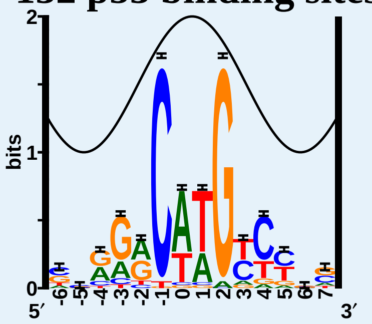
Information Theory and Molecular Biology

Thomas D. Schneider, Ph.D.

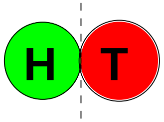
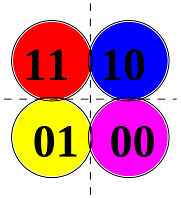
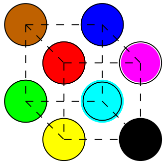
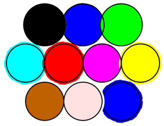
National Cancer Institute at Frederick
Gene Regulation and Chromosome Biology Laboratory
Molecular Information Theory Group



132 p53 binding sites

El Duomo, Florence, Italy

Information Theory: One-Minute Lesson

number of symbols	number of bits	example
M	B	
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	

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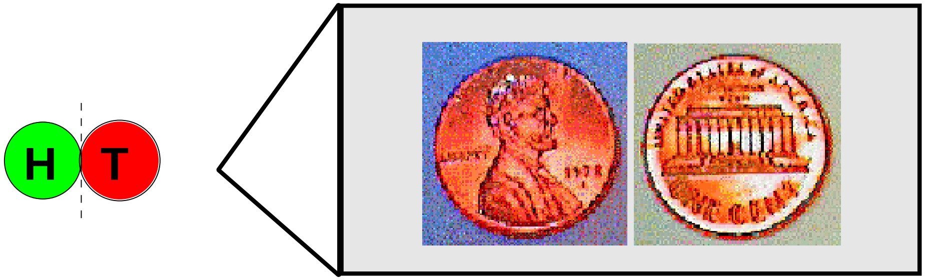
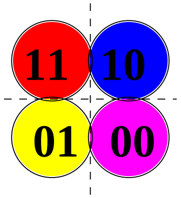
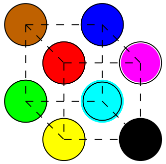
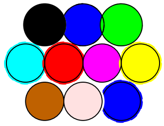
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	

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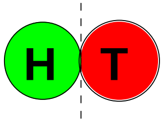
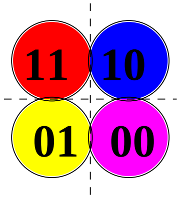
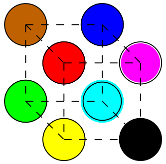
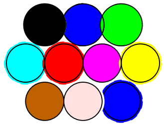
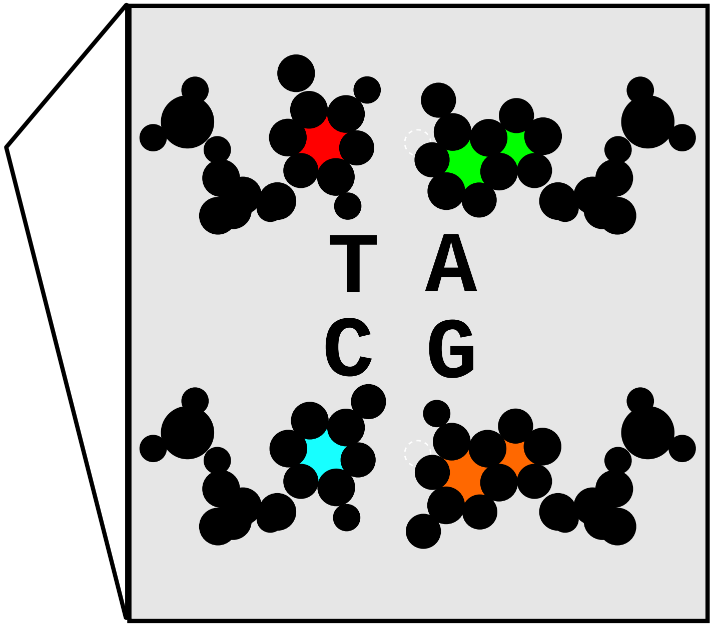
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	



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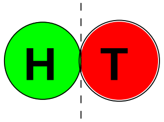
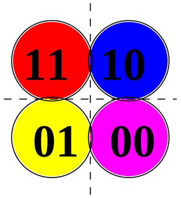
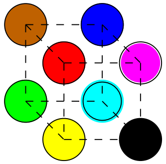
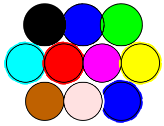
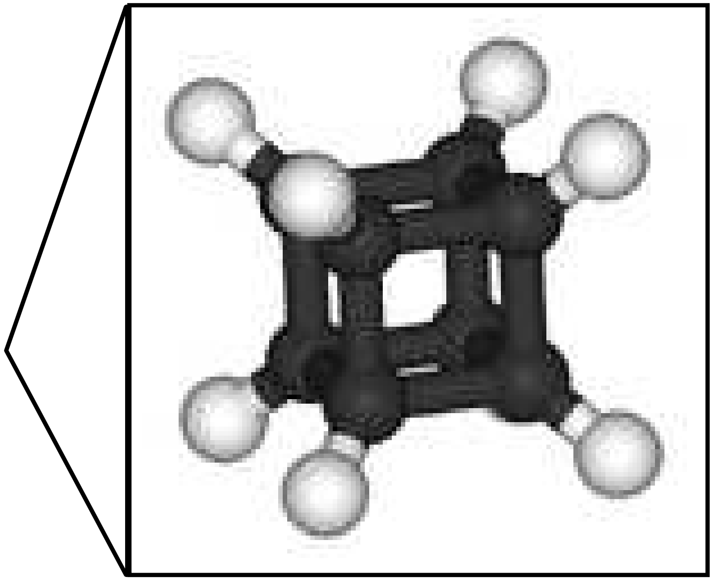
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	



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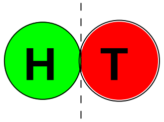
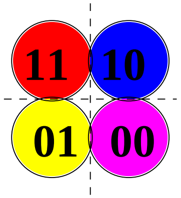
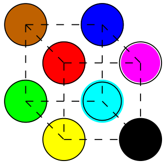
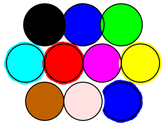
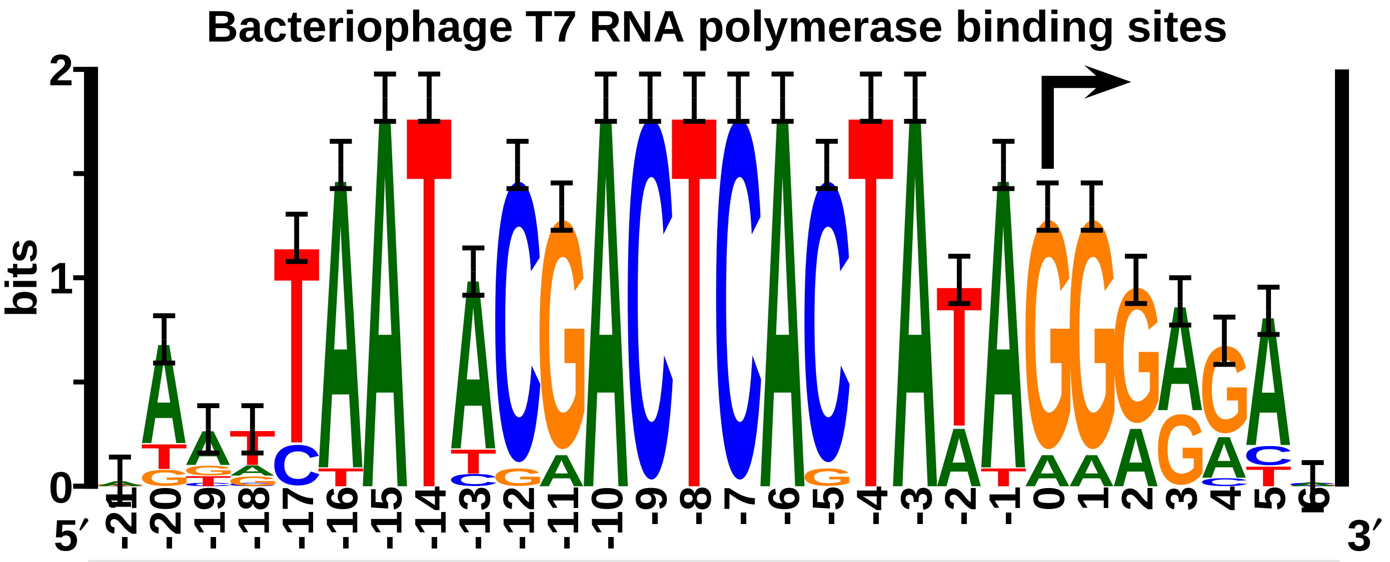
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	

Sequence Logo


Bacteriophage T7 RNA polymerase binding sites

Schneider &
Stephens
Nucl. Acids Res.
18: 6097-6100
1990

1 ttattaatacaactcactataaggagag

2 aaatcaatacgactcactatagagggac

3 cggttaatacgactcactataggagaac

4 gaagtaatacgactcagtatagggacaa

5 taattaattgaactcactaaagggagac

6 cgcttaatacgactcactaaaggagaca

6 of 17 sites

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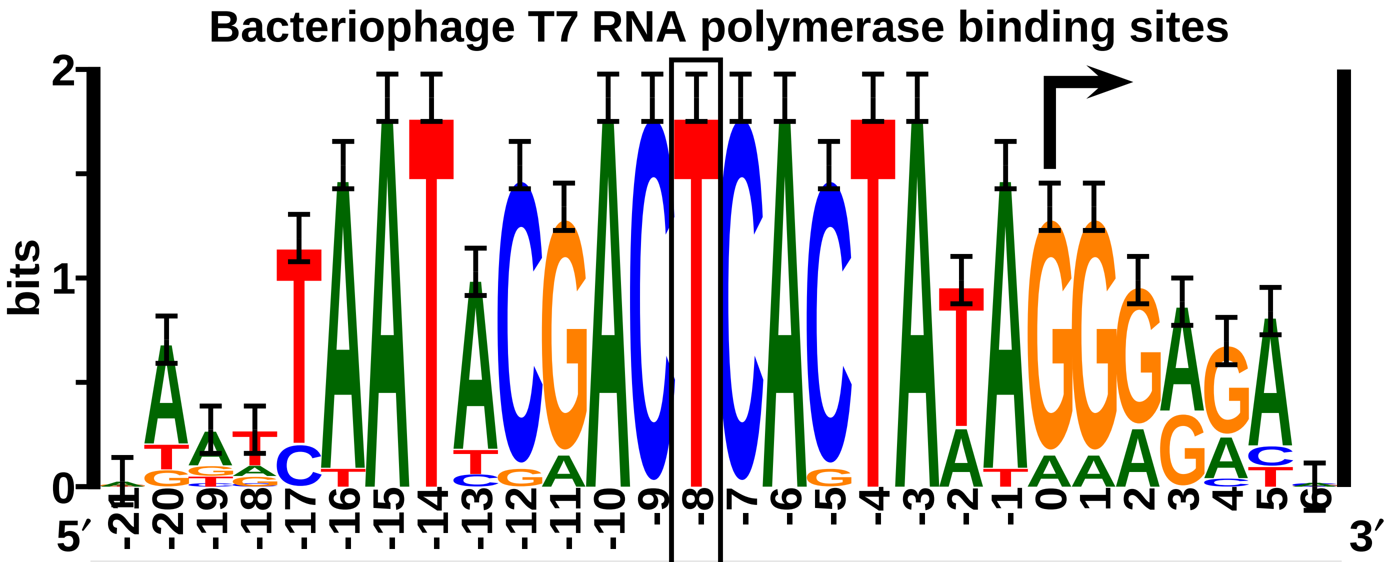

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1 ttattaatacaactcactataaggagag
2 aaatcaatacgactcactatagagggac
3 cggttaatacgactcactataggagaac
4 gaagtaatacgactcagtatagggacaa
5 taattaattgaactcactaaagggagac
6 cgcttaatacgactcactaaaggagaca

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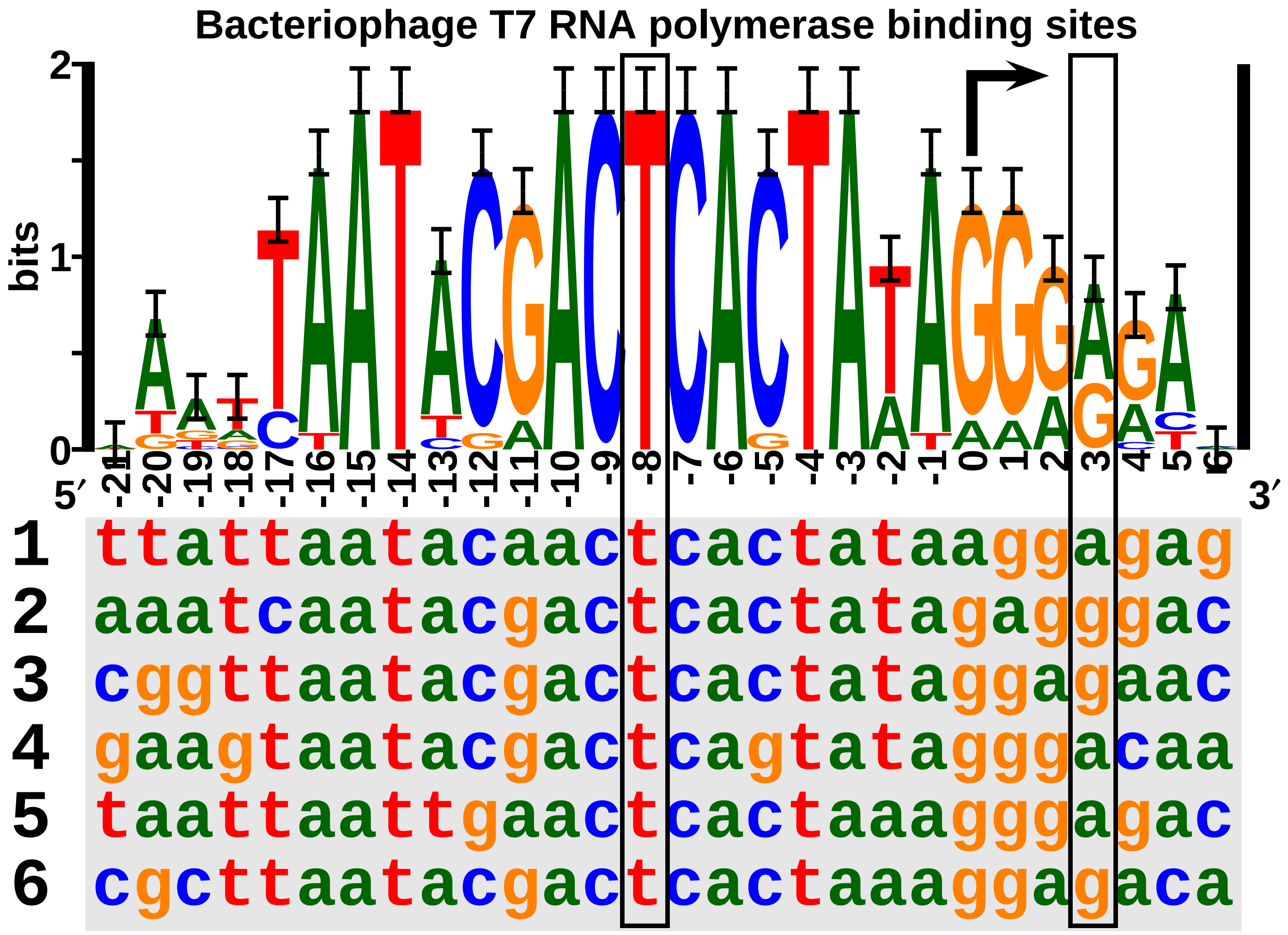
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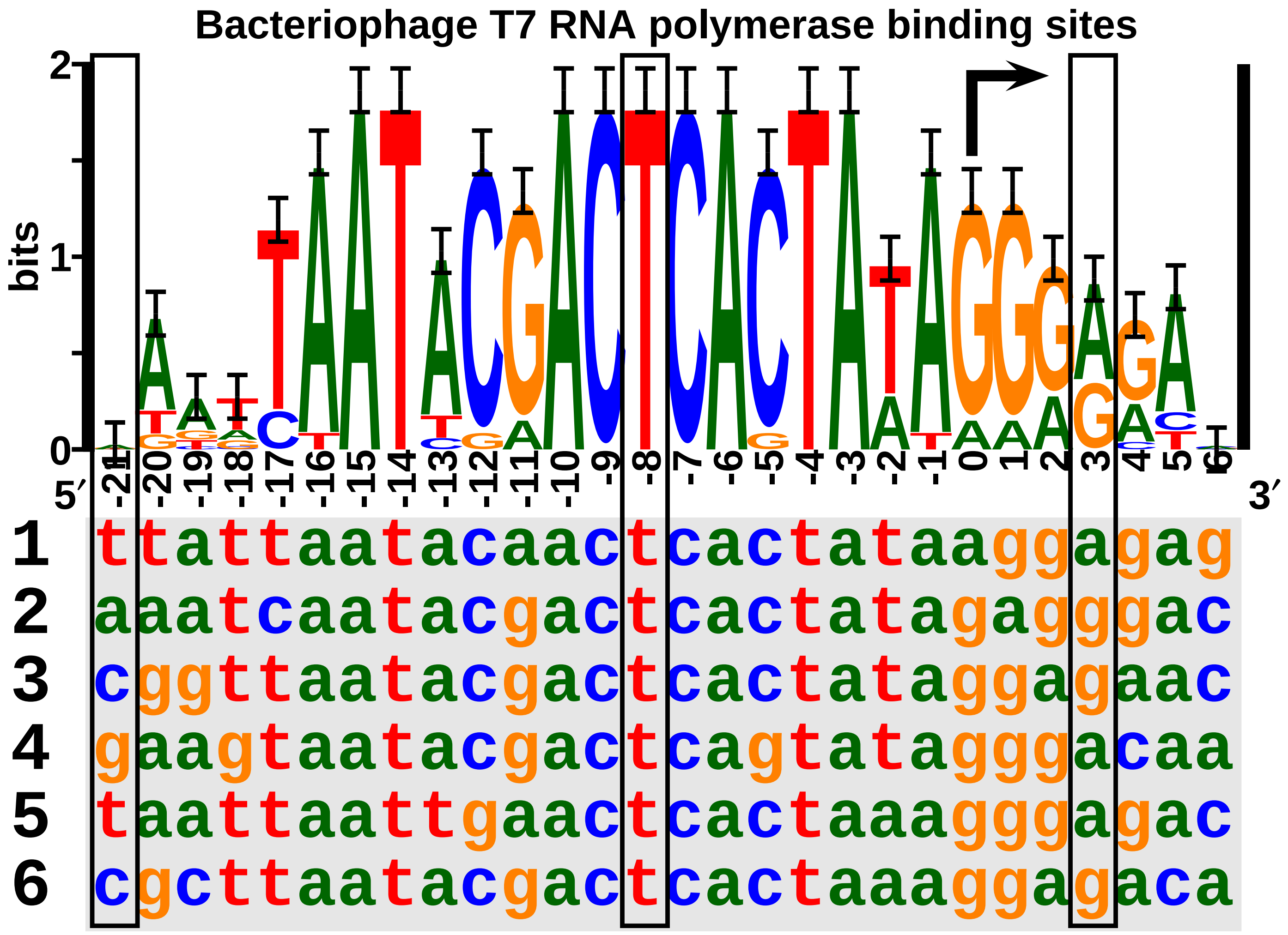

1 ttattaatacaactcactataaggagag

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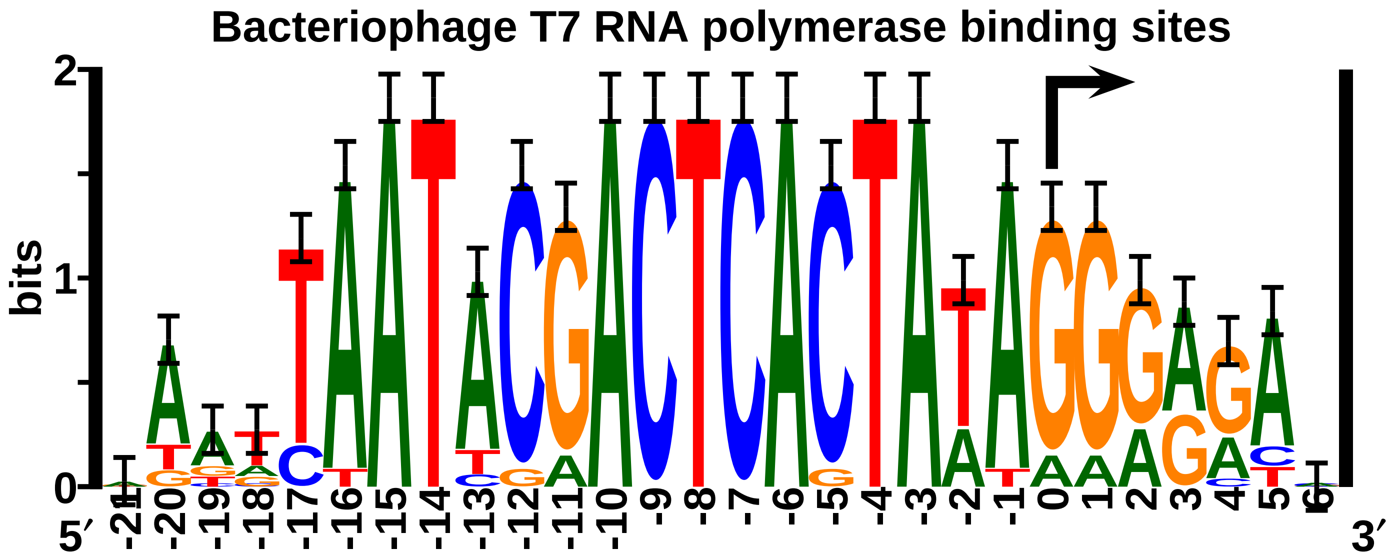
Sequence Logo and Sequence Walker



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		Bits
1	ttattaatacaactcactataaggagag	33.3
2	aaatcaatacgactcactatagagggac	37.4
3	cggttaatacgactcactataggagaac	34.4
4	gaagtaatacgactcagtatagggacaa	33.1
5	taattaattgaactcactaaagggagac	30.1
6	cgcttaatacgactcactaaaggagaca	29.1

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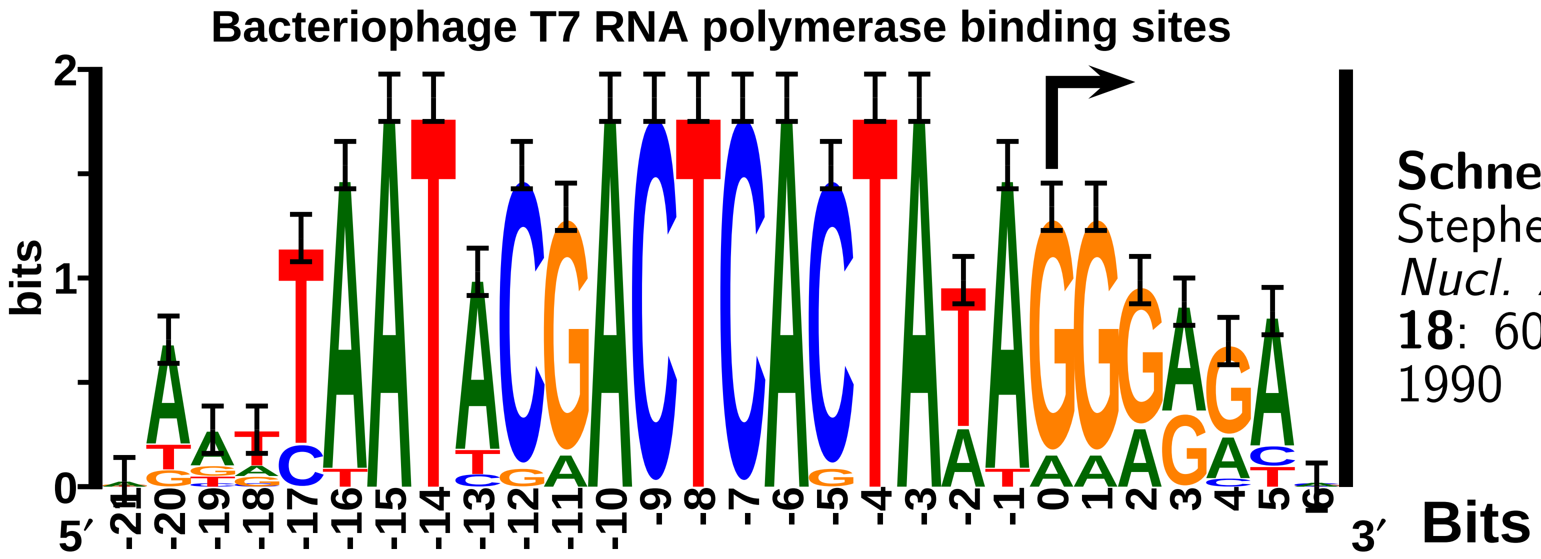

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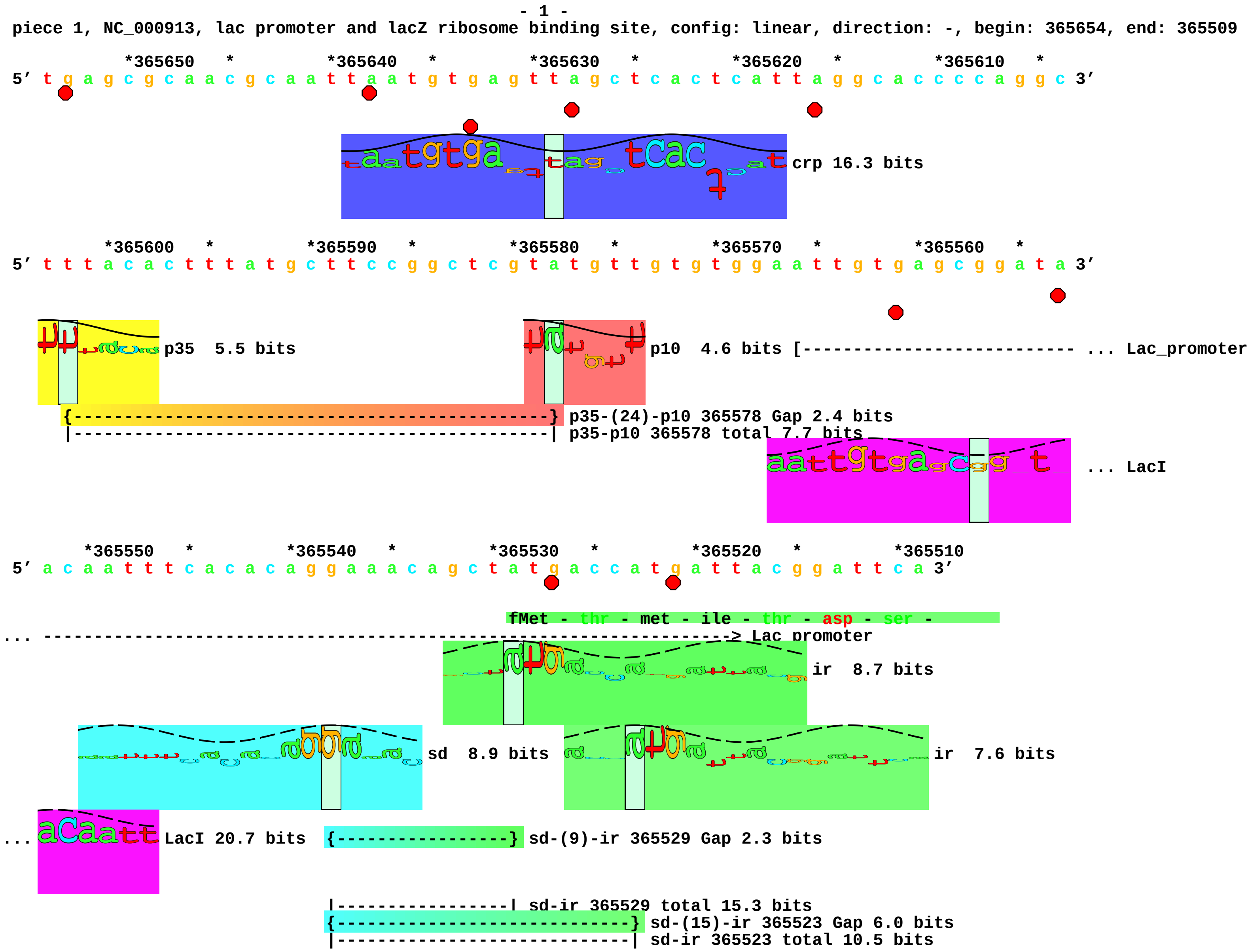
4	gaagtaatacgactcagtatagggacaa	33.1
5	taattaattgaactcactaaagggagac	30.1
6	cgcttaatacgactcactaaaggagaca	29.1

Sequence Walker
Patent
5,867,402

Sequence Walkers in the Lac Promoter



```
                                  - 1 -
piece 1, NC_000913, lac promoter and lacZ ribosome binding site, config: linear, direction: -, begin: 365654, end: 365509

          *365650    *         *365640    *         *365630    *         *365620    *         *365610    *
5' t g a g c g c a a c g c a a t t a a t g t g a g t t a g c t c a c t c a t t a g g c a c c c c a g g c 3'

                                                                                crp 16.3 bits

         *365600    *         *365590    *         *365580    *         *365570    *         *365560    *
5' t t t a c a c t t t a t g c t t c c g g c t c g t a t g t t g t g t g g a a t t g t g a g c g g a t a 3'

              p35   5.5 bits                      p10   4.6 bits [-------------------------- ... Lac_promoter
  {-----------------------------------------------} p35-(24)-p10 365578 Gap 2.4 bits
  |-----------------------------------------------| p35-p10 365578 total 7.7 bits
                                                                                   ... LacI

        *365550    *         *365540    *         *365530    *         *365520    *         *365510
5' a c a a t t t c a c a c a g g a a a c a g c t a t g a c c a t g a t t a c g g a t t c a 3'

                                            fMet - thr - met - ile - thr - asp - ser -
... ------------------------------------------------------------------> Lac promoter
                                                            ir   8.7 bits

                                sd   8.9 bits                                ir   7.6 bits

...         LacI 20.7 bits  {-----------------} sd-(9)-ir 365529 Gap 2.3 bits

                            |-----------------| sd-ir 365529 total 15.3 bits
                            {-----------------------------} sd-(15)-ir 365523 Gap 6.0 bits
                            |-----------------------------| sd-ir 365523 total 10.5 bits
```

Predicting splicing mutations using information theory

- Xeroderma Pigmentosum-Variant:
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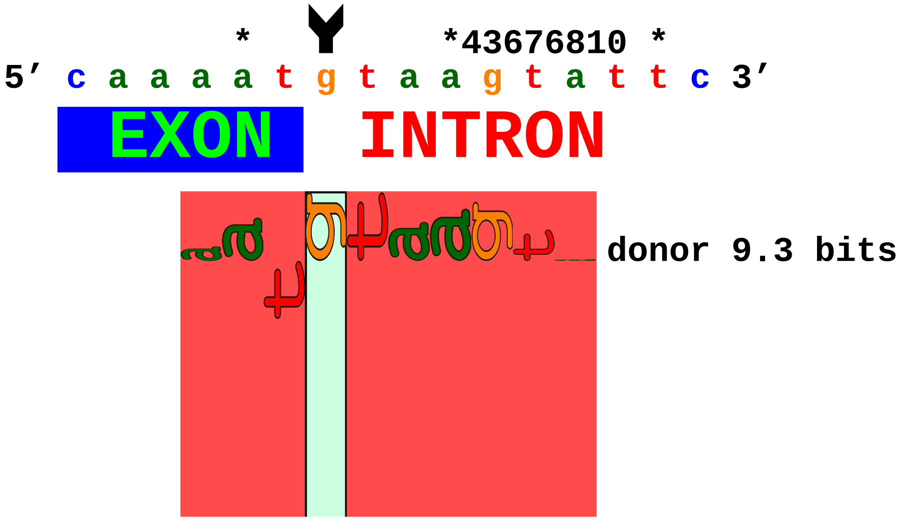

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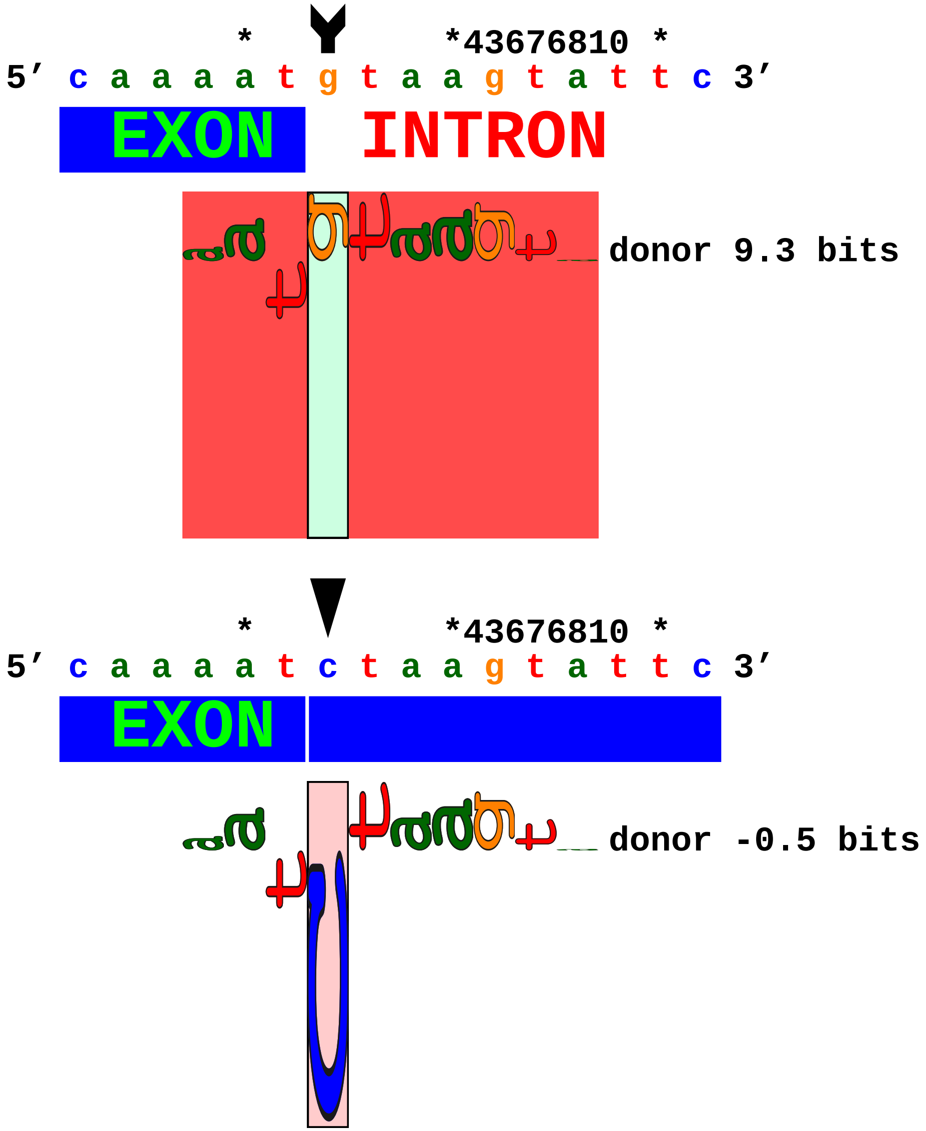

Inui, . . . , **Schneider** and Kraemer,
J Invest Dermatol. 128:2055-68 (2008)

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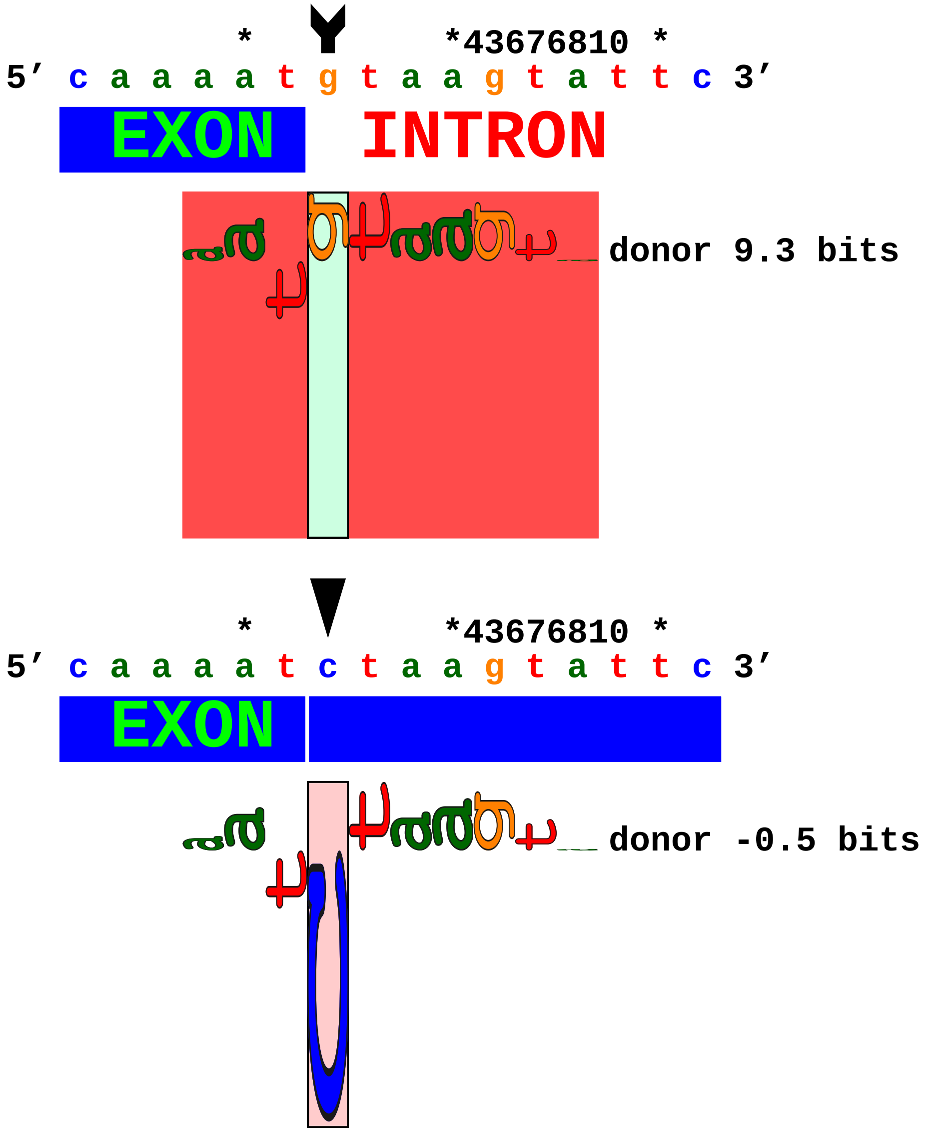

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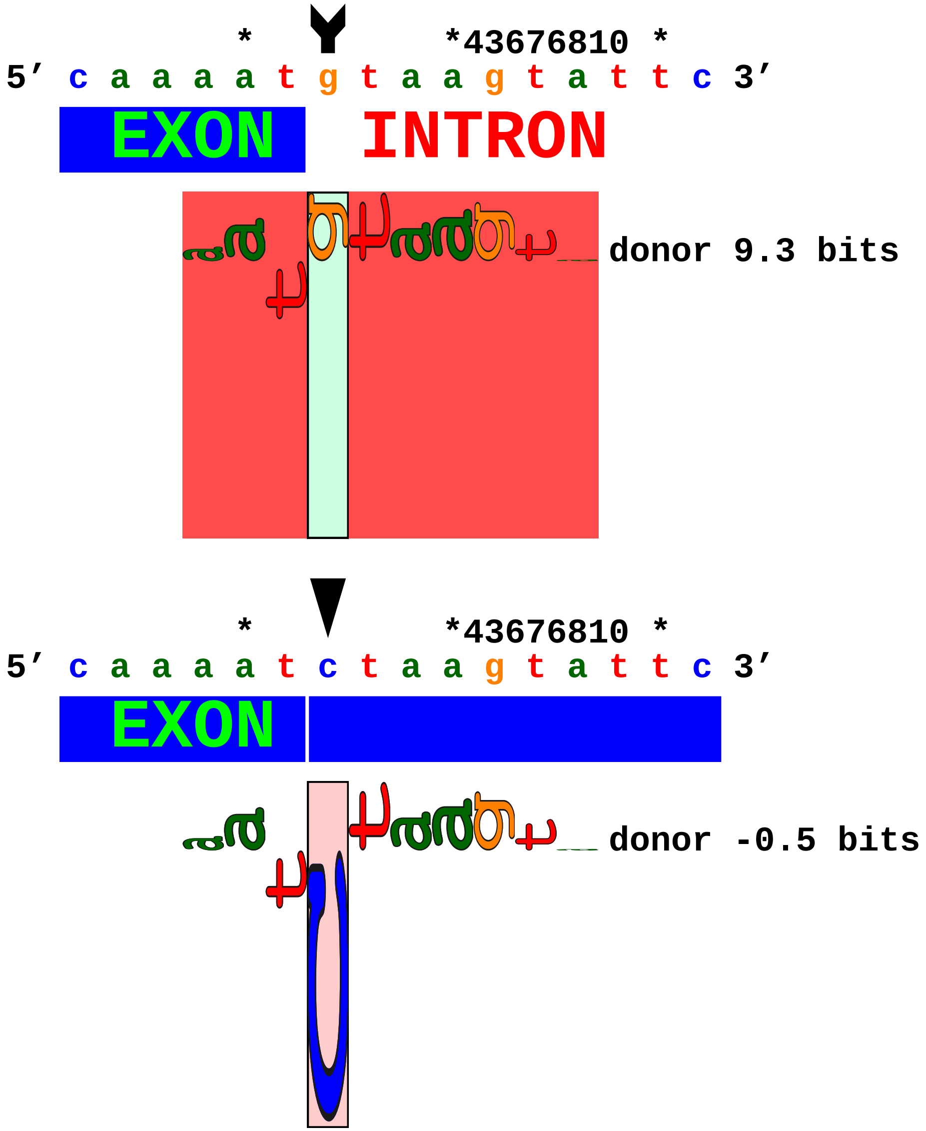

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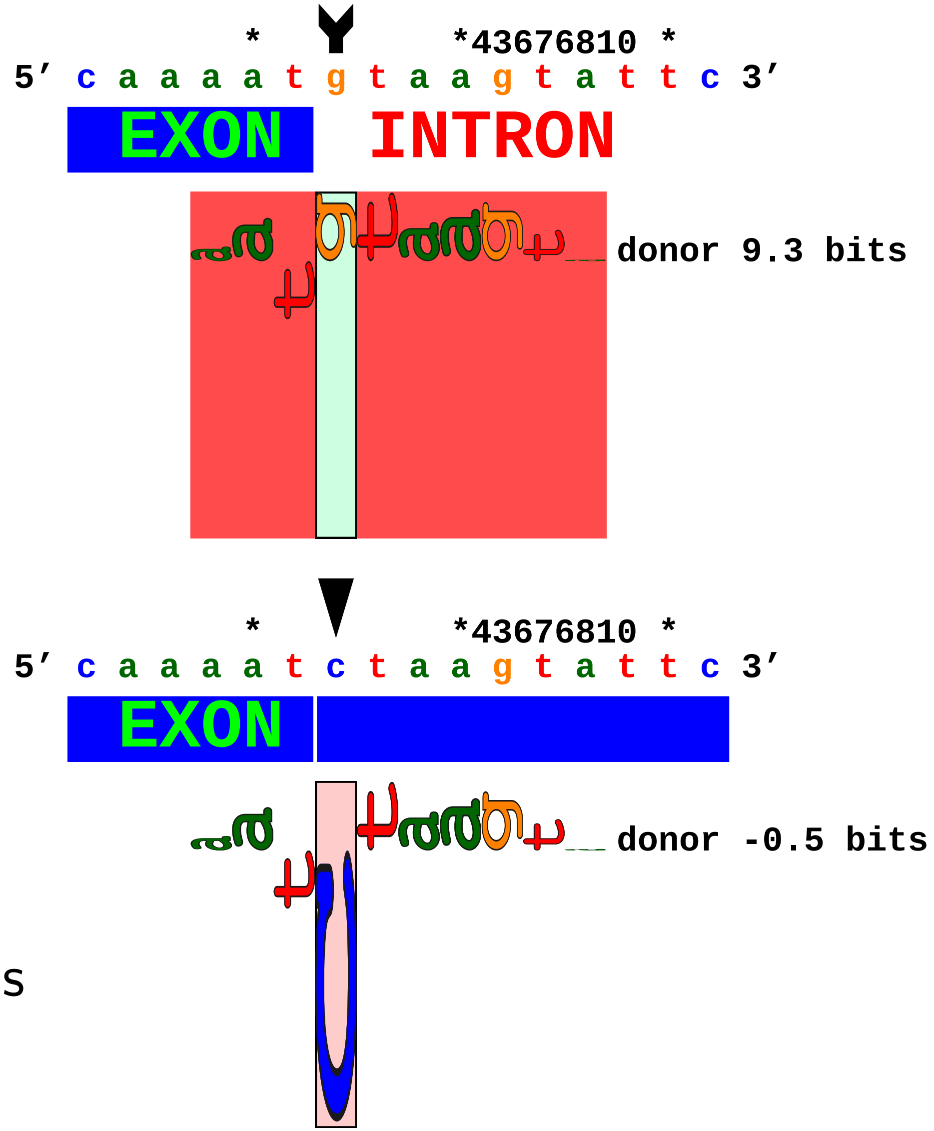

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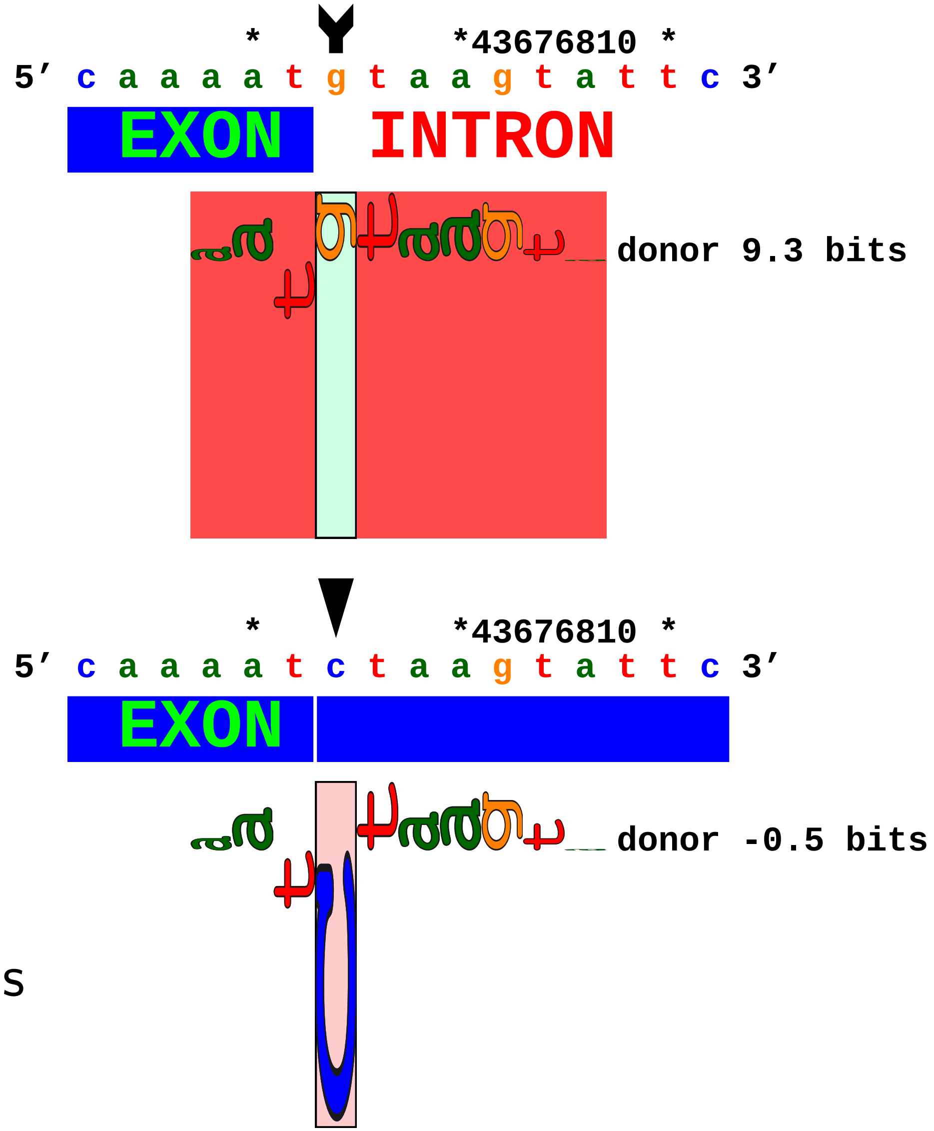
  Dr. Peter Rogan (Univ. Western Ontario)



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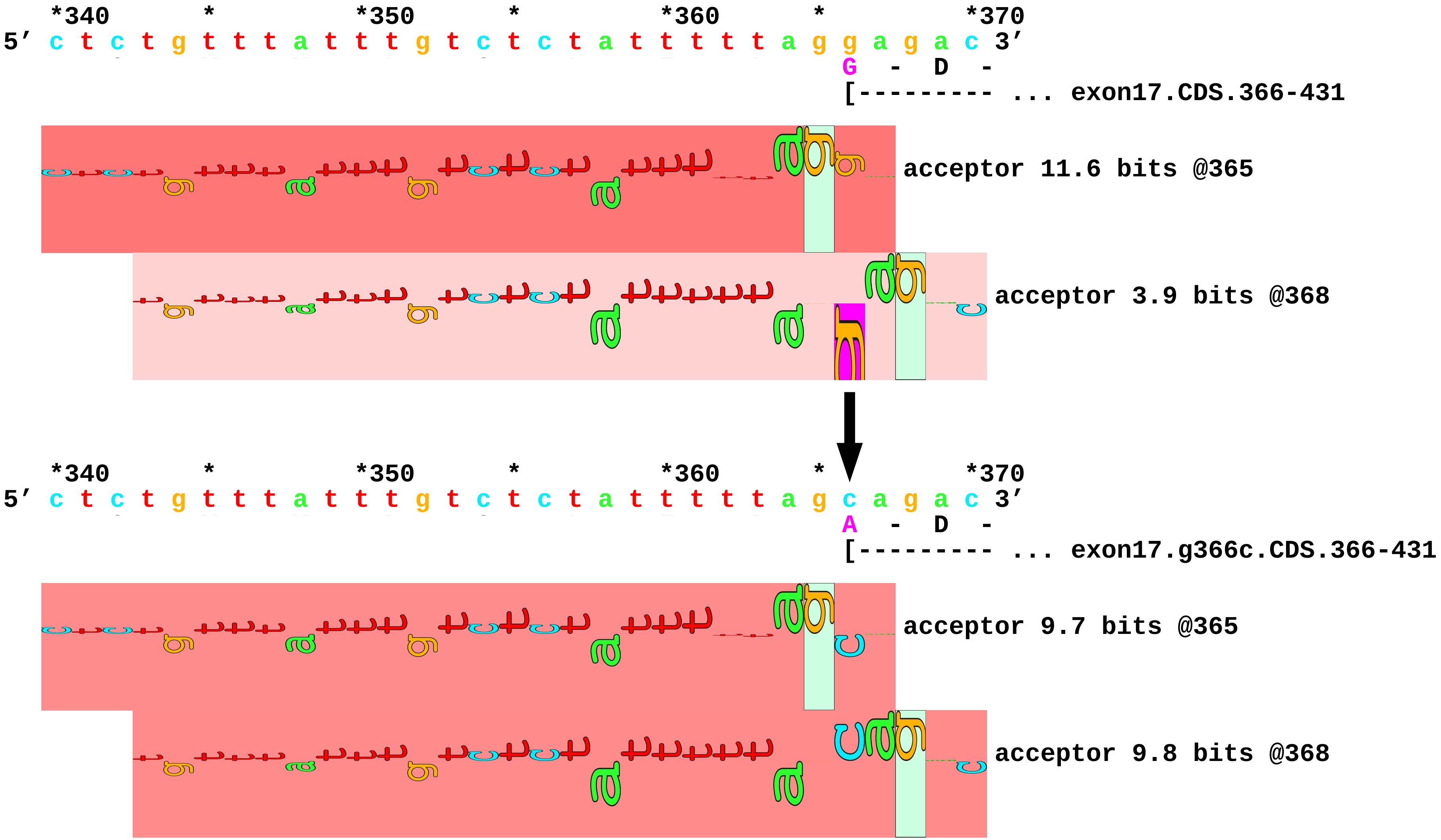
Medical Applications of Sequence Walkers



Mutation G863A: Stargardt disease = age-related macular degeneration

http://alum.mit.edu/www/toms/g863a.html

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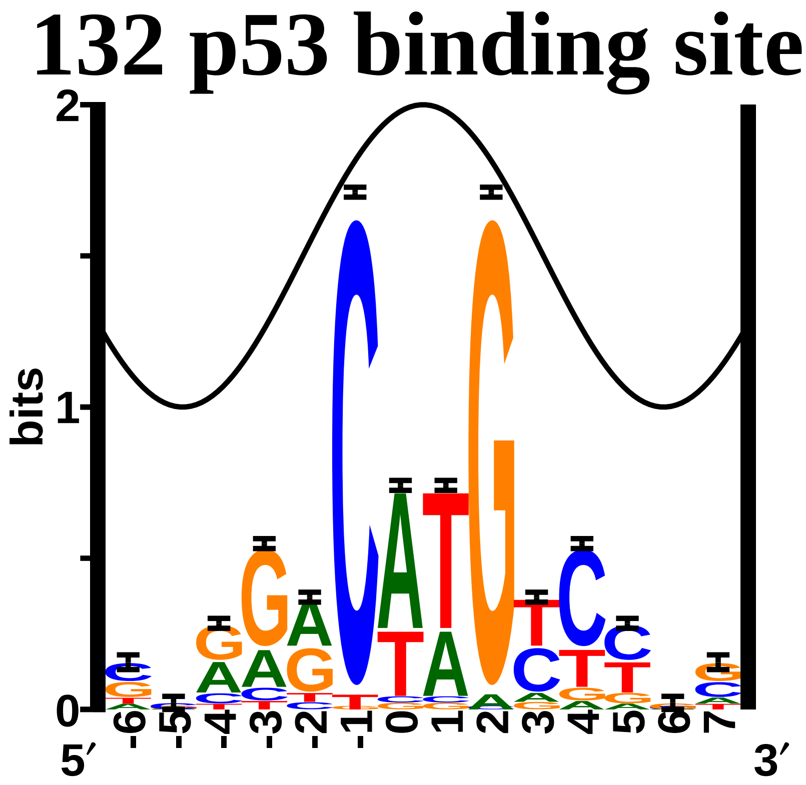

Lyakhov, Annangarachari and **Schneider**
Nucleic Acids Res. 36:3828-33 (2008)

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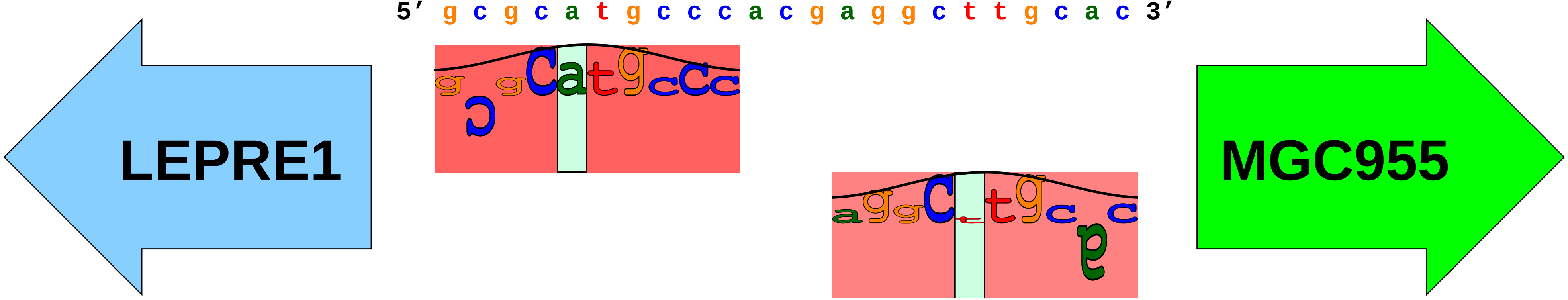
- LEPRE1 and MGC955 dual promoter



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- **Bacteriophage λ - a paradigm for gene control > 50 years**

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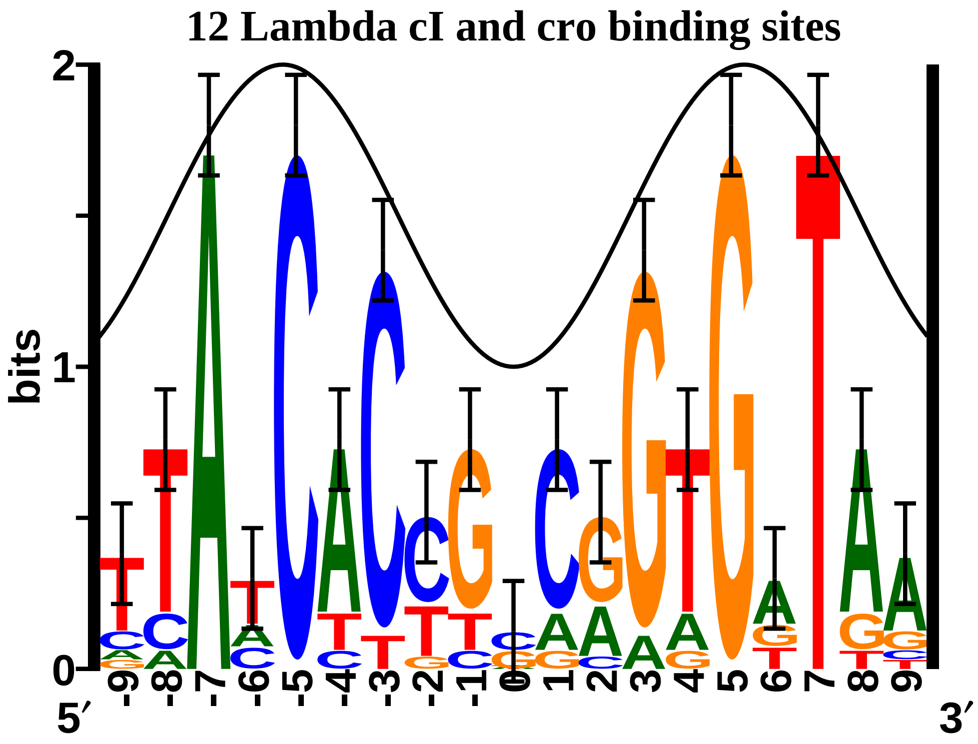

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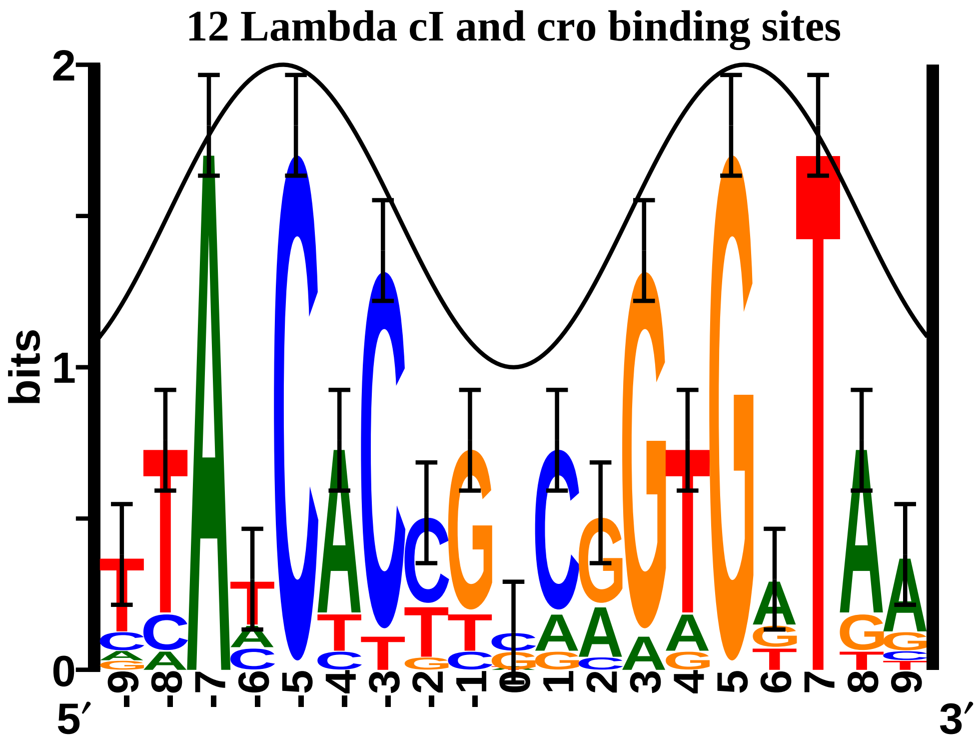

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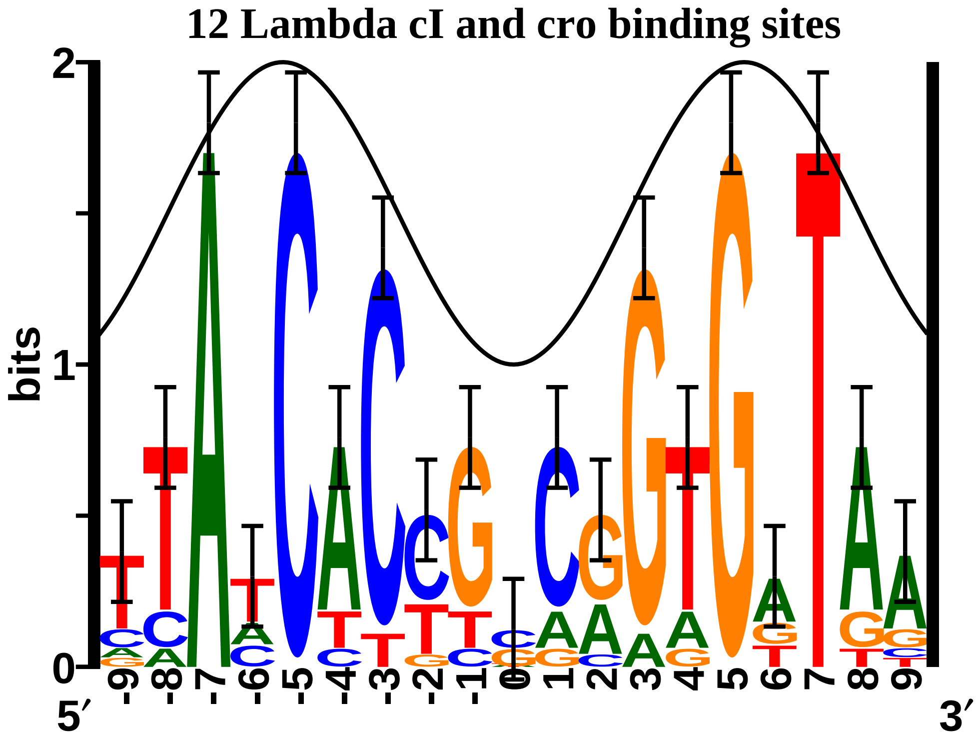

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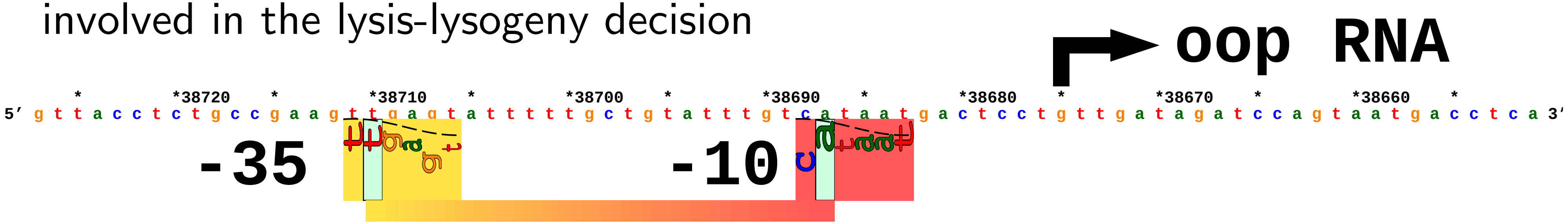
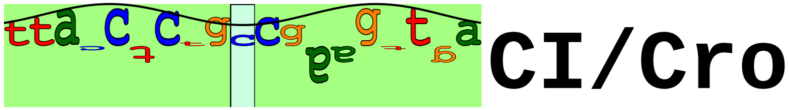
- A 7^{th} Operator found!

Bacteriophage λ Oop promoter: controlled by CI/Cro?

oop RNA is antisense to the $3'$ end of *cII* mRNA
involved in the lysis-lysogeny decision





CI/Cro	λ switch to lytic growth	predicted

Bacteriophage λ Oop promoter: controlled by CI/Cro?

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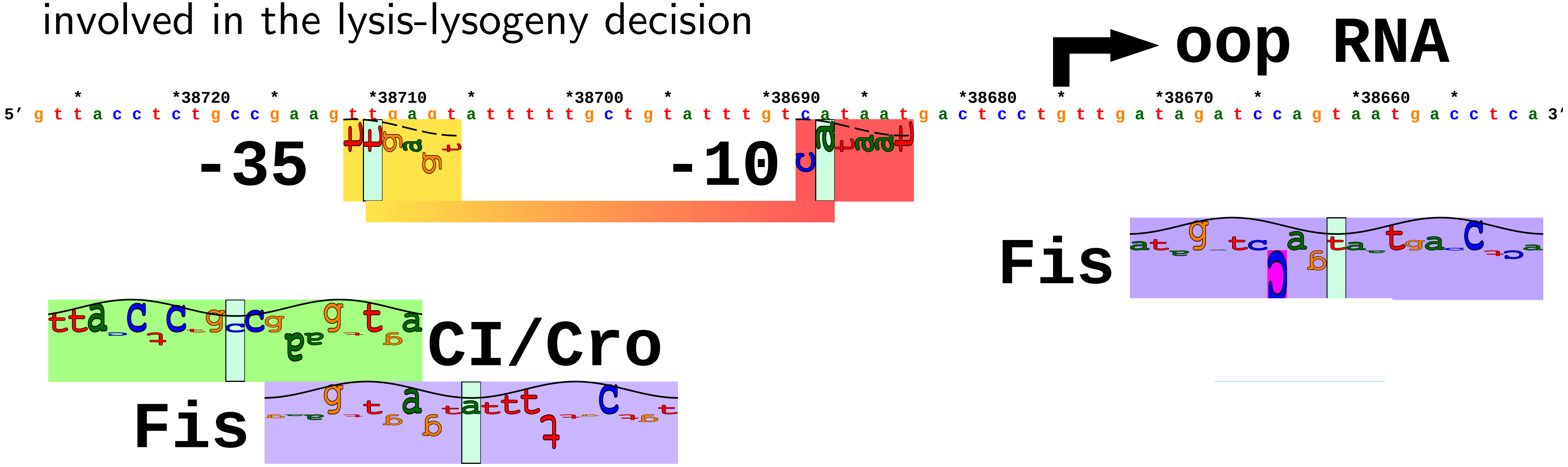

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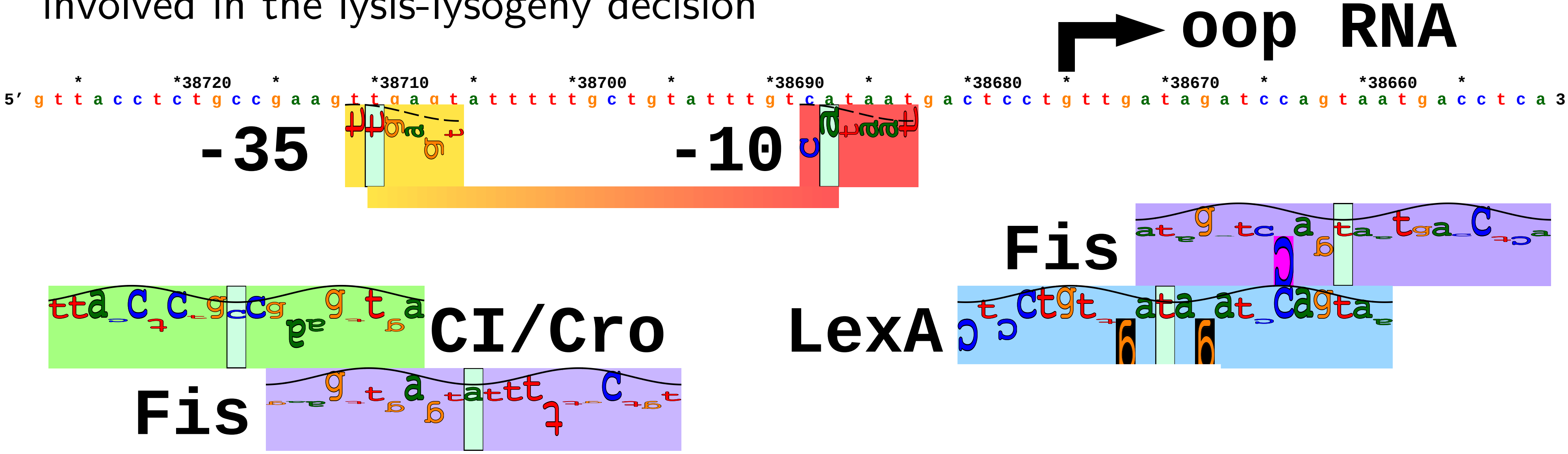

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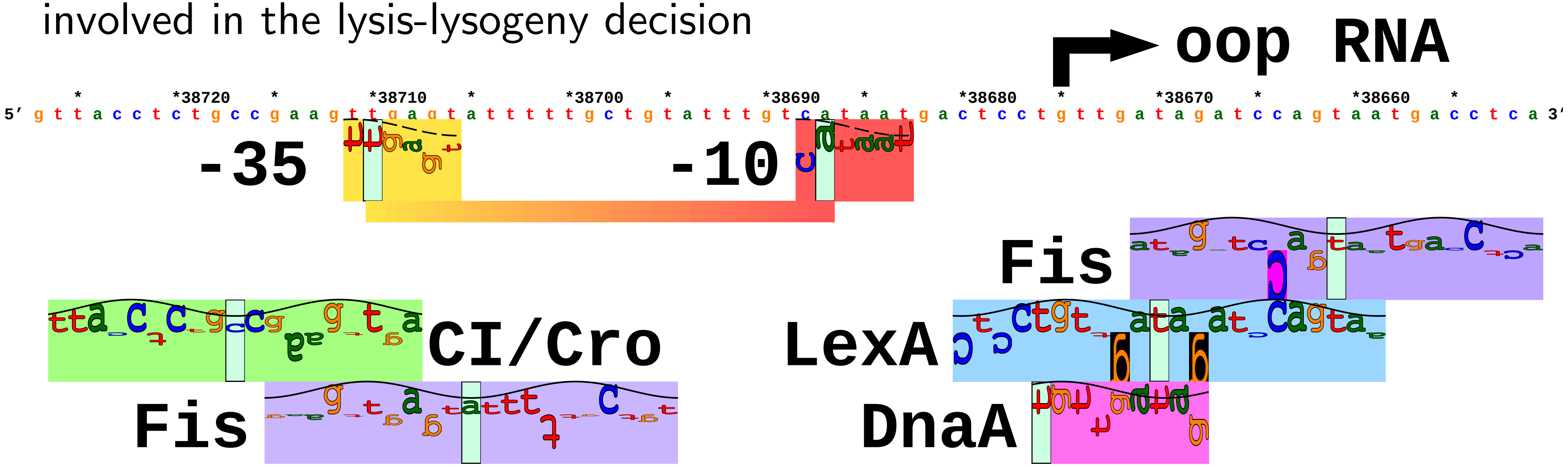

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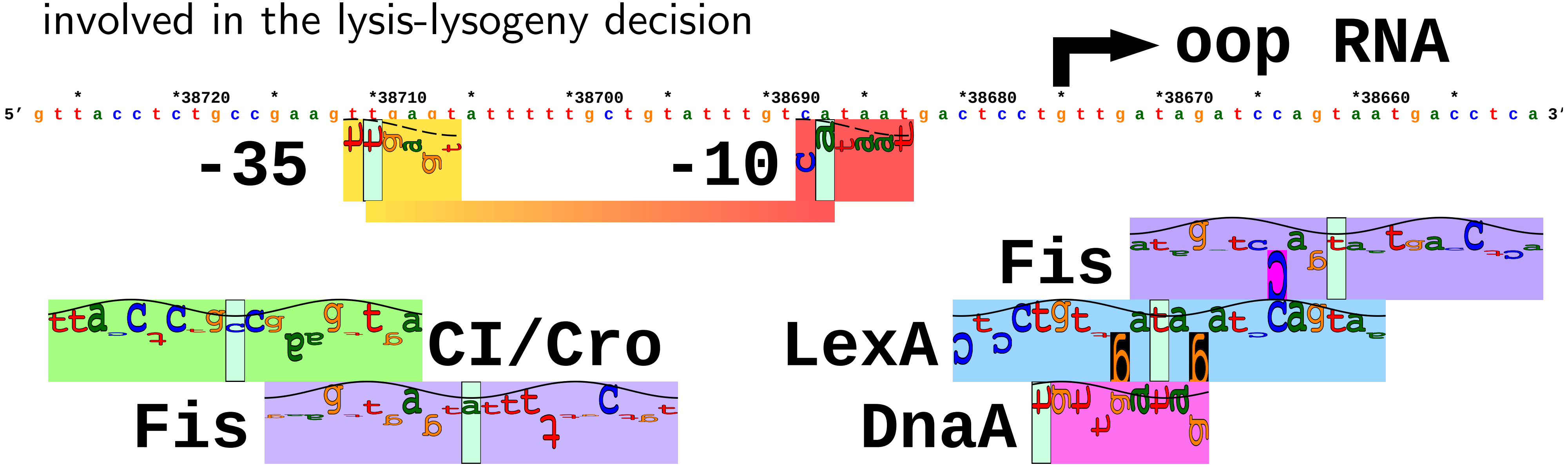

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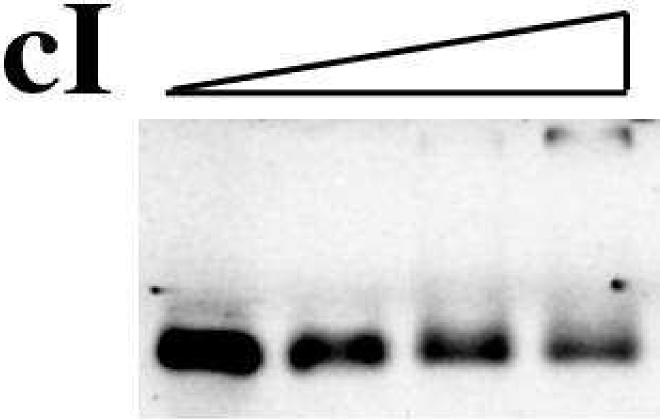
- **A cell-state detection/control center?**

Bacteriophage λ Oop promoter Cro site



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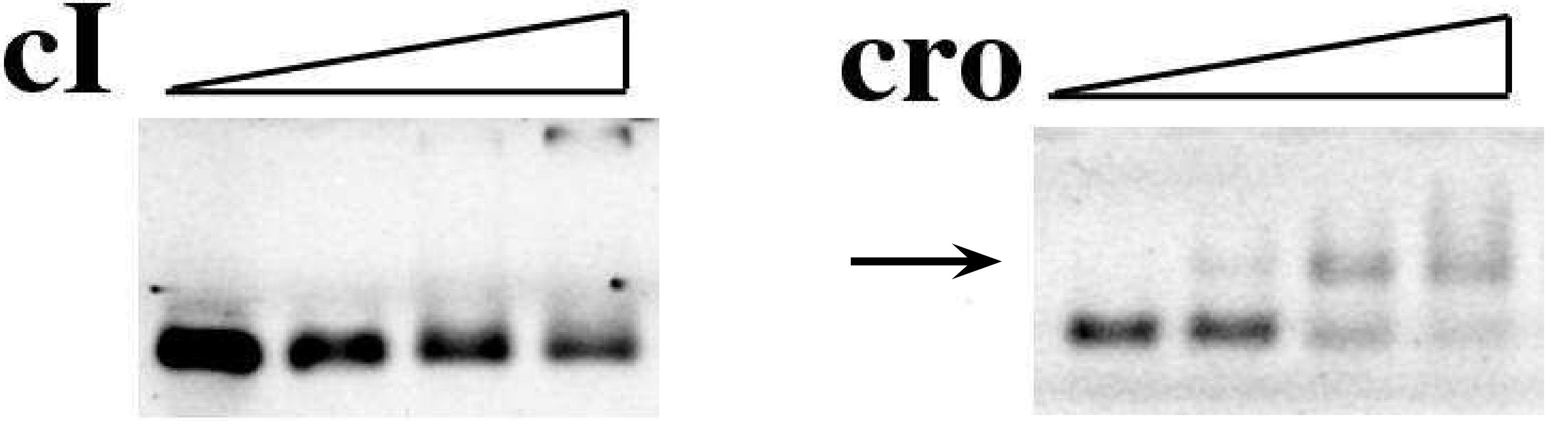

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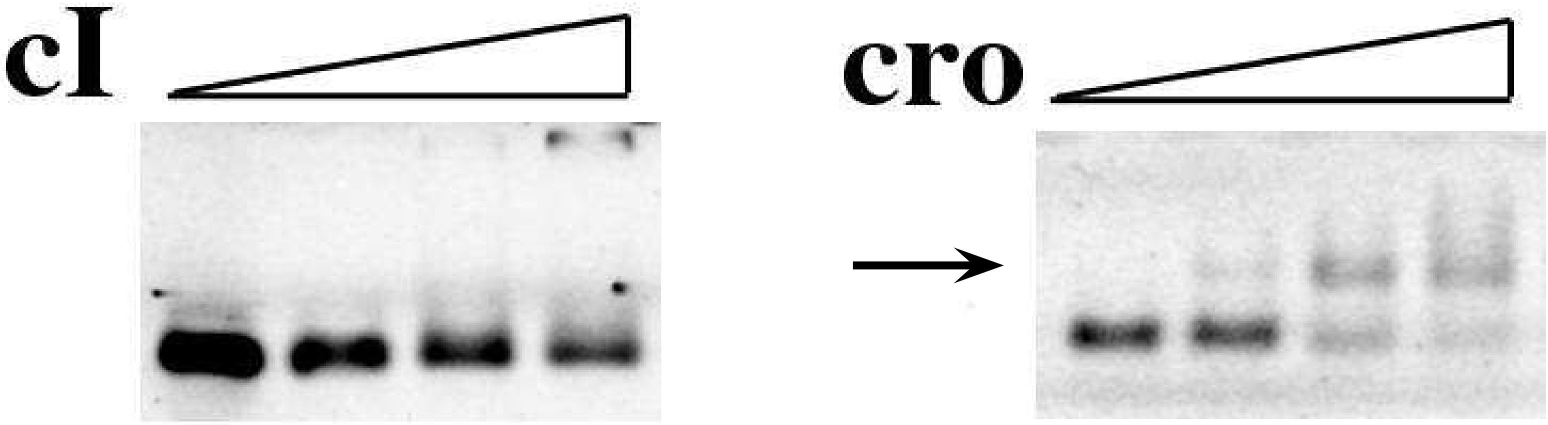

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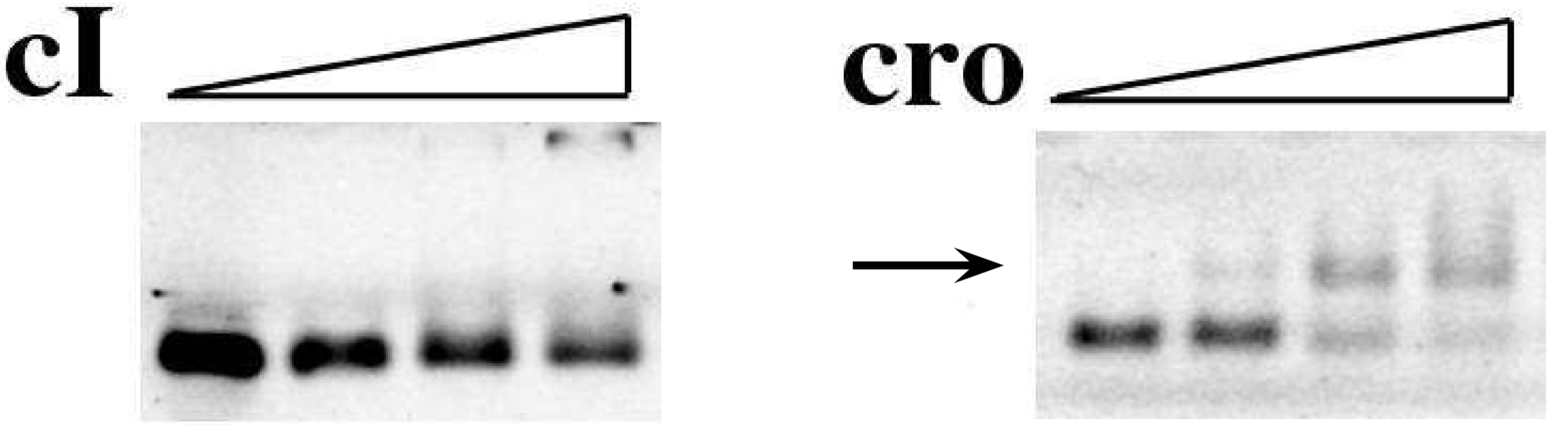

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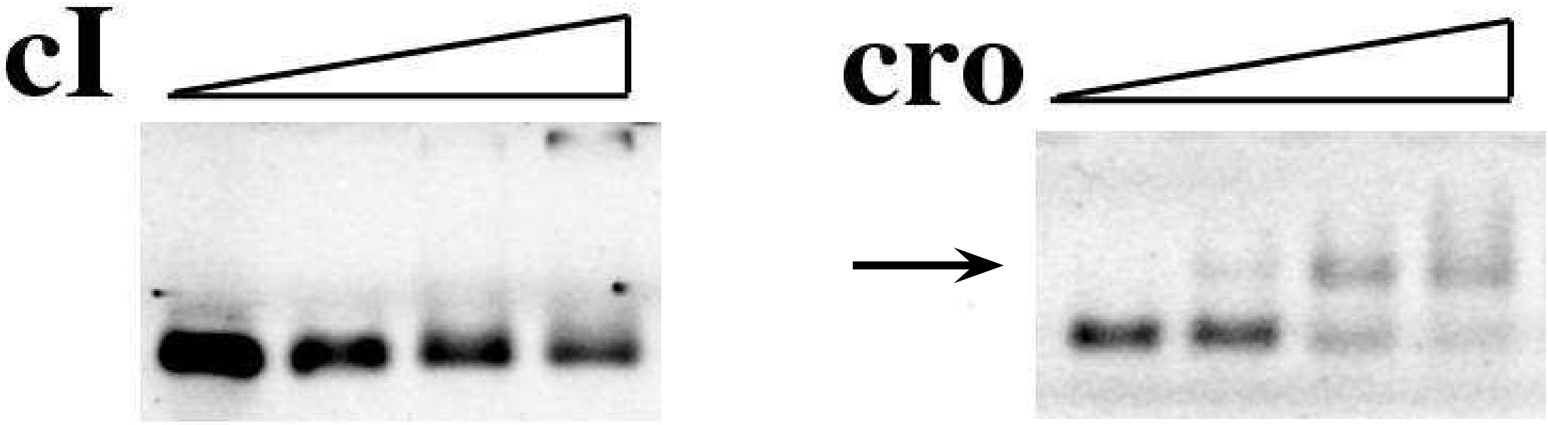

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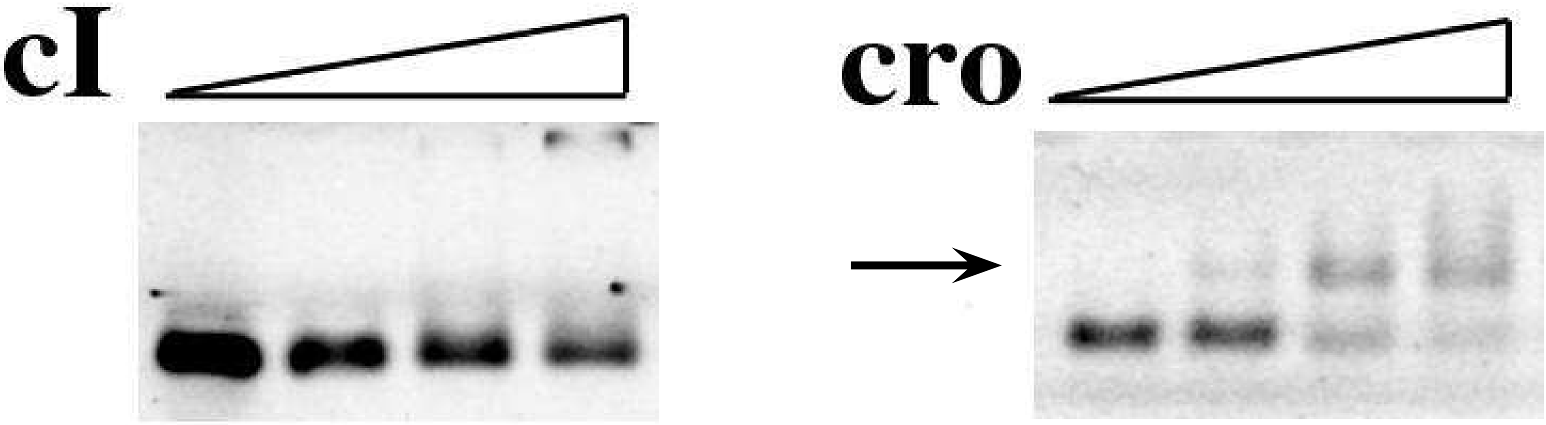

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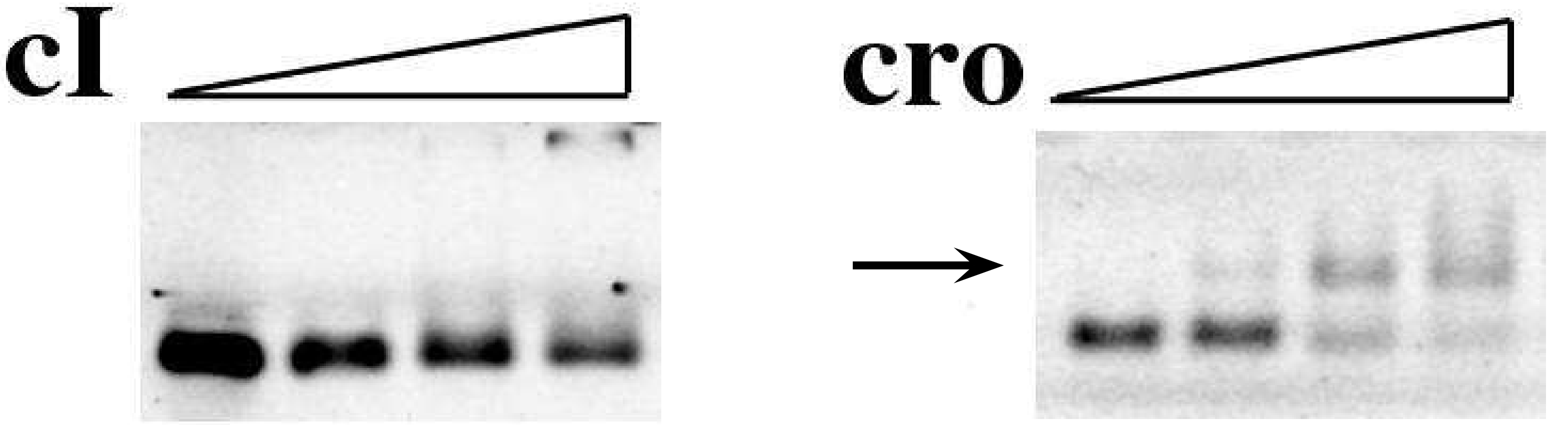

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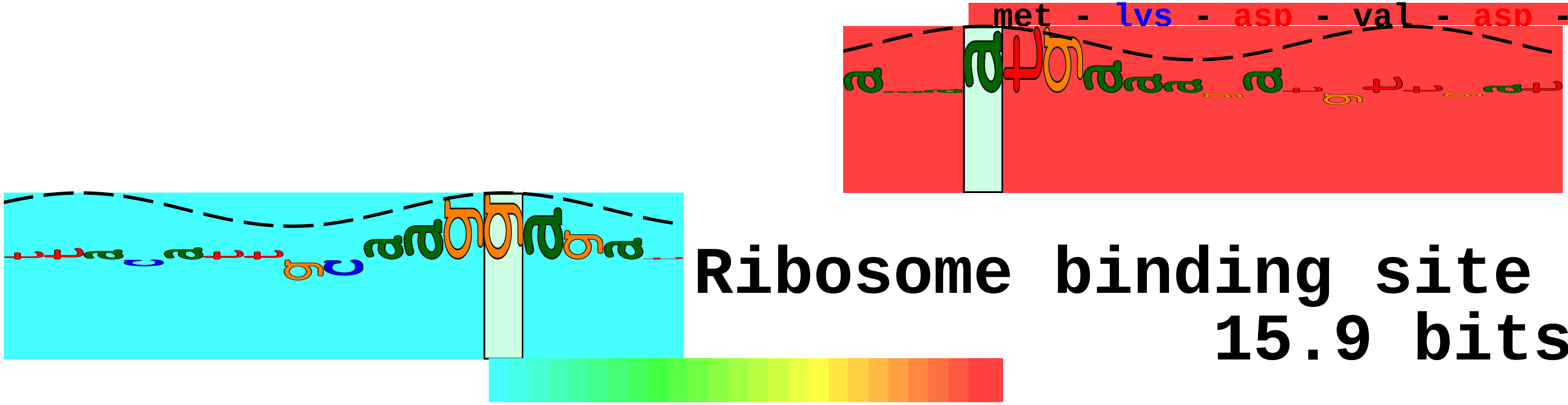
- Collaborator: Dr. Don Court (NCI) - λ expert, invented recombineering

Predicting Small Open Reading Frames in *E. coli*

```
   *         *2987940   *         *2987930   *         *2987920   *         *2987910   *
5′ t t a c a t t g c a a g g a g a t g t c t a a a a t g a a a g a t g t t g a t c a a a t c 3′
                                                       met - lys - asp - val - asp - gln - ile -
```



Ribosome binding site
15.9 bits

```
   *2987900   *         *2987890   *         *2987880   *         *2987870   *         *2987860
5′ t t t g a t g c t t t a g a c t g c c a t a t a c t g c g a g a a t a t t t a a t t t t a 3′
 - phe - asp - ala - leu - asp - cys - his - ile - leu - arg - glu - tyr - leu - ile - leu -

   *         *2987850   *         *2987840   *         *2987830   *         *2987820   *
5′ t t g t t t t a t g a t t a a c g a g g t t c c a t c t t t t t g t t a t c t a t t t t a 3′
 - leu - phe - tyr - asp -
```

27 codon open reading frame

Collaborators: Dr. Gisela Storz (NIH, NICHD, Bethesda, MD),
Dr. Kenneth Rudd (University of Miami School of Medicine, Miami, FL),
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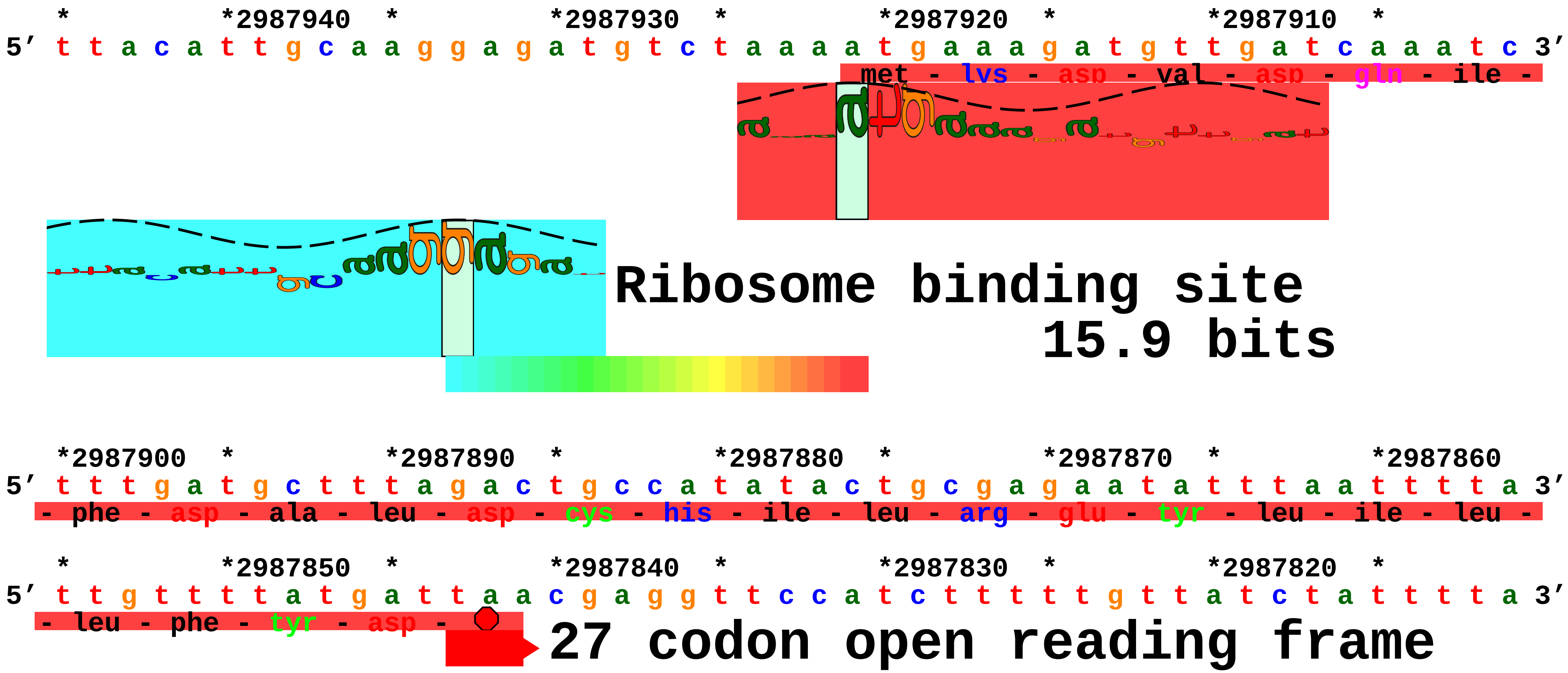

* *2987940 * *2987930 * *2987920 * *2987910 *

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- > 2000 **information theory predictions; test 24**

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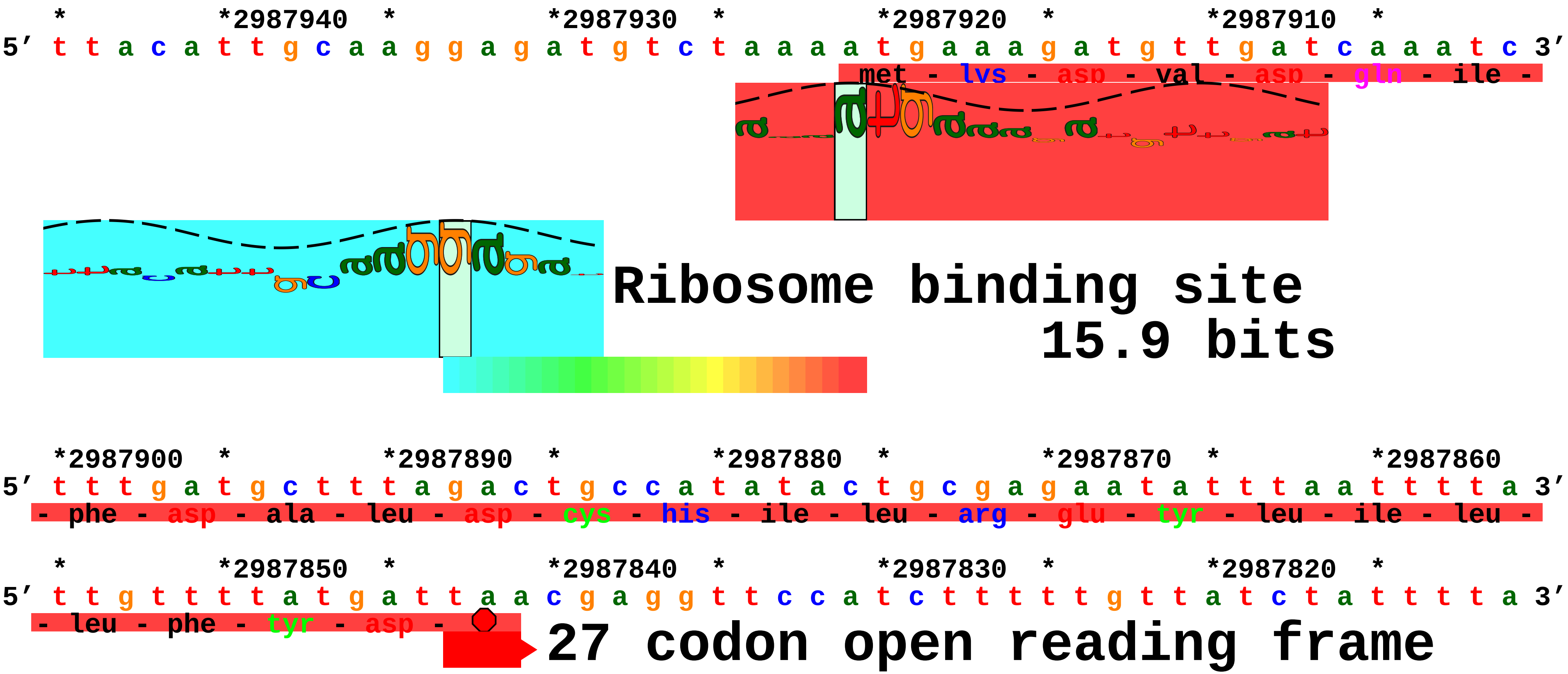

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- > 2000 information theory predictions; test 24
- tested by sequential peptide affinity (SPA) tag

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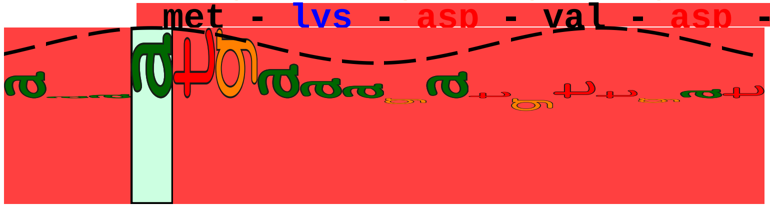

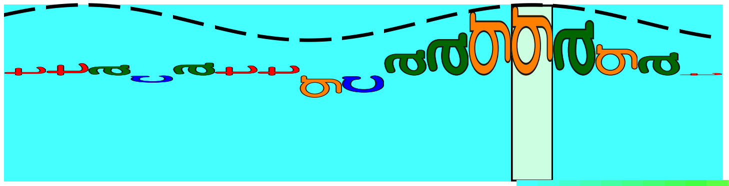

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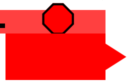

27 codon open reading frame

- > 2000 information theory predictions; test 24
- tested by sequential peptide affinity (SPA) tag
- 18 new genes < 50 aa long

Collaborators: Dr. Gisela Storz (NIH, NICHD, Bethesda, MD),
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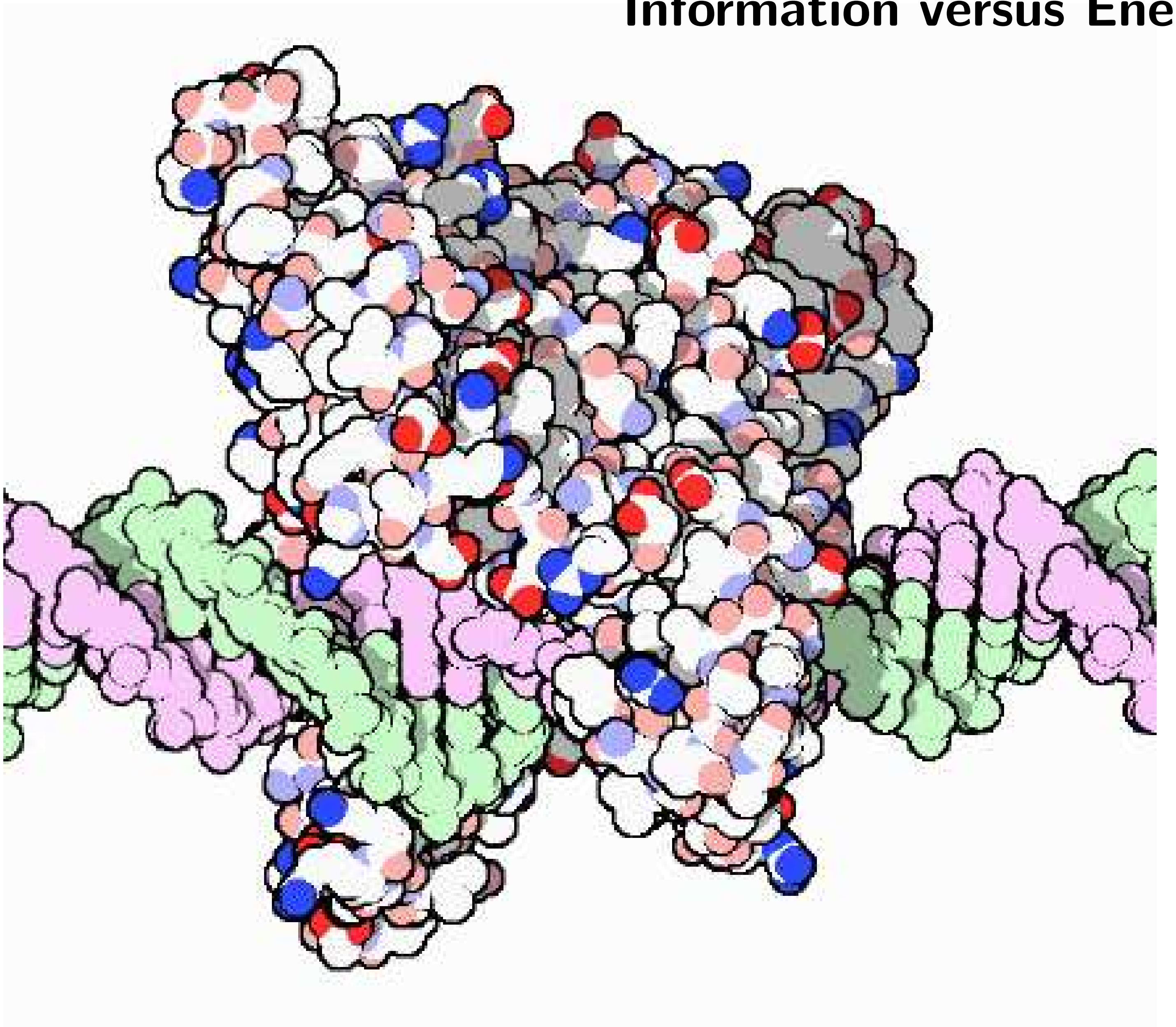
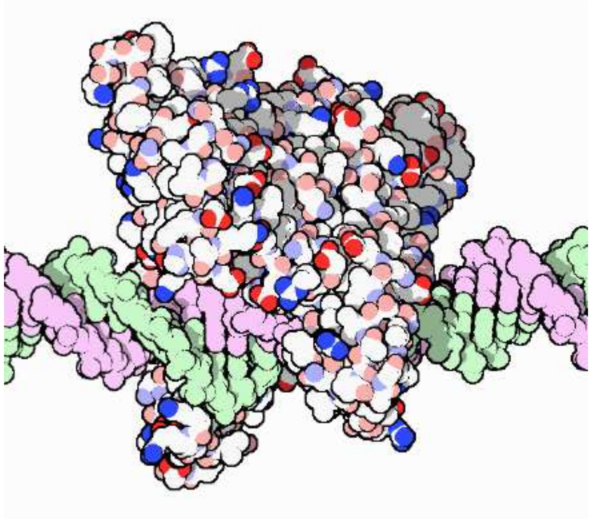
Information versus Energy



Information of EcoRI DNA Binding



- EcoRI - restriction enzyme

Information of EcoRI DNA Binding

- EcoRI - restriction enzyme
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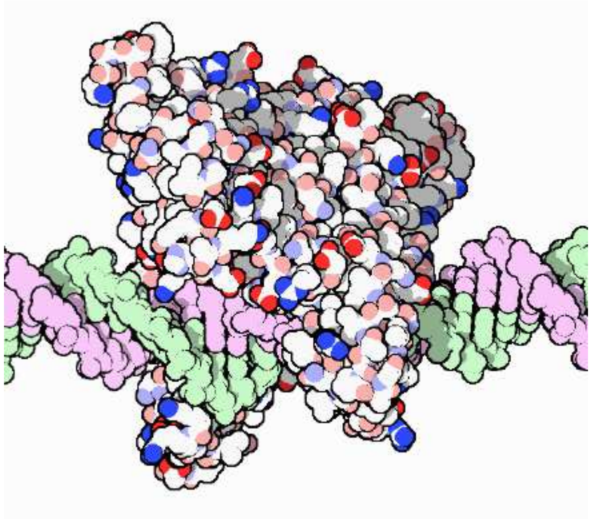

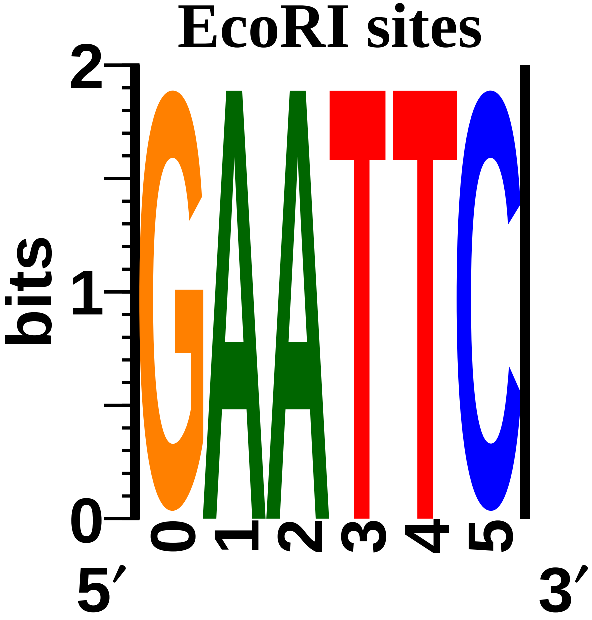

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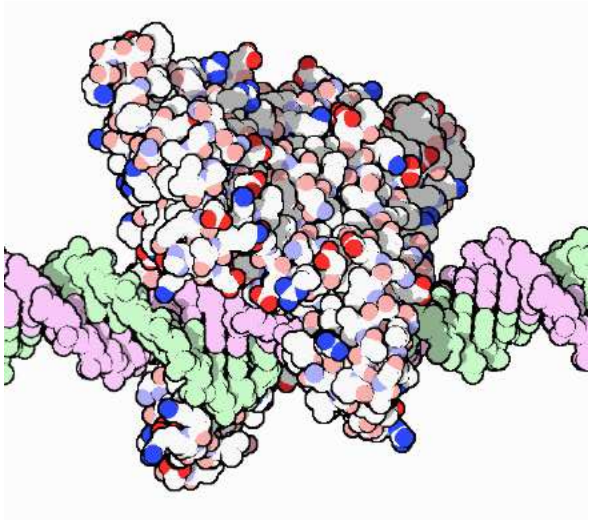
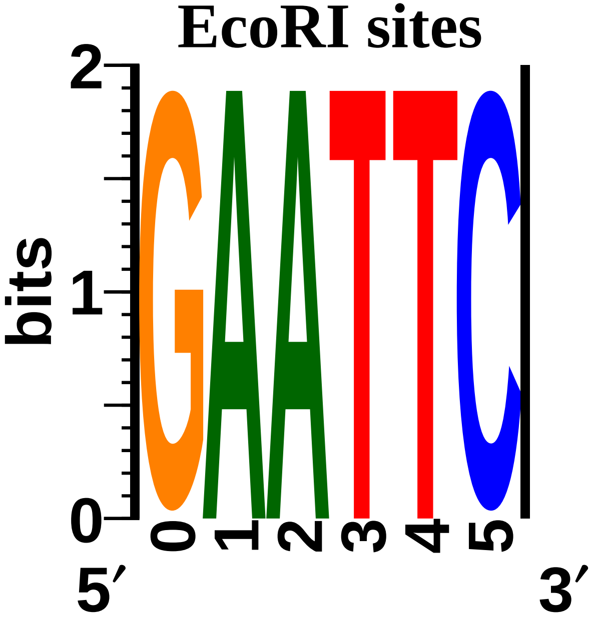
- $4^6 = 4096$ possible DNA hexamers





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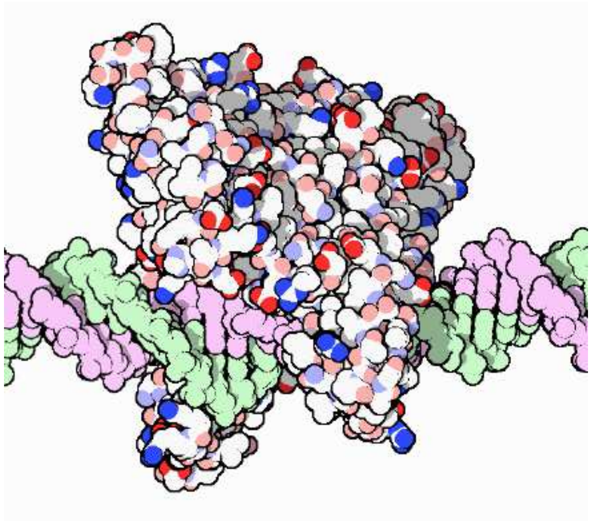
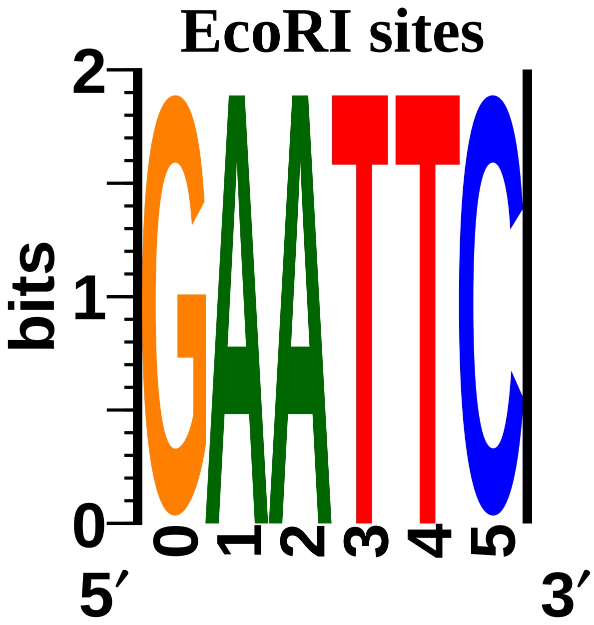


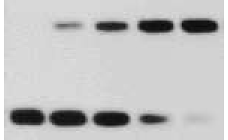
- EcoRI - restriction enzyme
- EcoRI binds DNA at $5'$ GAATTC $3'$
- $4^6 = 4096$ possible DNA hexamers
- information required:
  $\log_2 4096 = 12$ bits
  or
  6 bases $\times$ 2 bits per base $=$ $\boxed{\text{12 bits}}$



Energy Dissipation by EcoRI

- Measured specific binding constant:

$$K_{spec} = 1.6 \times 10^5$$



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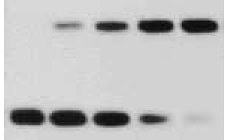

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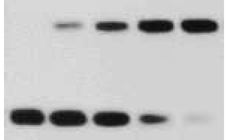

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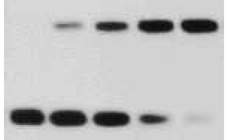

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- Number of bits that could have been selected:

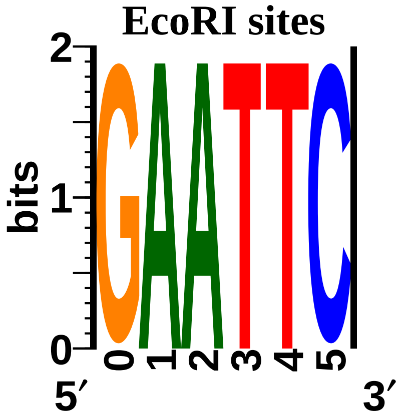
$$\begin{aligned} R_{energy} &= -\Delta G^\circ / \mathcal{E}_{min} \\ &= k_{\mathsf{B}} T \ln K_{spec} / k_{\mathsf{B}} T \ln 2 \\ &= \log_2 K_{spec} \qquad \Leftarrow \text{SO SIMPLE!} \\ &= \boxed{\text{17.3 bits per binding}} \end{aligned}$$

Information/Energy = Efficiency of EcoRI

EcoRI could have made 17.3 binary choices

Information/Energy = Efficiency of EcoRI

EcoRI could have made 17.3 binary choices
. . . but it only made 12 choices.



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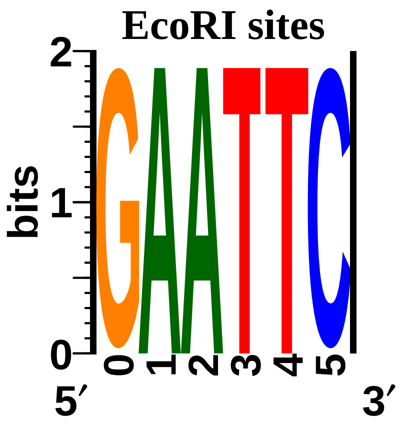

Efficiency is
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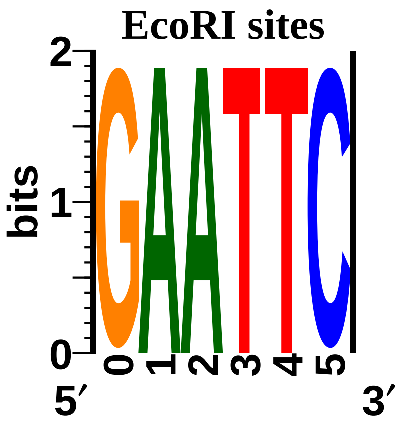

Efficiency is
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$$\frac{12 \text{ bits per binding}}{17.3 \text{ bits per binding}} = 0.7$$

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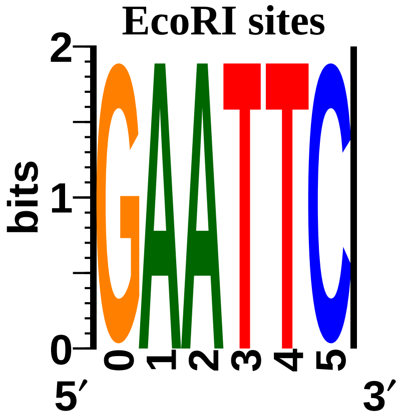

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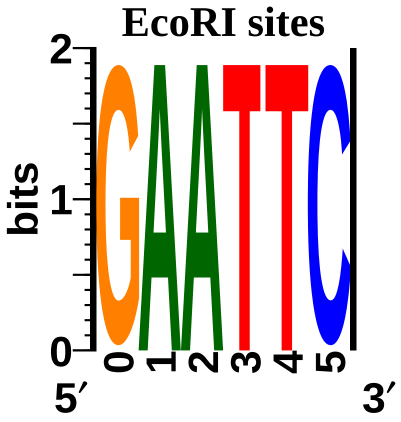

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18 out of 19 DNA binding proteins give ~70% efficiency.

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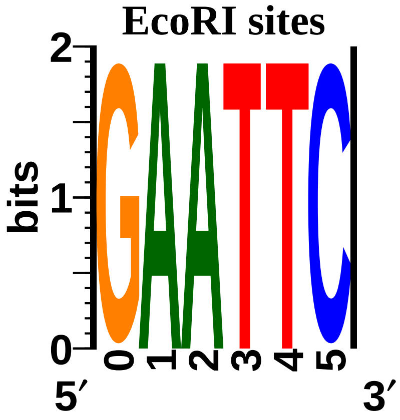

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**70% efficiency also appears widely in biology:
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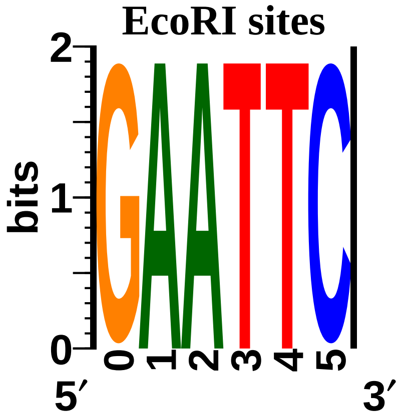

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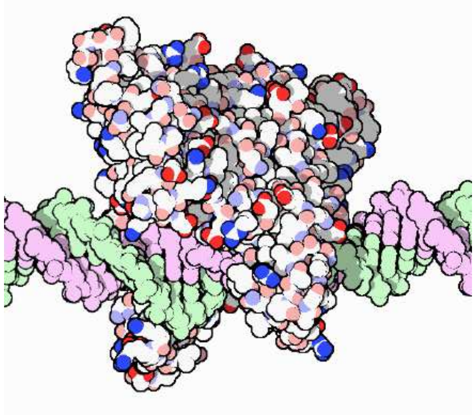
Why 70% efficiency?

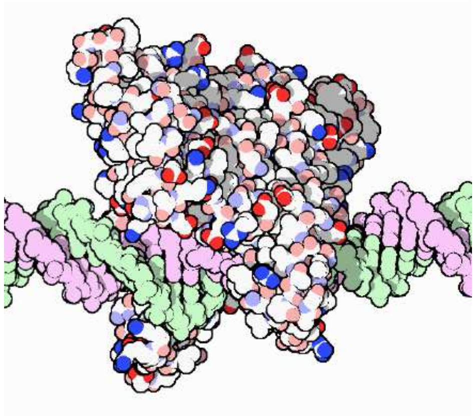
Theoretical Efficiency



- For molecular states of molecules with d_{space} 'parts' P_y energy is dissipated for noise N_y and

  $C = d_{space} \log_2(P_y/N_y + 1) \leftarrow$ machine capacity

Theoretical Efficiency



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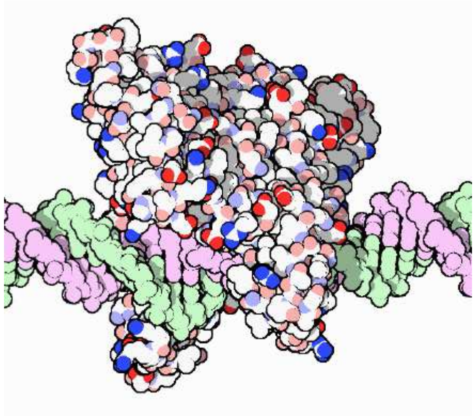
Theoretical Efficiency



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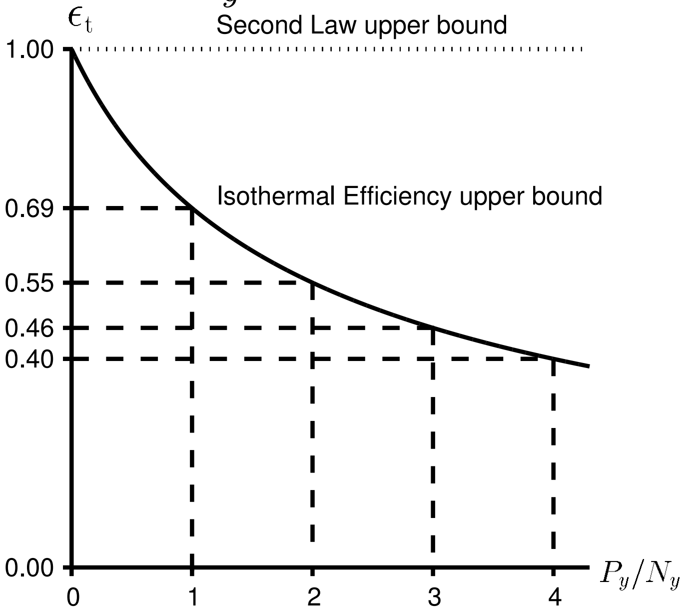
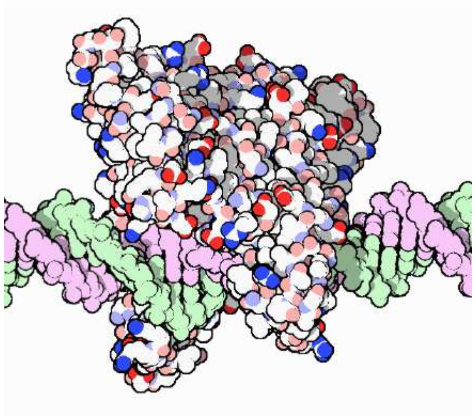


The curve is an upper bound

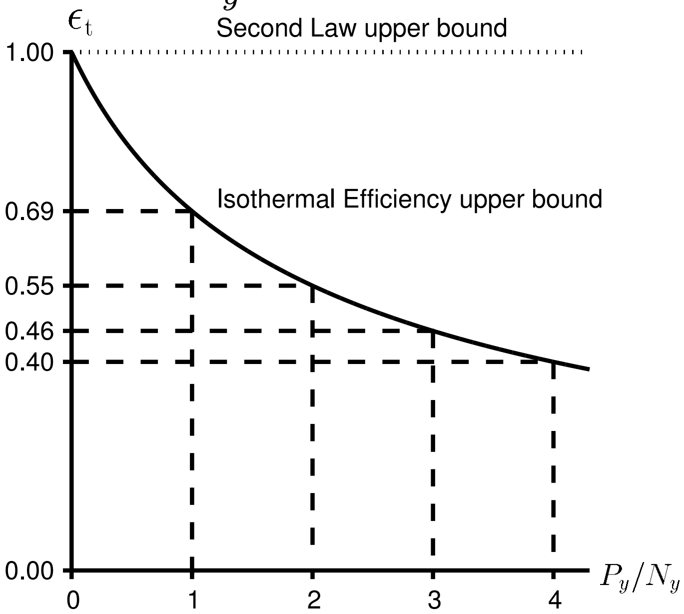
Theoretical Efficiency



- For molecular states of molecules with d_{space} 'parts' P_y energy is dissipated for noise N_y and

$$C = d_{space} \log_2(P_y/N_y + 1) \leftarrow \text{machine capacity}$$

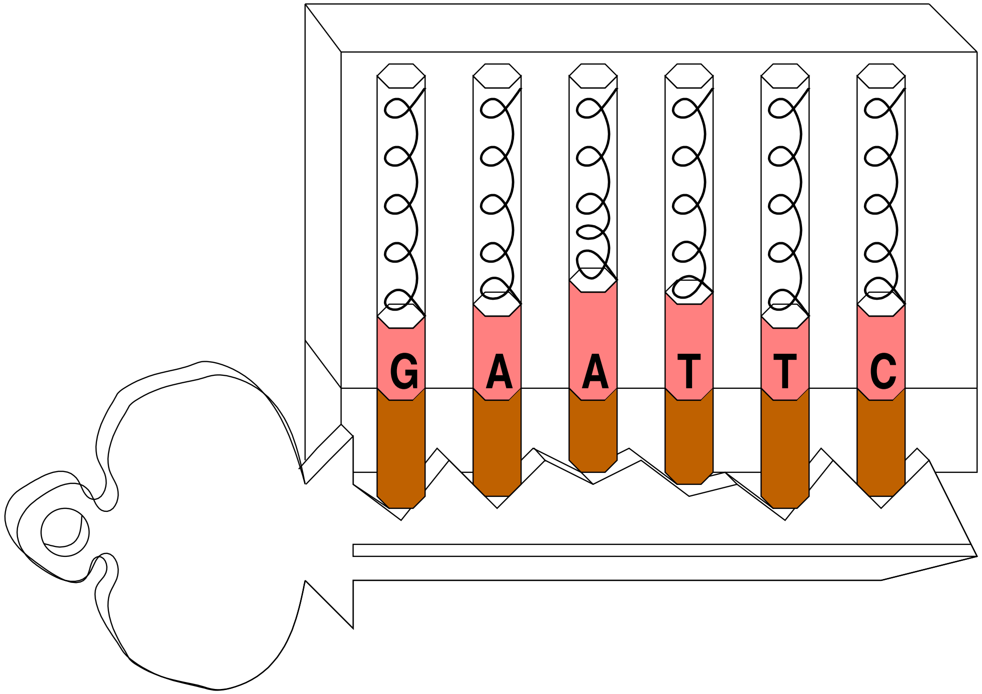
$$\epsilon_t \leq \frac{\ln\left(\frac{P_y}{N_y}+1\right)}{\frac{P_y}{N_y}} \leftarrow \text{molecular efficiency}$$



The curve is an upper bound

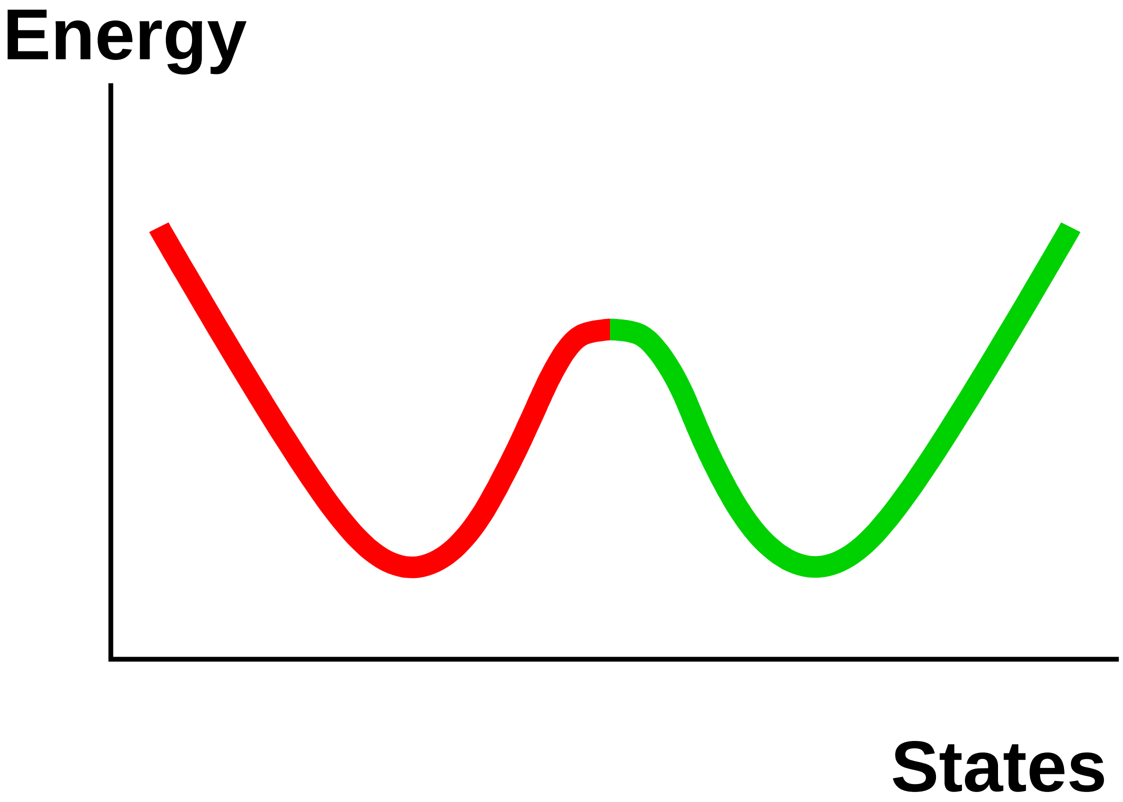
- $\boxed{\text{If } P_y/N_y = 1 \text{ the efficiency is 70\%!}}$

Lock and Key



Like a key in a lock
which has many independent pins,
it takes many numbers
to describe the vibrational state
of a molecular machine

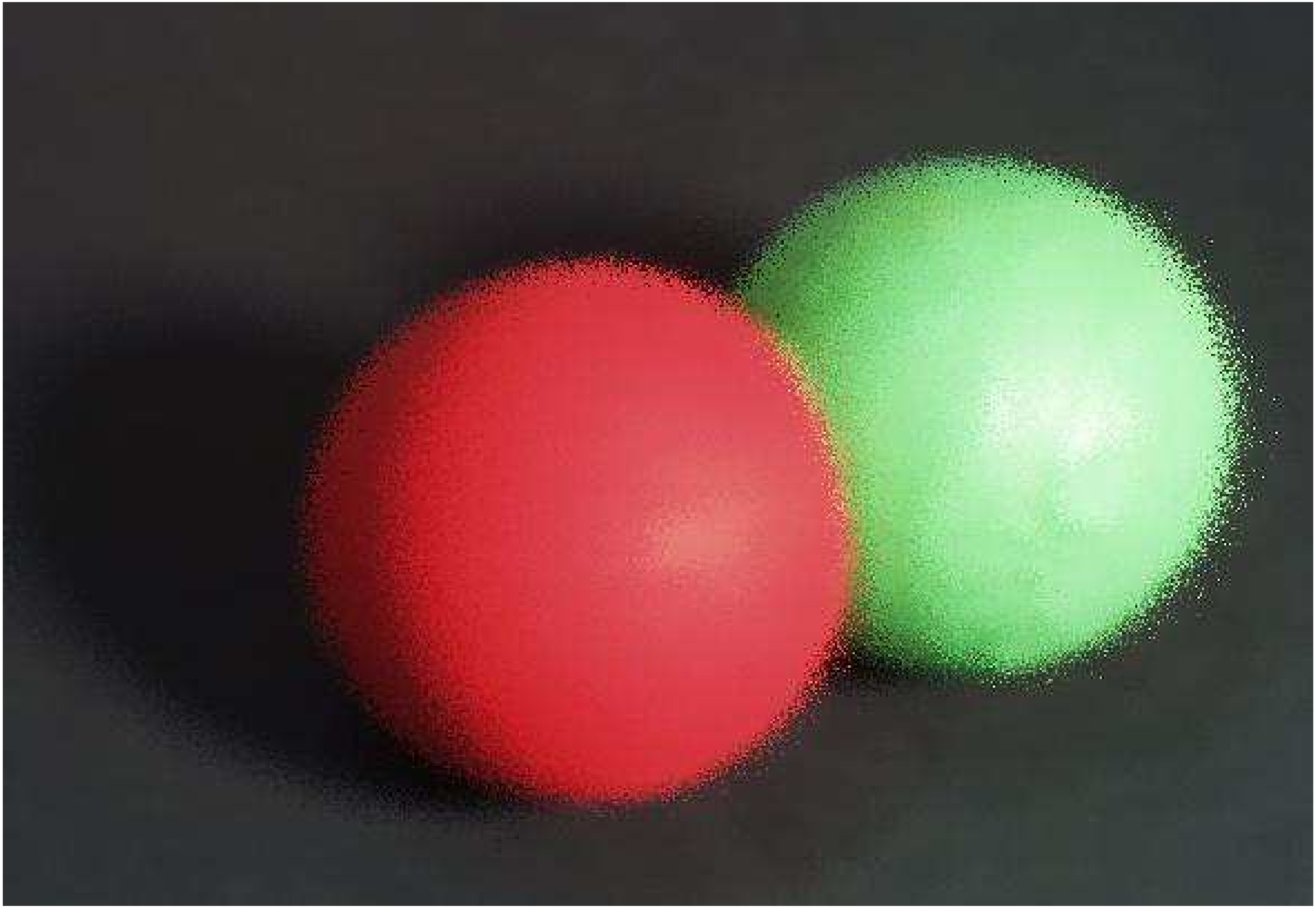
1 Dimension



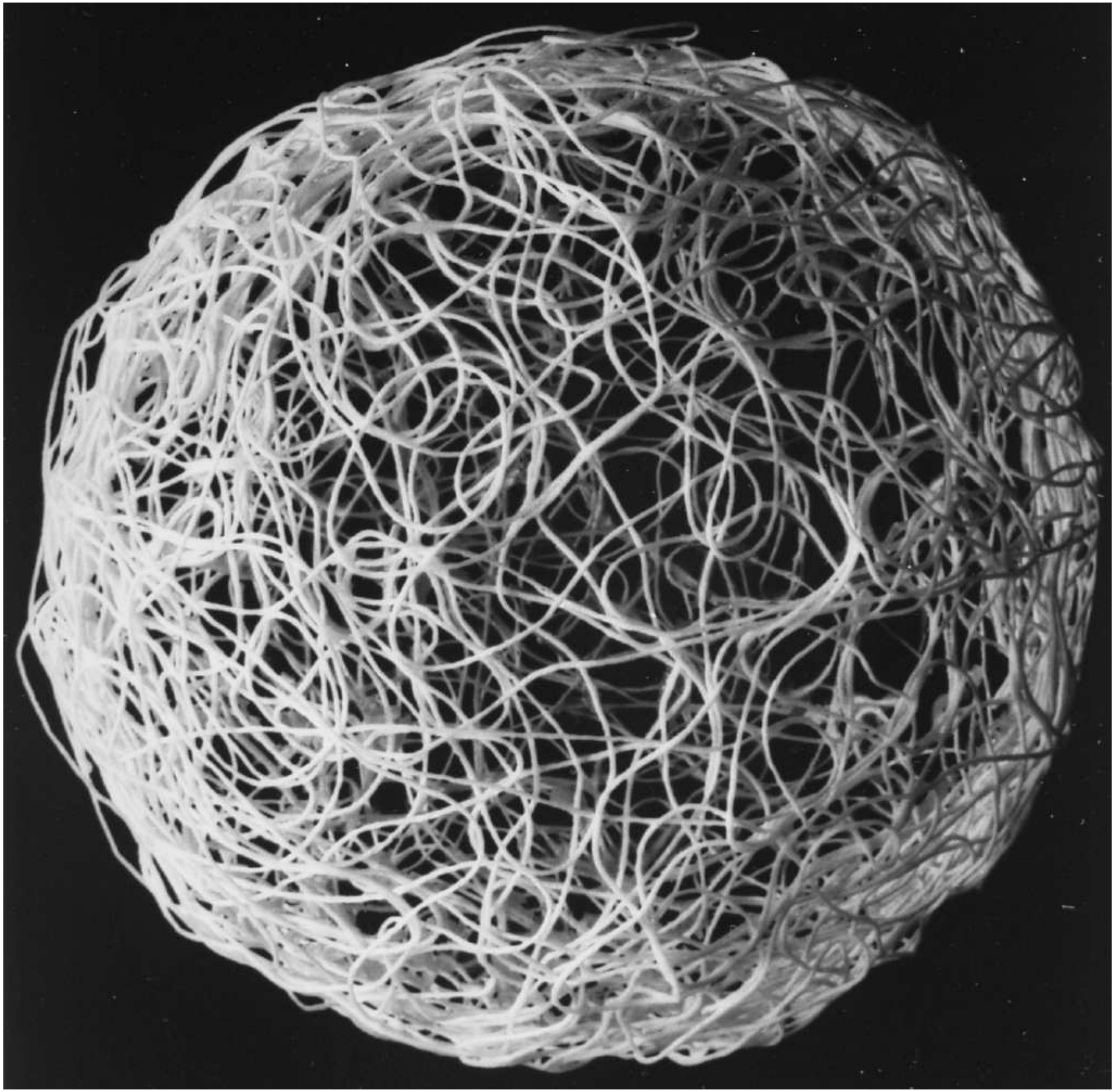
1 dimension is too simple!

Bowles in 2 Dimensions

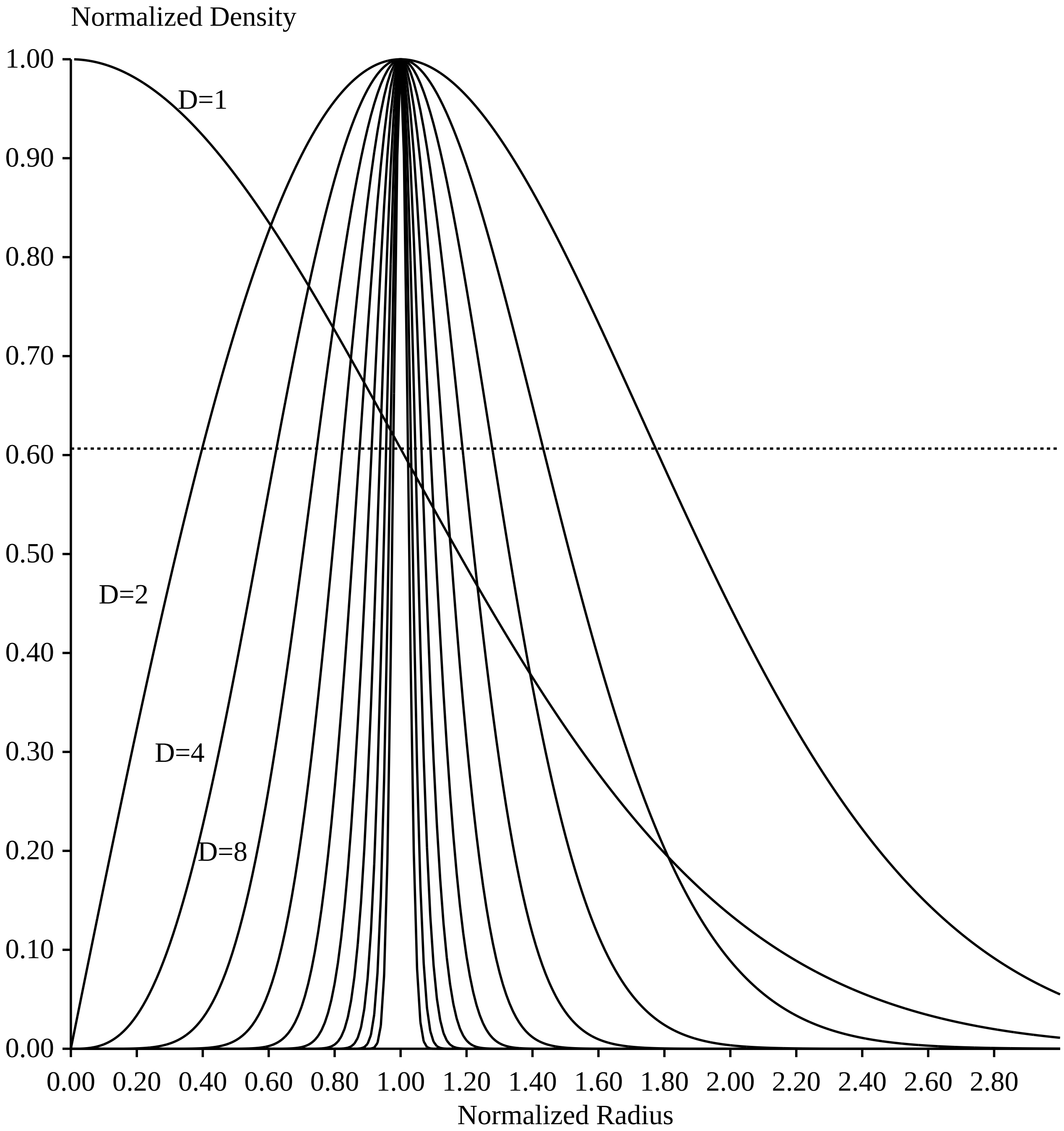
Spheres in 3 Dimensions



N Dimensional Sphere



Spheres tighten in high dimensions



Energy and velocity

$$\text{Energy} = \frac{1}{2}\text{Mass} \times \text{velocity}^2$$

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Energy and velocity

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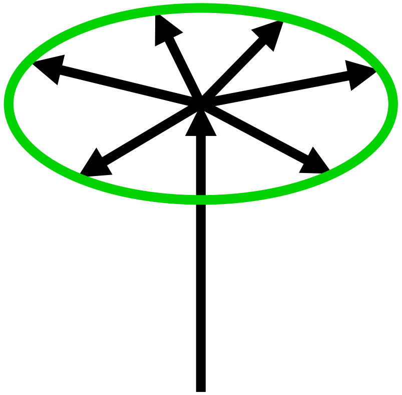
$$\text{Energy in the molecule} = \text{Noise} = \text{N}$$

$$\text{maximum velocity} \propto \sqrt{\text{N}}$$

$$\text{sphere radius} \propto \sqrt{\text{N}}$$

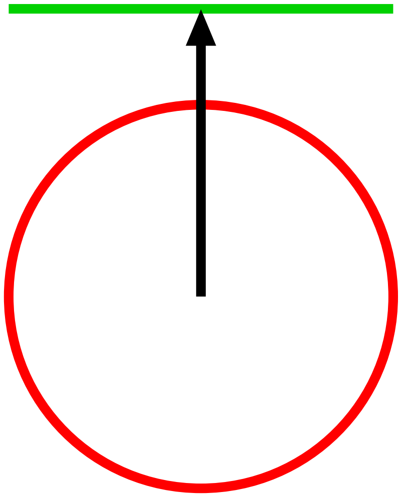
Sphere Packing

hyperdirection



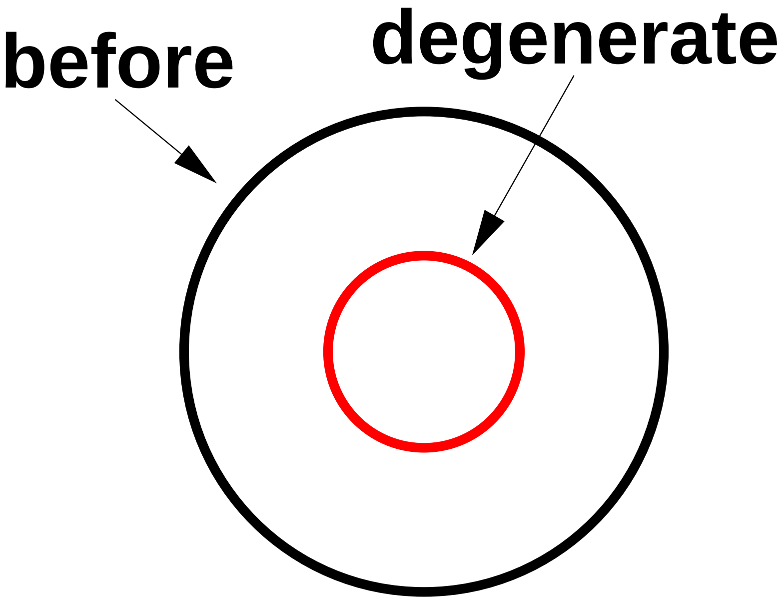
In 100 dimensions
99% of the thermal noise
is at right angles
to a given direction!

two



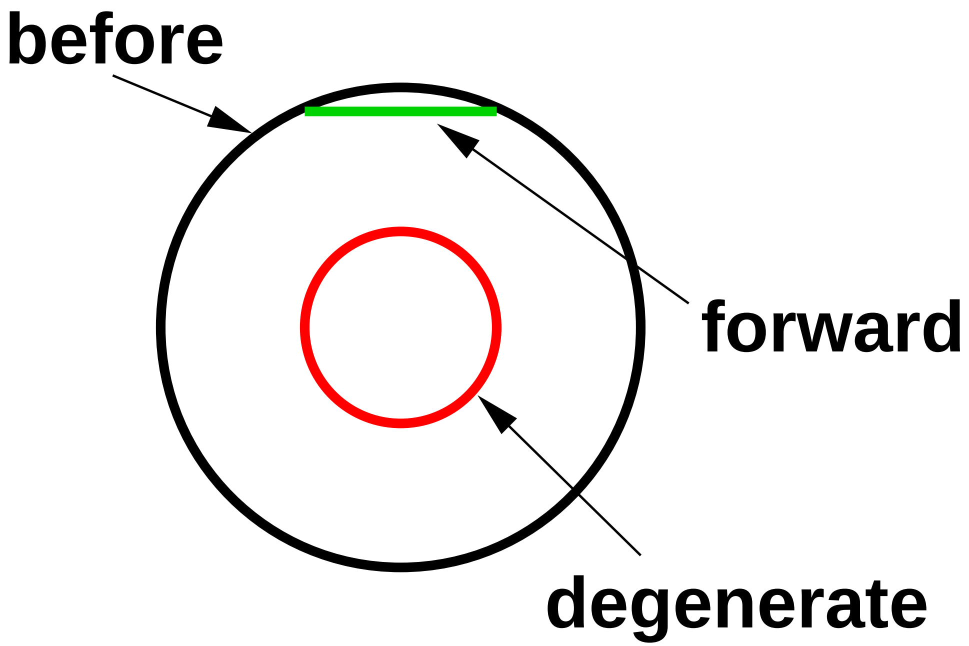
Two spheres in
high dimensional space

degenerate



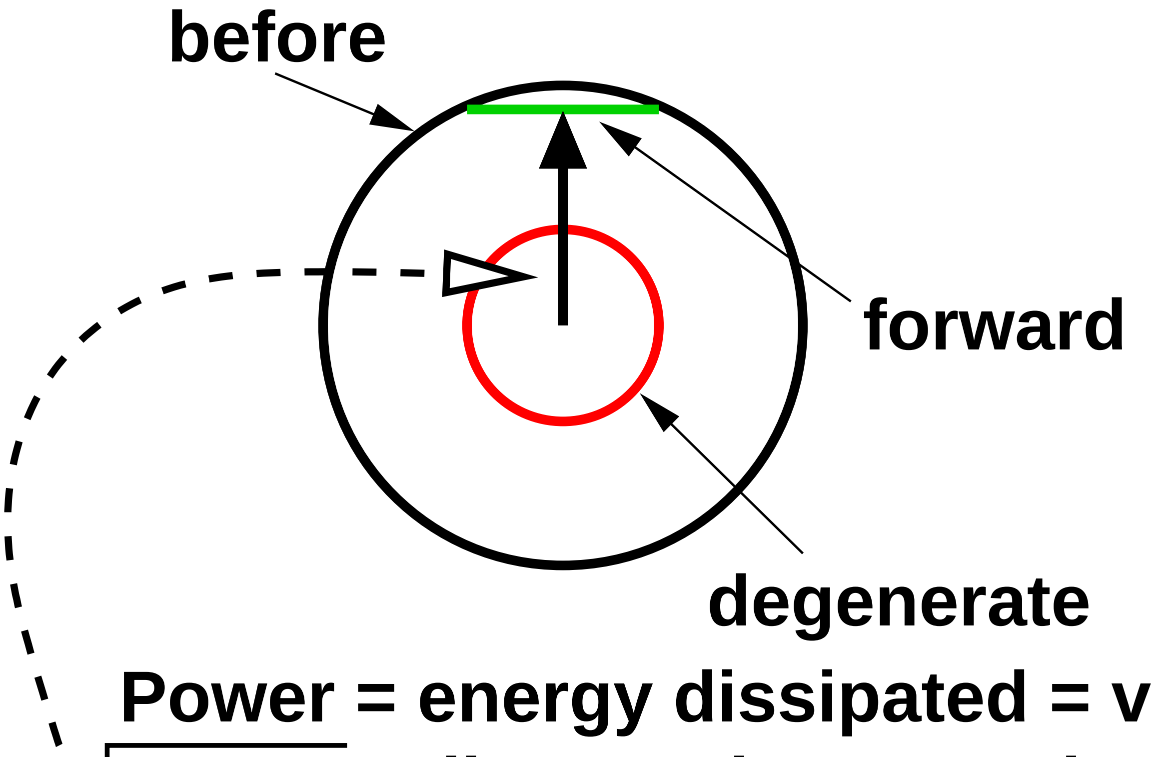
Hypothesis:
there is a sphere
in the middle
of the before sphere

forward



To do useful selections
the molecular machine
must avoid the degenerate sphere
It must choose the forward sphere

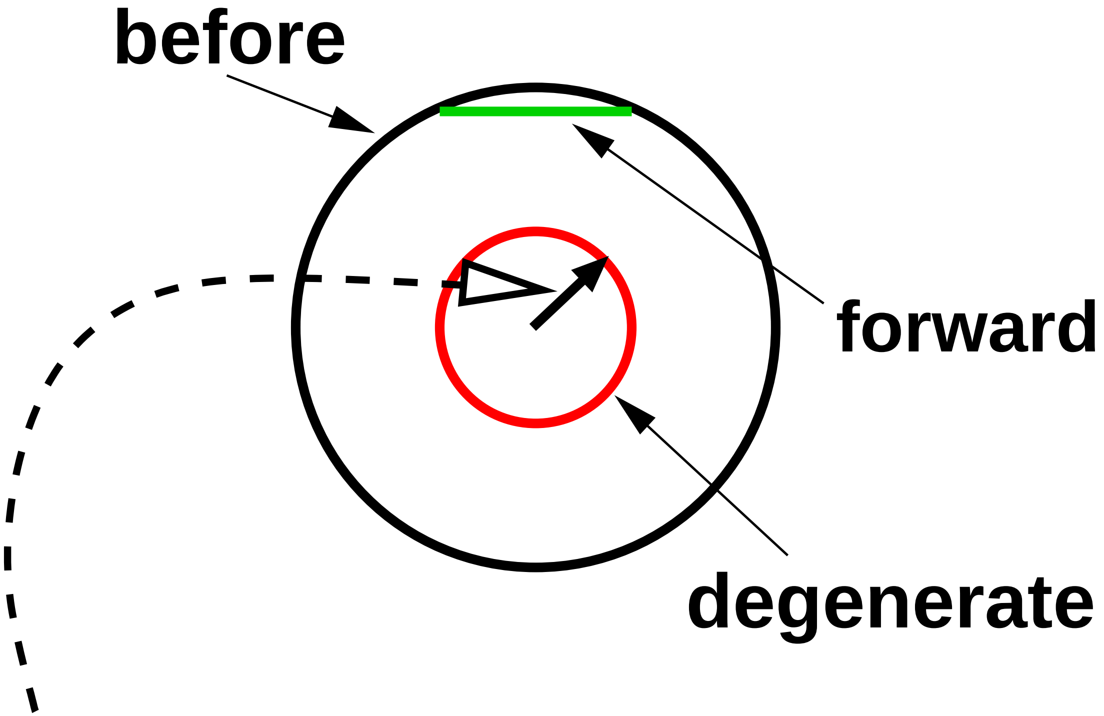
power



Power = energy dissipated = velocity^2

$\sqrt{\text{Power}}$ = distance between the forward and the degenerate sphere centers

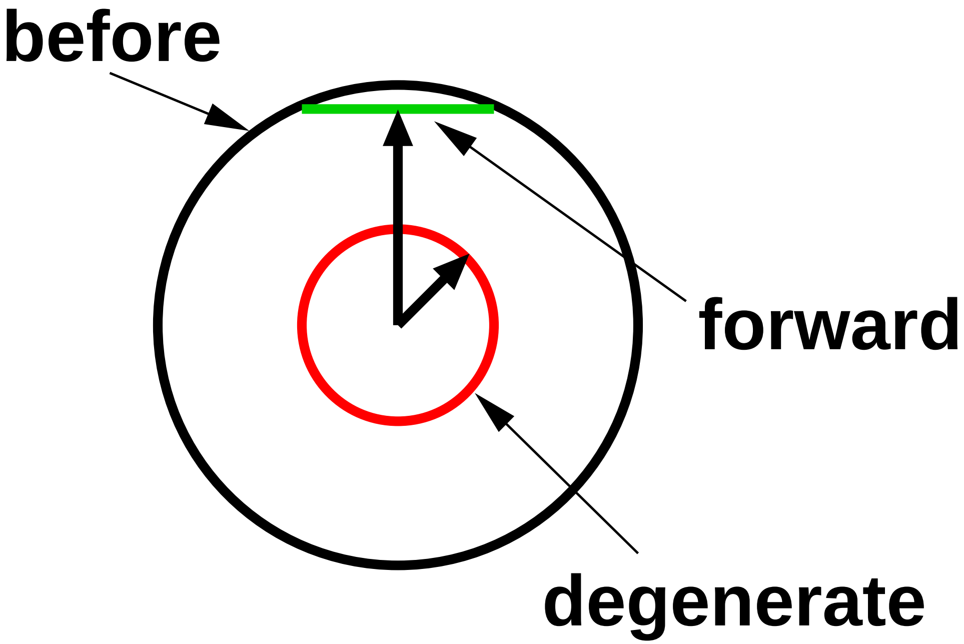
noise



$\sqrt{\text{Noise}}$ = degenerate sphere radius

**Thermal noise determines
the radius of the degenerate sphere**

criterion

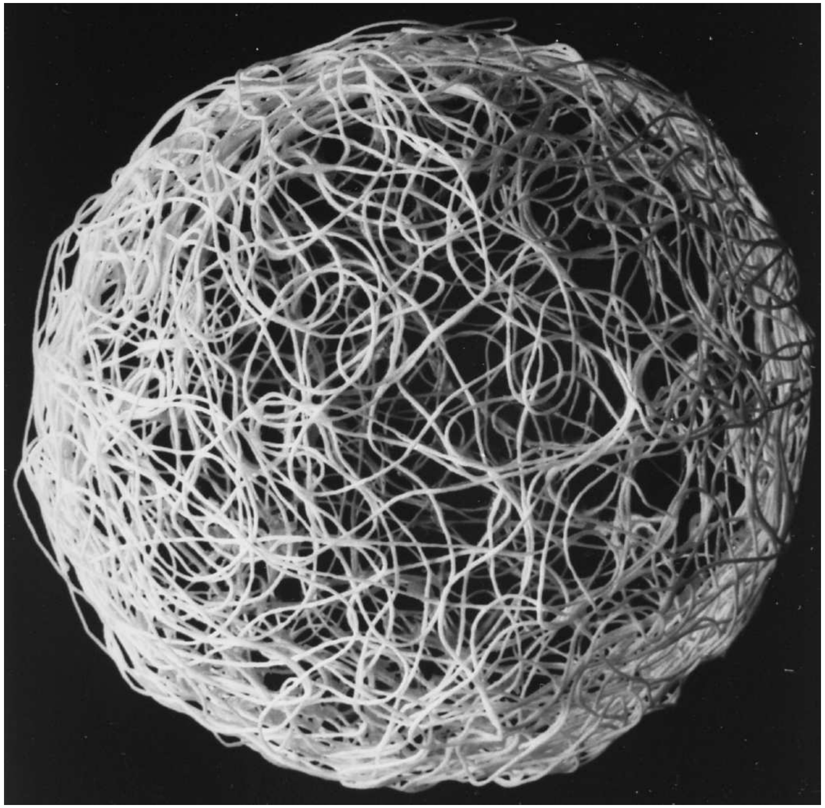


**Criterion for distinct states:
forward does not touch degenerate**

$$\sqrt{\textbf{Power}} > \sqrt{\textbf{Noise}}$$

N Dimensional Sphere Separation

Degenerate Sphere



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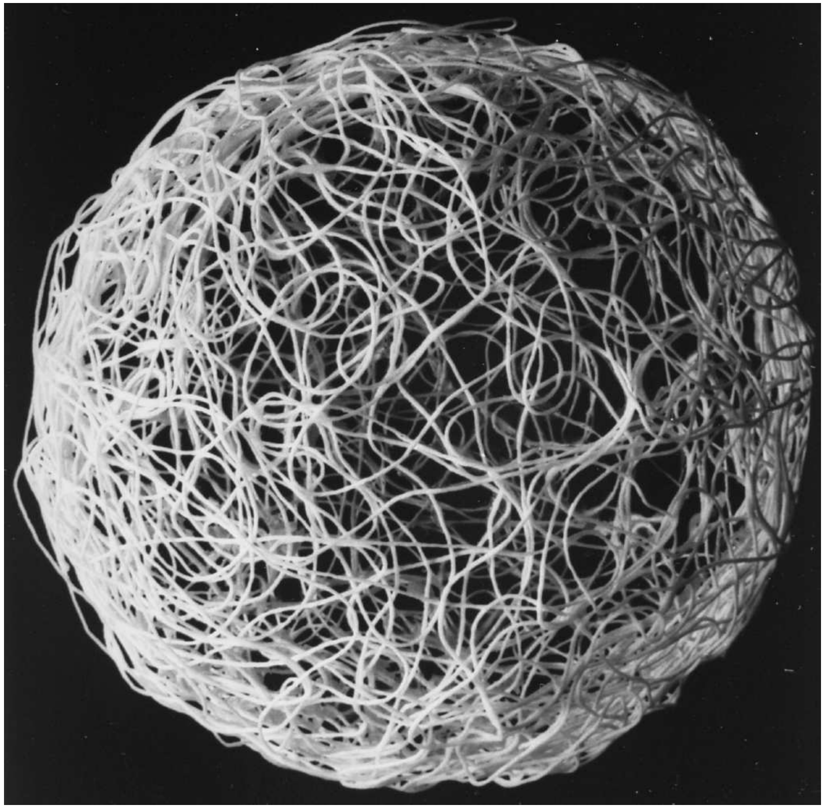
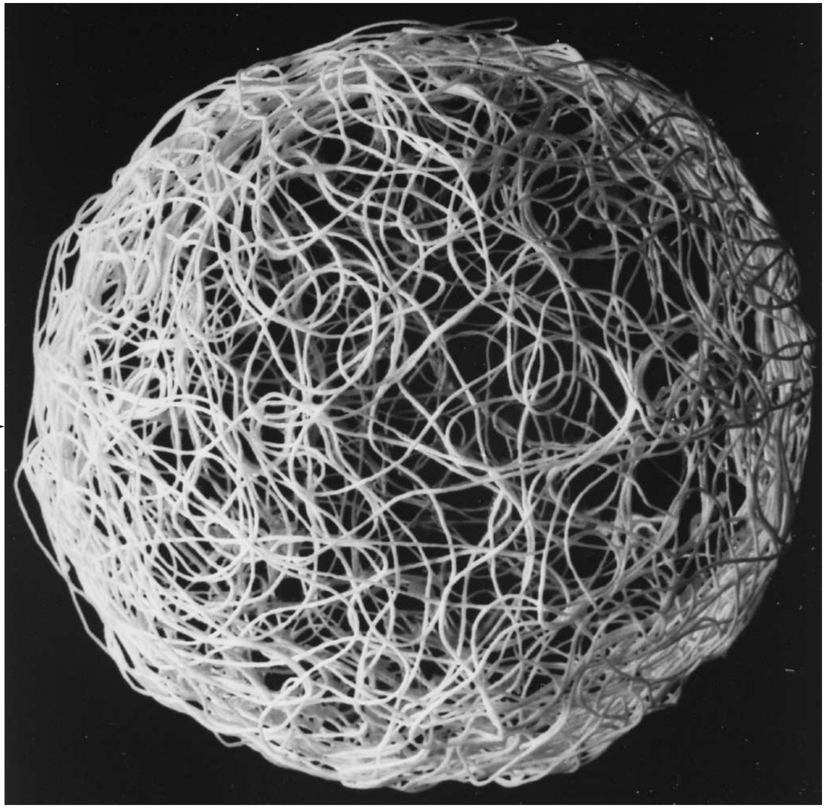


Forward Sphere



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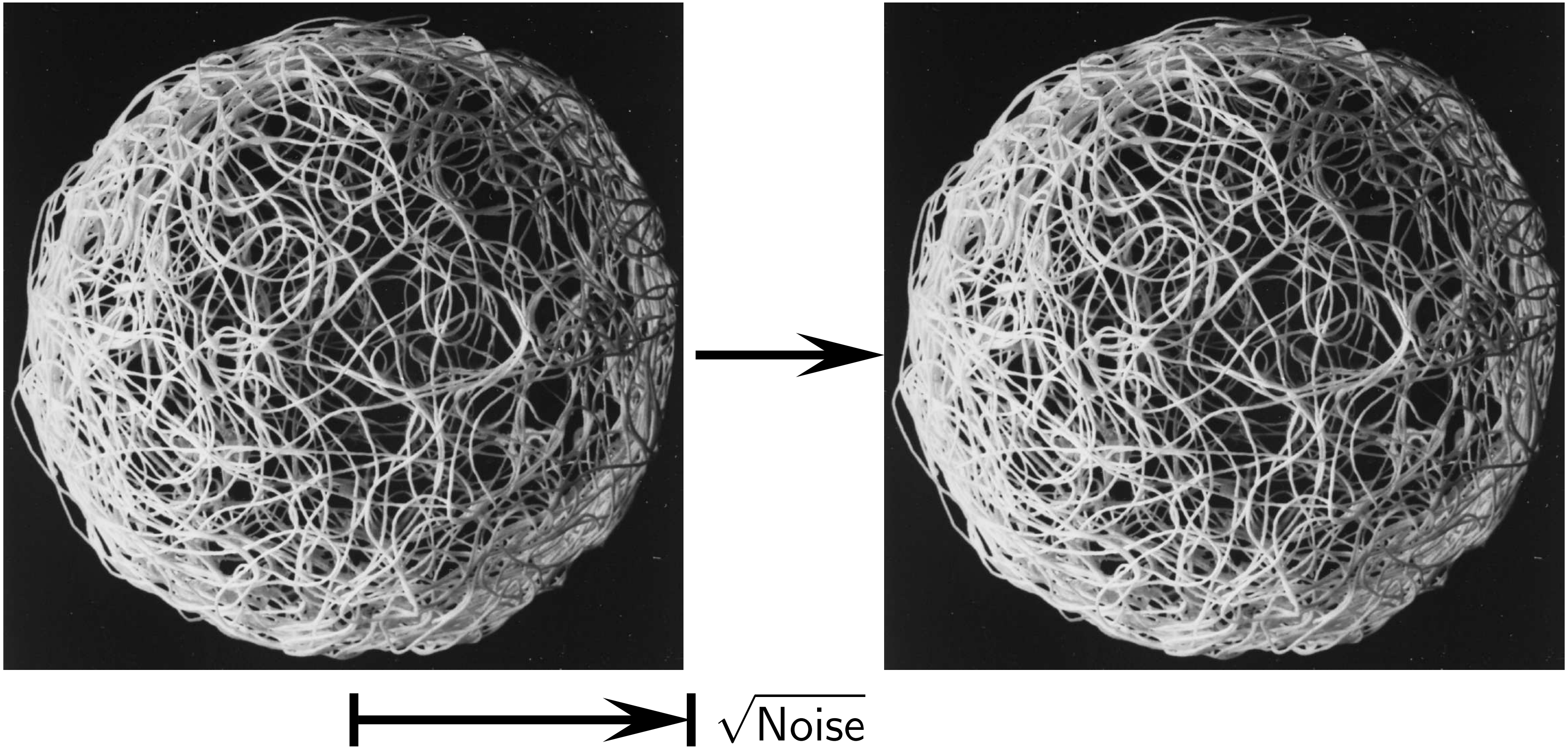
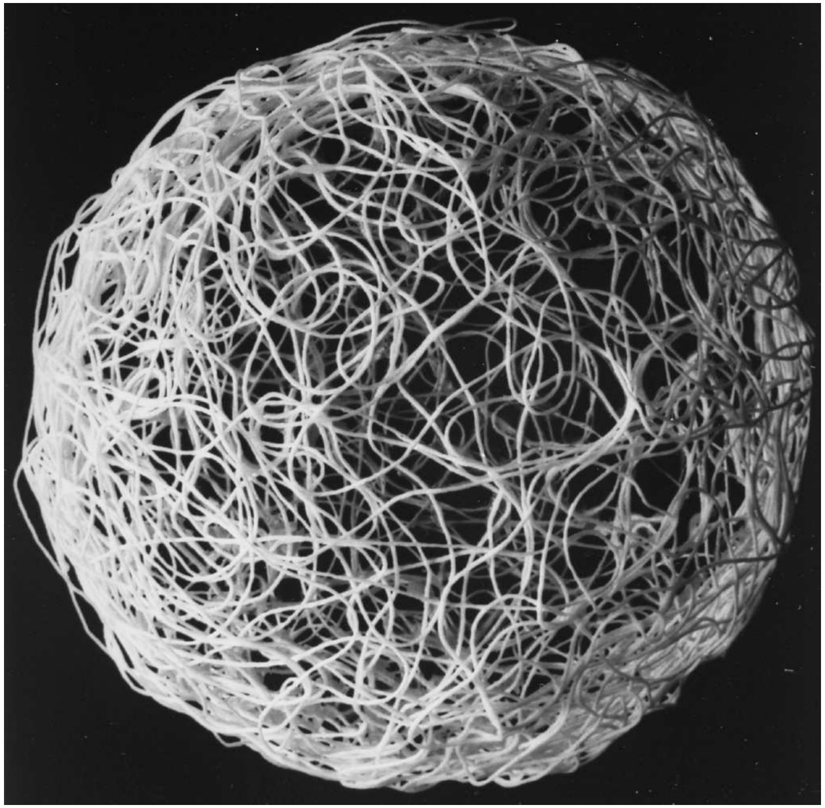


Degenerate Sphere

Forward Sphere

$\sqrt{\text{Noise}}$

N Dimensional Sphere Separation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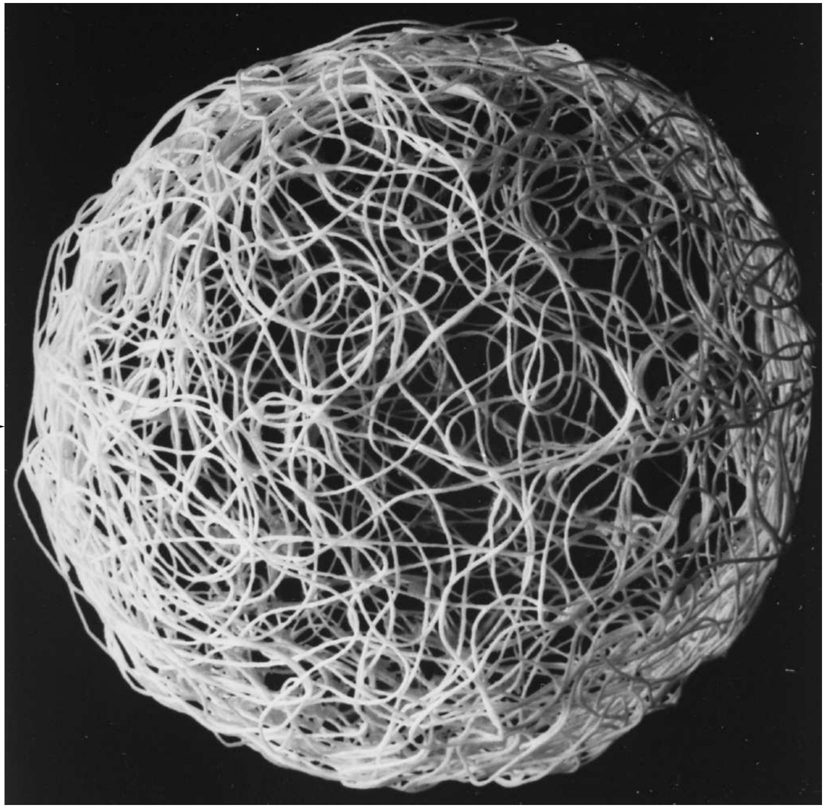
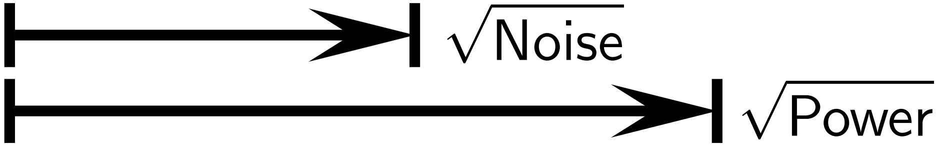

Forward Sphere


$\sqrt{\text{Noise}}$

$\sqrt{\text{Power}}$

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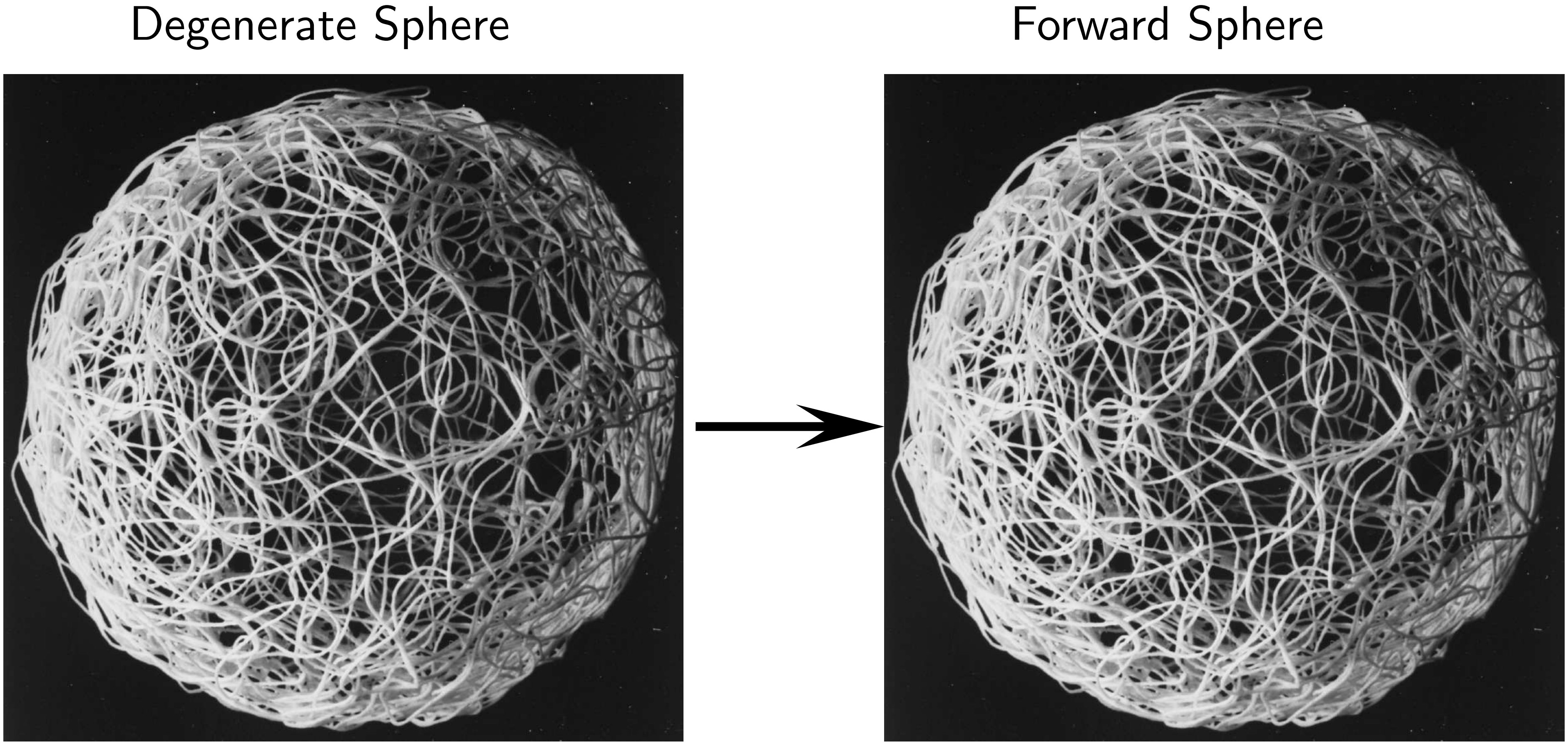
Degenerate Sphere

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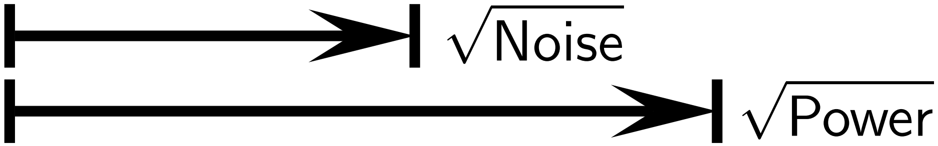

Energy dissipated to escape the Degenerate Sphere must exceed the Noise

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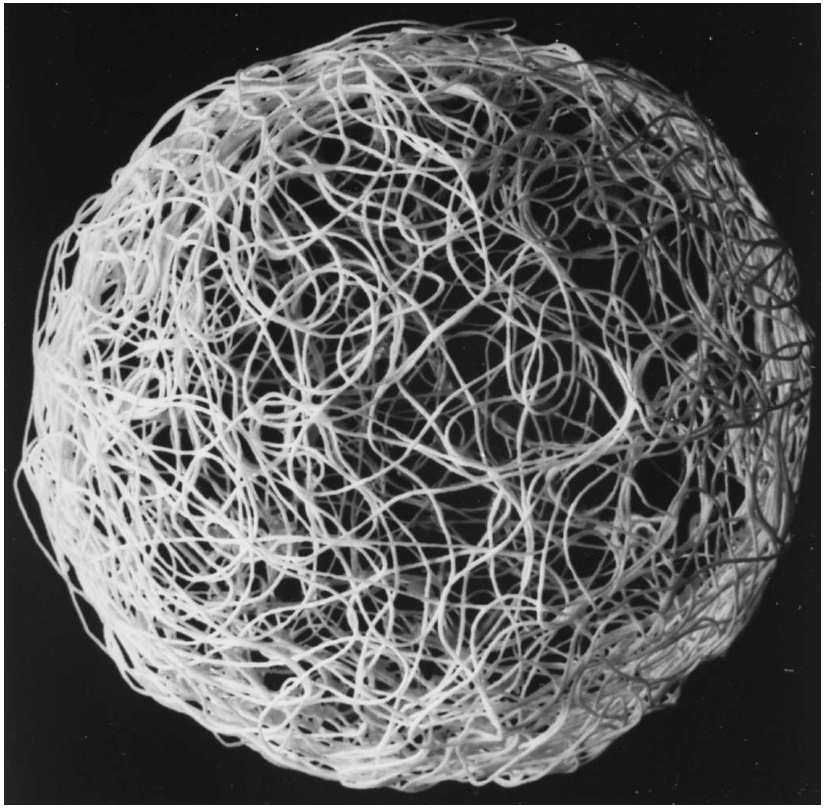

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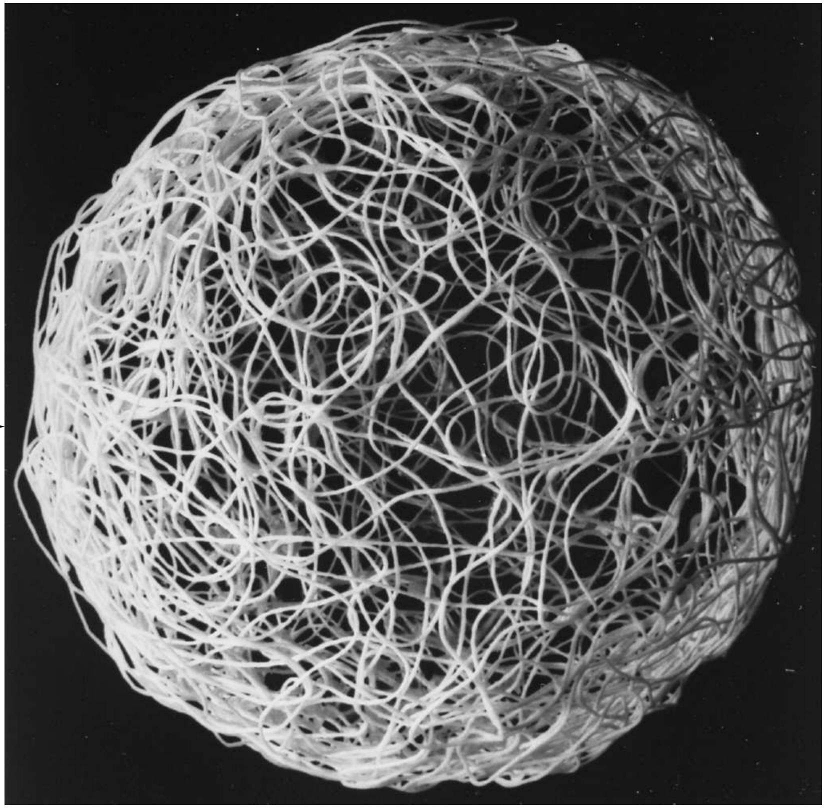

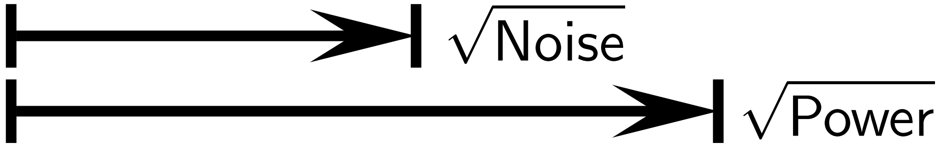

$\sqrt{\text{Noise}}$

$\sqrt{\text{Power}}$

Energy dissipated to escape the Degenerate Sphere must exceed the Noise

$$\sqrt{\text{Power}} > \sqrt{\text{Noise}}$$

CONSEQUENCES OF THE DEGENERATE SPHERE HYPOTHESIS

The geometry gives:

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which when plugged into the efficiency formula:

$$\epsilon_t \equiv \frac{\mathcal{E}_{min}}{\mathcal{E}} = \frac{\ln\left(\frac{\text{Power}}{\text{Noise}} + 1\right)}{\frac{\text{Power}}{\text{Noise}}} \qquad \frac{\text{(joules per bit)}}{\text{(joules per bit)}}$$

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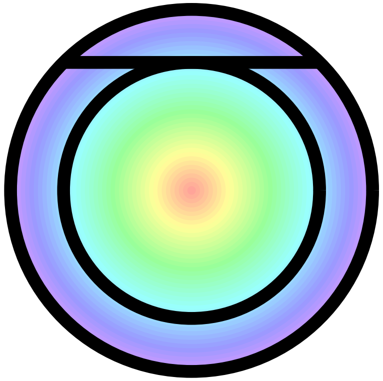

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T. D. Schneider
Nucl. Acids Res.
38: 5995-6006, 2010

Why is the Genetic Code Degenerate?

The Genetic Code

	Second base in codon				
First base in codon	U	C	A	G	Third base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	och	opa	A
	Leu	Ser	amb	Trp	G
C	Leu	Pro	His	Arg	U
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64 codons

$\log_2 64 = 6$ bits/amino acid

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Compute Efficiency

$$\begin{aligned} \epsilon_r &= \frac{\log_2 \text{actual choices}}{\log_2 \text{maximum choices}} \\ &= \frac{4.3}{6} = 0.72 \end{aligned}$$

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The Genetic Code fits the theory!

Amino Acid Frequencies

A	105312381
C	17427433
D	67454442
E	77603281
F	48627269
G	83989735
H	27315242
I	69538797
K	65592680
L	119947552
M	27534150
N	53024966
O	10
P	61536653
Q	49569998
R	71591890
S	91898484
T	69490771
U	397
V	80381739
W	15430467
Y	37433671

Refine the Calculation

Obtain actual amino acid frequencies from the 50% sequence identity non-redundant Protein Information Resource (PIR) UniRef50 database, January 2011.

$n = 1{,}240{,}702{,}008 = 1.2 \times 10^9$ amino acids

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Compute the uncertainty:

$$\begin{aligned} H_{\text{aa}} &= -\sum_{\text{aa}\,=\,\text{A}}^{\text{Y}} P_{\text{aa}} \log_2 P_{\text{aa}} \quad \text{bits per amino acid} \\ &= 4.170 \quad \text{bits per amino acid} \end{aligned}$$

That's what is actually accomplished by translation.

Translational Efficiency

Compute the efficiency:

$$\epsilon_r = \frac{4.170}{6}$$

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Translational Efficiency

Compute the efficiency:

$$\begin{aligned}
\epsilon_r &= \frac{4.170}{6} \\
&= 0.6949 \text{ Measured efficiency} \\
\epsilon_t &= 0.6931 \text{ Theoretical maximum} = \ln(2) \\
& 0.0018 \text{ difference}
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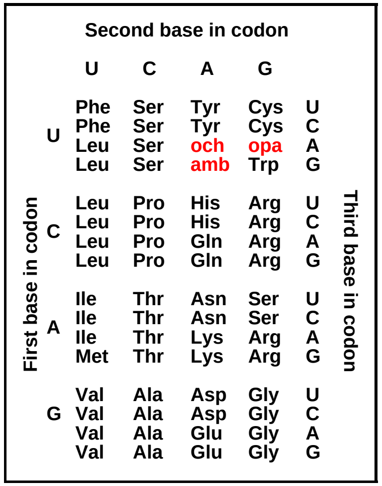

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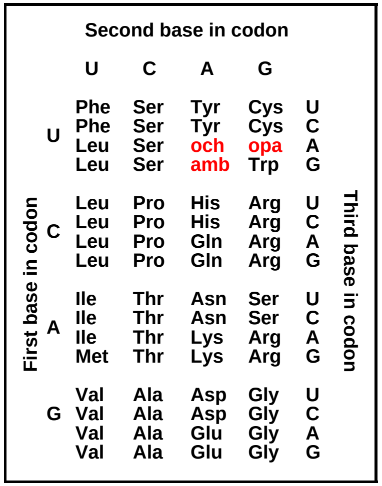

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A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

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Theory violation! . . . What's Missing?

- Rare amino acids don't contribute much.

Translational Efficiency

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A	Ile	Thr	Asn	Ser	U
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Since this comes from > 1 billion amino acids, 0.2% excess is significant!

Theory violation! . . . What's Missing?

- Rare amino acids don't contribute much.
- Removing the stop codons reduces the maximum from 6 bits to $\log_2 61 = 5.931$ bits and the efficiency would be $4.170/5.931 = 0.7031$, so this makes the situation worse and does not explain the discrepancy.

Translational Efficiency

Compute the efficiency:

$$\begin{aligned} \epsilon_r &= \frac{4.170}{6} \\ &= 0.6949 \text{ Measured efficiency} \\ \epsilon_t &= 0.6931 \text{ Theoretical maximum} = \ln(2) \\ & 0.0018 \text{ difference} \end{aligned}$$

	Second base in codon				
First base in codon	U	C	A	G	Third base in codon
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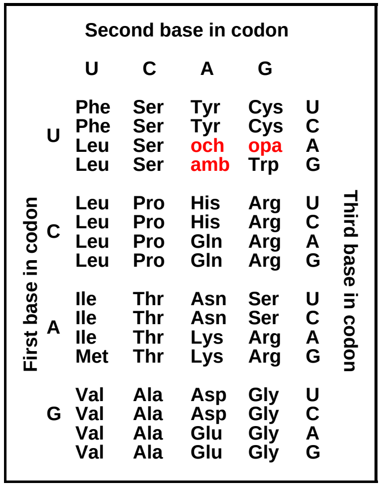
- Translational error rate was not accounted for?

Efficiency of the Genetic Code

Theory Violation! What's missing?
Error rate of transcription/translation was not accounted for.
See if we can compute it.



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Compute Error Rate
Proper Computation:

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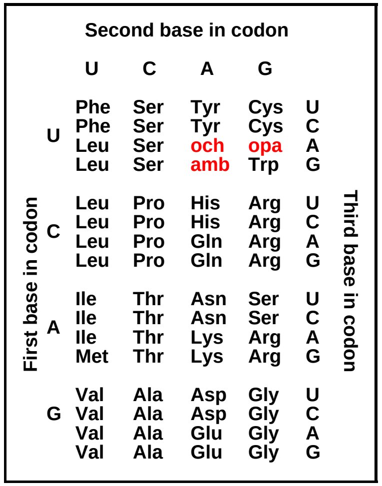

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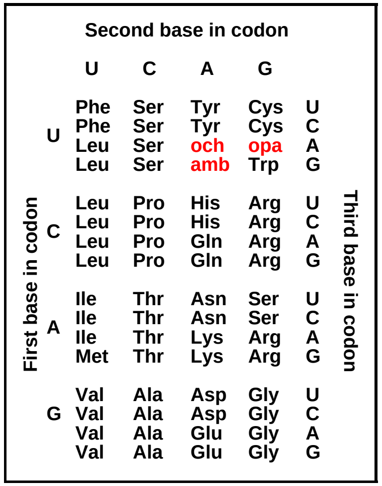

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The theory correctly predicts the error rate of translation

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Combine:

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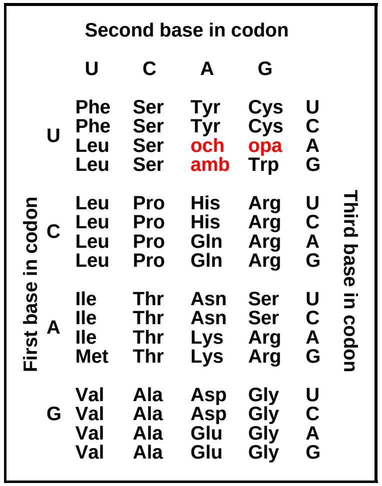

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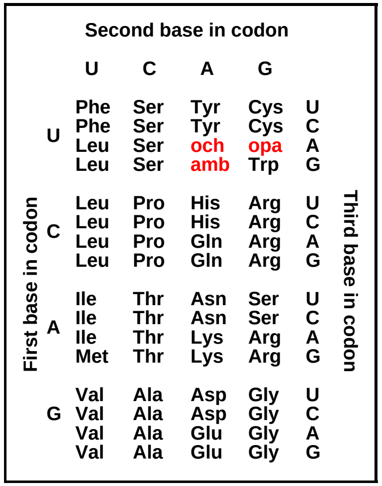

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Combine:
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The known translational error rate, 1×10^{-3}

$$\begin{aligned}(H_{aa} - H(P_{\text{error}}))/6 &= 0.69304765 = \text{measured efficiency}\\ \ln(2) &= 0.69314718 = \text{theoretical efficiency}\end{aligned}$$

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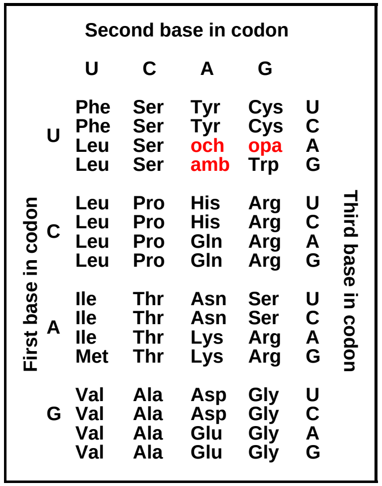

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The theory matches the data to 4 decimal places!

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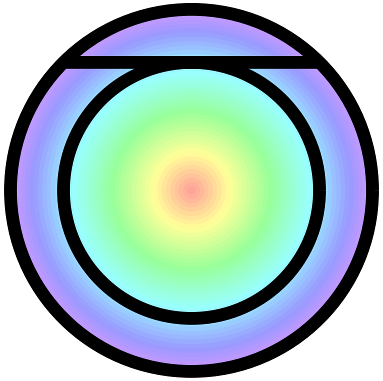

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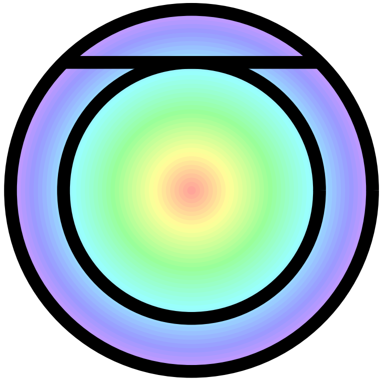

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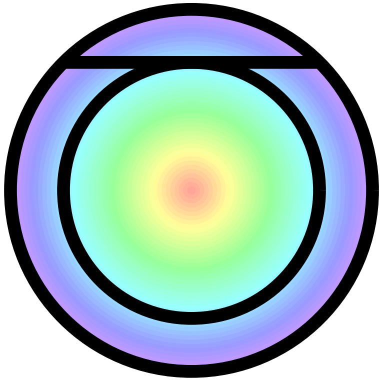

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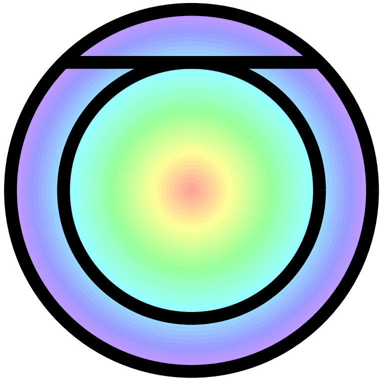

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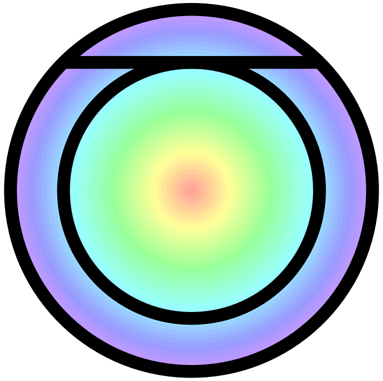

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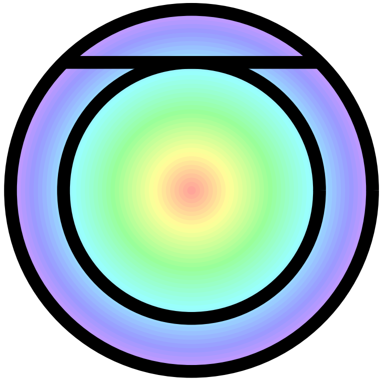

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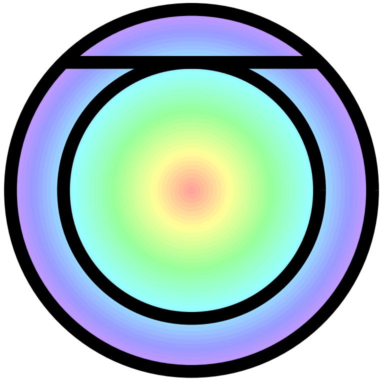

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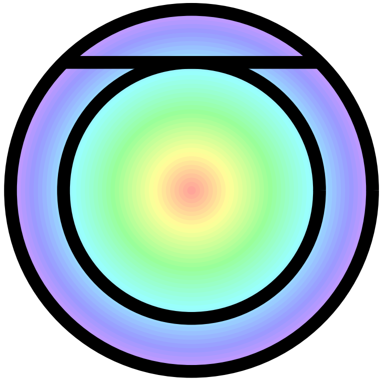

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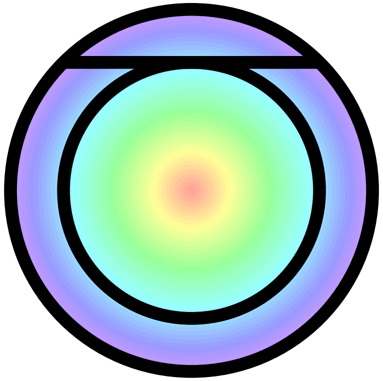

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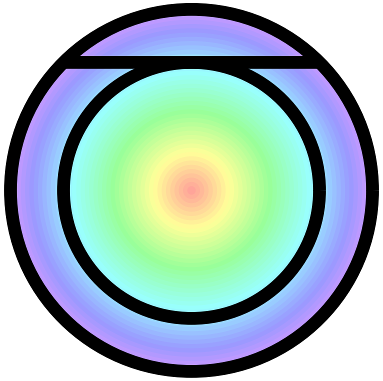

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Acknowledgments

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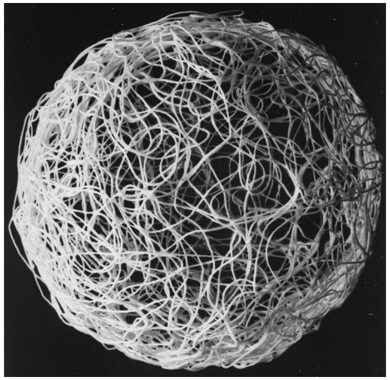
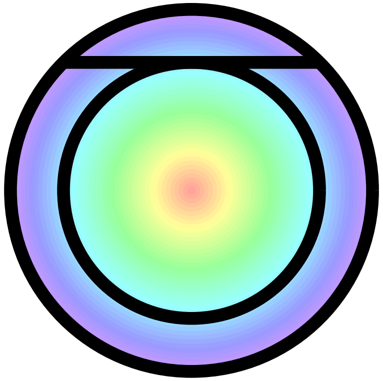
National Institutes of Health, National Cancer Institute

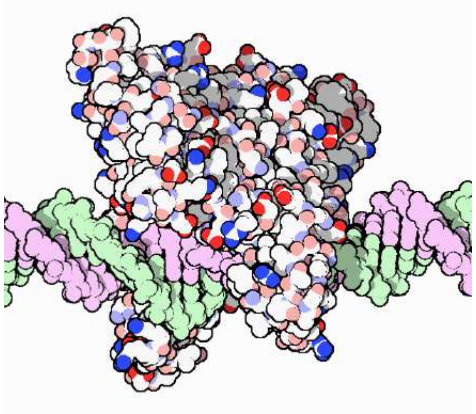
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

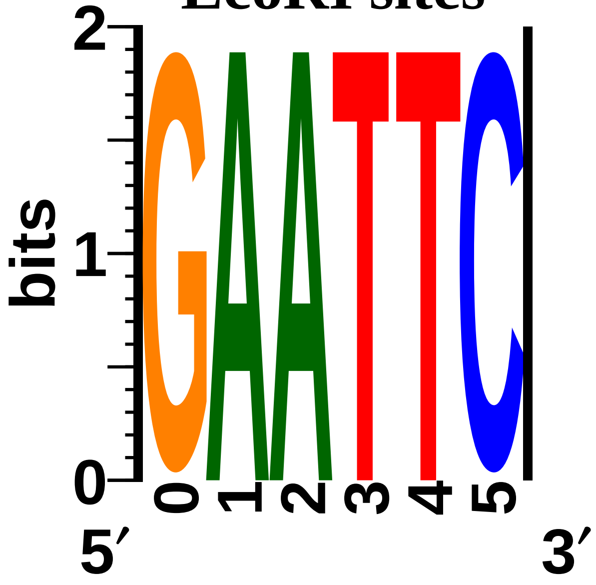
Web site:

TinyURL.com/tomschneider








EcoRI sites

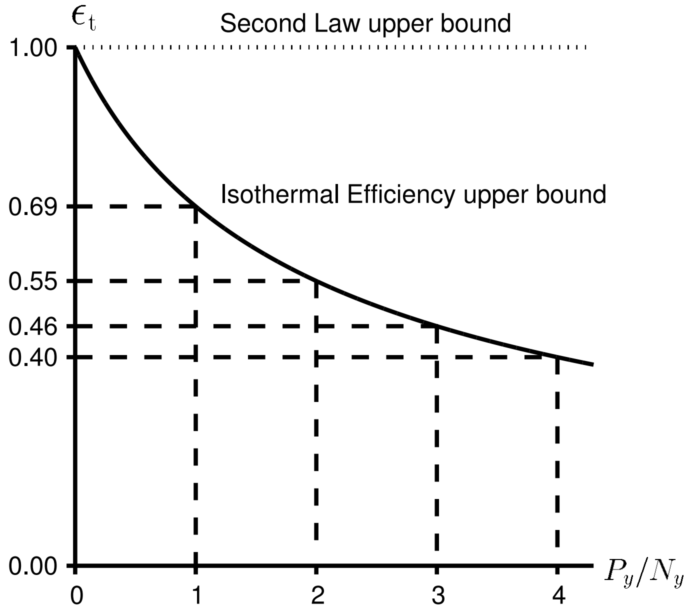
Second base in codon

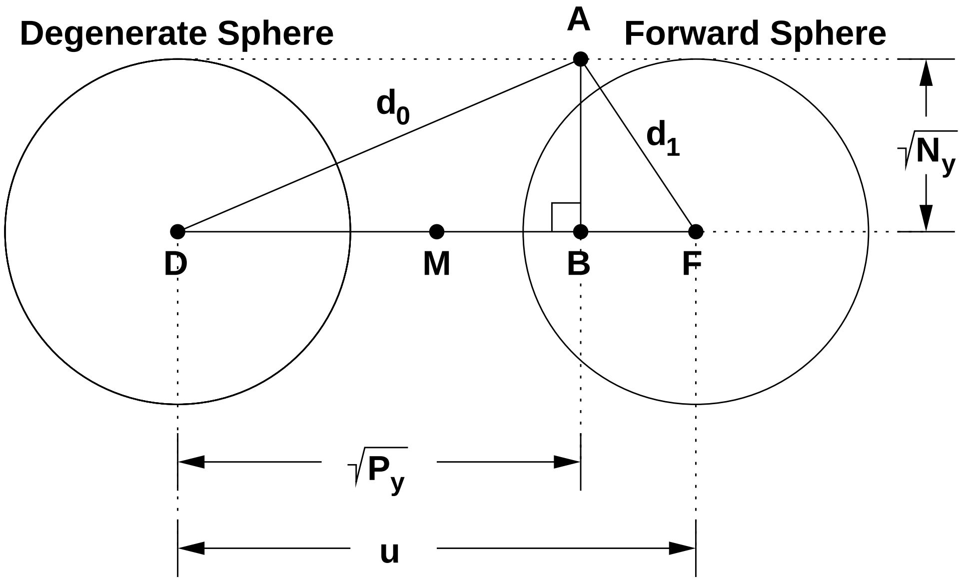
First base in codon	U	C	A	G	Third base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	och	opa	A
	Leu	Ser	amb	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Version

version = 1.33 of codetalk.tex 2011 Feb 25

Proof that $P_y > N_y$, $\epsilon < \ln(2)$





buffer zone: $u > 2\sqrt{N_y}$ (0)

distance² from A to D: $d_0^2 = \sqrt{P_y}^2 + \sqrt{N_y}^2 = P_y + N_y$ (1)

distance² from A to F: $d_1^2 = (u - \sqrt{P_y})^2 + \sqrt{N_y}^2$ (2)

decoding to forward sphere: $d_1 < d_0$ (3)

(1) and (2) into square of (3): $\sqrt{P_y} > u/2$ (4)

from (0) and (4): $\sqrt{P_y} > \sqrt{N_y}$ **so** $P_y > N_y$ (5)

$$\epsilon = \frac{\ln\left(\frac{P_y}{N_y} + 1\right)}{\frac{P_y}{N_y}} \quad \textbf{so} \quad \epsilon < \ln(2) \approx 0.6931$$

More Information Theory - 1

An Intuitive Approach

Information to chose one symbol from M symbols:

$$\log_2 M \tag{6}$$

More Information Theory - 1

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Information to chose one symbol from M symbols:

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$1/M$ is like the probability of a symbol.

More Information Theory - 1

An Intuitive Approach

Information to chose one symbol from M symbols:

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$$= \quad -\log_2 1/M.$$

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If the probabilities P_i of different symbols, i, are not equal, then the **surprisal** is:

$$u_i \equiv -\log_2 P_i. \tag{7}$$

how surprised one is to see a symbol

More Information Theory - 2

EXAMPLE

A phone rings once every 1024 seconds.

$$P_{\text{ring}} = 1/1024 \quad (8)$$

$$P_{\text{silent}} = 1023/1024 \quad (9)$$

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More Information Theory - 3

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More Information Theory - 3

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$$
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H &= \sum_{i=1}^{M} P_i \times (\text{surprisal for} P_i) && (14) \\
&= \sum_{i=1}^{M} P_i \times (-\log_2 P_i) && (15) \\
&= -\sum_{i=1}^{M} P_i \log_2 P_i \quad \text{bits per symbol} && (16)
\end{aligned}
$$

More Information Theory - 4

$\boxed{\text{Information is a decrease in uncertainty}}$

$$R = H_{\text{before}} - H_{\text{after}} \tag{17}$$

More Information Theory - 4

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Example a sequence logo is computed from equiprobable bases before:

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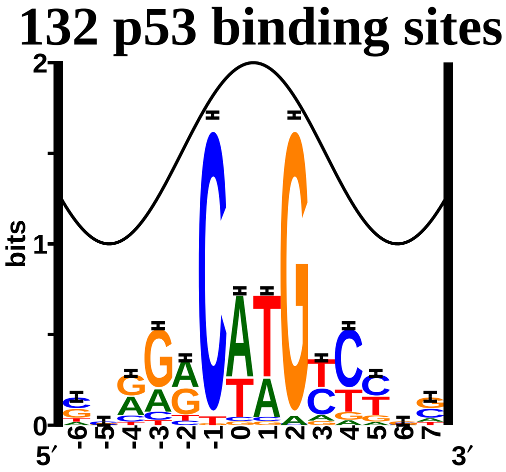

More Information Theory - 4

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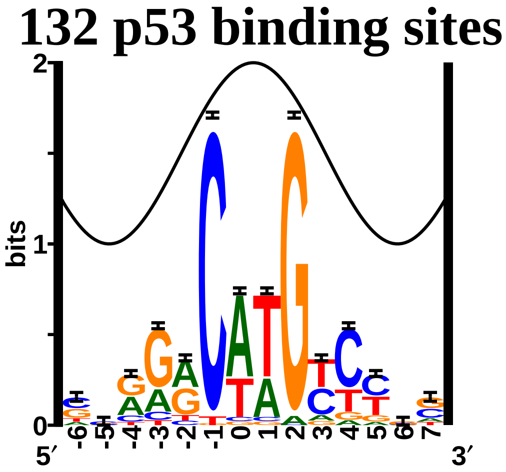

More Information Theory - 4

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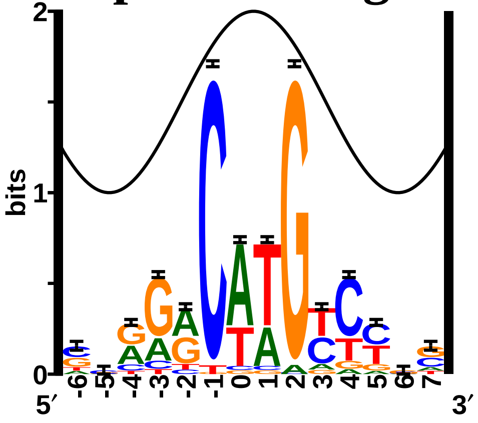
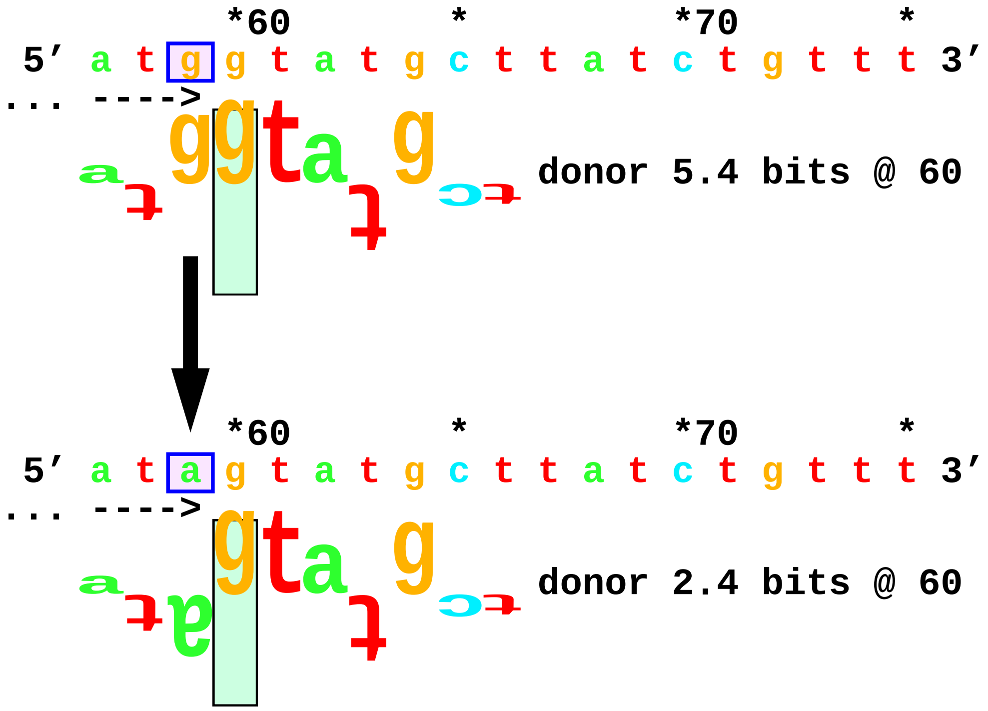
Note: with only one base, $H_{\text{after}} = 0$
so $R = 2$ bits/base.

132 p53 binding sites



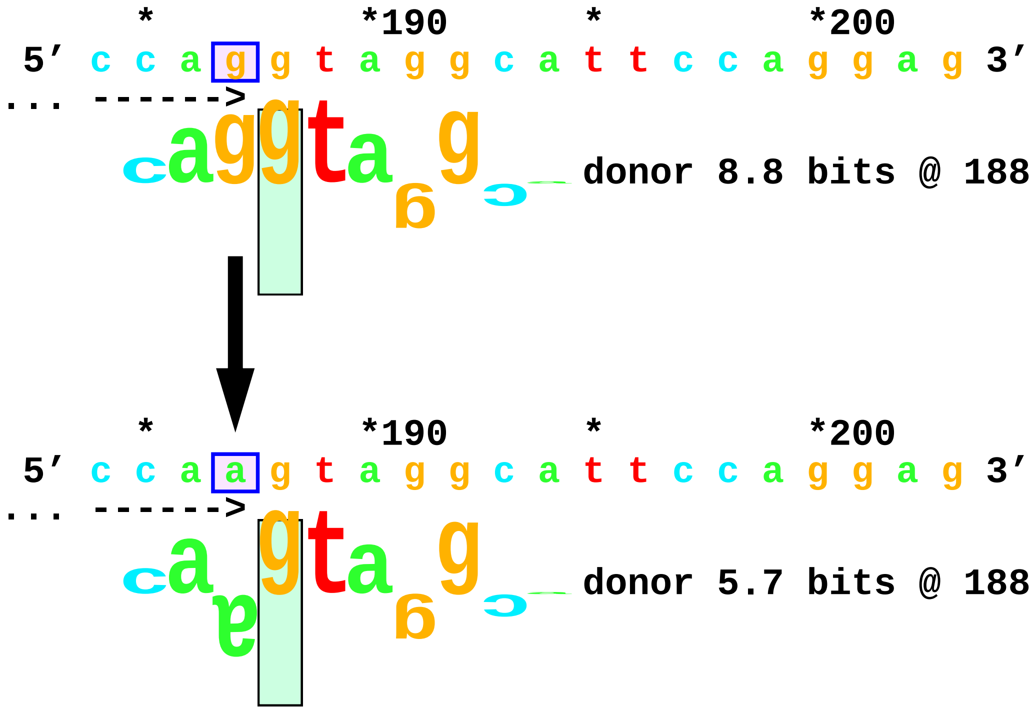
Splice Junction Mutation by Sequence Walkers



COL1A2 gene results in 50% exon skipping and Ehlers-Danlos syndrome

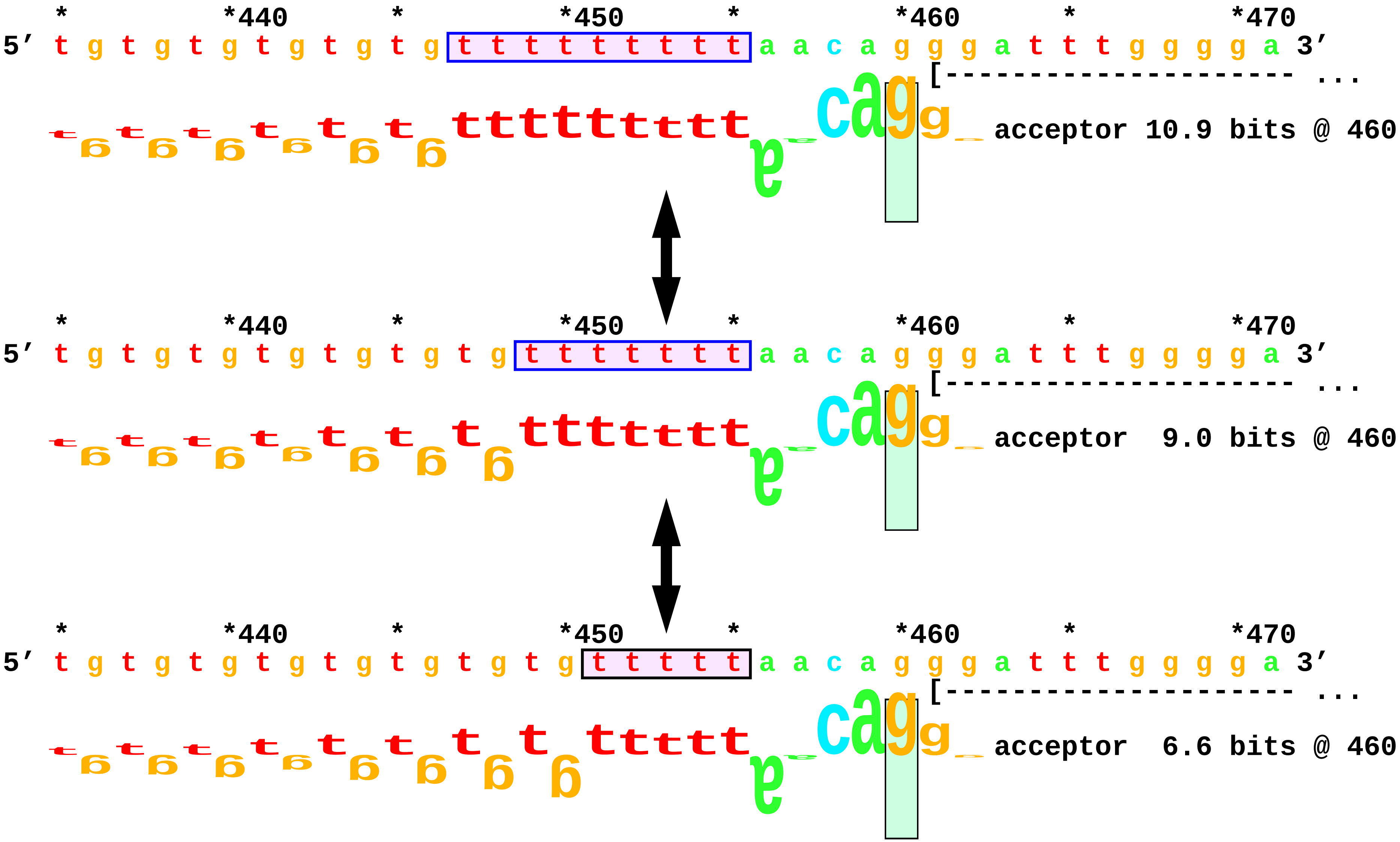
Rogan, Faux, Schneider, Human Mutation 12: 153-171 (1998)

Leaky Splice Junction Mutation



Lysosomal lipase gene [LIPA]
mild cholesterol ester storage disease with 4-9% enzymatic activity
Rogan, Faux, Schneider, Human Mutation 12: 153-171 (1998)

Polymorphic Variation Affects Splicing

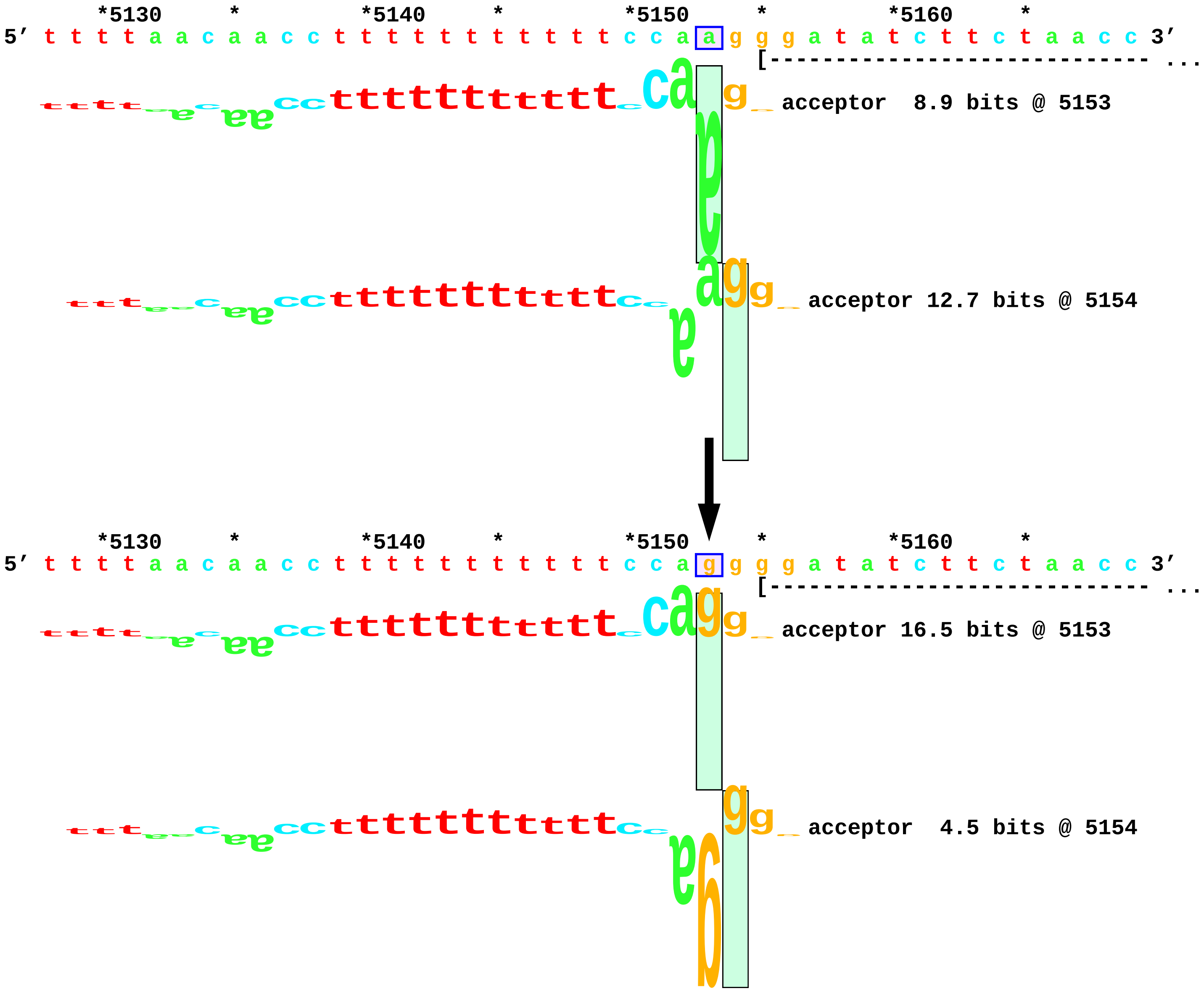


```
   *          *440        *          *450        *          *460        *          *470
5′ t g t g t g t g t g t g t t t t t t t t t a a c a g g g a t t t g g g g a 3′
                                                       [---------------------- ...
                                                         acceptor 10.9 bits @ 460

   *          *440        *          *450        *          *460        *          *470
5′ t g t g t g t g t g t g t g t t t t t t t a a c a g g g a t t t g g g g a 3′
                                                       [---------------------- ...
                                                         acceptor  9.0 bits @ 460

   *          *440        *          *450        *          *460        *          *470
5′ t g t g t g t g t g t g t g t g t t t t t a a c a g g g a t t t g g g g a 3′
                                                       [---------------------- ...
                                                         acceptor  6.6 bits @ 460
```

Cystic fibrosis transmembrane regulator [CFTR]

Rogan, Faux, Schneider, Human Mutation 12: 153-171 (1998)

Cryptic Site Generation and Mutation of Natural Site



Iduronidase synthetase gene [IDS]

Rogan, Faux, Schneider, Human Mutation 12: 153-171 (1998)