Markov chains, part 2

Ben Langmead

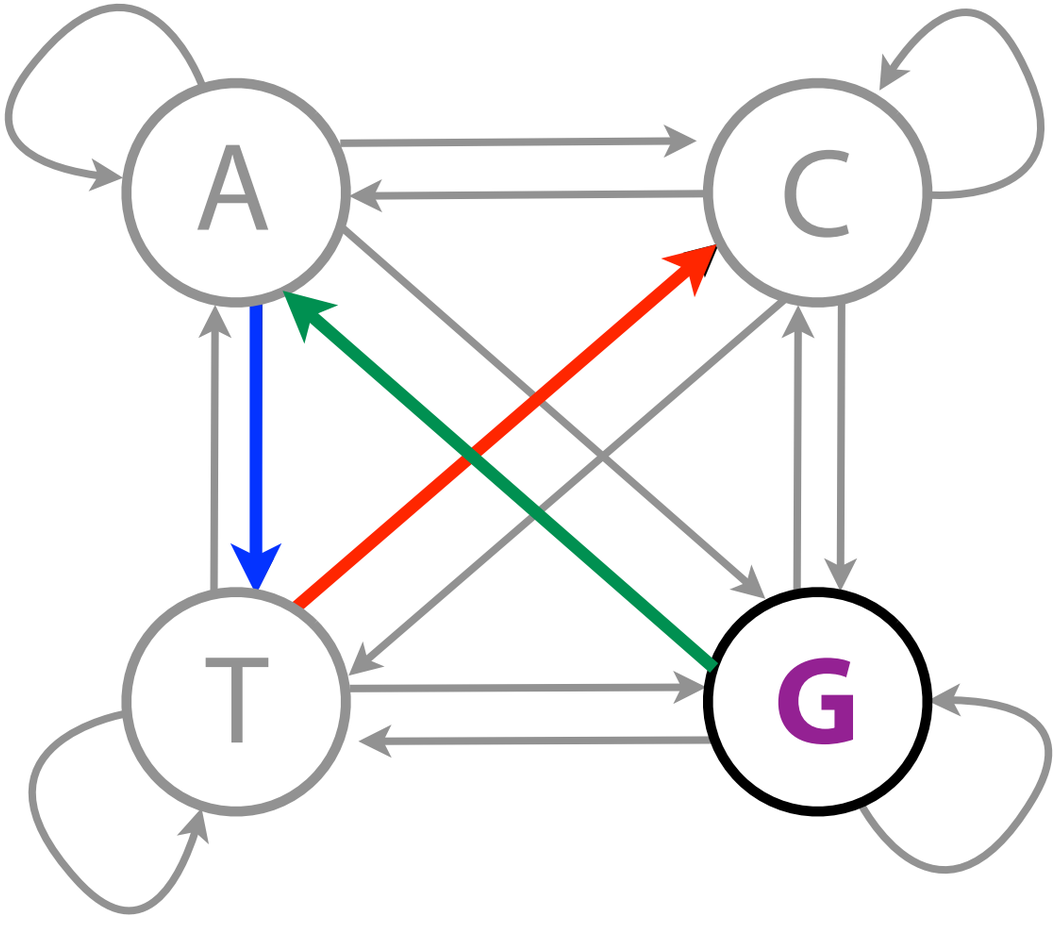
Markov chain

```
>>> iTab, oTab = islandTransitionTables(fn, ifn)
>>> print(iTab)
[[ 0.18427153, 0.27129525, 0.4055757 , 0.13885752],
 [ 0.19081672, 0.36113346, 0.24897947, 0.19907035],
 [ 0.17440554, 0.32764433, 0.35676759, 0.14118254],
 [ 0.09348595, 0.3474561 , 0.36885   , 0.19020795]]
```

X_{i-1} A C G T

A C G T

X_i



$x = \text{GATC}$

$P(x) = P(x_4 \mid x_3)\, P(x_3 \mid x_2)\, P(x_2 \mid x_1)\, P(x_1)$

$P(x) = P(\text{C} \mid \text{T})\, P(\text{T} \mid \text{A})\, P(\text{A} \mid \text{G})\, P(\text{G})$

$= 0.347 * 0.139 * 0.174 * 0.25$

$= 0.0021$

Markov chain

** is exponentiation

```
>>> 0.5 ** 1
0.5
>>> 0.5 ** 10
0.0009765625
>>> 0.5 ** 100
7.888609052210118e-31
>>> 0.5 ** 1000
9.33263618503218 9e-302
>>> 0.5 ** 1100
```

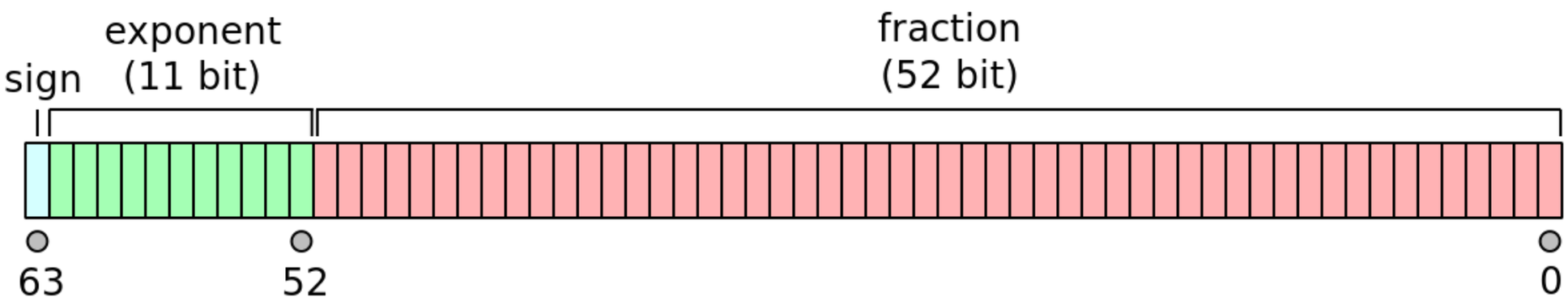
Markov chain

Underflow: when result is a number so small, it cannot be represented in a limited-precision floating point number and is **rounded to 0**

** is exponentiation

```
>>> 0.5 ** 1
0.5
>>> 0.5 ** 10
0.0009765625
>>> 0.5 ** 100
7.888609052210118e-31
>>> 0.5 ** 1000
9.33263618503218 9e-302
>>> 0.5 ** 1100
0.0
```

😱😱😱



https://en.wikipedia.org/wiki/Double-precision_floating-point_format

Markov chain

To avoid underflow, switch to log domain

$$\log P(x) \approx \log [\, P(x_k \mid x_{k-1})\, P(x_{k-1} \mid x_{k-2}) \ldots P(x_2 \mid x_1)\, P(x_1)\,]$$

$$= \log P(x_k \mid x_{k-1}) + \log P(x_{k-1} \mid x_{k-2}) + \ldots$$

…product becomes sum!

$$= \sum_{i=2}^{k} \log P(x_i \mid x_{i-1}) + \log P(x_1)$$

Assume logs are base 2

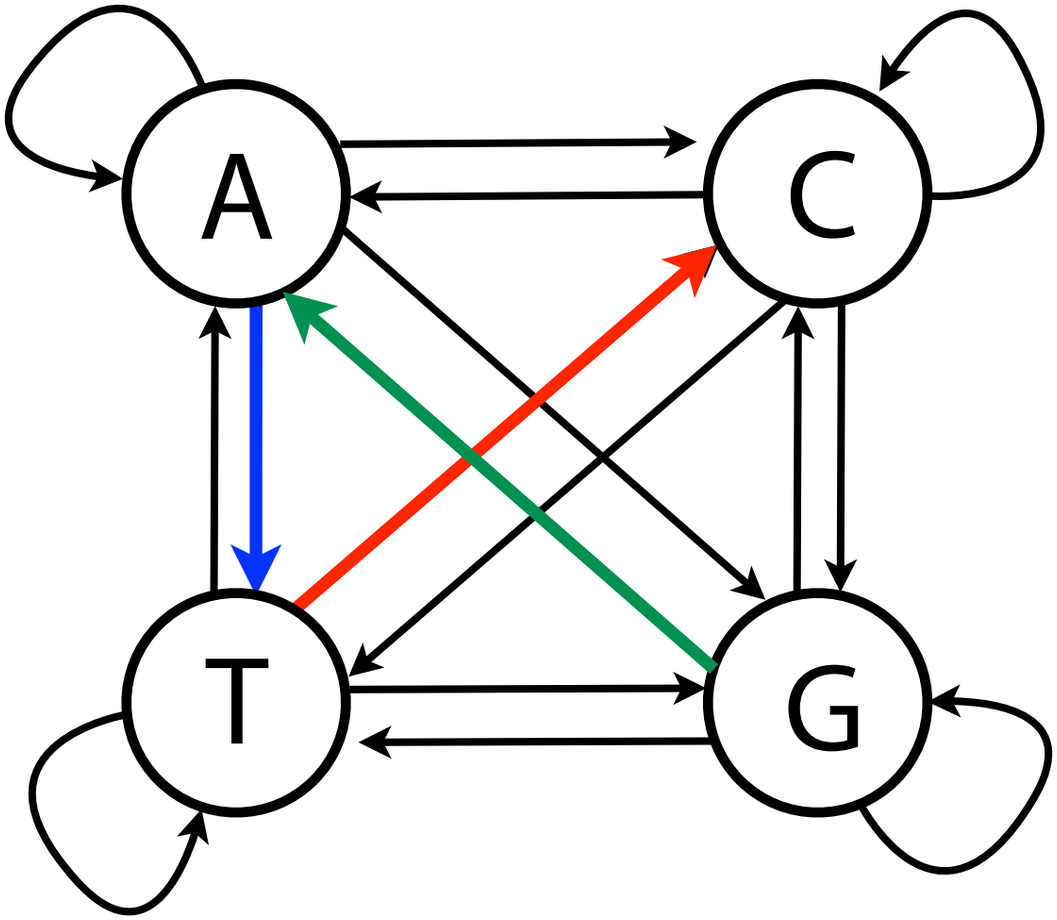
Markov chain

```
>>> iTab, nTab = islandTransitionTables(fn, ifn)
>>> print(numpy.log2(iTab))
[[-2.44009488, -1.8820643 , -1.30195688, -2.84832282],
 [-2.38974049, -1.469396  , -2.00590131, -2.32864974],
 [-2.51948223, -1.60979755, -1.48694353, -2.82436637],
 [-3.41910668, -1.52509737, -1.43889385, -2.39435058]]
```

X_{i-1}: **A** **C** **G** **T**

A **C** **G** **T**

X_i



$x = \text{GATC}$

$$\log P(x) = \sum_{i=2}^{4} \log P(x_i \mid x_{i-1}) + \log P(x_1)$$

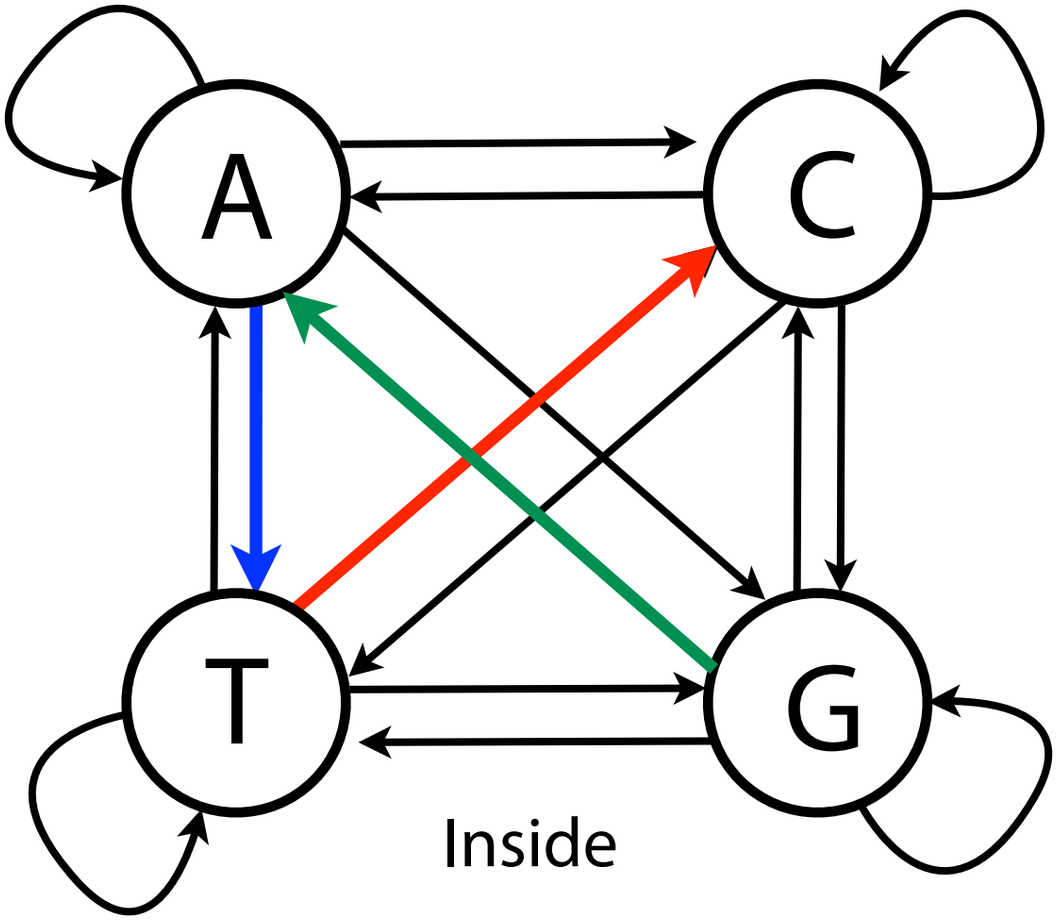
$$= -1.525 + -2.848 + -2.519 + -2.0$$

$$= -8.892$$

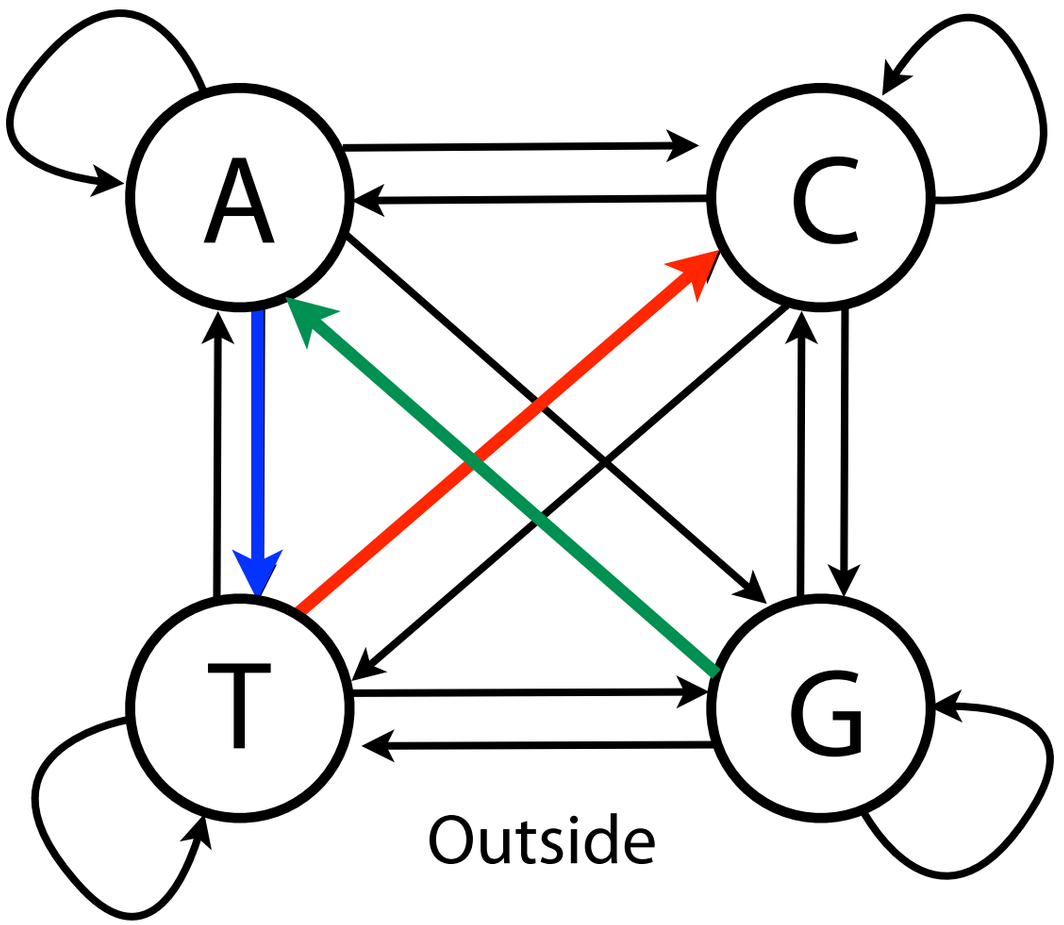
Markov chain

P(x) given the inside-CpG model is helpful, but we really want to know which model is better, inside CpG or outside CpG?

Use *ratio:* $$\frac{\text{P(} x \text{) using model on the left}}{\text{P(} x \text{) using model on the right}}$$



Inside



Outside

Markov chain

Take log, get a *log ratio*: $$S(x) = \log \frac{P(x) \text{ inside CpG}}{P(x) \text{ outside CpG}}$$

If inside more probable than outside, fraction is > 1, log ratio is > 0.
Otherwise, fraction is ≤ 1 and log ratio is ≤ 0.

$$S(x) = \log \frac{P(x) \text{ inside CpG}}{P(x) \text{ outside CpG}}$$

$$= \log [\, P(x) \text{ inside CpG} \,] - \log [\, P(x) \text{ outside CpG} \,]$$

(Marginal probabilities ignored here)

$$= \sum_{i=2}^{k} \left(\log [\, P(x_i \mid x_{i-1}) \text{ inside CpG} \,] \right) - \sum_{i=2}^{k} \log \left([\, P(x_i \mid x_{i-1}) \text{ outside CpG} \,] \right)$$

$$= \sum_{i=2}^{k} \underbrace{\left(\log [\, P(x_i \mid x_{i-1}) \text{ inside CpG} \,] - \log [\, P(x_i \mid x_{i-1}) \text{ outside CpG} \,] \right)}$$

New table: elementwise log ratios between inside/outside

Markov chain

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 [ 0.17440554, 0.32764433, 0.35676759, 0.14118254],
 [ 0.09348595, 0.3474561 , 0.36885   , 0.19020795]]
>>> print(oTab)
 [[0.33804066, 0.17971034, 0.23104207, 0.25120694],
  [0.37777025, 0.25612117, 0.03987225, 0.32623633],
  [0.30257815, 0.20326794, 0.24910719, 0.24504672],
  [0.21790184, 0.20942905, 0.2642385 , 0.3084306 ]]
>>> combinedTab = numpy.log2(iTab) - numpy.log2(oTab)
>>> print(combinedTab)
 [[-0.87536356,  0.59419041,  0.81181564, -0.85527103],
  [-0.98532149,  0.49570561,  2.64256972, -0.7126391 ],
  [-0.79486196,  0.68874785,  0.51821792, -0.79549511],
  [-1.22085697,  0.73036913,  0.48119354, -0.69736839]]
```

Inside: A C G T

Outside: A C G T

Log ratio: A C G T

A C G T

Markov chain

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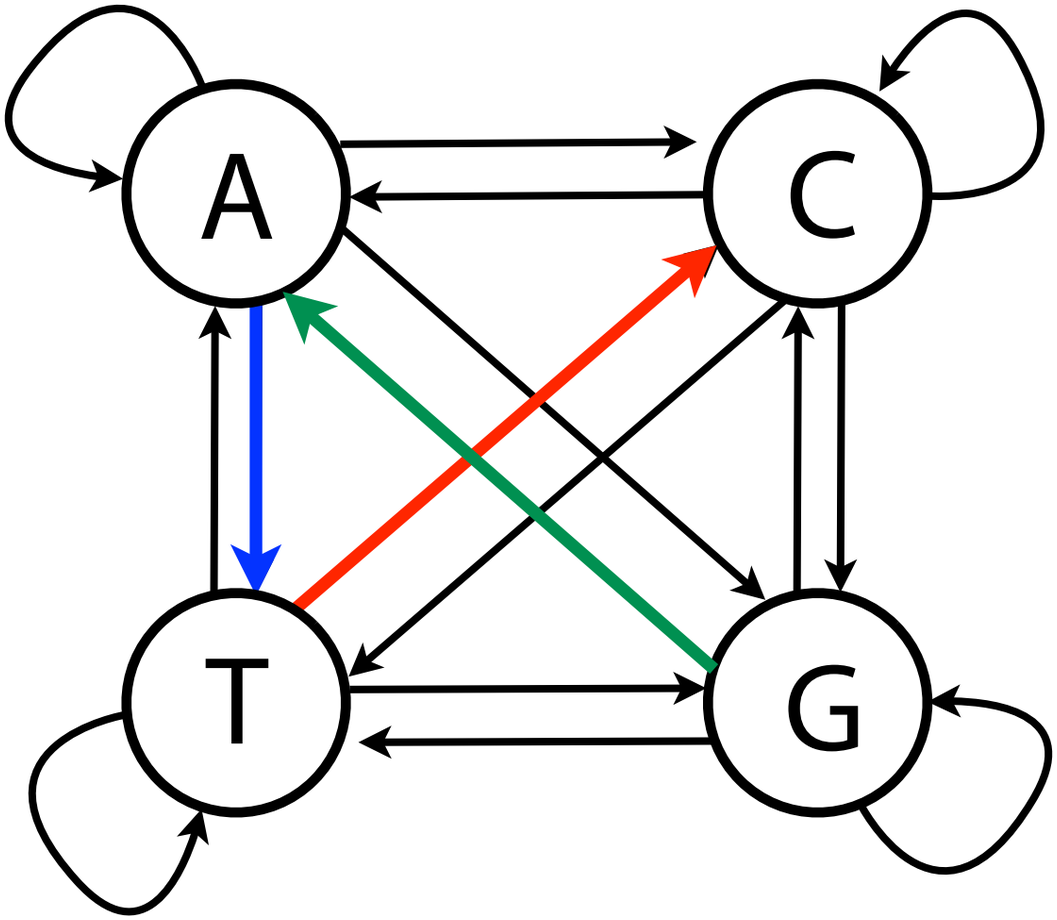


(Marginal probabilities ignored here)

x = GATC

S(x) = 0.730 +
-0.855 +
-0.795

= -0.92

Negative, therefore probability with *outside* model is greater

Markov chain

$$S(x) = \log \frac{P(x) \text{ inside CpG}}{P(x) \text{ outside CpG}}$$

S(CGCGCGCGCGCGCGCGCGCGCGCG) = 32.246609048

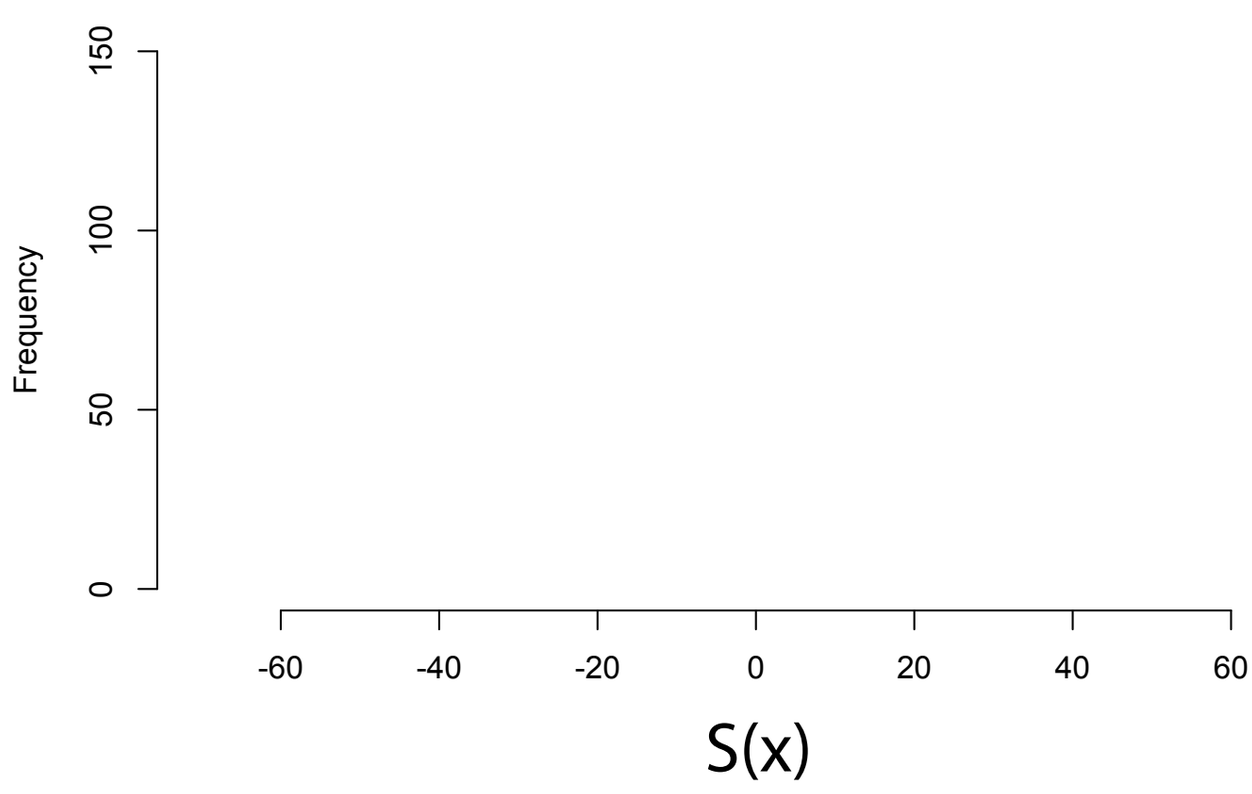
S(ATTCTACTATCATCTATCTATCTTCT) = -9.501209765

Markov chain

How well does S(x) distinguish strings drawn from inside versus outside CpG islands?

Draw 1,000 100-mers from inside CpG islands on chromosome 1, and another 1,000 from outside, calculate log ratios for all

Markov chain trained on chromosome 22 islands



Markov chain

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