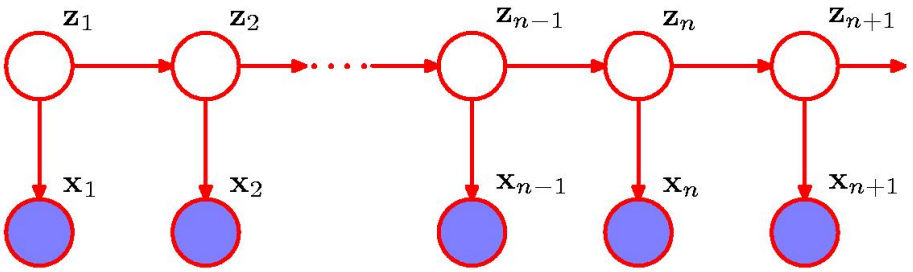
Hidden Markov Models

Selecting the initial model parameters

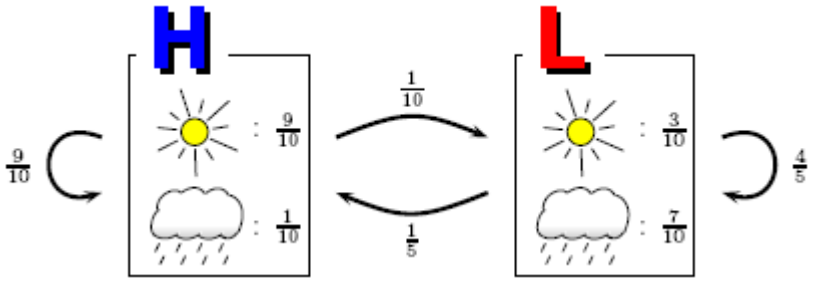
Using HMMs for (simpel) gene finding



HMMs as a generative model

A HMM ***generates a sequence of observables*** by moving from latent state to latent state according to the transition probabilities and ***emitting an observable*** (from a discrete set of observables, i.e. a finite alphabet) from each latent state visited ***according to the emission probabilities*** of the state ...

Model *M*:



A run follows a sequence of states:

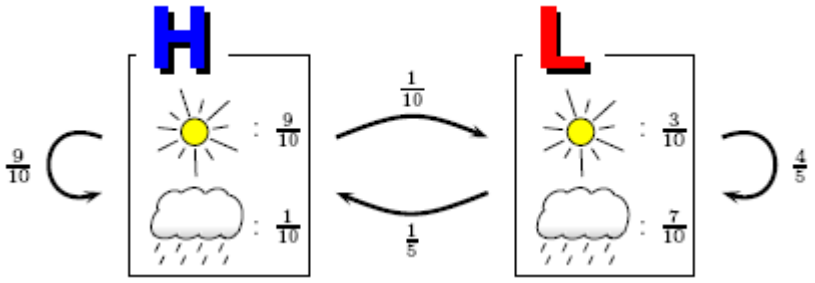
H H L L H

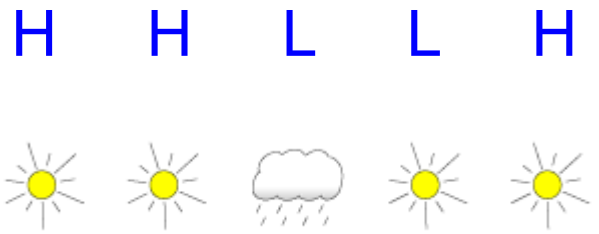
And emits a sequence of symbols:

For a HMM that generates finite strings (e.g. a HMM with an end-state), the language L = {**X** | p(**X**) > 0} is regular ...

Selecting initial model parameters

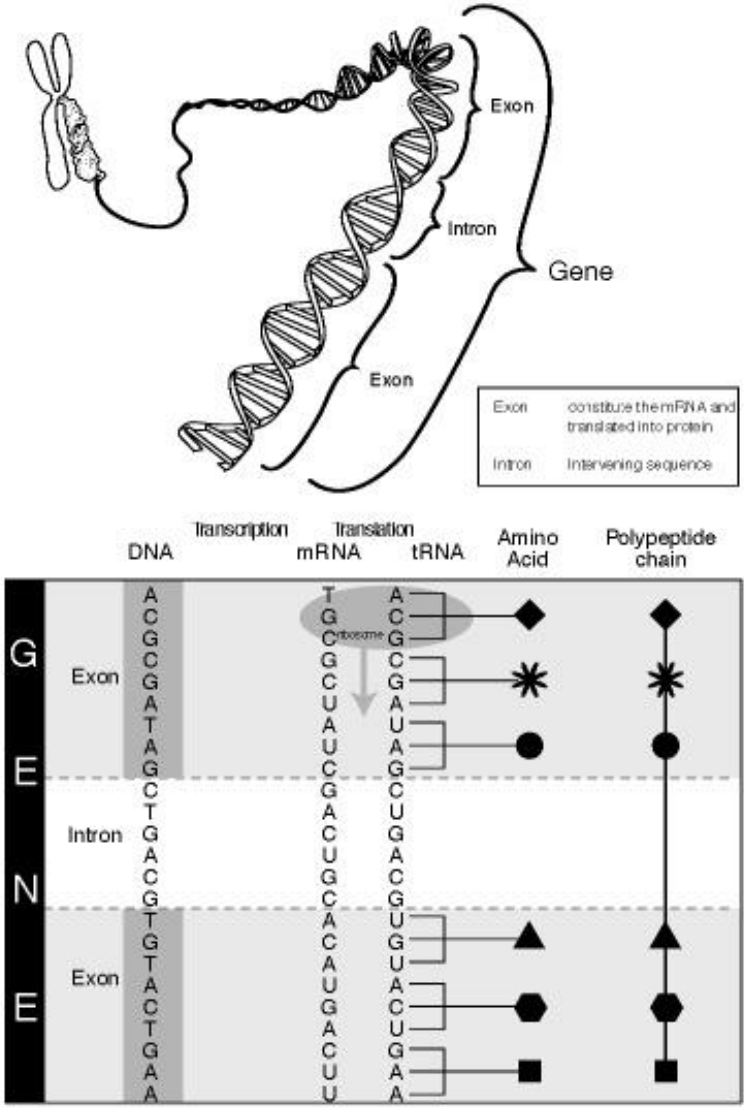
The initial selection of transition and emission probabilities, i.e. A, π, Φ, should model (how we see) the underlying structure of the observations, i.e. the syntax of possible sequences of observations, recall that the language L = {x | P(x | θ) > 0} is regular.





The initial selection of parameters is essential just to decide which parameters are 0 (or 1), i.e. to decide which transitions of emission should never (or always) be possible ...

Example – Gene finding



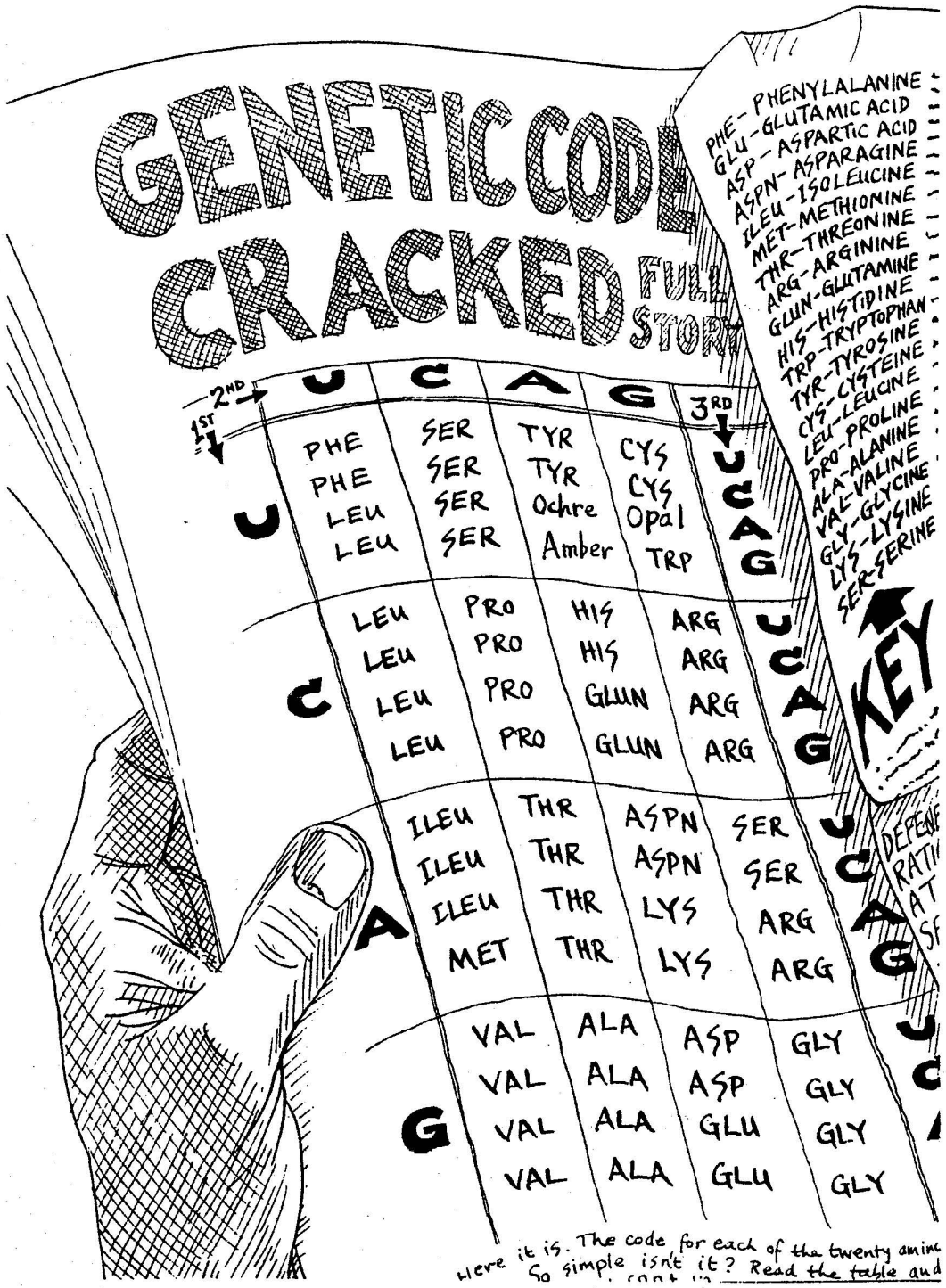
Each protein is encoded in a stretch of DNA. A gene ...

Which is expressed when the protein is needed ...

Important problem

Locating genes on the genome and determining how they get expressed ...

Recognizing the patterns that indicates a gene ...


GENETIC CODE
CRACKED
FULL
STORY
PHE - PHENYLALANINE
GLU - GLUTAMIC ACID
ASP - ASPARTIC ACID
ASPN - ASPARAGINE
ILEU - ISOLEUCINE
MET - METHIONINE
THR - THREONINE
ARG - ARGININE
GLUN - GLUTAMINE
HIS - HISTIDINE
TRP - TRYPTOPHAN
TYR - TYROSINE
CYS - CYSTEINE
LEU - LEUCINE
PRO - PROLINE
ALA - ALANINE
VAL - VALINE
GLY - GLYCINE
LYS - LYSINE
SER - SERINE
KEY
1ST
2ND
3RD
U C A G
U: PHE SER TYR CYS U | PHE SER TYR CYS C | LEU SER Ochre Opal A | LEU SER Amber TRP G
C: LEU PRO HIS ARG U | LEU PRO HIS ARG C | LEU PRO GLUN ARG A | LEU PRO GLUN ARG G
A: ILEU THR ASPN SER U | ILEU THR ASPN SER C | ILEU THR LYS ARG A | MET THR LYS ARG G
G: VAL ALA ASP GLY U | VAL ALA ASP GLY C | VAL ALA GLU GLY A | VAL ALA GLU GLY G
Here it is. The code for each of the twenty amino
So simple isn't it? Read the table and

>NC_002737.1 Streptococcus pyogenes M1 GAS
TTGTTGATATTCTGTTTTTTCTTTTTTAGTTTTCCACATGAAAAATAGTTGAAAACAATA
GCGGTGTCCCCTTAAAATGGCTTTTCCACAGGTTGTGGAGAACCCAAATTAACAGTGTTA
ATTTATTTTCCACAGGTTGTGGAAAAACTAACTATTATCCATCGTTCTGTGGAAAACTAG
AATAGTTTATGGTAGAATAGTTCTAGAATTATCCACAAGAAGGAACCTAGTATGACTGAA
AATGAACAAATTTTTTGGAACAGGGTCTTGGAATTAGCTCAGAGTCAATTAAAACAGGCA
ACTTATGAATTTTTTGTTCATGATGCCCGTCTATTAAAGGTCGATAAGCATATTGCAACT
ATTTACTTAGATCAAATGAAAGAGCTCTTTTGGGAAAAAAATCTTAAAGATGTTATTCTT
ACTGCTGGTTTTGAAGTTTATAACGCTCAAATTTCTGTTGACTATGTTTTCGAAGAAGAC
CTAATGATTGAGCAAAATCAGACCAAAATCAACCAAAAACCTAAGCAGCAAGCCTTAAAT
TCTTTGCCTACTGTTACTTCAGATTTAAACTCGAAATATAGTTTTGAAAACTTTATTCAA
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GAAAAATTTCGTAATTTAGATTTACTCCTTATTGATGATATCCAATCTTTAGCTAAAAAA
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AAACAAATTGTCCTAACAAGCGACCGTACACCAGATCATCTCAATGATTTAGAAGATCGA
TTAGTTACTCGTTTTAAATGGGGATTAACAGTCAATATCACACCTCCTGATTTTGAAACA
CGAGTGGCTATTTTGACAAATAAAATTCAAGAATATAACTTTATTTTTCCTCAAGATACC
ATTGAGTATTTGGCTGGTCAATTTGATTCTAATGTCAGAGATTTAGAAGGTGCCTTAAAA
GATATTAGTCTGGTTGCTAATTTCAAACAAATTGACACGATTACTGTTGACATTGCTGCC
GAAGCTATTCGCGCCAGAAAGCAAGATGGACCTAAAATGACAGTTATTCCCATCGAAGAA
ATTCAAGCGCAAGTTGGAAAATTTTACGGTGTTACCGTCAAAGAAATTAAAGCTACTAAA
CGAACACAAAATATTGTTTTAGCAAGACAAGTAGCTATGTTTTTAGCACGTGAAATGACA
GATAACAGTCTTCCTAAAATTGGAAAAGAATTTGGTGGCAGAGACCATTCAACAGTACTC
CATGCCTATAATAAAATCAAAAACATGATCAGCCAGGACGAAAGCCTTAGGATCGAAATT
GAAACCATAAAAAACAAAATTAAATAACATGTGGAAAAGAATATCTTTTATGAAATAGTT
ATCCACAAGTTGTGAACATCCATTTAGTCTTGGATTCTCTCGTTTATTTAGAGTTATCCA
CTATATACACAAGACCTACTACTACTACTTATTATTATACTTATTAAATAAAGGAGTTCT

Viterbi decoding

```
>NC_002737.1 Streptococcus pyogenes M1 GAS
TTGTTGATATTCTGTTTTTTCTTTTTTAGTTTTCCACATGAAAAATAGTTGAAAACAATA
GCGGTGTCCCCTTAAAATGGCTTTTCCACAGGTTGTGGAGAACCCAAATTAACAGTGTTA
ATTTATTTTCCACAGGTTGTGGAAAAACTAACTATTATCCATCGTTCTGTGGAAAACTAG
AATAGTTTATGGTAGAATAGTTCTAGAATTATCCACAAGAAGGAACCTAGTATGACTGAA
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CTAATGATTGAGCAAAATCAGACCAAAATCAACCAAAAACCTAAGCAGCAAGCCTTAAAT
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GAAAACTTTATTAATGAGTTTGTTATCCATATTCGCCTTGATACCATGGATGAATTGAAA
GAAAAATTTCGTAATTTAGATTTACTCCTTATTGATGATATCCAATCTTTAGCTAAAAAA
ACGCTCTCTGGAACACAAGAAGAGTTCTTTAATACTTTTAATGCACTTCATAATAATAAC
AAACAAATTGTCCTAACAAGCGACCGTACACCAGATCATCTCAATGATTTAGAAGATCGA
TTAGTTACTCGTTTTAAATGGGGATTAACAGTCAATATCACACCTCCTGATTTTGAAACA
CGAGTGGCTATTTTGACAAATAAAATTCAAGAATATAACTTTATTTTTCCTCAAGATACC
ATTGAGTATTTGGCTGGTCAATTTGATTCTAATGTCAGAGATTTAGAAGGTGCCTTAAAA
GATATTAGTCTGGTTGCTAATTTCAAACAAATTGACACGATTACTGTTGACATTGCTGCC
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CATGCCTATAATAAAATCAAAAACATGATCAGCCAGGACGAAAGCCTTAGGATCGAAATT
GAAACCATAAAAAACAAAATTAAATAACATGTGGAAAAGAATATCTTTTATGAAATAGTT
ATCCACAAGTTGTGAACATCCATTTAGTCTTGGATTCTCTCGTTTATTTAGAGTTATCCA
CTATATACACAAGACCTACTACTACTACTTATTATTATACTTATTAAATAAAGGAGTTCT
```

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>NC_002737.1 gene annotation Streptococcus pyogenes M1 GAS
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNCCCCCCCC
CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
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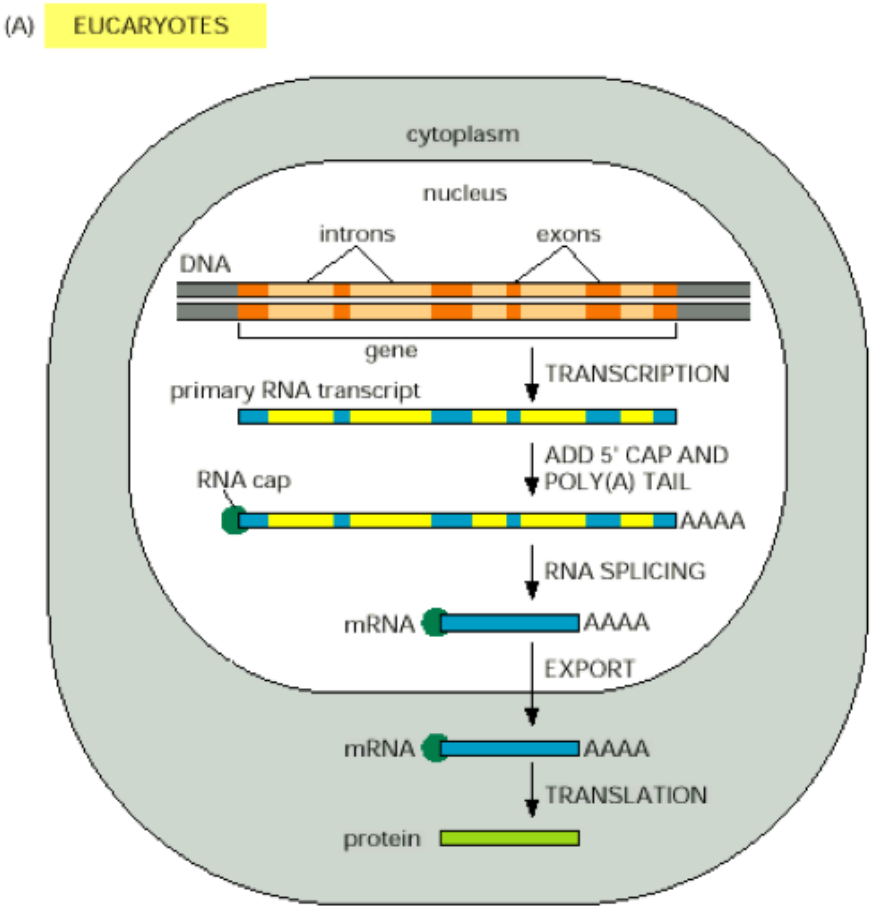
CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
CCCCCCCCCCCCCCCCCCCCCCCCCCCNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
```

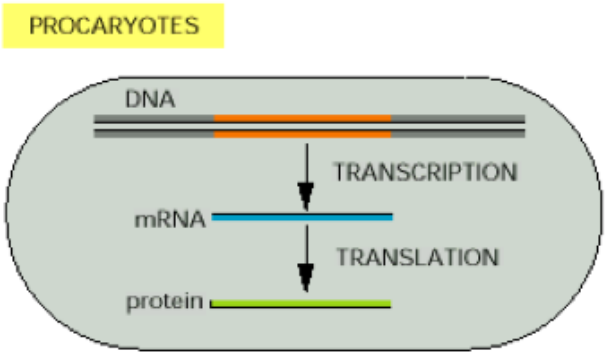
Design a HMM that models the syntax of genes

Gene structure

Depends on the organism (eucaryote or procaryote)

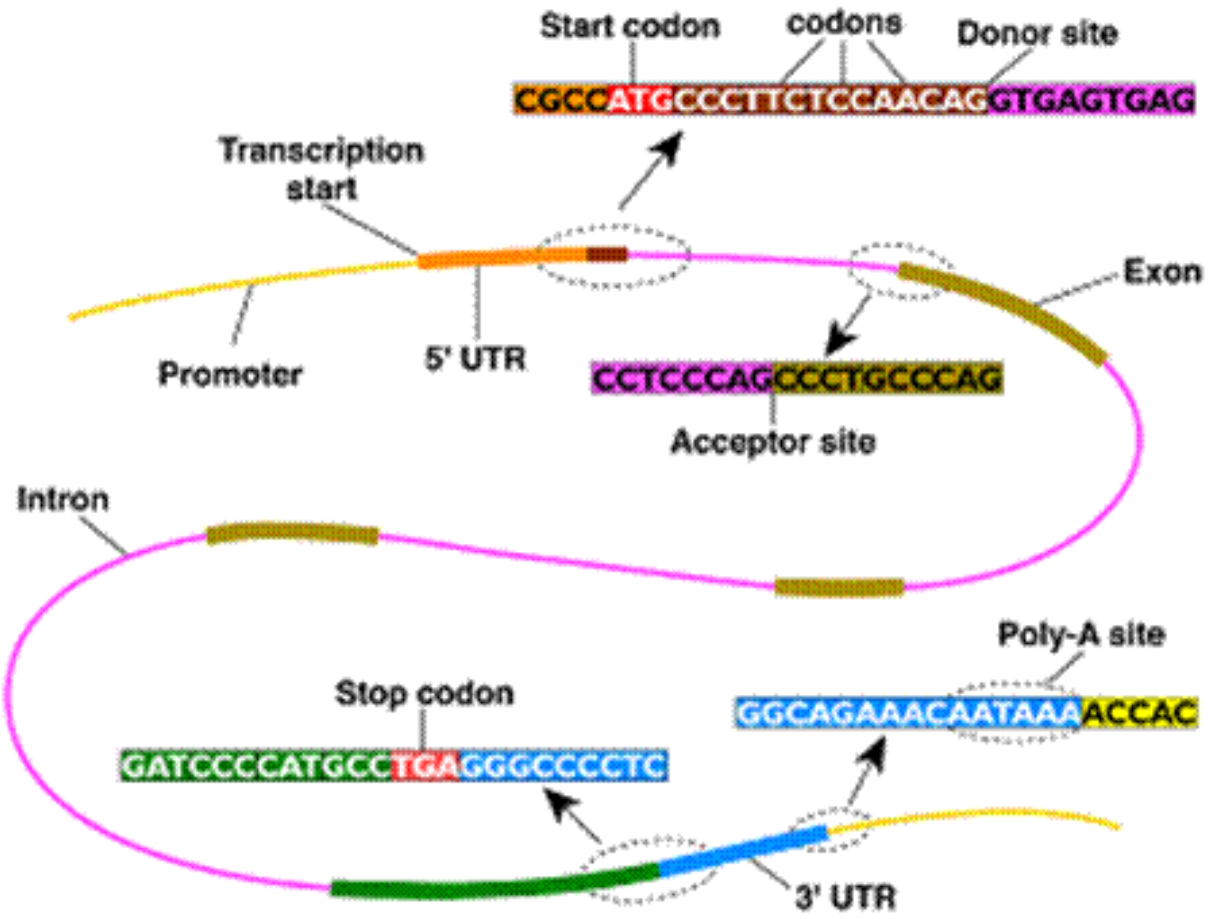


Large genomes. Intron/exon structure and low coding density



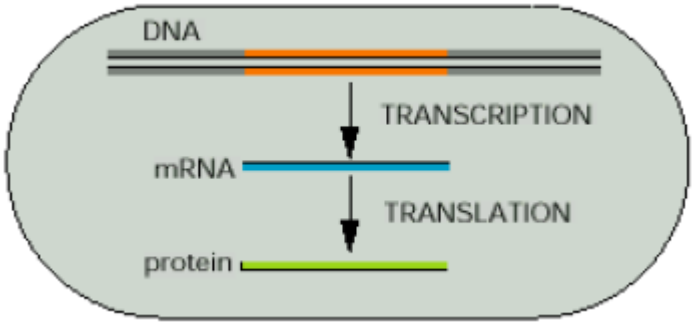
Smaller genomes and high coding density.

Gene structure in eukaryotes



Eukaryotic gene structure in more details

Gene structure in procaryotes

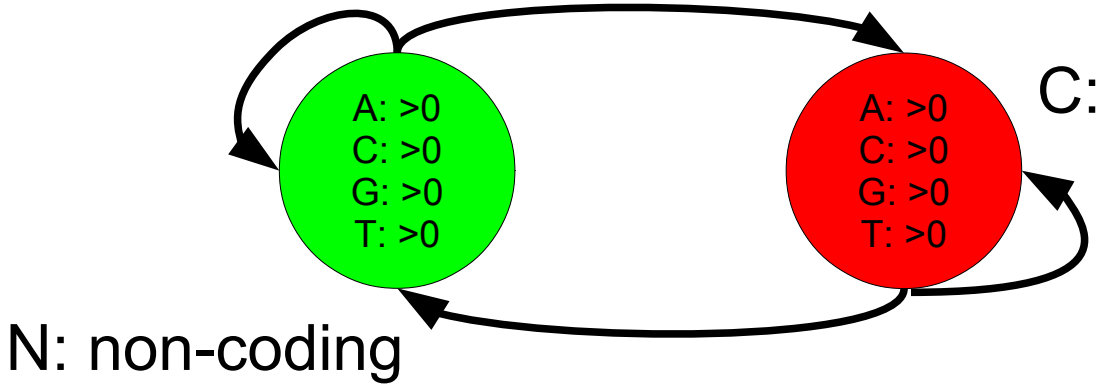


Biological facts

- The gene is a substring of the DNA sequence of A,C,G,T's

Z: NNNCCCCCCCCCCNNNNNNNNCCCCCCCCCCCCCCCCCCNNNNNNNNNNN

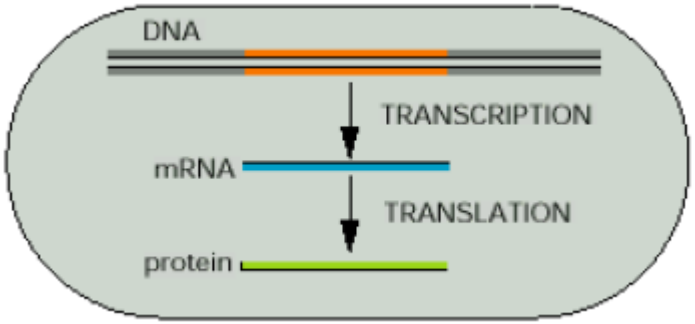
X: acgatgcgctaatatgtccgatgacgtgagcataagcgacatgcag



$\pi_N = 1$

$\pi_C = 0$

Gene structure in procaryotes

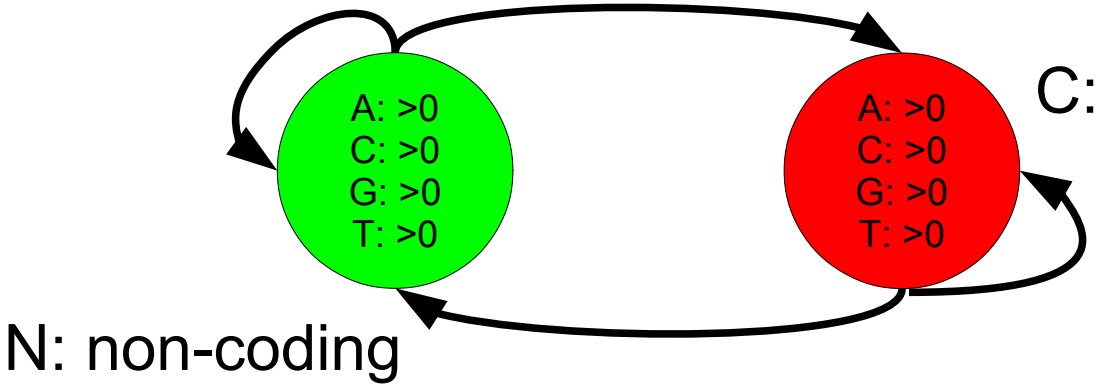


Biological facts

- The gene is a substring of the DNA sequence of A,C,G,T's
- The gene starts with a start-codon **atg**

Z: NNNCCCCCCCCCCNNNNNNNNNCCCCCCCCCCCCCCCCCCNNNNNNNNNNN

X: acgatgcgctaatatgtccgatgacgtgagcataagcgacatgcag



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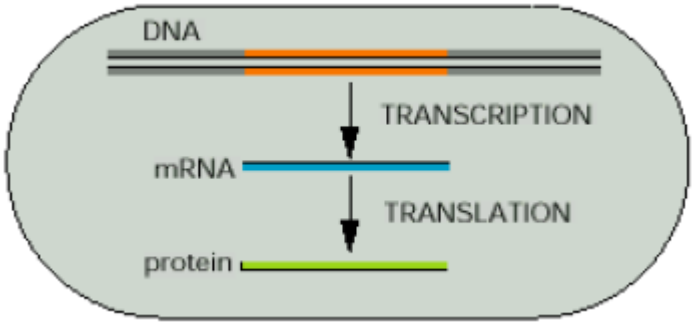
Gene structure in procaryotes



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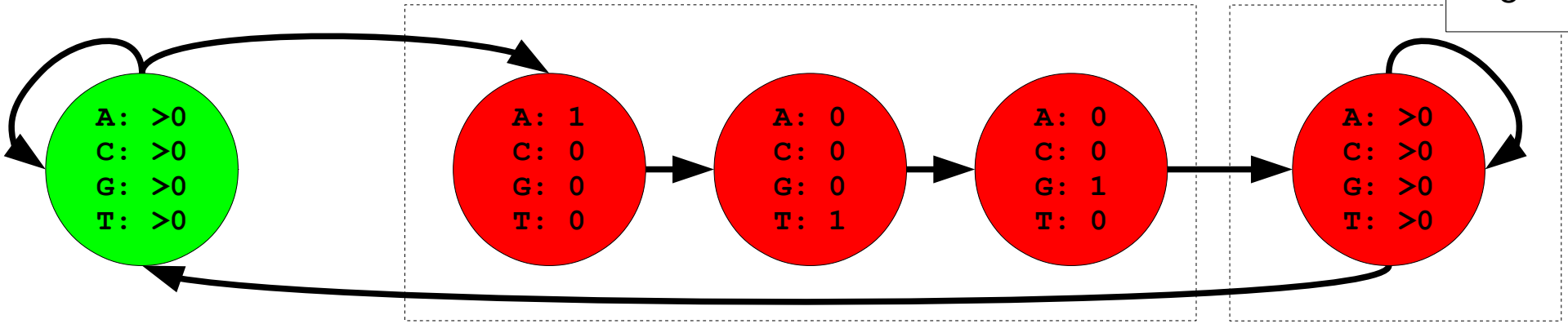
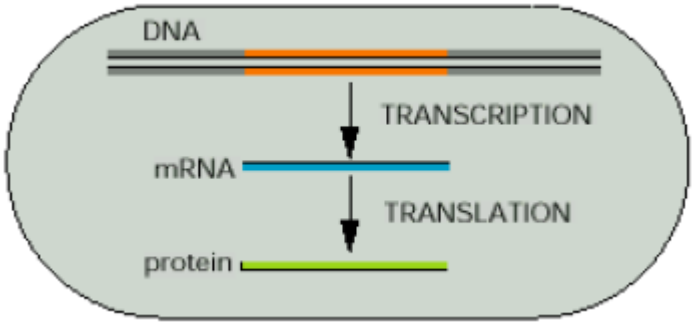


N: non-coding

C: coding

Gene structure in procaryotes



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- The gene starts with a start-codon **atg**
- The gene ends with a stop-codon **taa**, **tag** or **tga**

Z: NNNCCCCCCCCCCNNNNNNNNCCCCCCCCCCCCCCCCCCNNNNNNNNNNN

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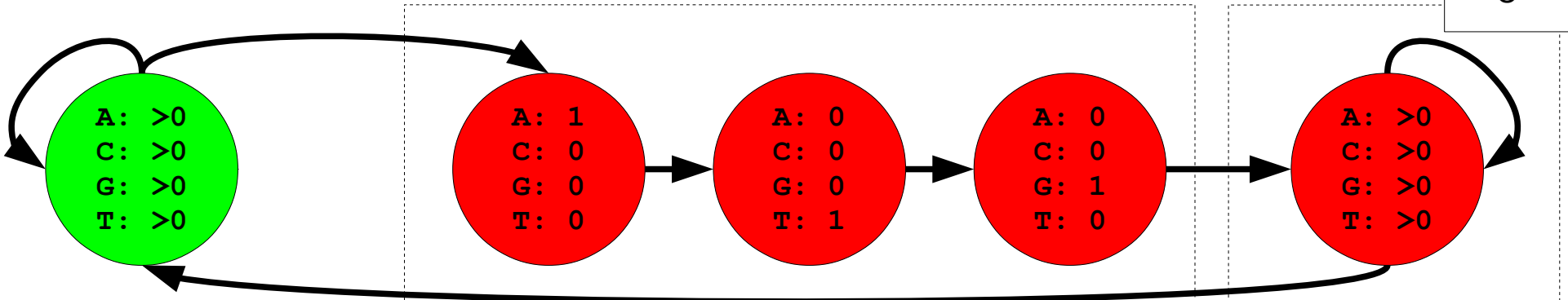

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Gene structu

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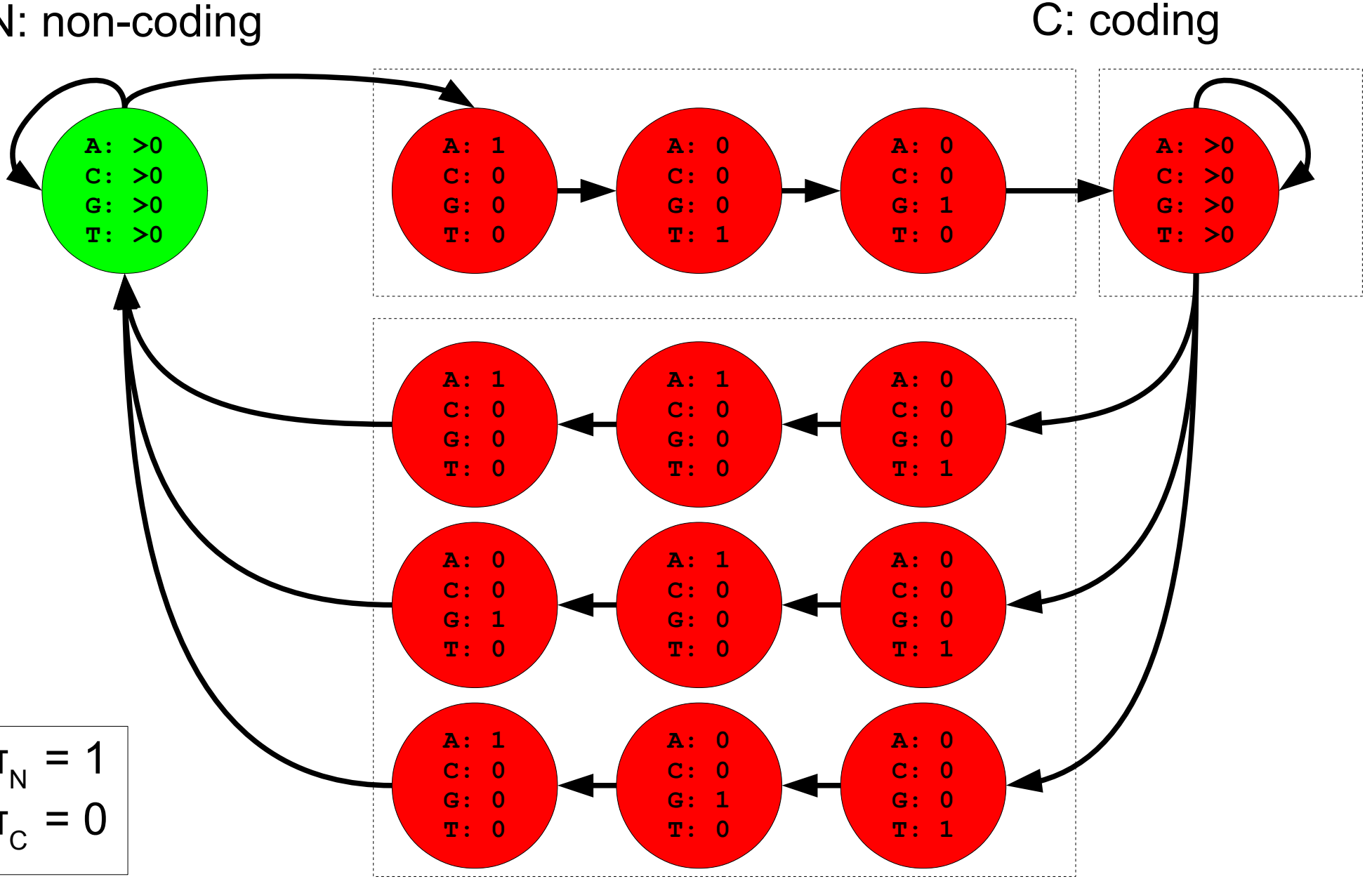

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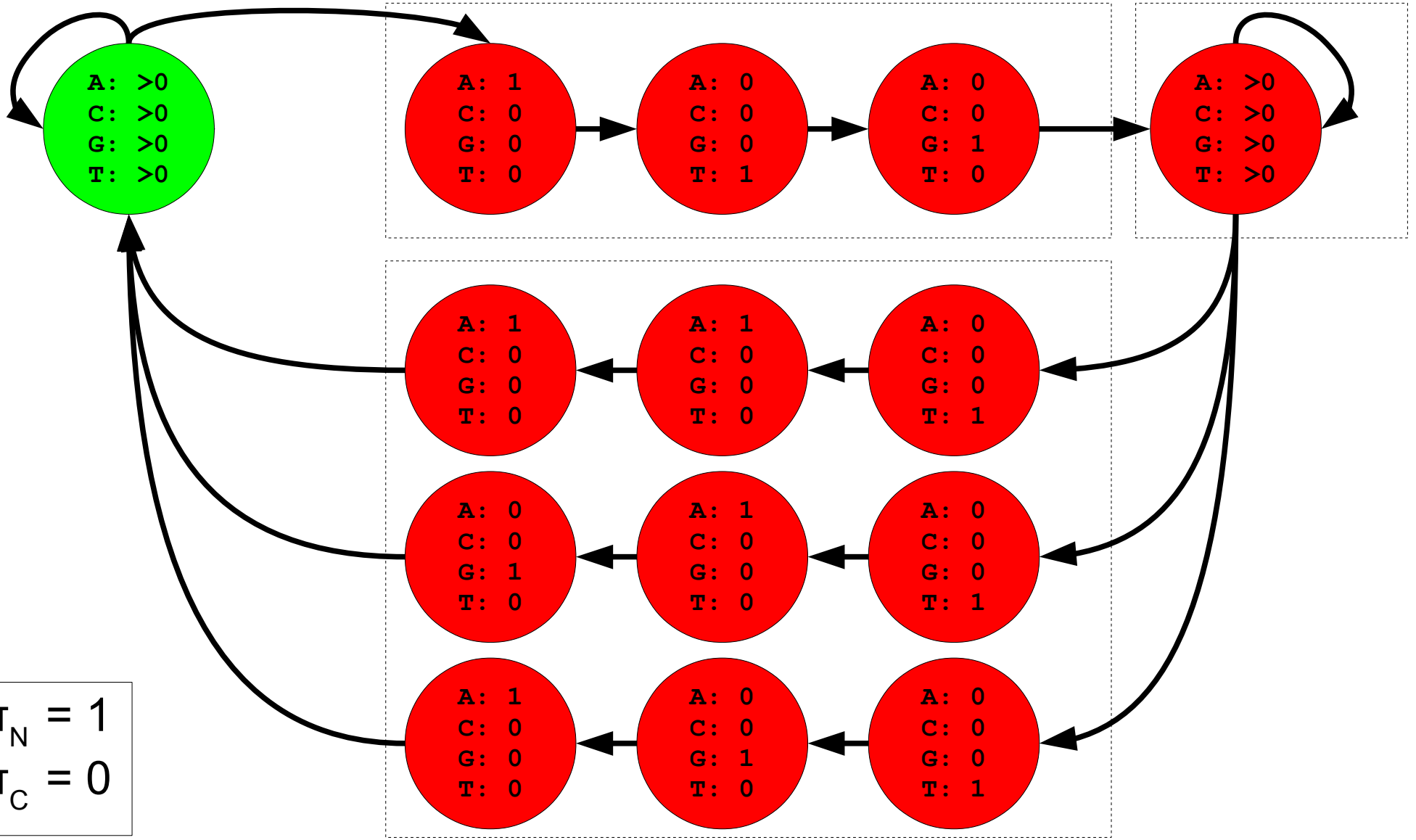
- The number of nucleotides in a gene is a multiplum of 3

N: non-coding

C: coding



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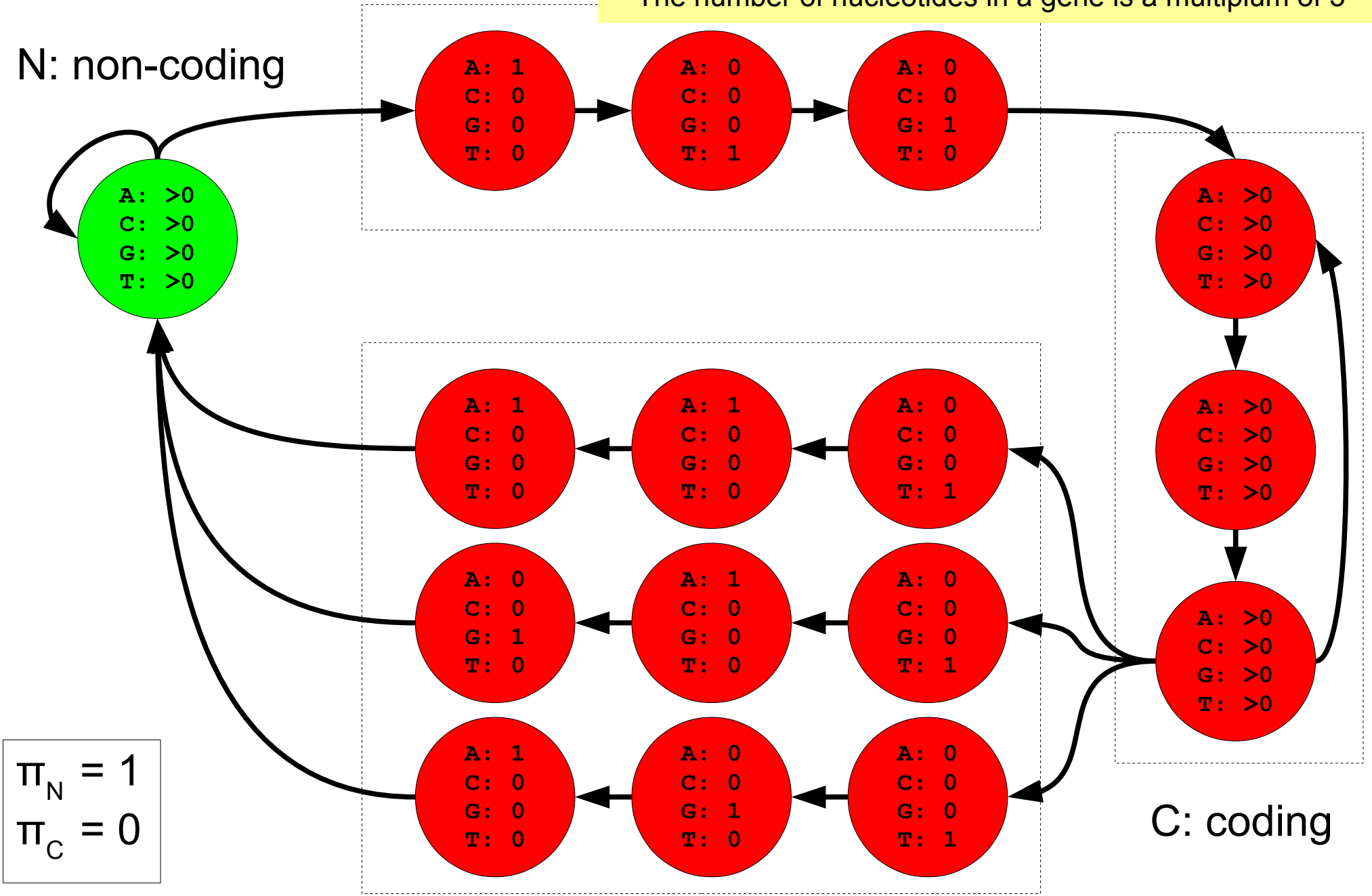

$\pi_N = 1$

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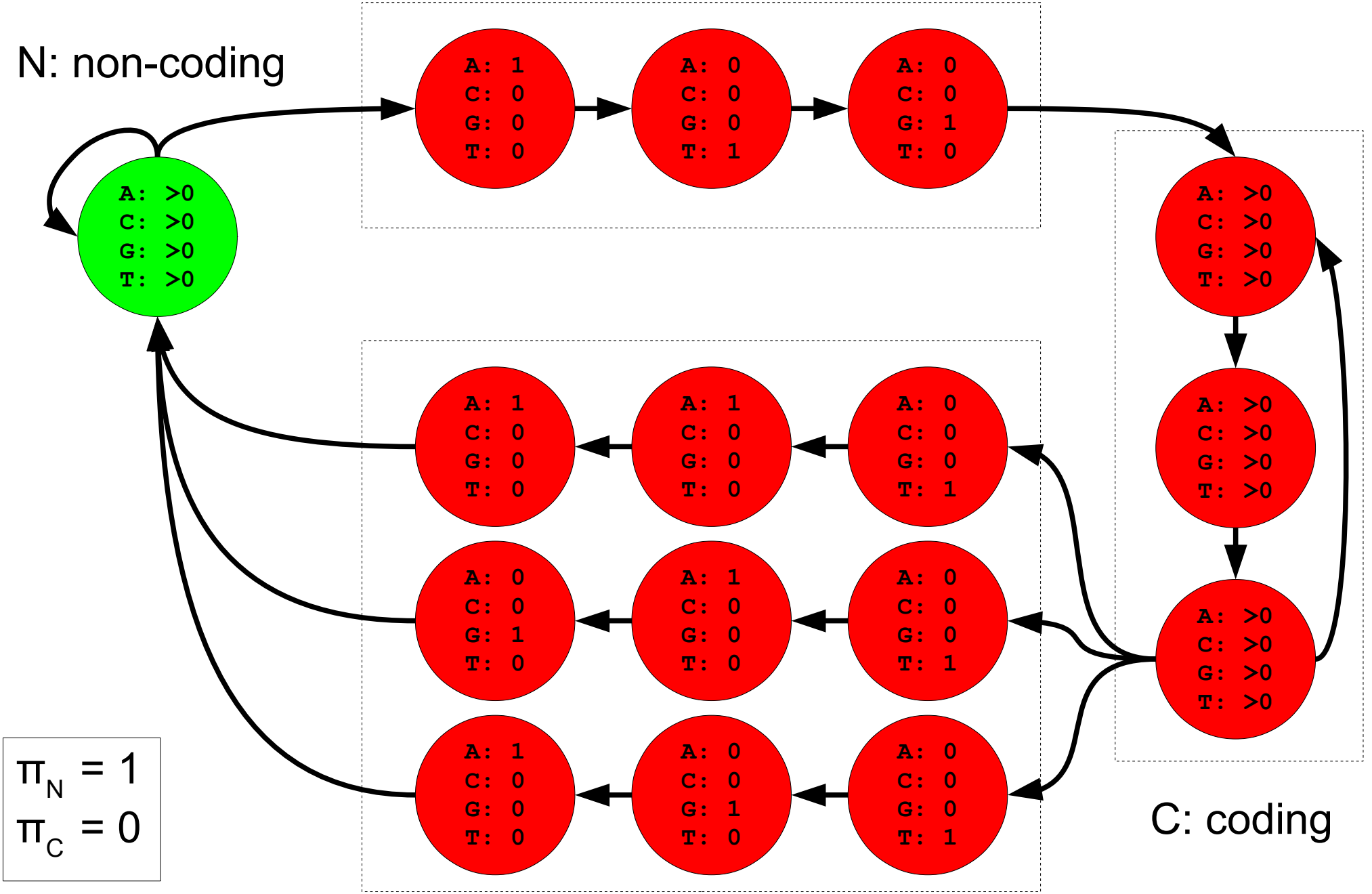
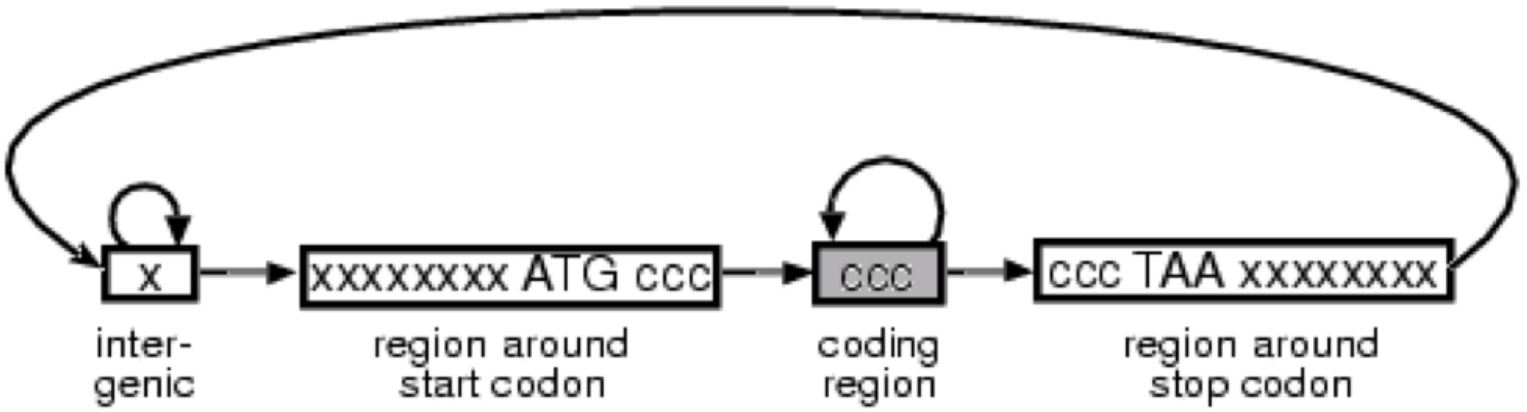
Gene structure in procaryotes

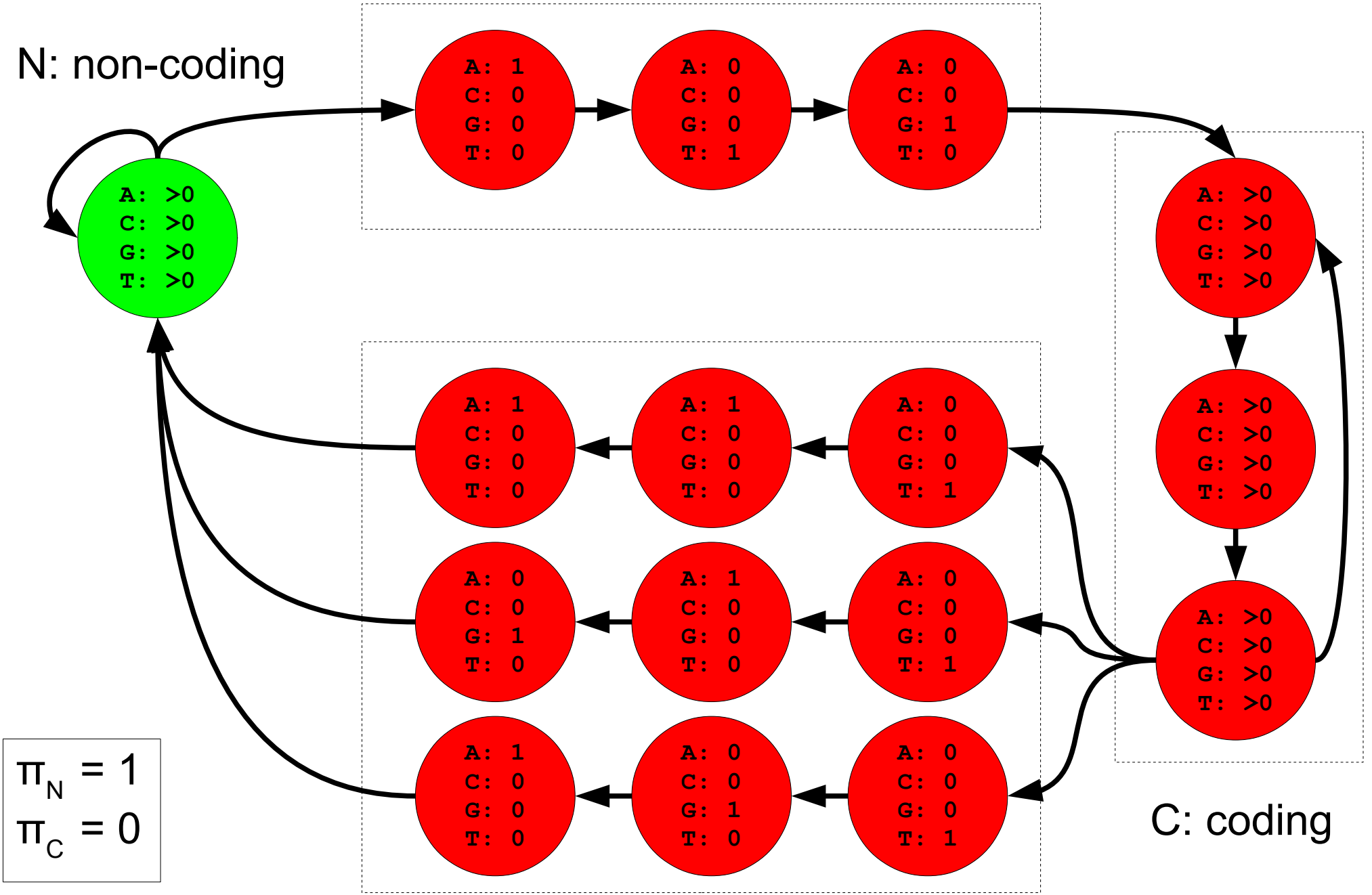


Gene structure in procaryotes

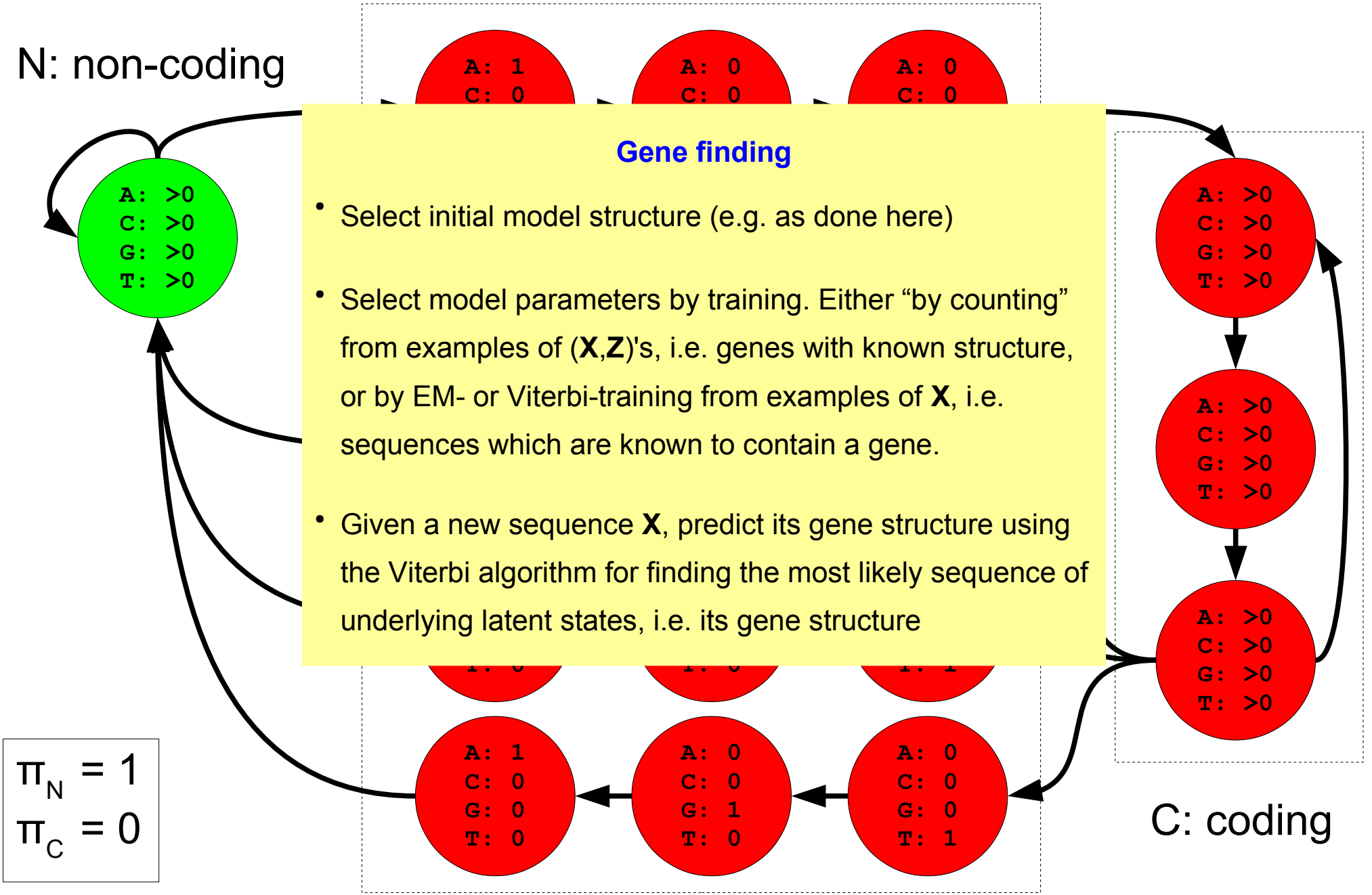


From "An Introduction to HMMs for Biological Sequences", A. Krogh, 1998

Gene structure in procaryotes



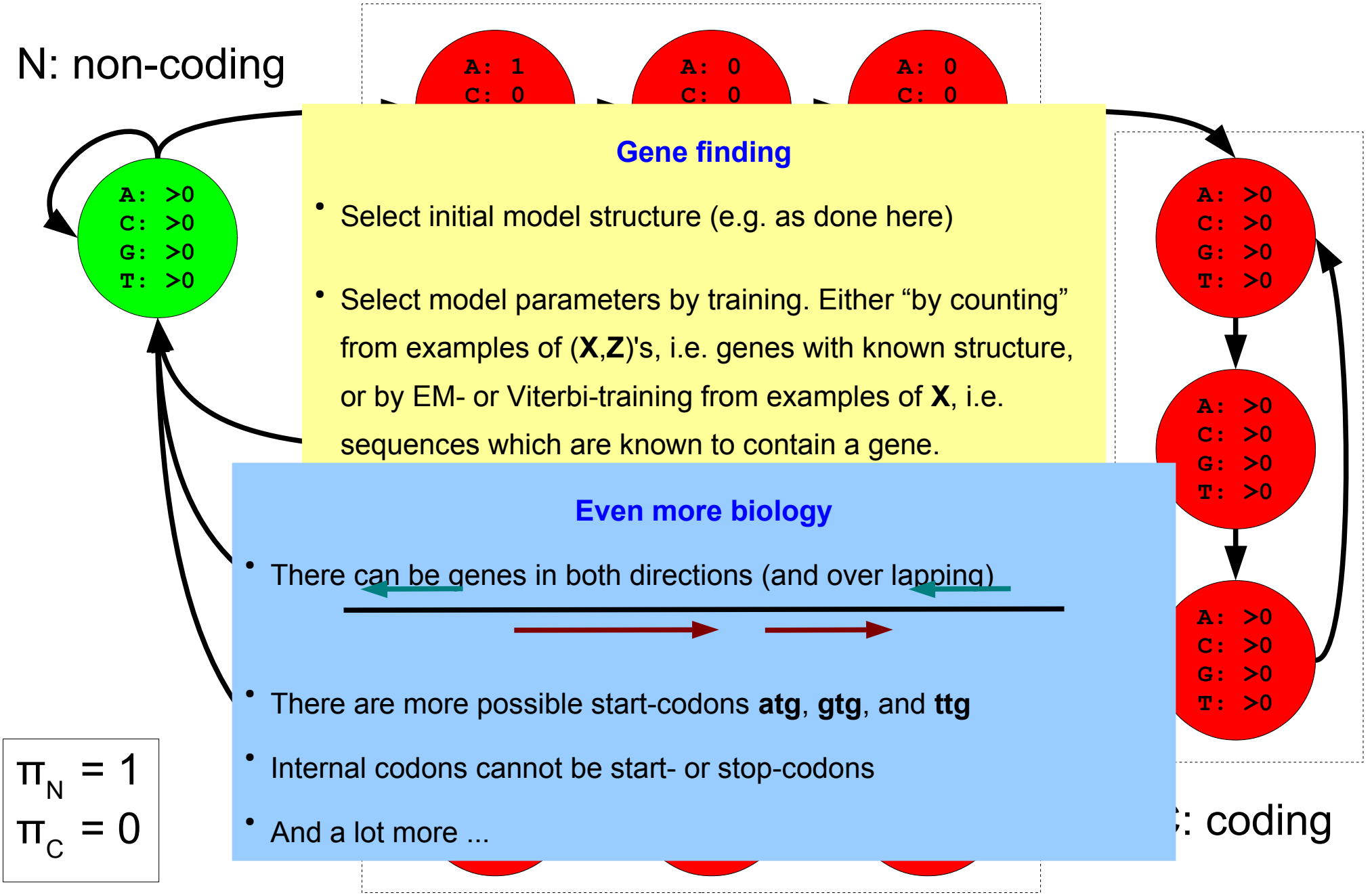
Gene structure in procaryotes



Gene finding

- Select initial model structure (e.g. as done here)
- Select model parameters by training. Either “by counting” from examples of (**X**,**Z**)'s, i.e. genes with known structure, or by EM- or Viterbi-training from examples of **X**, i.e. sequences which are known to contain a gene.
- Given a new sequence **X**, predict its gene structure using the Viterbi algorithm for finding the most likely sequence of underlying latent states, i.e. its gene structure

Example – Gene finding



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Even more biology

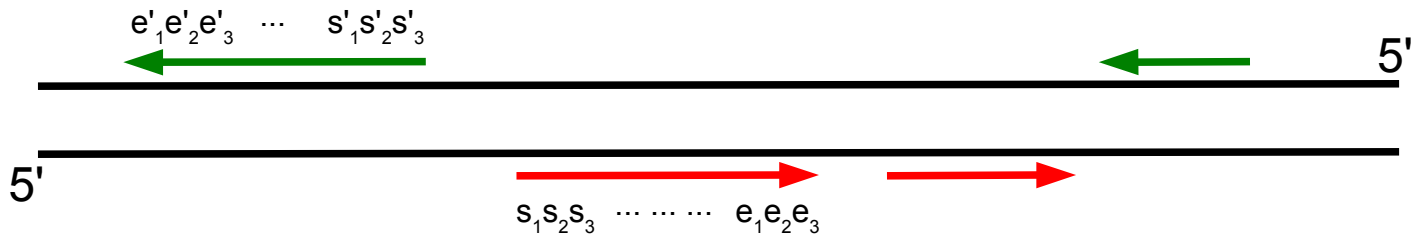
- There can be genes in both directions (and over lapping)

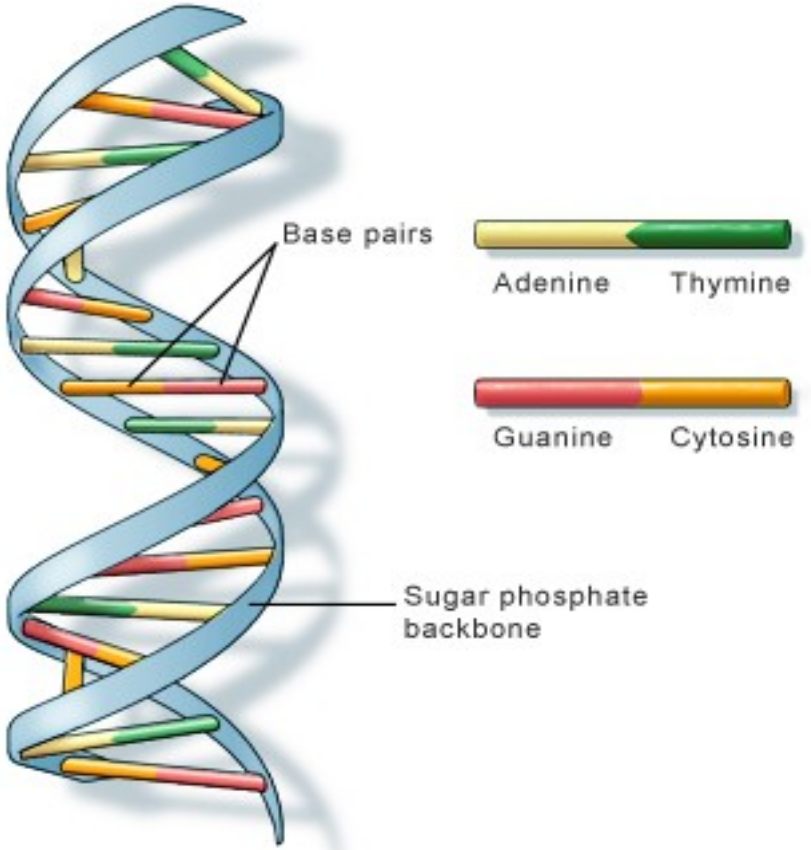
- There are more possible start-codons **atg**, **gtg**, and **ttg**
- Internal codons cannot be start- or stop-codons
- And a lot more ...

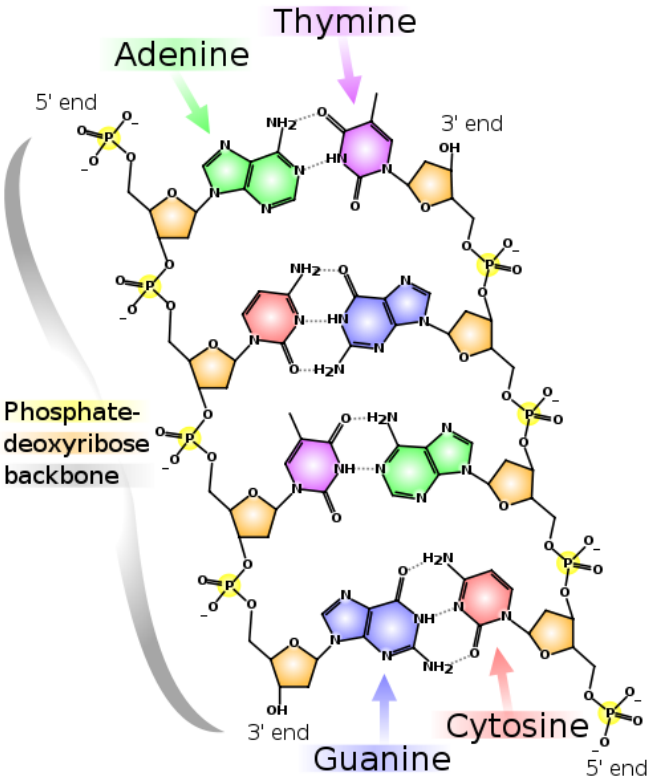
$\pi_N = 1$

$\pi_C = 0$

DNA

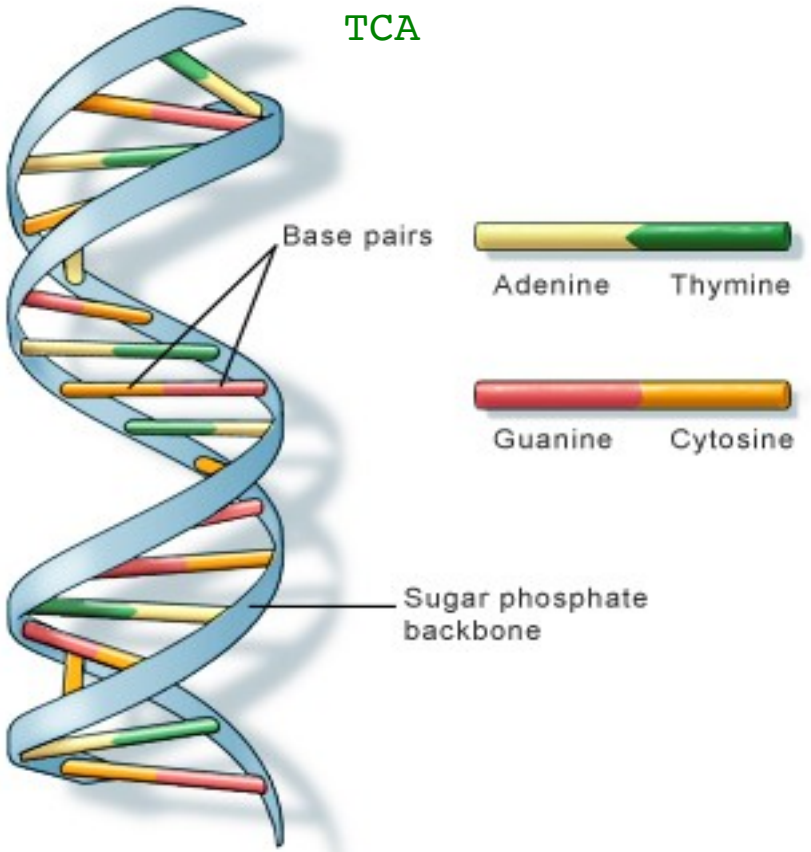


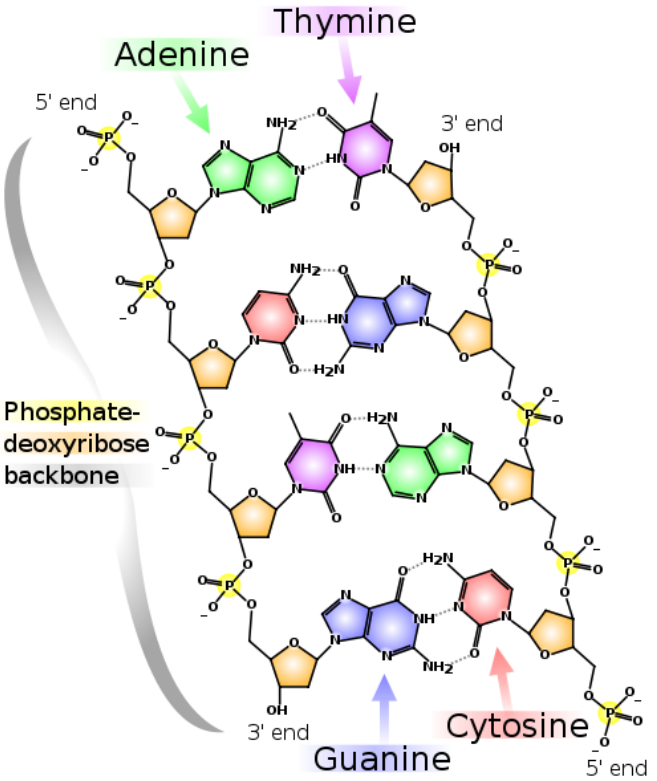




U.S. National Library of Medicine

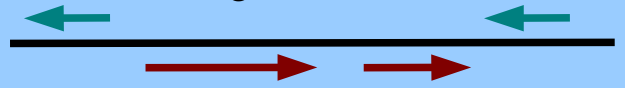
DNA





Even more biology

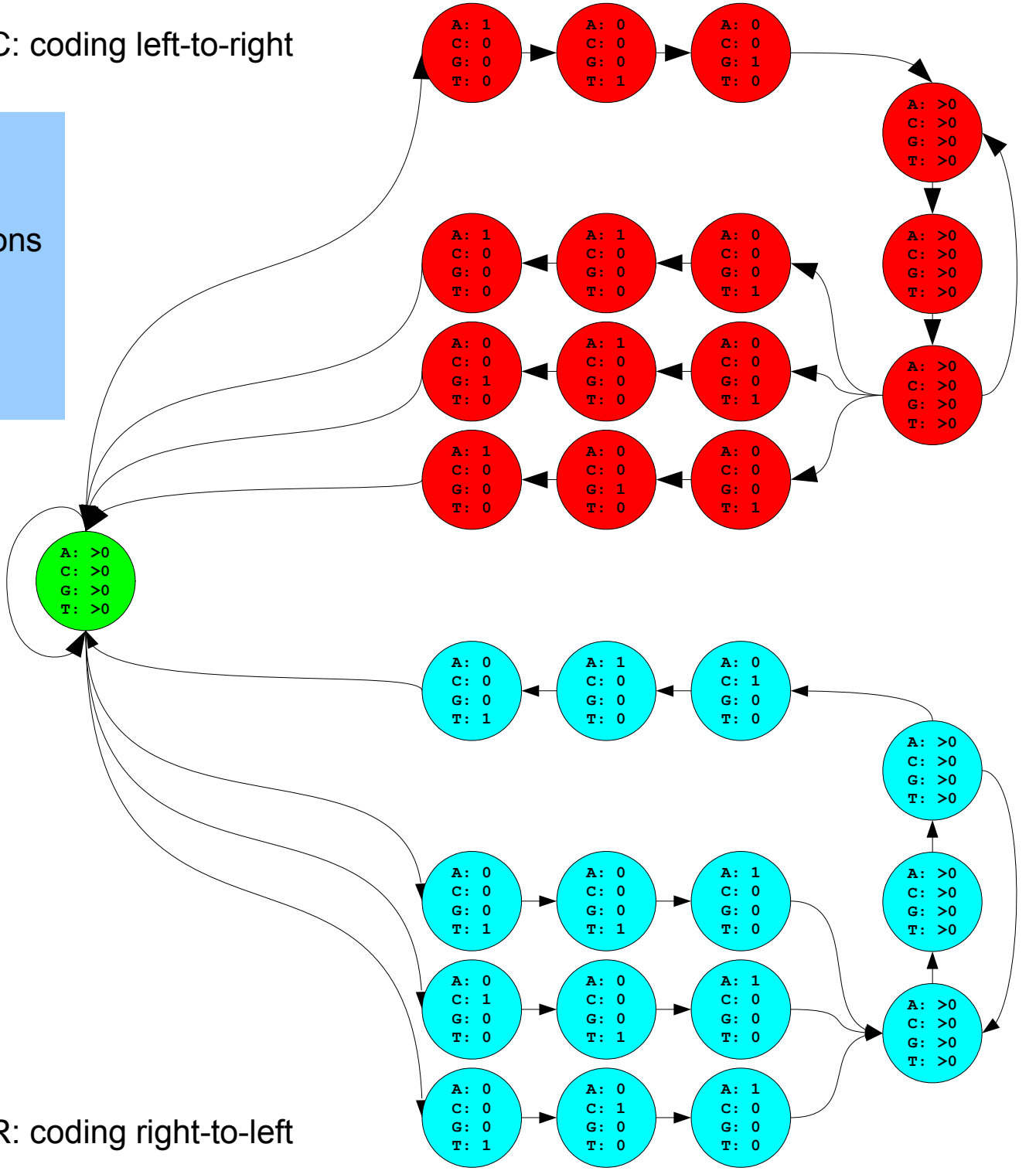
There can be genes in both directions



C: coding left-to-right

N: Non-coding

R: coding right-to-left



$\pi_N = 1$

$\pi_C = 0$

Example – 7-state HMM

Observable: {A, C, G, T}, States: {0,1, 2, 3, 4, 5, 6}

A

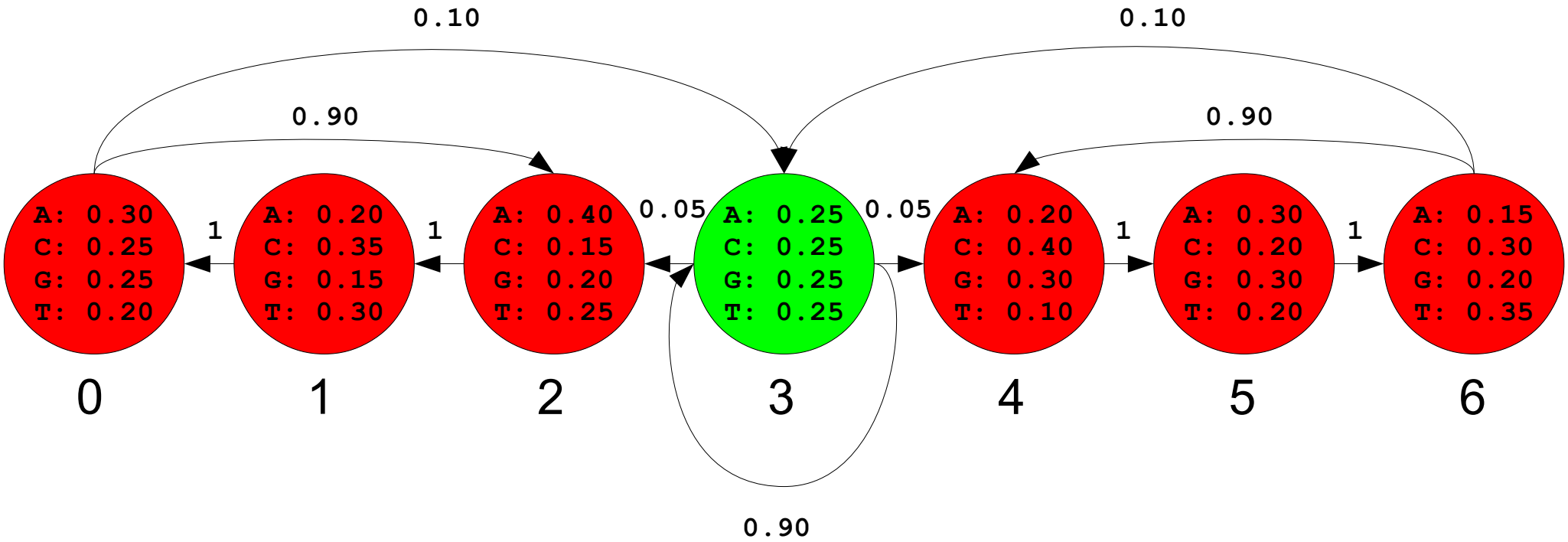
0.00	0.00	0.90	0.10	0.00	0.00	0.00
1.00	0.00	0.00	0.00	0.00	0.00	0.00
0.00	1.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.05	0.90	0.05	0.00	0.00
0.00	0.00	0.00	0.00	0.00	1.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00	1.00
0.00	0.00	0.00	0.10	0.90	0.00	0.00

π

0.00
0.00
0.00
1.00
0.00
0.00
0.00

φ

0.30	0.25	0.25	0.20
0.20	0.35	0.15	0.30
0.40	0.15	0.20	0.25
0.25	0.25	0.25	0.25
0.20	0.40	0.30	0.10
0.30	0.20	0.30	0.20
0.15	0.30	0.20	0.35



This model is also applicable for gene finding.

It does not model start- and stop-codons explicitly, but models that genes in both directions are a sequence of triplets.

A

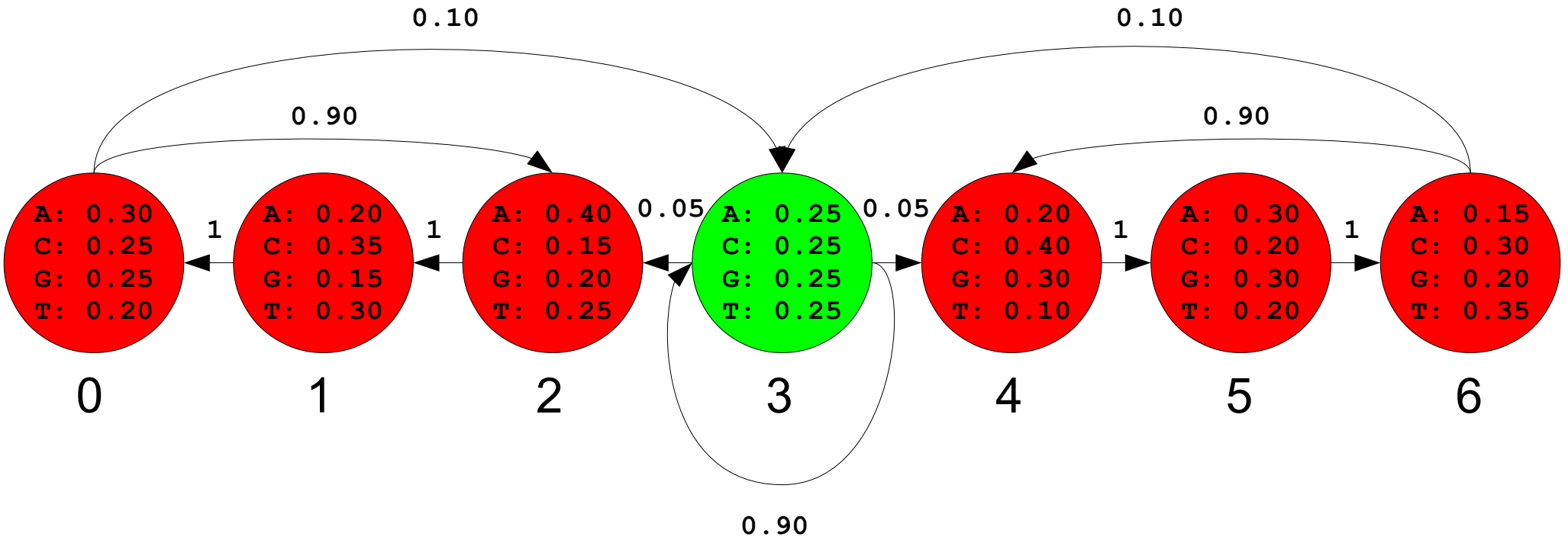
0.00	0.00	0.90	0.10	0.00	0.00	0.00
1.00	0.00	0.00	0.00	0.00	0.00	0.00
0.00	1.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.05	0.90	0.05	0.00	0.00
0.00	0.00	0.00	0.00	0.00	1.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00	1.00
0.00	0.00	0.00	0.10	0.90	0.00	0.00

π

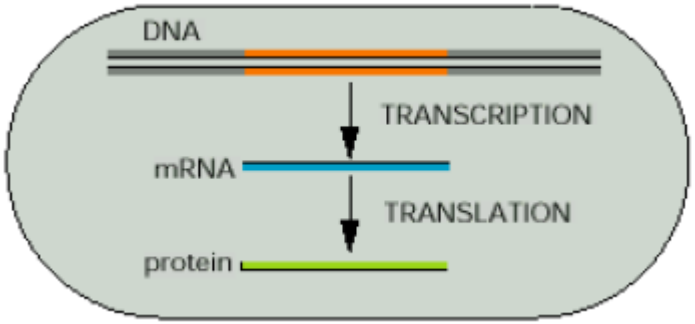
0.00
0.00
0.00
1.00
0.00
0.00
0.00

φ

0.30	0.25	0.25	0.20
0.20	0.35	0.15	0.30
0.40	0.15	0.20	0.25
0.25	0.25	0.25	0.25
0.20	0.40	0.30	0.10
0.30	0.20	0.30	0.20
0.15	0.30	0.20	0.35



Problem: From annotation to Z



Biological facts

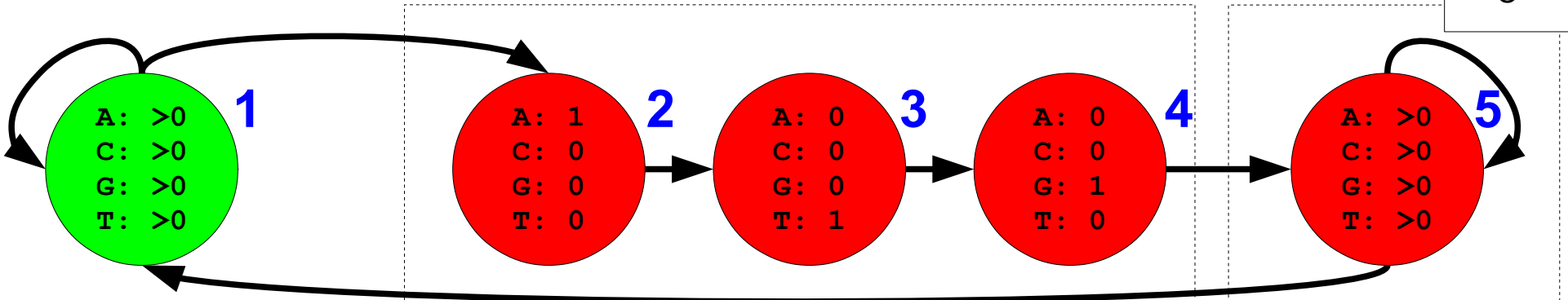
- The gene is a substring of the DNA sequence of A,C,G,T's
- The gene starts with a start-codon **atg**

Z: NNNCCCCCCCCCCNNNNNNNNNCCCCCCCCCCCCCCCCCCNNNNNNNNNNN

X: acgatgcgctaatatgtccgatgacgtgagcataagcgacat

$\pi_N = 1$

$\pi_C = 0$



N: non-coding

C: coding

Problem: From annotation to Z

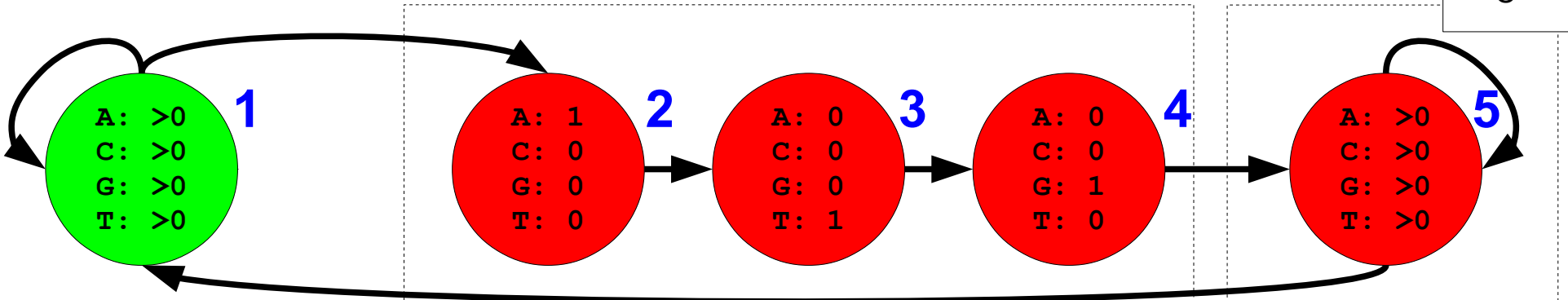
Problem: The string **Z=**NNNCCC.... is not a prober sequence of states in the illustrated HMM, but is can easily be converted into one (because there in this case is a 1-1 matching between a sequence of Ns and Cs and a sequence of states).

ence of A,C,G,T's

Z: NNNCCCCCCCCCNNNNNNNNNCCCCCCCCCCCCCCCCCNNNNNNNNNNN

X: acgatgcgctaatatgtccgatgacgtgagcataagcgacat

$\pi_N = 1$
$\pi_C = 0$



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Problem: From annotation to Z

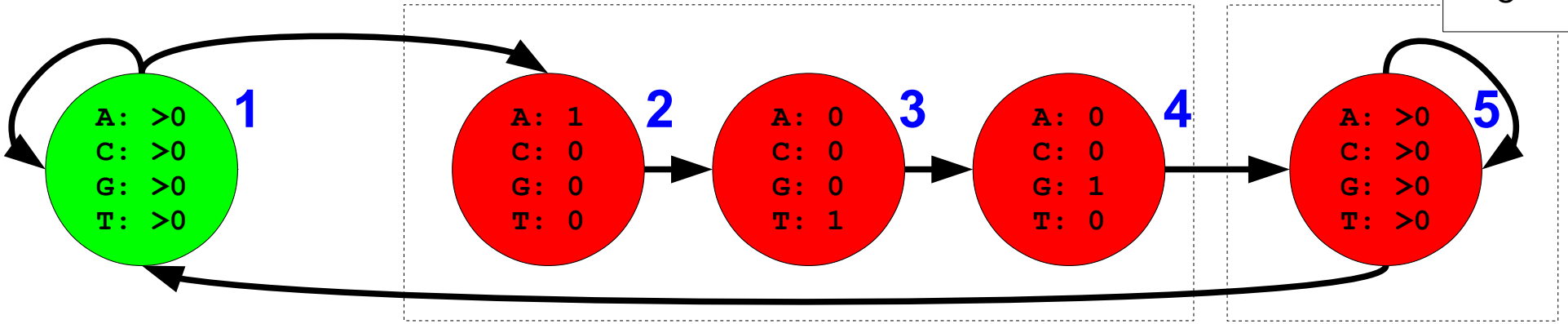
Problem: The string **Z=**NNNCCC.... is not a prober sequence of states in the illustrated HMM, but is can easily be converted into one (because there in this case is a 1-1 matching between a sequence of Ns and Cs and a sequence of states).

ence of A,C,G,T's

```
     11123455555511111111234555555555511111111111
Z:   NNNCCCCCCCCCCNNNNNNNNNCCCCCCCCCCCCCCCCCCNNNNNNNNNNN

X:   acgatgcgctaatatgtccgatgacgtgagcataagcgacatc
```

$\pi_N = 1$
$\pi_C = 0$

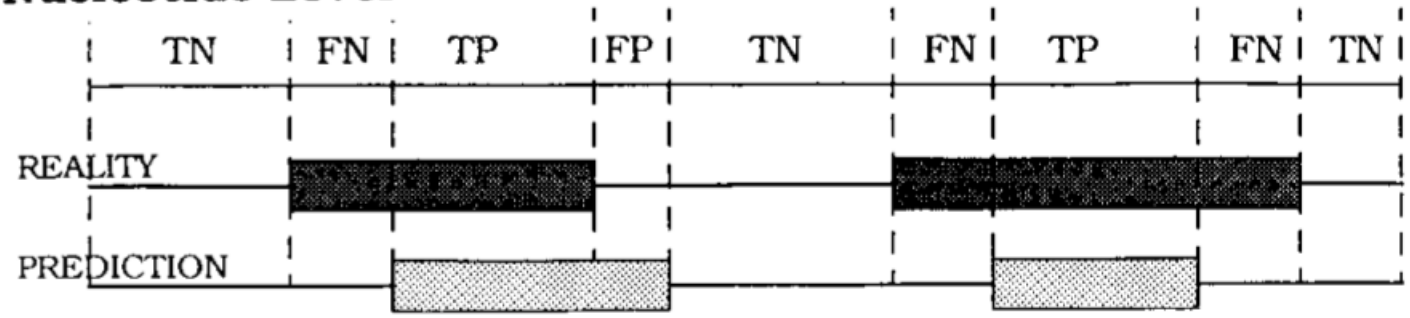


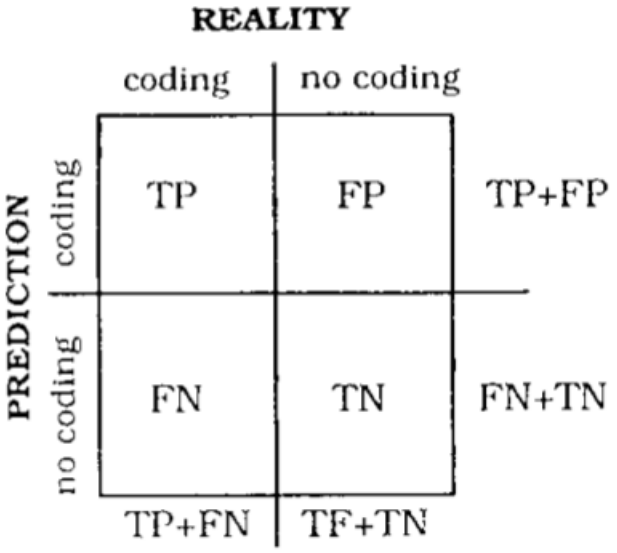
N: non-coding

C: coding

Evaluating performance

Nucleotide Level





$$Sn = \frac{TP}{TP + FN}$$

Sensitivity

$$Sp = \frac{TP}{TP + FP}$$

Specificity

$$CC = \frac{(TP \times TN) - (FN \times FP)}{\sqrt{(TP + FN) \times (TN + FP) \times (TP + FP) \times (TN + FN)}}$$

Correlation Coefficient

$$ACP = \frac{1}{4}\left[\frac{TP}{TP + FN} + \frac{TP}{TP + FP} + \frac{TN}{TN + FP} + \frac{TN}{TN + FN}\right]$$

$$AC = (ACP - 0.5) \times 2$$

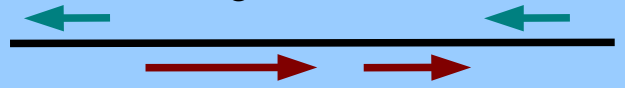
Approximate Correlation

compare_anns.py

```
Genome 6
Cs   (tp=757332, fp=164766, tn=305197, fn=57217): Sn = 0.9298, Sp = 0.8213, AC = 0.6213
Rs   (tp=715865, fp=127462, tn=304830, fn=57584): Sn = 0.9255, Sp = 0.8489, AC = 0.6603
Both (tp=1473197, fp=292228, tn=247613, fn=114801): Sn = 0.9277, Sp = 0.8345, AC = 0.4520
Genome 7
Cs   (tp=868820, fp=236008, tn=517048, fn=79049): Sn = 0.9166, Sp = 0.7864, AC = 0.6285
Rs   (tp=815026, fp=226580, tn=511963, fn=84134): Sn = 0.9064, Sp = 0.7825, AC = 0.6205
Both (tp=1683846, fp=462588, tn=432914, fn=163183): Sn = 0.9117, Sp = 0.7845, AC = 0.4529
Genome 8
Cs   (tp=705403, fp=137180, tn=351159, fn=74782): Sn = 0.9041, Sp = 0.8372, AC = 0.6424
Rs   (tp=607762, fp=169829, tn=351738, fn=74203): Sn = 0.8912, Sp = 0.7816, AC = 0.5865
Both (tp=1313165, fp=307009, tn=276956, fn=148985): Sn = 0.8981, Sp = 0.8105, AC = 0.4166
Genome 9
Cs   (tp=776640, fp=203664, tn=340882, fn=88415): Sn = 0.8978, Sp = 0.7922, AC = 0.5550
Rs   (tp=759048, fp=219786, tn=336181, fn=93116): Sn = 0.8907, Sp = 0.7755, AC = 0.5270
Both (tp=1535688, fp=423450, tn=247766, fn=181531): Sn = 0.8943, Sp = 0.7839, AC = 0.3122
Genome 10
Cs   (tp=612457, fp=106124, tn=253878, fn=88014): Sn = 0.8744, Sp = 0.8523, AC = 0.5872
Rs   (tp=371869, fp=138143, tn=291605, fn=50287): Sn = 0.8809, Sp = 0.7291, AC = 0.5707
Both (tp=984326, fp=244267, tn=203591, fn=138301): Sn = 0.8768, Sp = 0.8012, AC = 0.3640
```

Even more biology

There can be genes in both directions



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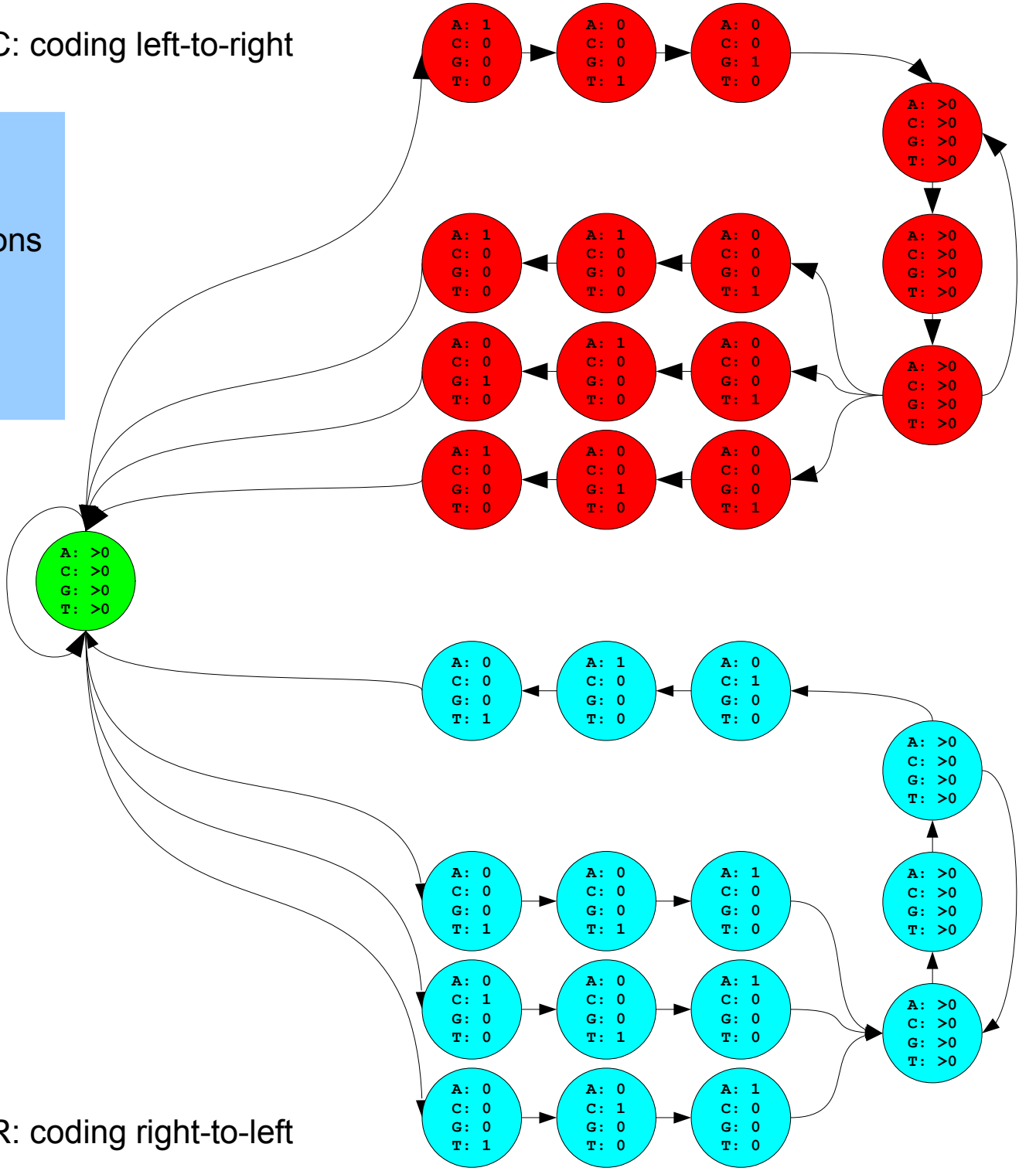

$\pi_N = 1$

$\pi_C = 0$

Analysis of some genomes

```
Length of genome1: 1852441 (1852441)
Length of genome2: 2211485 (2211485)
Length of genome3: 2499279 (2499279)
Length of genome4: 1796846 (1796846)
Length of genome5: 2685015 (2685015)
Length of genome6: 2127839 (2127839)
Length of genome7: 2742531 (2742531)
Length of genome8: 2046115 (2046115)
Length of genome9: 2388435 (2388435)
Length of genome10: 1570485 (1570485)
Length of genome11: 2096309 (2096309)
```

```
Start-codon in normal genes:
ATG [8423, 'NCCC']
ATC [3, 'NCCC']
ATA [1, 'RCCC']
GTG [713, 'NCCC']
ATT [3, 'NCCC']
CTG [2, 'NCCC']
GTT [1, 'NCCC']
CTC [1, 'NCCC']
TTA [1, 'NCCC']
TTG [1020, 'NCCC']

Stop-codon in normal genes:
TAG [1949, 'CCCN']
TGA [1531, 'CCCN']
TAA [6686, 'CCCN']

Reversed stop-codon in reversed genes:
TTA (reverse-complement: TAA) [6596, 'NRRR']
CTA (reverse-complement: TAG) [2014, 'NRRR']
TCA (reverse-complement: TGA) [1148, 'NRRR']

Reversed start-codon in reversed genes:
TAT (reverse-complement: ATA) [2, 'RRRN']
ATG (reverse-complement: CAT) [1, 'RRRN']
GAT (reverse-complement: ATC) [1, 'RRRN']
CAT (reverse-complement: ATG) [8077, 'RRRN']
AAT (reverse-complement: ATT) [4, 'RRRN']
TAC (reverse-complement: GTA) [1, 'RRRN']
CAC (reverse-complement: GTG) [715, 'RRRN']
CAA (reverse-complement: TTG) [953, 'RRRN']
CAG (reverse-complement: CTG) [4, 'RRRN']
```