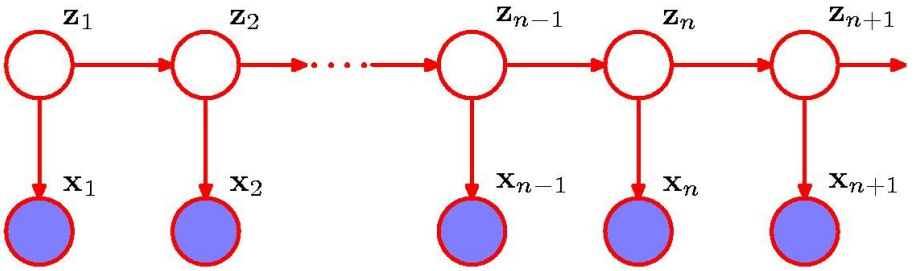
Hidden Markov Models

Some useful extensions



Christian Nørgaard Storm Pedersen

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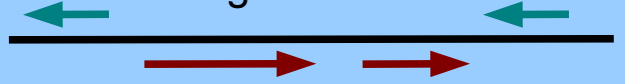
Last time

We developed an HMM for gene finding ...

- A gene is a substring of the DNA sequence of A,C,G,T's
- A gene starts with a start-codon **atg**
- A gene ends with a stop-codon **taa**, **tag** or **tga**
- The number of nucleotides in a gene is a multiplum of 3

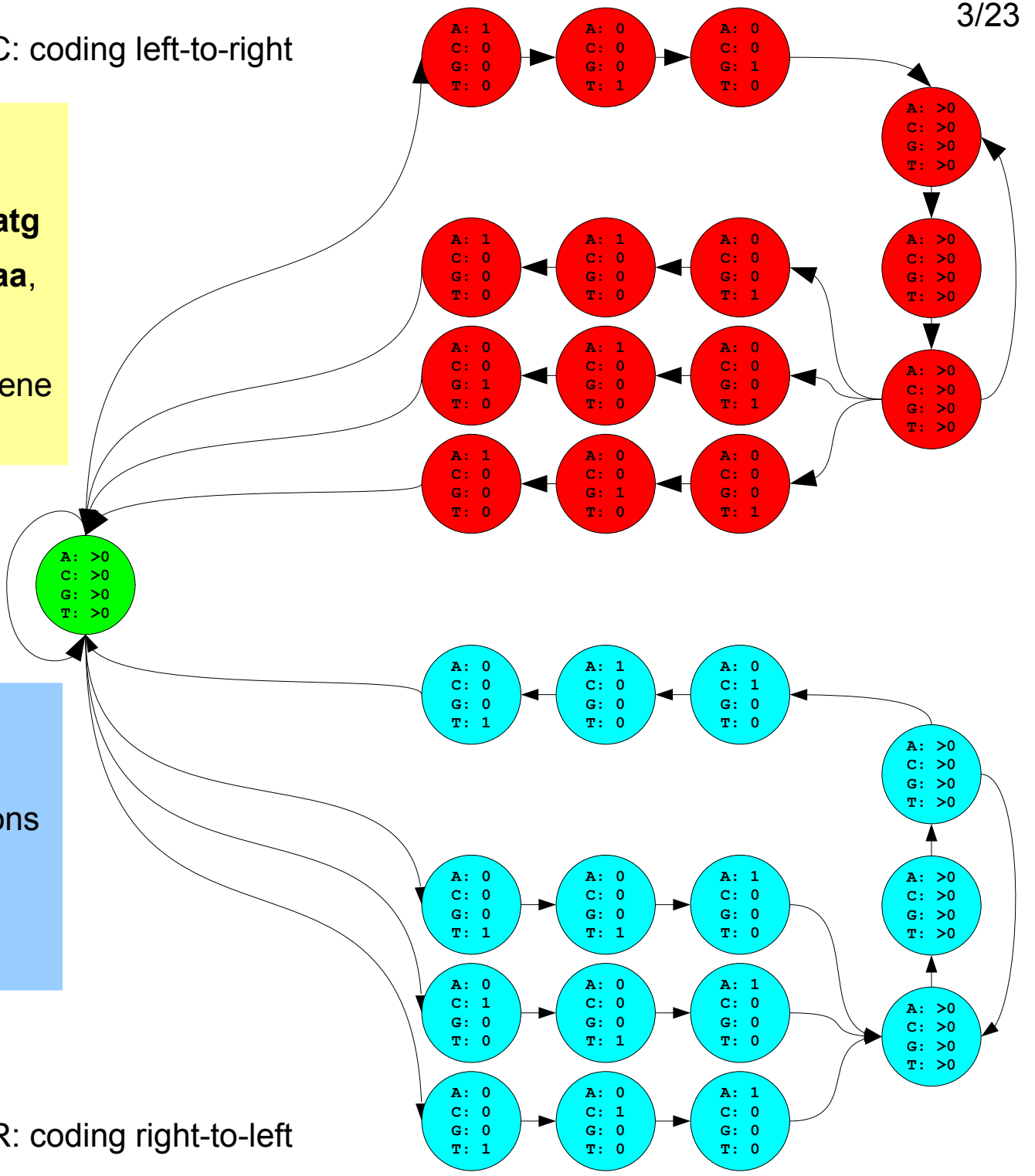
Even more biology

There can be genes in both directions



$\pi_N = 1$

$\pi_C = 0$



C: coding left-to-right

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N: No…

Even more b…

There can be genes in…

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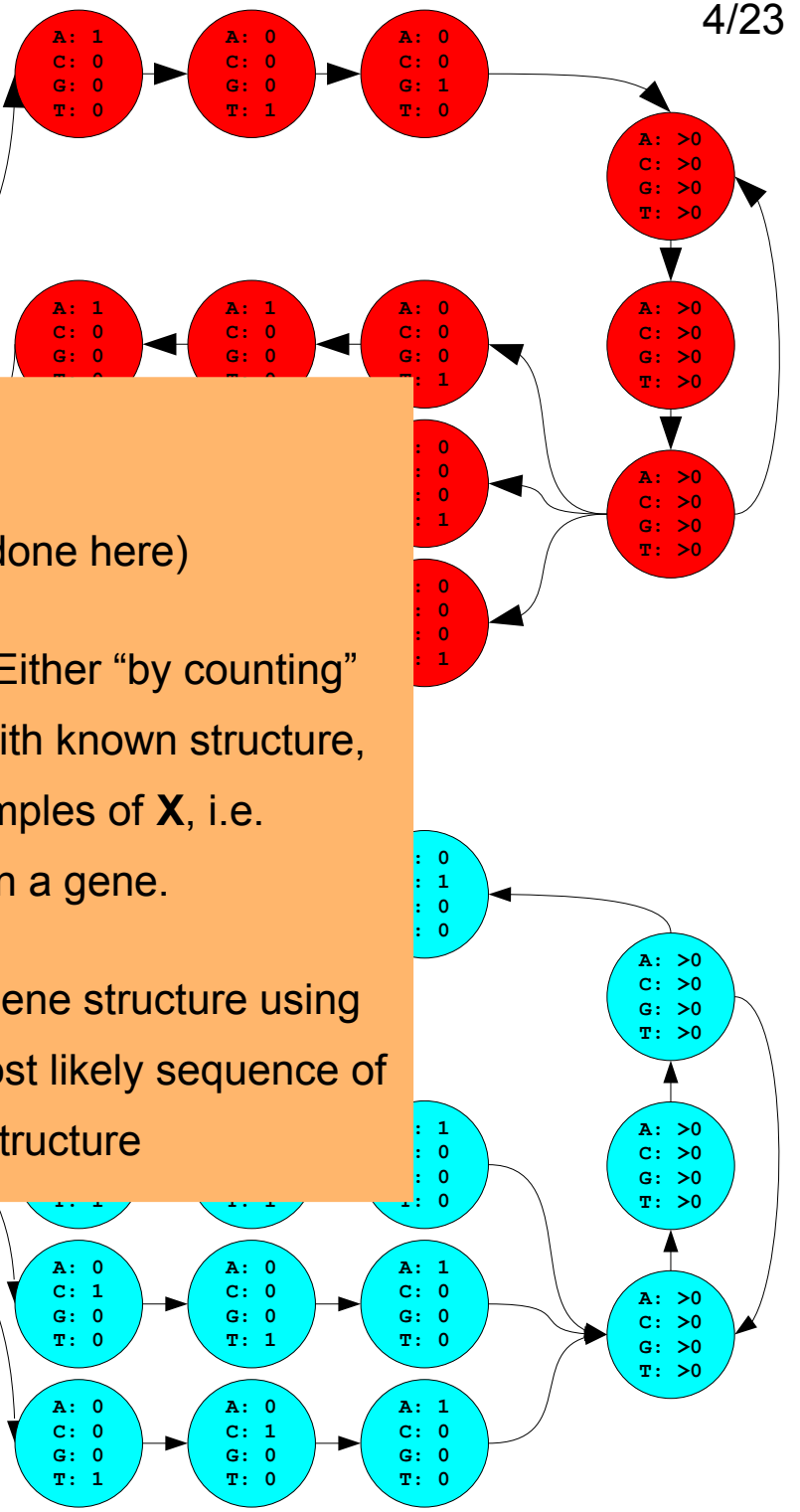
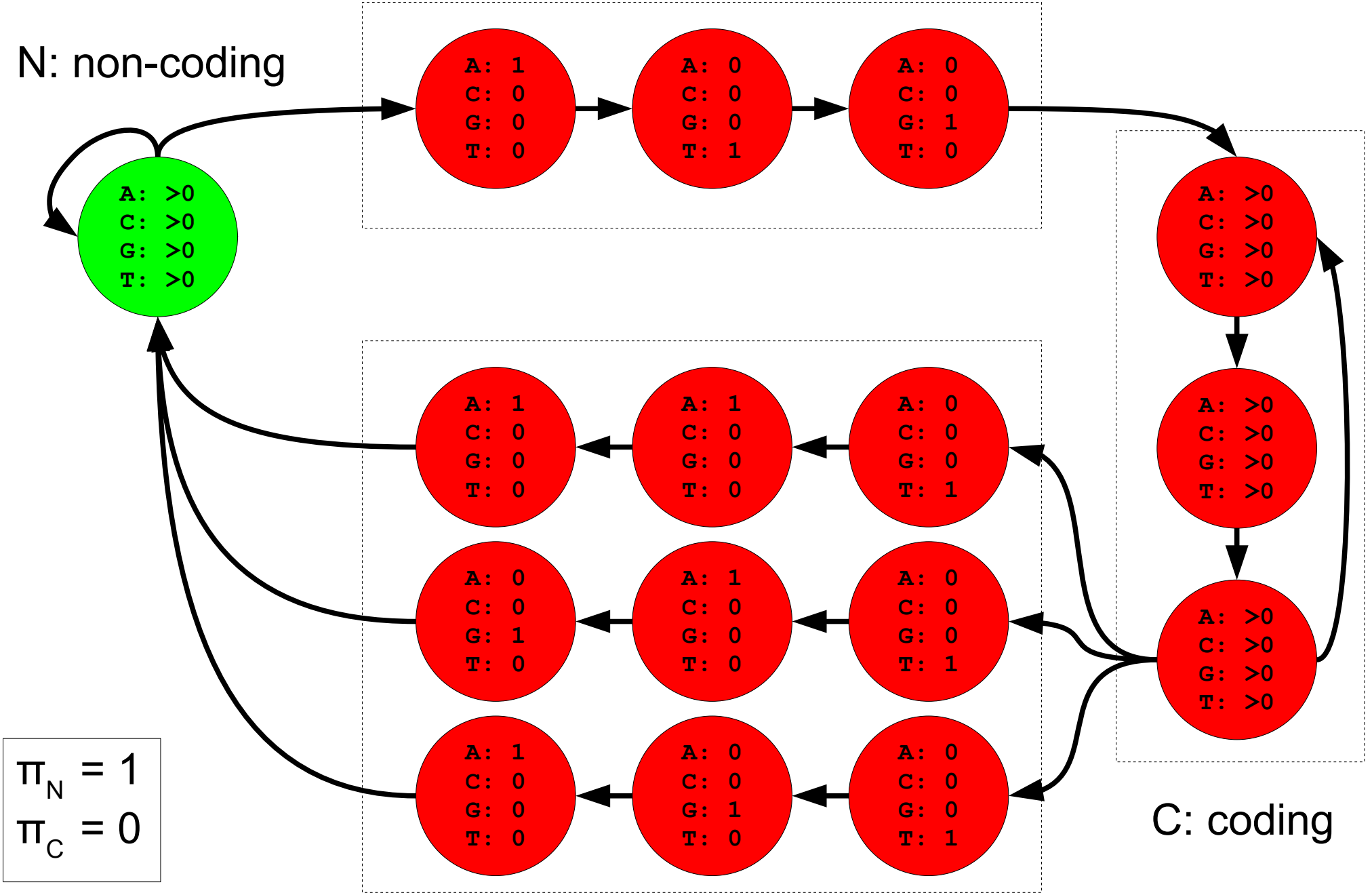
Gene finding

- 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



R: coding right-to-left

The “forward-coding” part



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The "forwa

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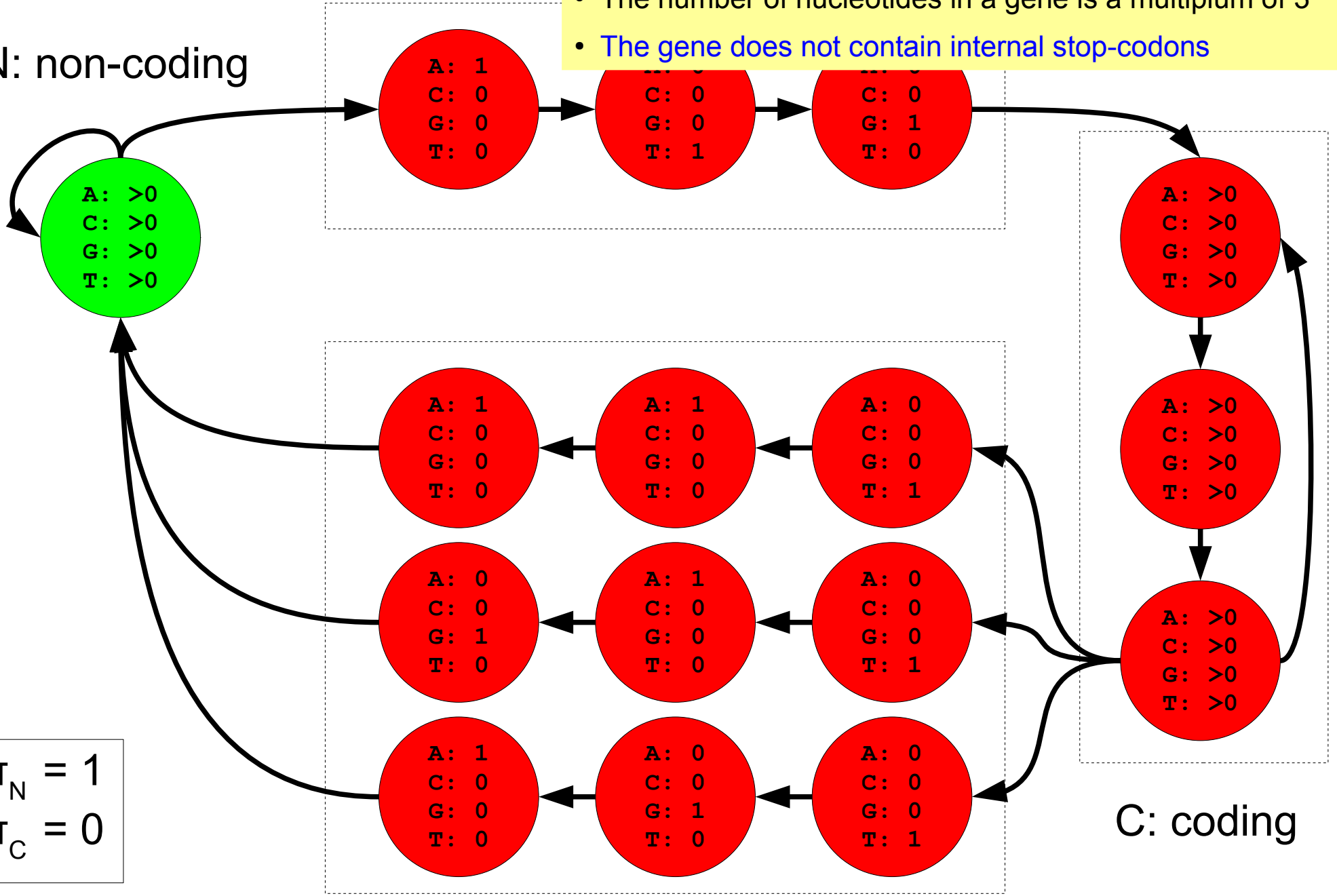
- The number of nucleotides in a gene is a multiplum of 3
- The gene does not contain internal stop-codons



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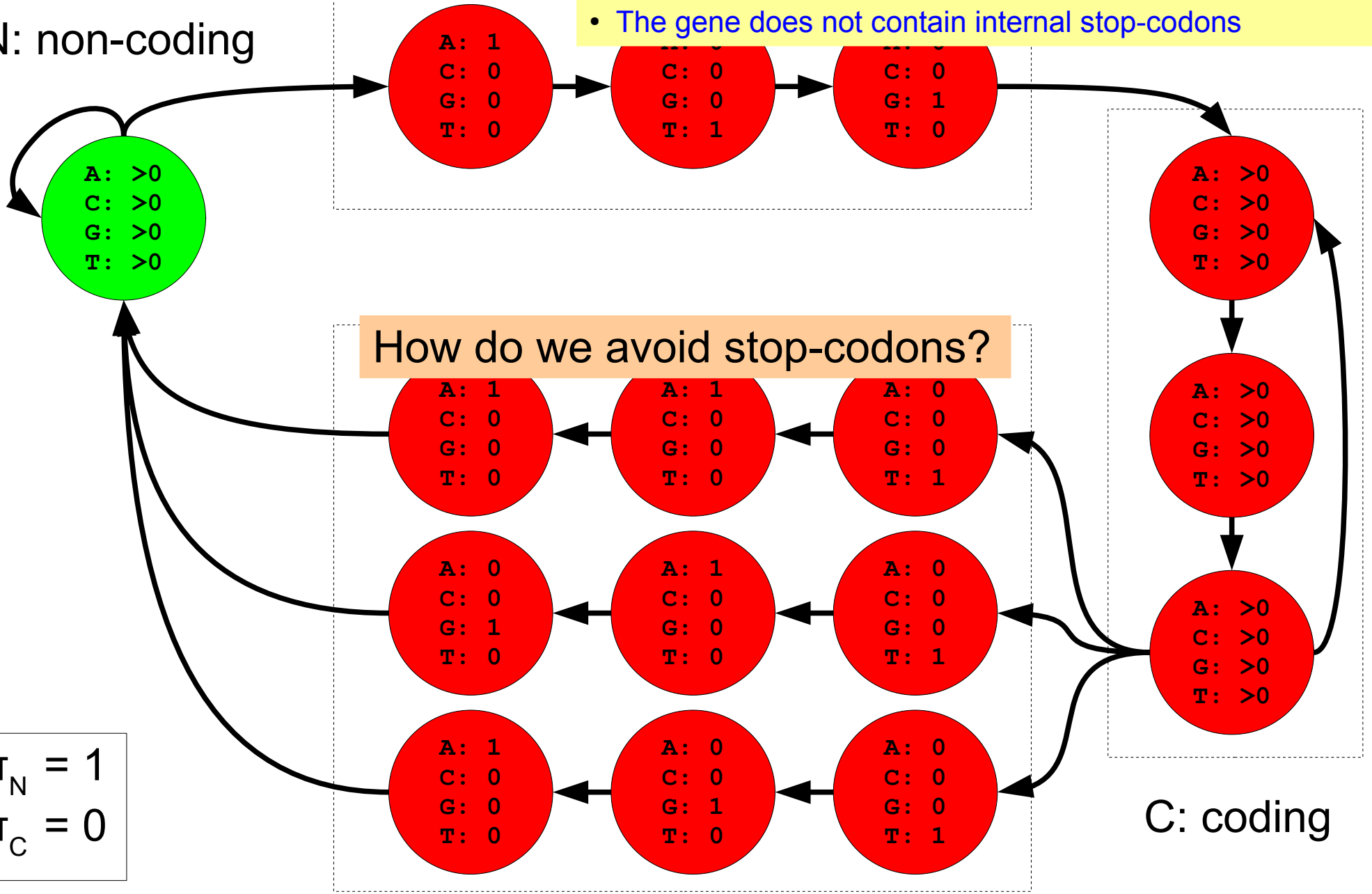
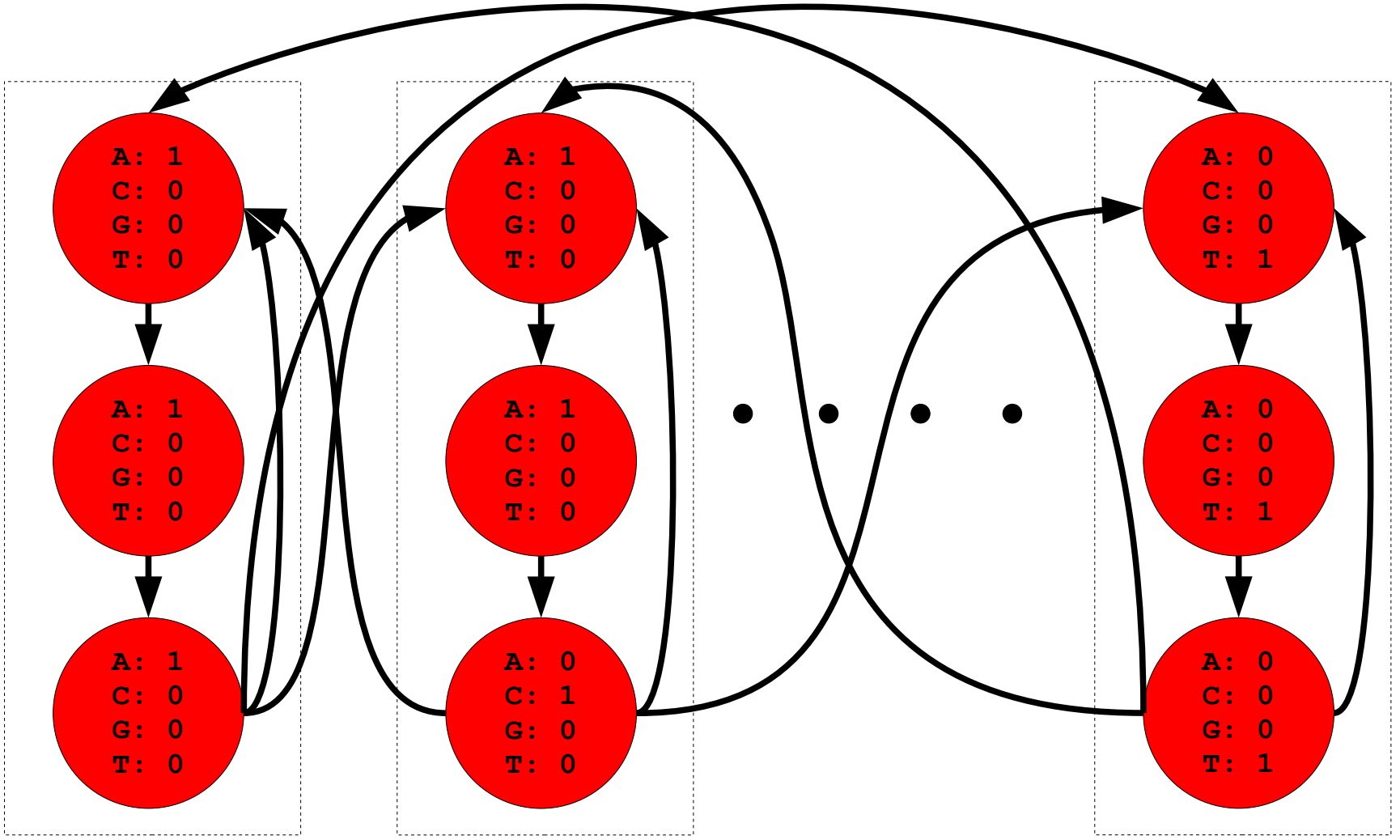


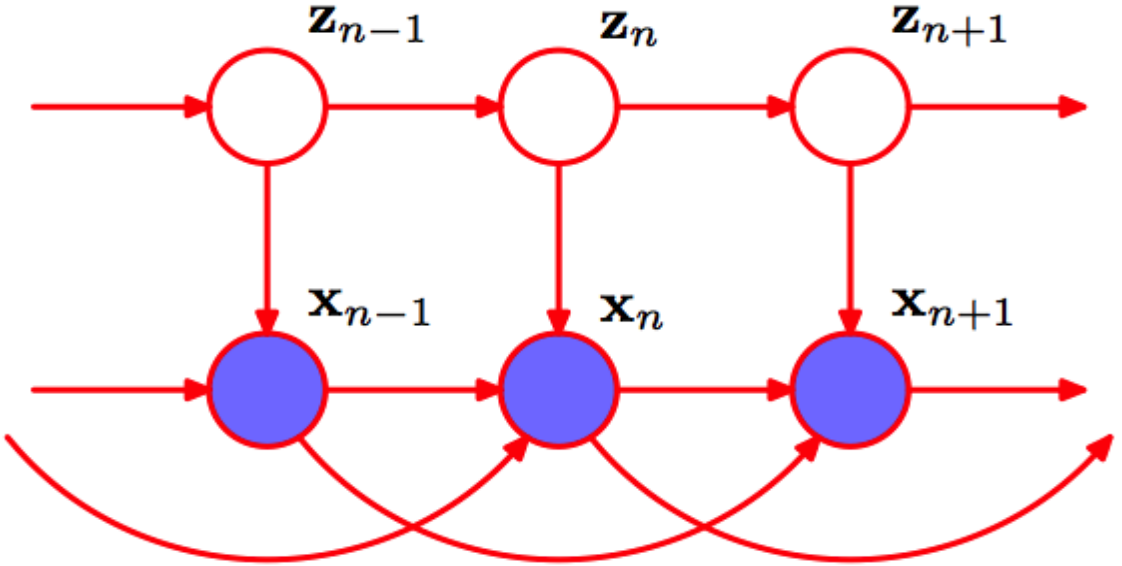
Avoiding internal stop-codons



Encode the emission of each legal codon as a sequence of states.
Many states (61*3=183) and non-trivial transitions (61*60=3660)!

Other ideas?

Autoregressive HMMs

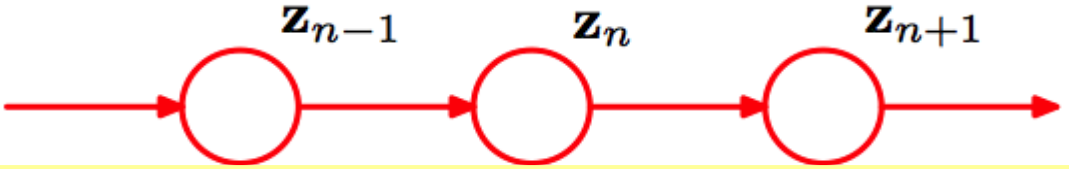


The probability of emitting $\mathbf{x}_n$ depends also on $\mathbf{x}_{n-1}$ and $\mathbf{x}_{n-2}$
The basic algorithms remain the same:

$$\alpha(\mathbf{z}_n) = p(\mathbf{x}_n|\mathbf{x}_{n-1}, \mathbf{x}_{n-2}, \mathbf{z}_n) \sum_{\mathbf{z}_{n-1}} \alpha(\mathbf{z}_{n-1}) p(\mathbf{z}_n|\mathbf{z}_{n-1})$$

$$\omega(\mathbf{z}_n) = p(\mathbf{x}_n|\mathbf{x}_{n-1}, \mathbf{x}_{n-2}, \mathbf{z}_n) \max_{\mathbf{z}_{n-1}} \omega(\mathbf{z}_{n-1}) p(\mathbf{z}_n|\mathbf{z}_{n-1})$$

Autoregressive HMMs



For each state, we just have to state the conditional probabilities. For a 4-letter DNA alphabet this corresponds to 4*4*4 emission prob.

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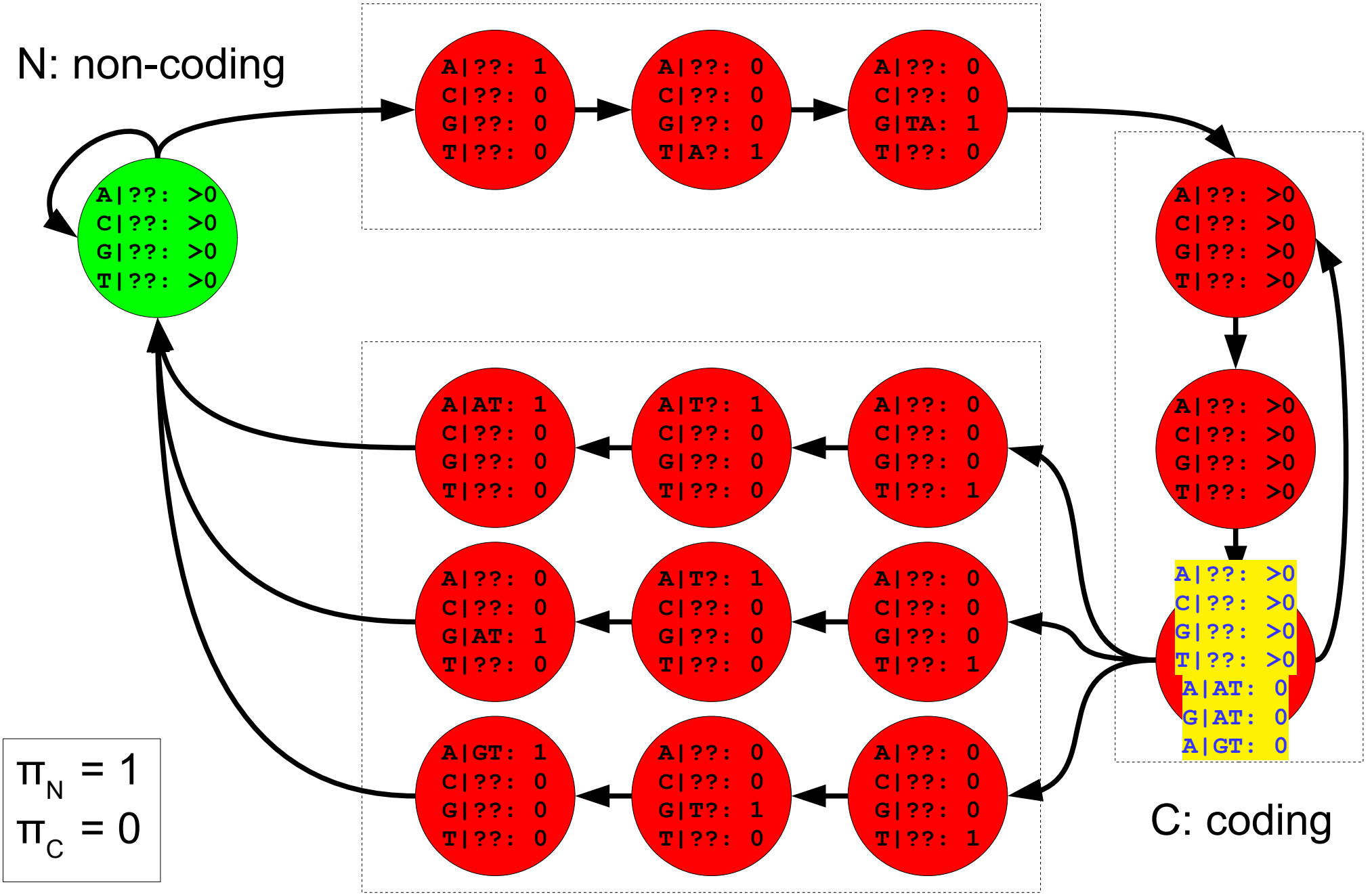
Adjusting our simple HMM



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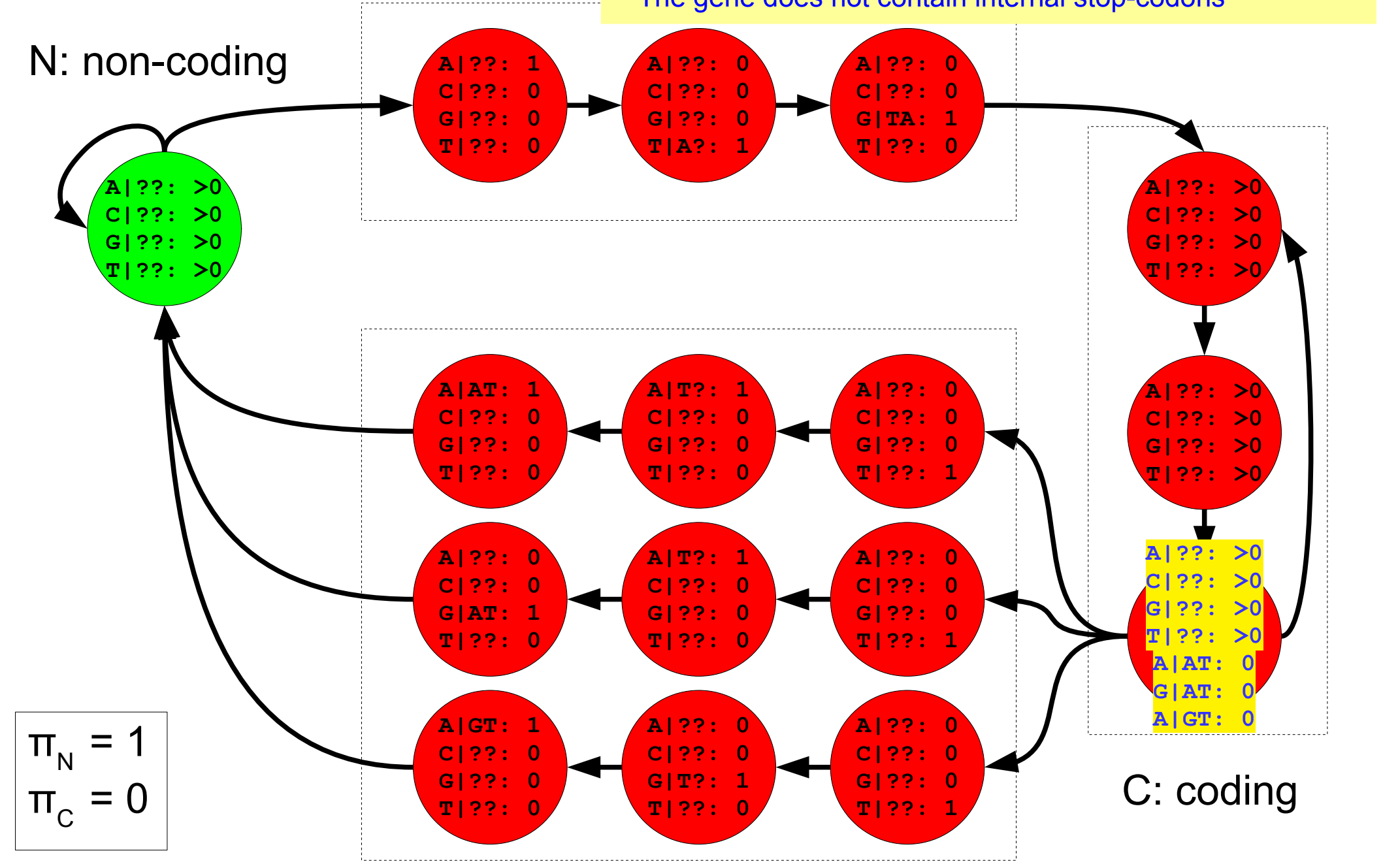
Adjusting



Emitting a variable number of symbols

Make it possible to emit a variable number of symbols depending on the state. Fx when being in state $\mathbf{z}_n$ the model emits $d_{\mathbf{z}n}$ symbols, where $d_{\mathbf{z}n}$ is an integer ≥ 0.

The basic algorithms can easily be reformulated, fx Viterbi:

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$\omega(n,k)$: The probability of the most likely path generating the first *n* symbols and ending in state *k*.

$$\omega(n,k) = \max_{k' \to k} \omega(n - d_k, k') p(k' \to k) p(\mathbf{x}_n \ldots \mathbf{x}_{n-d_k+1} | k)$$

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Transition prob from state *k'* to *k*

Emission prob of emitting d_k symbols from state *k*.

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$\omega(n,k)$: The probability of the mos… the first *n* symbols and en…

Special case: If $d_k = 0$ then the state is called a *silent state*.

$$\omega(n,k) = \max_{k' \to k} \omega(n - d_k, k') p(k' \to k) p(\mathbf{x}_n \ldots \mathbf{x}_{n-d_k+1} | k)$$

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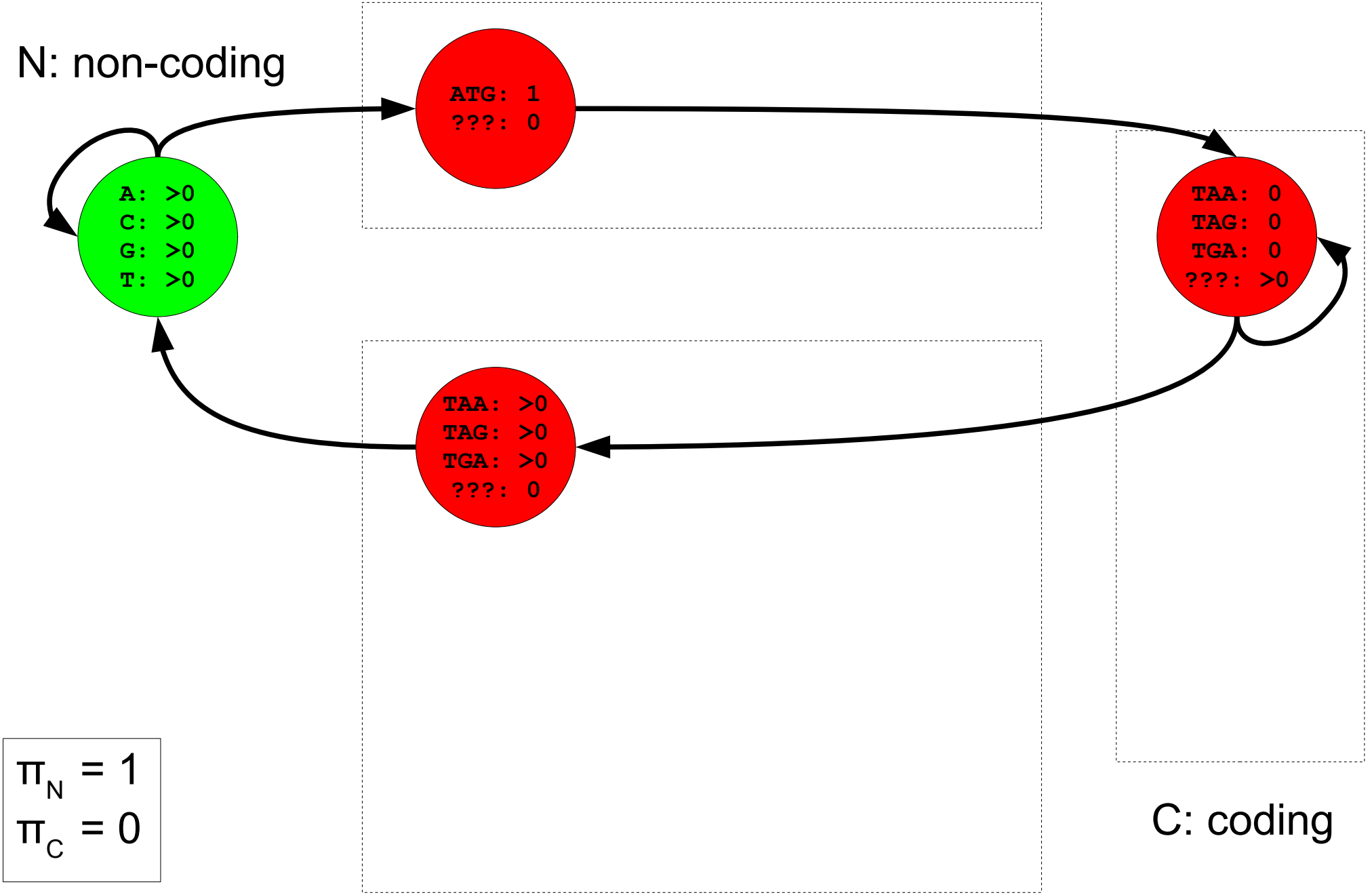
Adjusting our simple HMM



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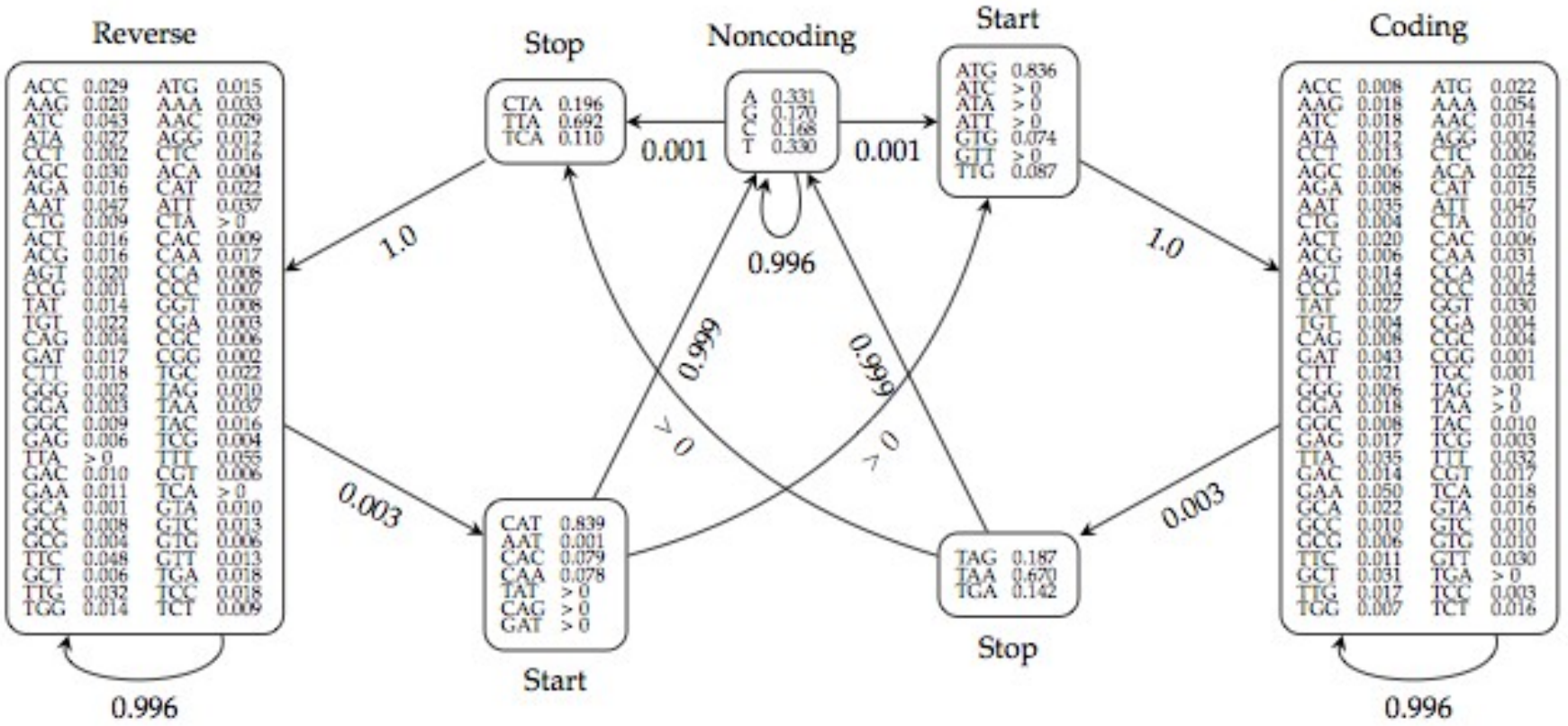
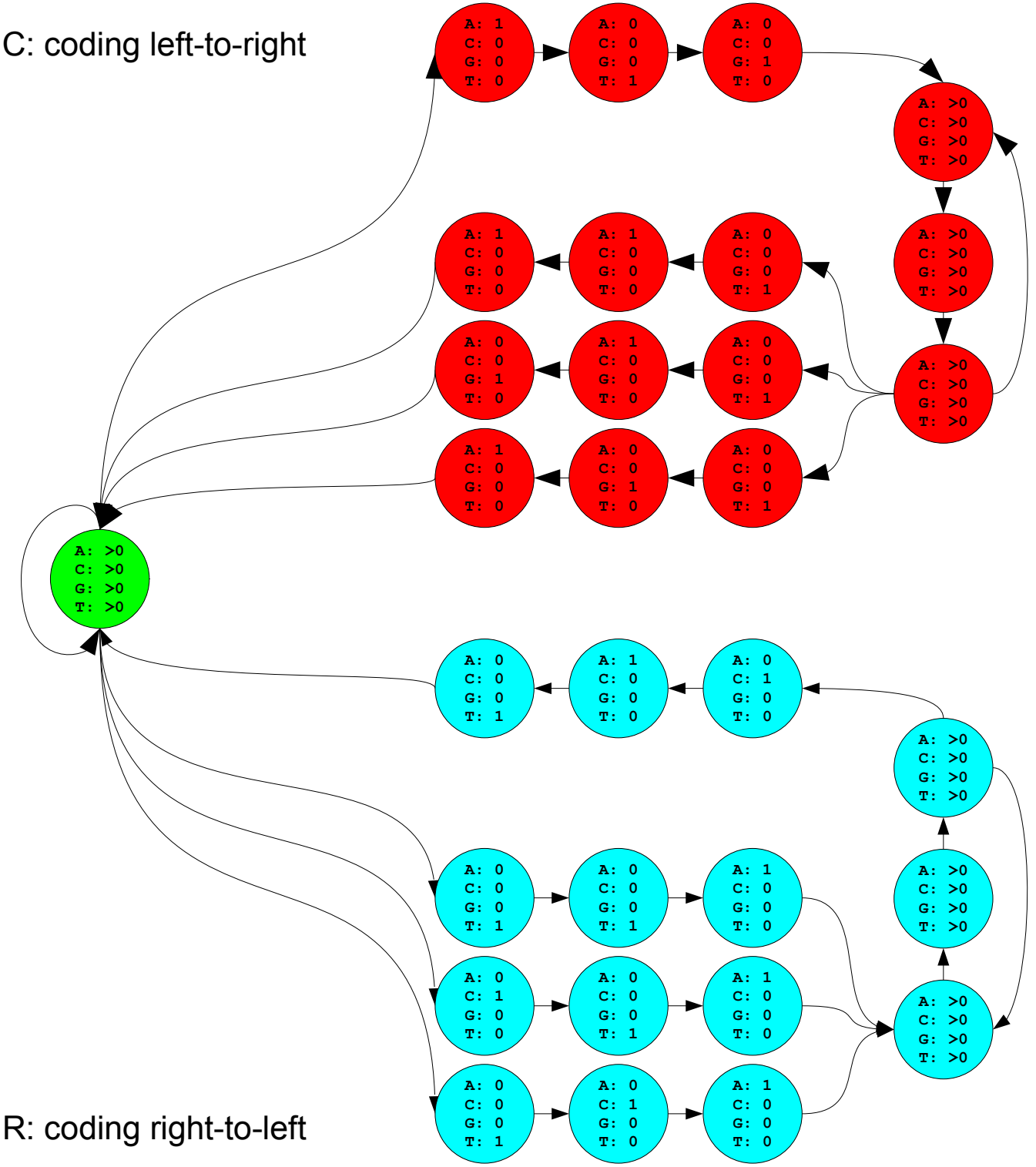
A “codon” model



C: coding left-to-right



R: coding right-to-left

ACs between predictions and true annotations sorted by average

	Genome 6	Genome 7	Genome 8	Genome 9	Genome 10	Average
3	0,6313	0,6378	0,6007	0,5310	0,4762	**0,5754**
22	0,6313	0,6378	0,6007	0,5310	0,4762	**0,5754**
9	0,6053	0,6147	0,5708	0,4919	0,4197	**0,5405**
10	0,4628	0,4587	0,4245	0,3244	0,3611	**0,4063**
21	0,4619	0,4582	0,4219	0,3239	0,3603	**0,4052**
13	0,4539	0,4547	0,4159	0,3121	0,3650	**0,4003**
11	0,4522	0,4504	0,4172	0,3139	0,3648	**0,3997**
1	0,4520	0,4529	0,4165	0,3122	0,3646	**0,3996**
25	0,4543	0,4515	0,4144	0,3133	0,3596	**0,3986**
18	0,4521	0,4481	0,4112	0,3095	0,3619	**0,3966**
15	0,4501	0,4449	0,4187	0,2974	0,3586	**0,3939**
24	0,4237	0,4326	0,4063	0,2769	0,3816	**0,3842**
14	0,4359	0,4383	0,3974	0,2642	0,3467	**0,3765**
2	0,4286	0,4548	0,3725	0,2473	0,3733	**0,3753**
19	0,3856	0,4075	0,3727	0,2926	0,3059	**0,3529**
23	0,3854	0,4073	0,3551	0,2336	0,3710	**0,3505**
5	0,3850	0,4008	0,3619	0,2559	0,3119	**0,3431**
6	0,3821	0,3914	0,3504	0,2365	0,3263	**0,3373**
16	0,2917	0,3462	0,2618	0,2240	0,3213	**0,2890**
7	0,0247	0,0978	0,0311	0,0642	0,1441	**0,0724**
4	0,0254	0,0939	0,0253	0,0631	0,1387	**0,0693**
20	0,0775	0,0526	0,1344	-0,0246	0,0765	**0,0633**
12	0,0344	0,0820	0,0089	0,0549	0,1144	**0,0589**
17	-0,2748	-0,2571	-0,2635	-0,2657	-0,3075	**-0,2737**
8						

Codon-models

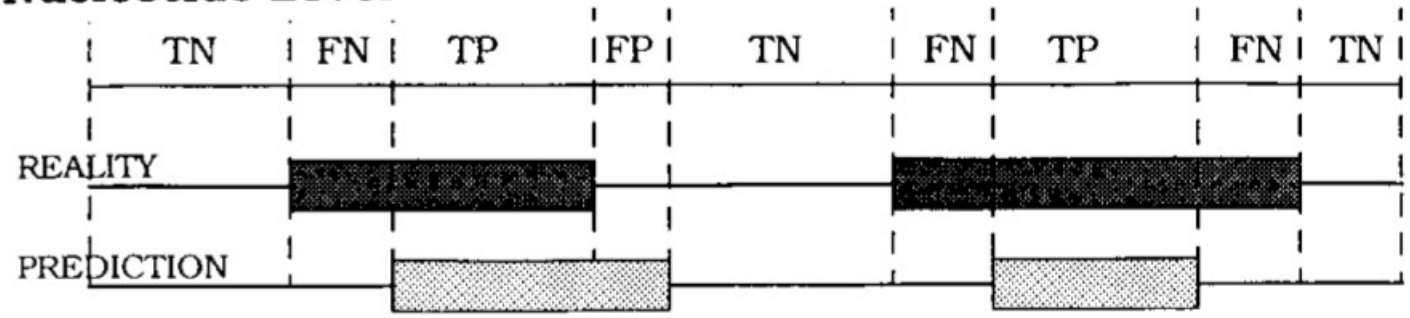
Models inspired by the model presented in class maybe allowing more start/stop codons.

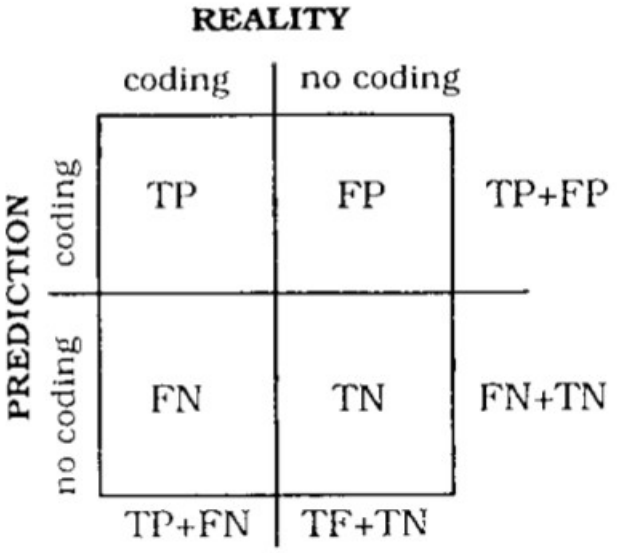
Problems with training or prediction

Evaluation of Gene Structure Prediction Programs (Burset and Guigo, 1996)

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

History and applications of HMMs

History of HMMs

Hidden Markov Models were introduced in statistical papers by Leonard E. Baum and others in the late1960s. One of the first applications of HMMs was speech recognition in the mid-1970s.

In the late 1980s, HMMs were applied to the analysis of biological sequences. Since then, many applications in bioinformatics...

Applications of HMMs in bioinformatics

prediction of protein-coding regions in genome sequences

modeling families of related DNA or protein sequences

prediction of secondary structure elements in proteins

... and many others ...