Creating an Evolution Simulator for Protein Low Complexity Regions and Attempting to Utilize it for an Approximate Bayesian Computation

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Overview

- Background Information
- Simulating LCR Evolution
- Applications to ABC-MCMC
- Conclusions
- Future Work

What are Low Complexity Regions?

Saccharomyces cerevisiae SRP40 Protein LCRs

>CAA82171.1(25-125) complexity=0.92 (15/1.90/2.20)
sssssssssssssssssssssssgessssssssssssssdssdssdsessssssssss
ssssssdsesssesdssssgsssssssssdesssesesede

>CAA82171.1(149-282) complexity=1.33 (15/1.90/2.20)
essssesssssgsssssesesgsesdsdsssssssssdsesdsesdsqsssssssssdsss
dsdsssdsssdsdsssssssssssdsdsdsdsssdsdssgssdsssssdsssdestssds
sdsdsdsdsgssse

>CAA82171.1(298-316) complexity=2.18 (15/1.90/2.20)
tpassnestpsasssssan

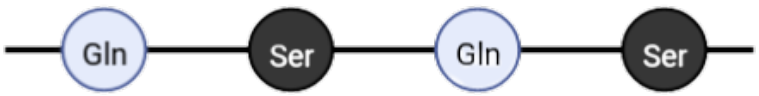
LCRs Present in Unique Ways

Homorepeats

Consecutive iterations of a single residue

Direpeats

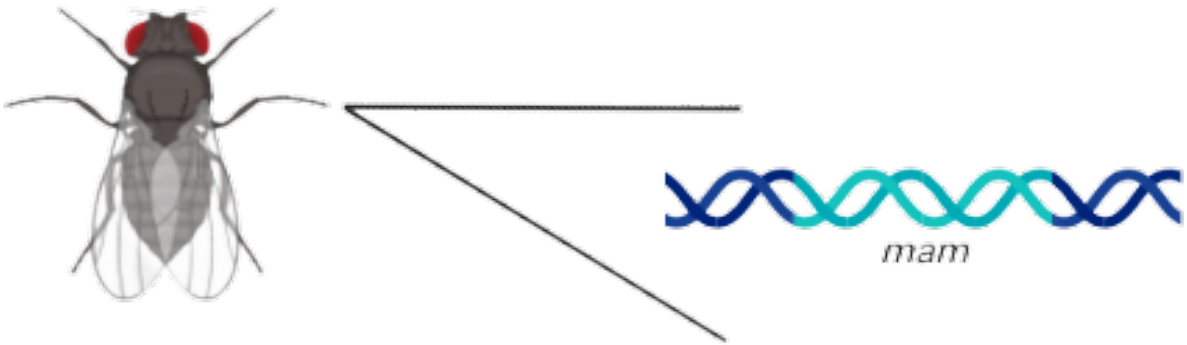
Consecutive iterations of two ordered, different residues



Imperfect Repeats

Regions in which the repeat units are not the same

LCRs are Hypermutable

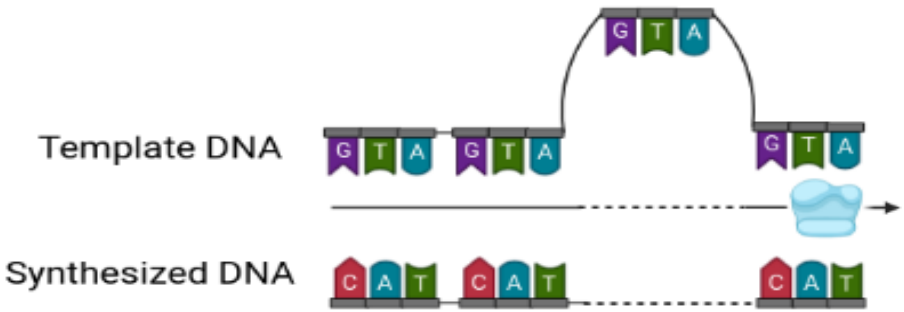


mam domain	Size (bp)	Amino Acid Substitutions	Amino Acid/ Total Substitutions
Unique	933	26	0.15
Repetitive	810	47	0.42

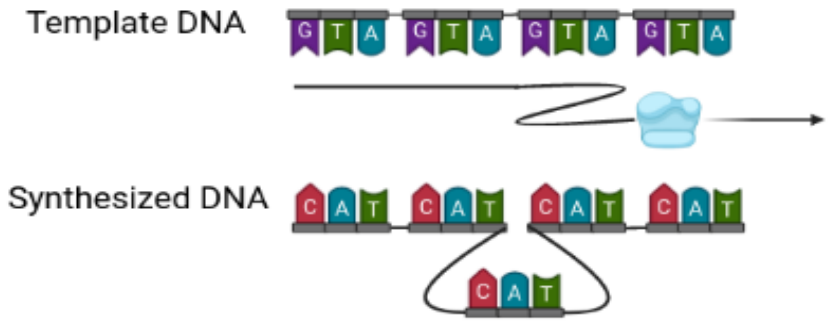
[1] Newfeld, Smoller, and Yedvobnick, 1991

Proposed Mechanisms of LCR Evolution

1. Polymerase Slippage/Slipped Strand Mispairing



Polymerase Slips Forward

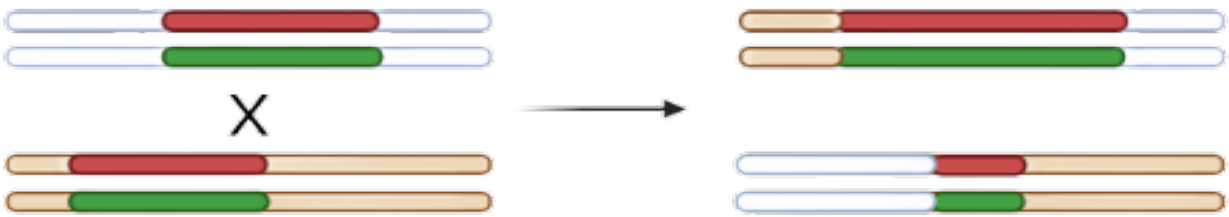


Polymerase Slips Backwards

[2] Levinson and Gutman, 1987; Sehn, 2015

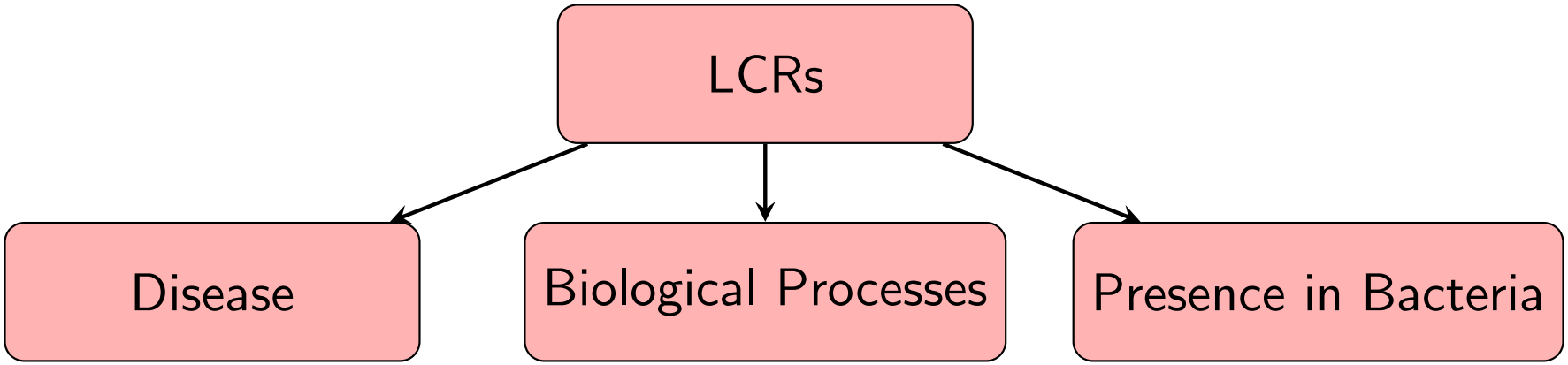
Proposed Mechanisms of LCR Evolution

2. Unequal Recombination

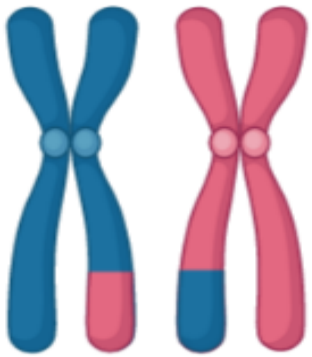


[3] Mirkin, 2007

Why Care about LCRs and their Evolution?



Huntington's Disease



Genetic Recombination

Neisseria meningitidis

What we Did in this Study

LCR Simulator Overall Process

1. Random Protein Sequence
   GGAGGGAQ
   mutation rate = 0.14 indel rate = 0.14

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   mutation rate = 0.14 indel rate = 0.14

2. Assign Exponential Deviates
   mutation deviates = (0.83, 1.82, 2.35, 0.54, 0.98, 0.76, 1.53, 2.34)
   indel deviates = (0.21, 1.21, 1.49, 0.86, 0.97, 1.13, 0.53, 0.35)
   exp(β), where β = mutation rate
   exp(β), where β = length of repeat * indel rate

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   Lowest value deviate = Residue that mutates fastest

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4. Upon point mutation, insertion, or deletion, scan the sequence again to see if the landscape of the sequence was affected, assign new deviates to affected amino acids only.

LCR Simulator Results

LCR Simulator Results 2

LCR Simulator Results 3

LCR Simulator Results 4

Bayesian Statistics Overview

Bayesian Statistics: Model-based statistical inference

$$p(D|\theta) \tag{1}$$

Likelihood

Bayesian Statistics Overview

Bayesian Statistics: Model-based statistical inference

$$p(D|\theta) \tag{1}$$

Likelihood

$$p(\theta|D) \tag{2}$$

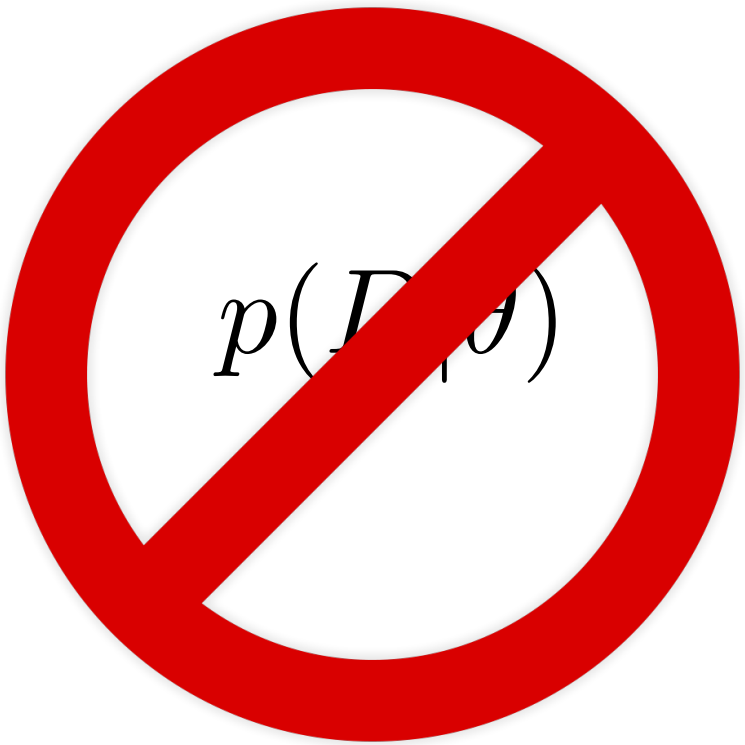
Posterior

Why use an ABC-MCMC

- The increasing complexity and magnitude of available data can make the likelihood difficult to calculate

$$p(D|\theta)$$

Why use an ABC-MCMC



- Calculation of the likelihood is replaced with a simulation step

MCMC for ABC

1. Propose a move from θ to θ' according to a transition kernel $q(\theta, \theta')$.
2. Generate simulated dataset D' using θ' and calculate S'.
3. If $\rho(S', S) \leq \epsilon$ continue to 4, otherwise remain at θ and go to 1.
4. Calculate

$$\alpha(\theta, \theta') = min(1, \frac{\pi(\theta')q(\theta', \theta)}{\pi(\theta)q(\theta, \theta')})$$

5. Accept θ' with probability α, otherwise stay at θ.
6. Return to 1.

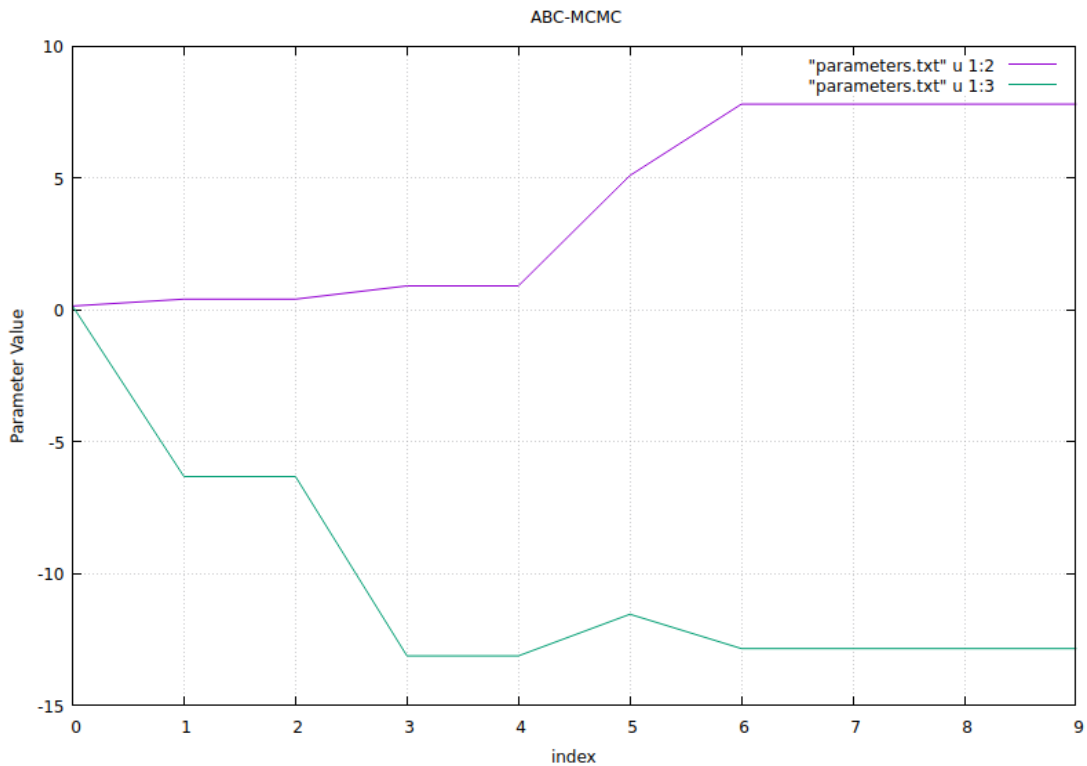
[4] Marjoram et al., 2003

MCMC for ABC: Modified Algorithm

1. Propose a move from θ to θ' according to the normal distribution $N(0.0, 1.0)$
2. Create and mutate a random protein sequence using θ' to generate the simulated Dataset D' - do this 1000 times per newly proposed parameter value.
3. Calculate summary statistics for simulated dataset D' (average of all 1000 vectors of summary statistics)
4. If $d(S', S) < previous\_distance$, go to next step, otherwise employ a one-sample t-test to assess the probability of accepting a larger distance. If the newly proposed distance is close to the previous distance, there is a higher chance we accept the value, otherwise we reject.
5. Accept θ'
6. Return to step 1

Future Work

- Graphical representations of simulation iteration versus parameter values
- Implementation of weighted summary statistics in distance calculation
- Adjustment of values such as mean and standard deviation of the proposal distribution



Acknowledgements

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