
- They assumed slippage was linearly proportional to repeat number,
- and that point mutation would occur in any repeat at a constant rate a.

$$q_{ij} = \begin{cases} c & \text{for } i = 1, j = 2 \\ (i-1)b & \text{for } i > 1, j = i+1 \\ (i-1)b + a & \text{for } i > 1, j = i-1 \\ a & \text{for } i > 1, j < i-1 \\ 0 & \text{otherwise.} \end{cases}$$

Kruglyak's proportional slippage model

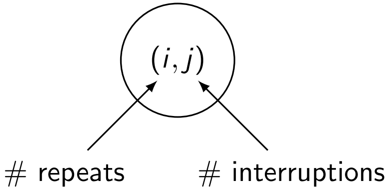
- Kruglyak and Durrett proved in a later paper [Durret, 1999] that the stationary distribution exists.
- Stationary distribution can be shown to satisfy

$$c\pi_1 = b\pi_2 + a\sum_{j=2}^{\infty}\pi(j),$$

$$b(i-1)\pi_i = bi\pi_{i+1} + ia\sum_{i=i+1}^{\infty}\pi_j \text{ for } i \geq 2.$$

Purity-dependant Model

- We move up a dimension in the state space.



(i,j)

# repeats

interruptions

$$\boxed{AT}\ \boxed{AT}\ \boxed{AT}\ \boxed{AC}\ \boxed{AT}\ \boxed{AT}$$

$$= (6,1)$$

Key Assumptions

- Effect of impurity is independent of location.

$$\boxed{AT}\ \boxed{AT}\ \boxed{AT}\ \fcolorbox{black}{red}{AC}\ \boxed{AT} \quad = \quad \boxed{AT}\ \fcolorbox{black}{red}{AC}\ \boxed{AT}\ \boxed{AT}\ \boxed{AT}$$

- Each base pair is either ‘correct’ or ‘incorrect’.

$$\boxed{A}\boxed{T} \neq \boxed{A}\boxed{C} = \boxed{A}\boxed{G} = \boxed{A}\boxed{A}$$

Extra Assumptions

- A repeat *unit* is either pure or impure - binary.

$$\boxed{AT} \neq \boxed{AX} = \boxed{YT} = \boxed{YX}$$

- Slippage events of length 1 only.

Heuristic model development

Slipped-strand mispairing

- Process may transition from a state (i, j) to $(i + 1, j)$ at a rate given by $r_s(i, j)$.

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Point mutation

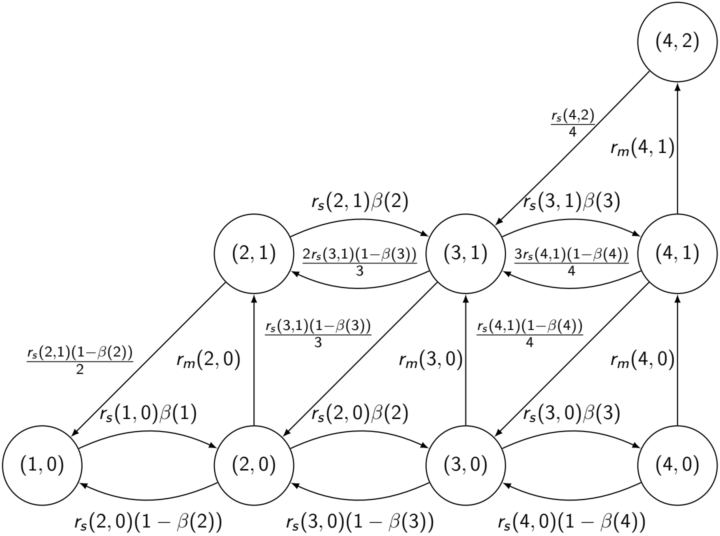
- Process may transition from a state (i, j) to $(i, j + 1)$ at a rate given by $r_m(i, j)$.

The General Purity-Dependant Model

In its most general form, our model is given by generator $\mathbf{Q} = [q_{ij}]$ where

$$q_{(i,j)(k,l)} = \begin{cases} r_s(i,j)\beta(i) & \text{for } k = i+1, l = j \\ r_s(i,j)(1-\beta(i))\frac{(i-j)}{i} & \text{for } k = i-1, l = j \\ r_s(i,j)(1-\beta(i))\frac{j}{i} & \text{for } k = i-1, l = j-1 \\ r_m(i,j) & \text{for } k = i, l = j+1. \end{cases}$$

The General Purity-Dependant Model



Some Restrictions

By making some restrictions we can judge the benefits of modeling point mutation/purity.

Purity-independant model

Set $r_s(i,j) \equiv r_s(i)$.

- Models point mutation.
- Purity has no effect on mutation rates.

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One-dimensional model

Set $r_m(i,j) \equiv 0$ (and fix $j = 0$)

- No point mutation.
- No purity dependance
- Reduced to 1D, one-phase model.

Applications

We choose some specific functions r_s, β, r_m

- $r_s(i,j) = (u_0 + u_1(i-1))c^{-j}$,
- $\beta(i) = \frac{1}{1+e^{-(b_0+(i-1)b_1}}$,
- $r_m(i,j) = d(i-j)$.

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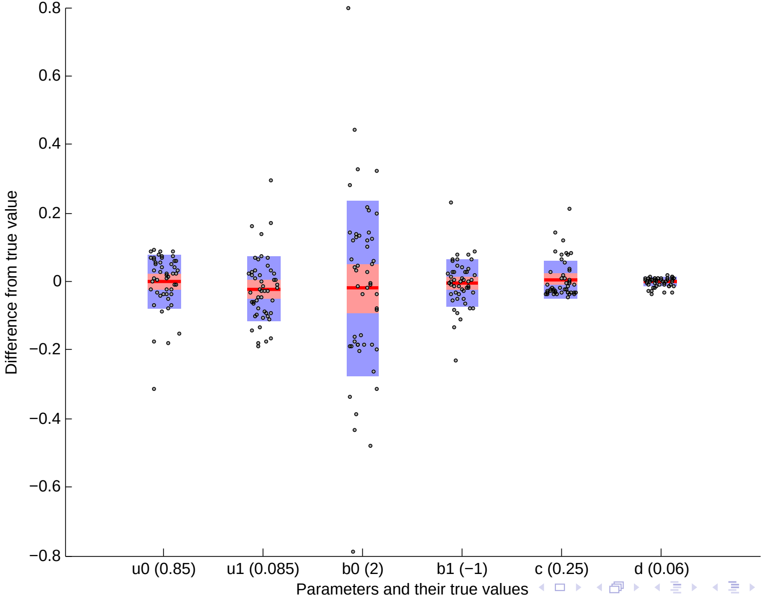
- If we set $c = 1$ then $r_s(i,j) = r_s(i)$.
- If we set $r_m = 0$ then we have Wu and Drummond's one-phase linear-rate logistic bias model.

Simulation (Purity-dependant Model)



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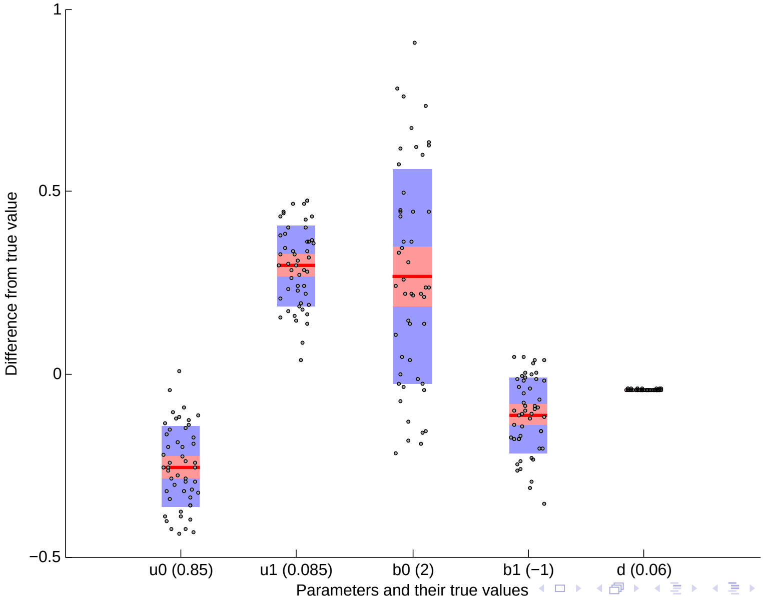

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