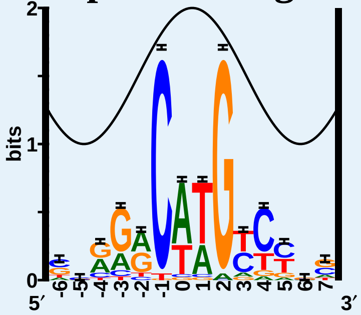
Efficiency of Molecular Machines

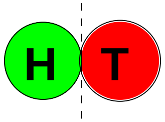
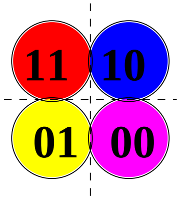
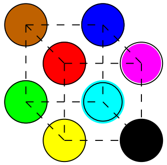
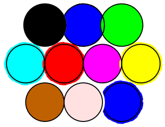
Thomas D. Schneider, Ph.D.

National Cancer Institute at Frederick
Center for Cancer Research Nanobiology Program
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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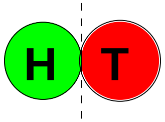
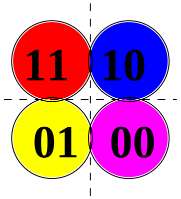
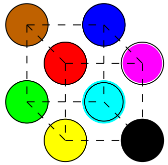
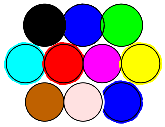
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	

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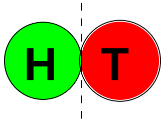
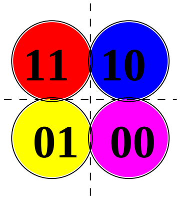
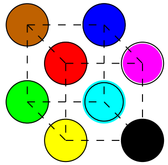
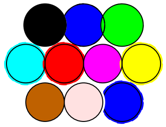
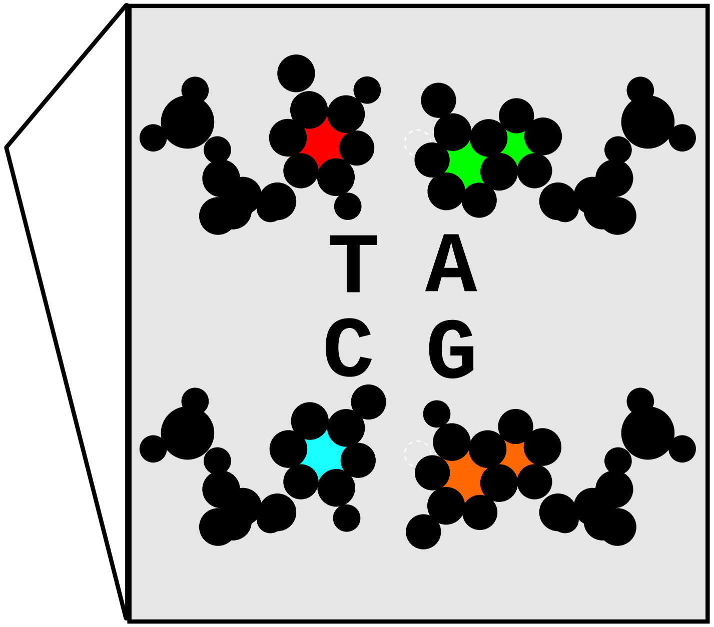
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	



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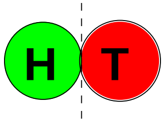
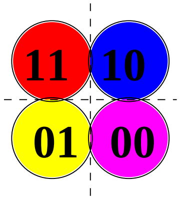
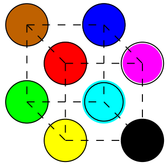
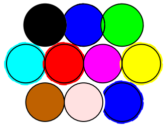
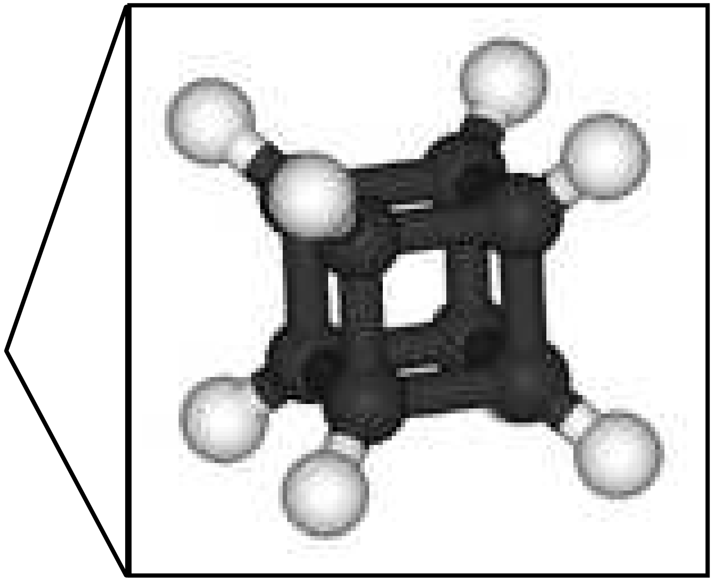
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	



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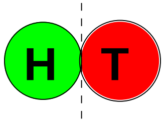
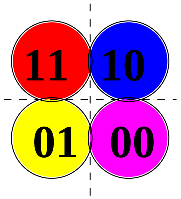
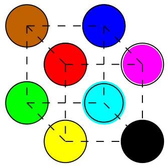
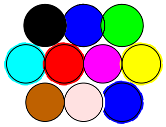
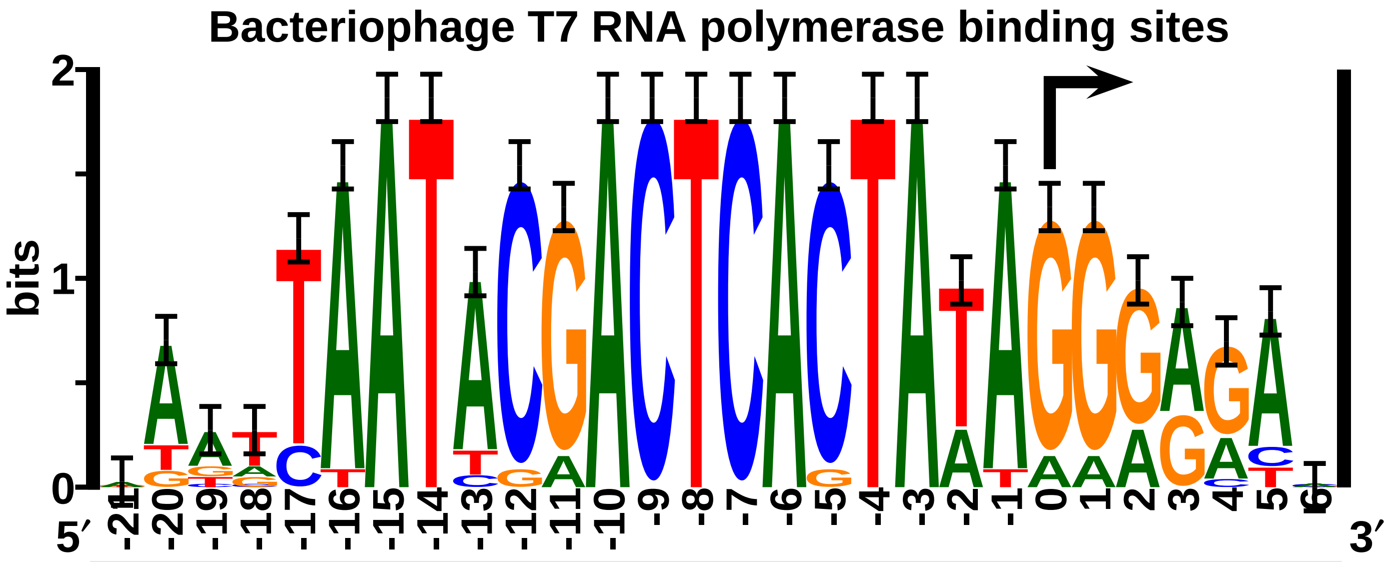
2	1	
4	2	
8	3	
$M=2^B$	$B=\log_2 M$	

Sequence Logo

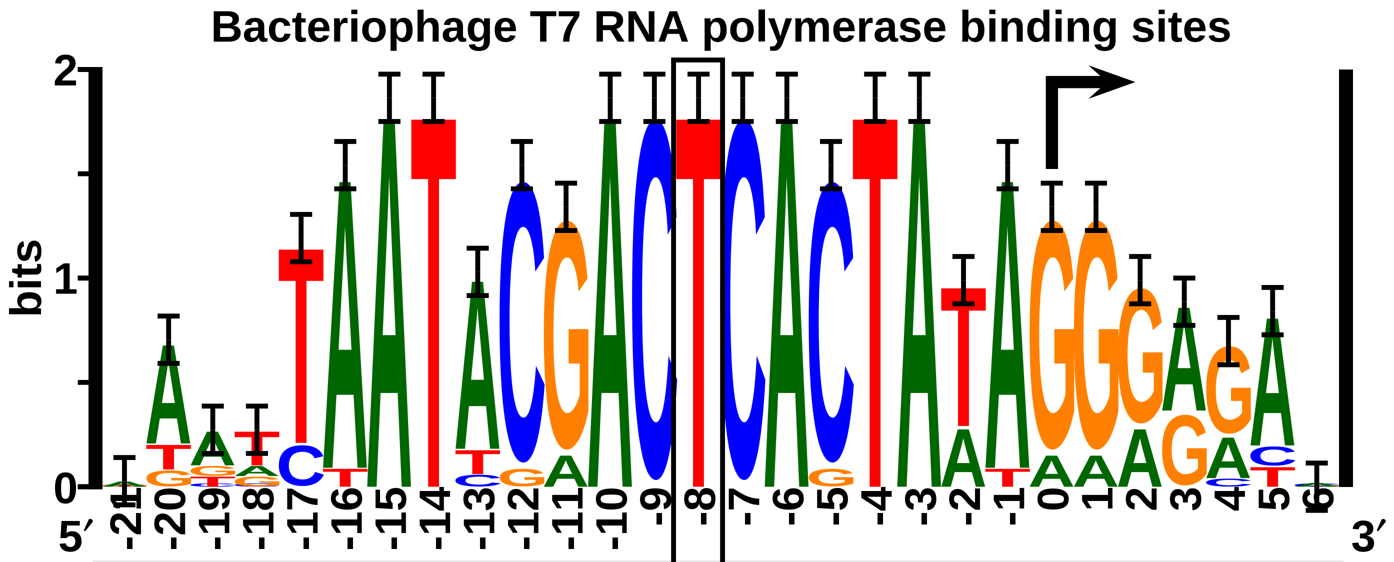


Schneider &
Stephens
Nucl. Acids Res.
18: 6097-6100
1990

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

6 of 17 sites

Sequence Logo



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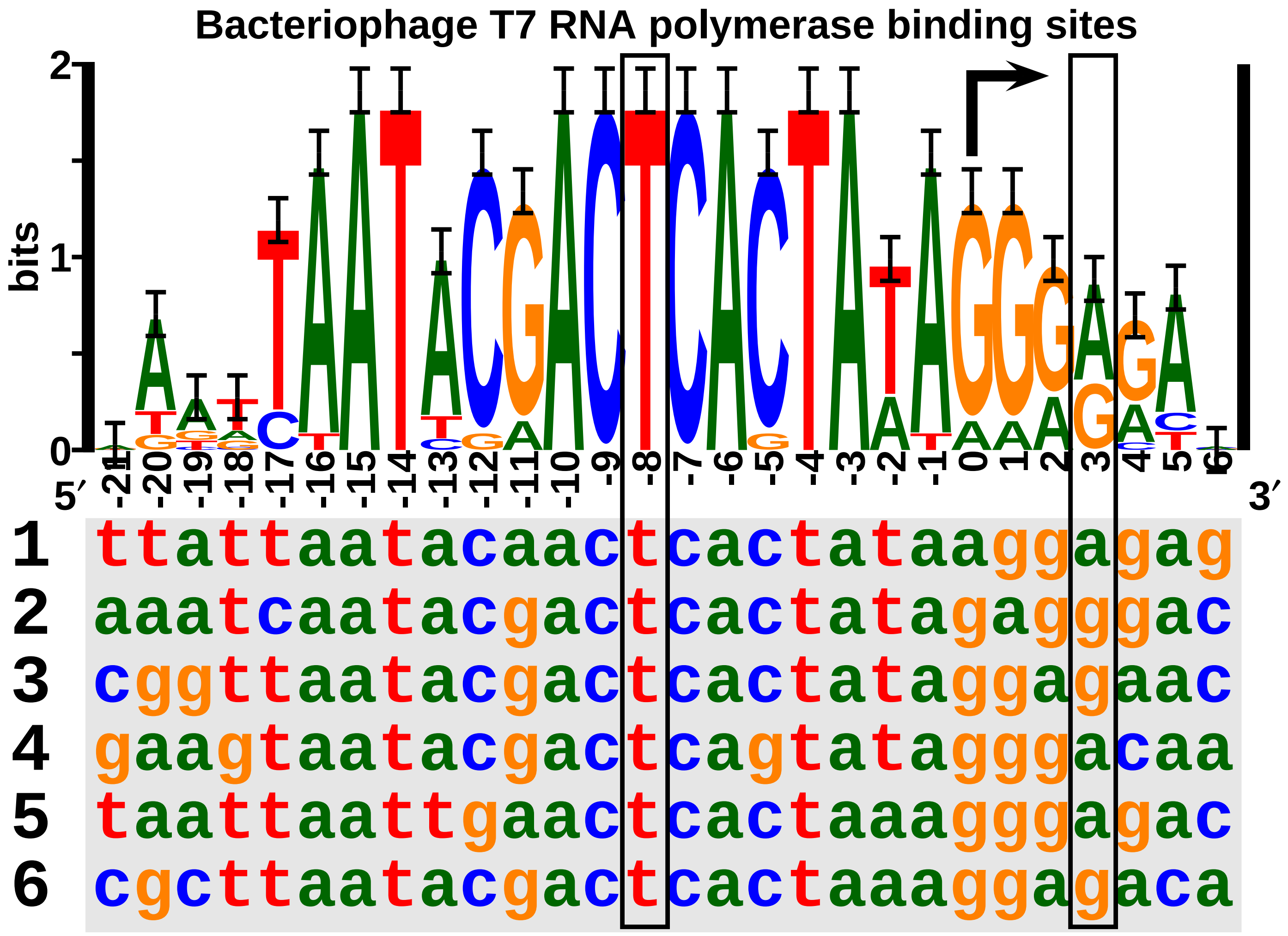
```
1  ttattaatacaactcactataaggagag
2  aaatcaatacgactcactatagagggac
3  cggttaatacgactcactataggagaac
4  gaagtaatacgactcagtatagggacaa
5  taattaattgaactcactaaagggagac
6  cgcttaatacgactcactaaaggagaca
```

6 of 17 sites

Sequence Logo



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

6 of 17 sites

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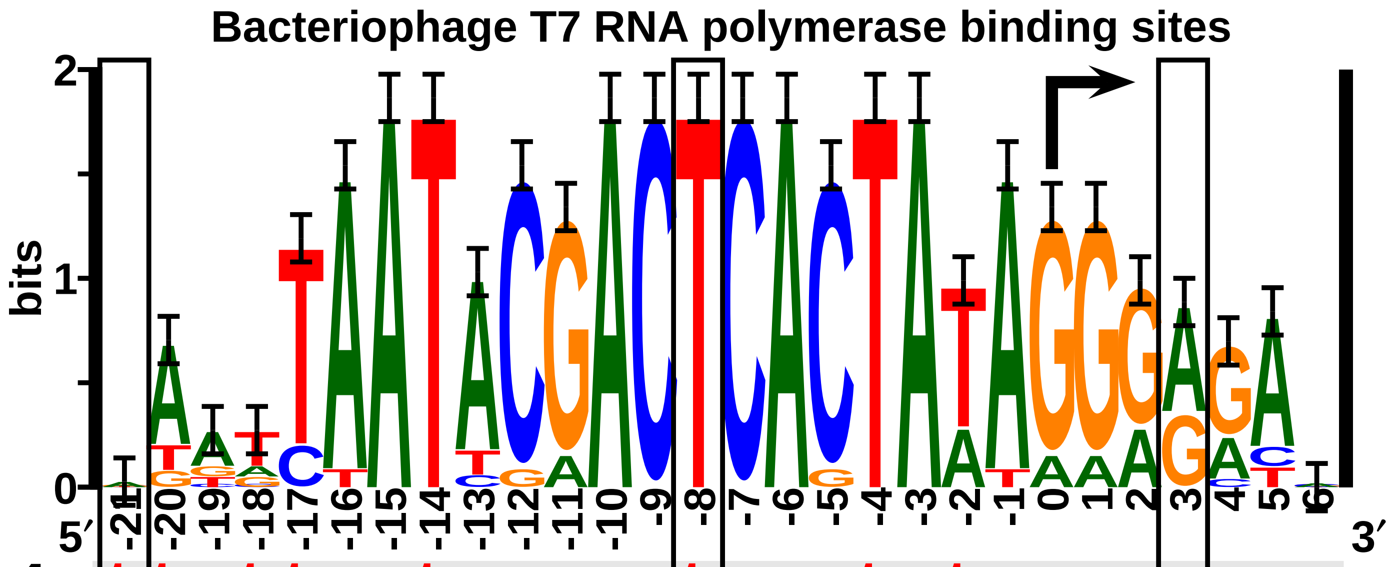

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```
1 ttattaatacaactcactataaggagag
2 aaatcaatacgactcactatagagggac
3 cggttaatacgactcactataggagaac
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5 taattaattgaactcactaaagggagac
6 cgcttaatacgactcactaaaggagaca
```
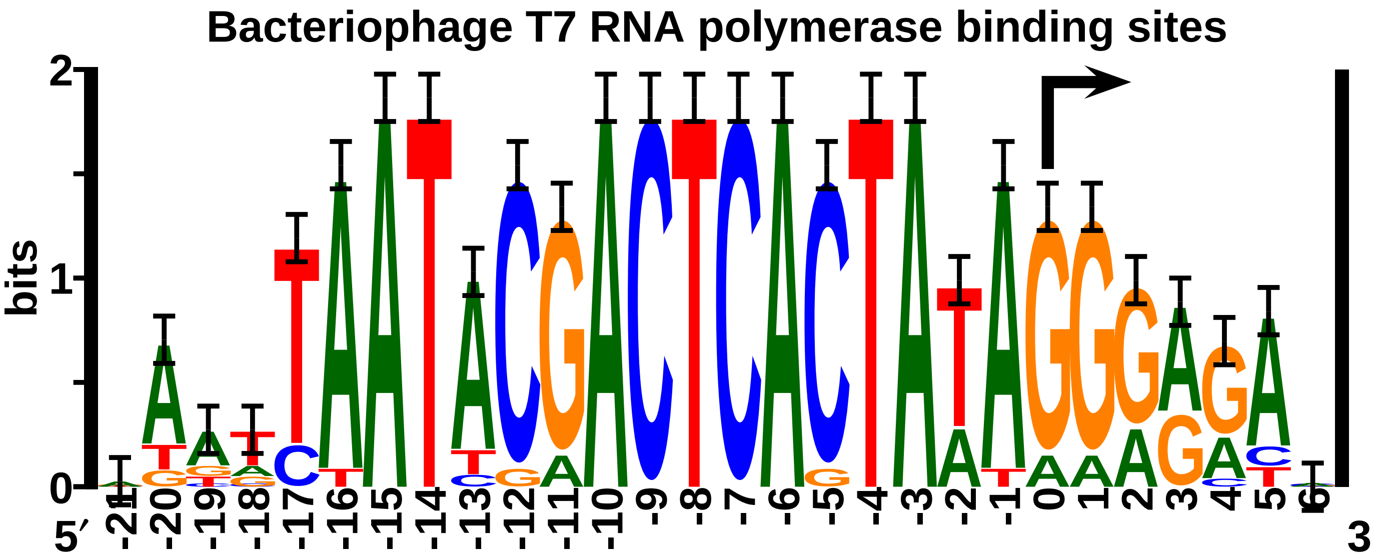

6 of 17 sites

Sequence Logo and Sequence Walker



Schneider &
Stephens
Nucl. Acids Res.
18: 6097-6100
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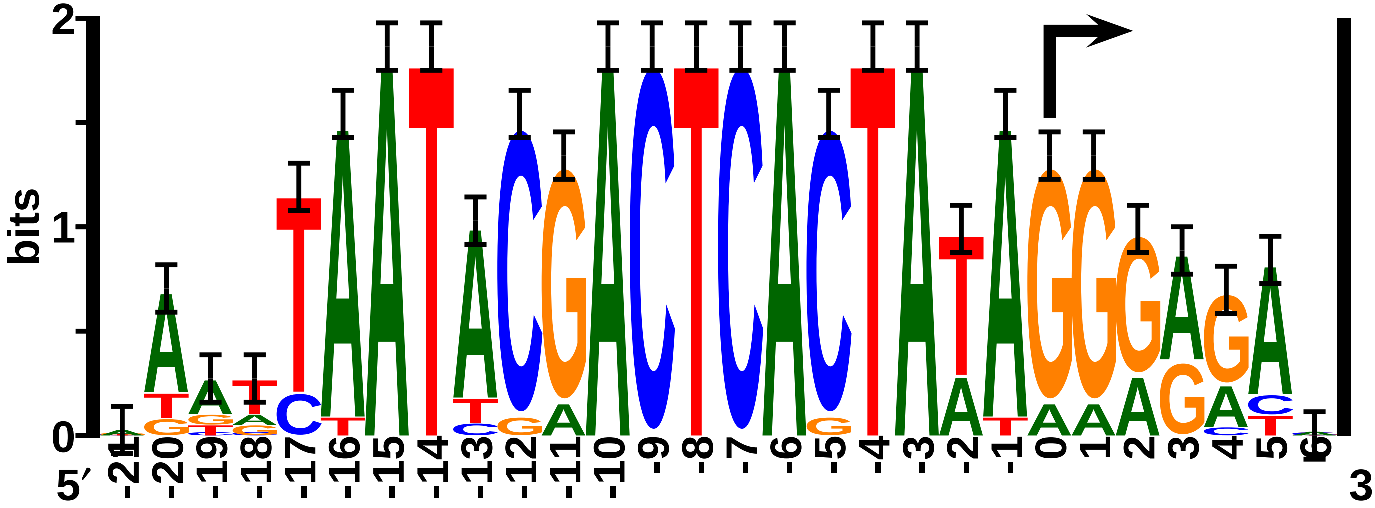
		Bits
1	ttattaatacaactcactataaggagag	33.3
2	aaatcaatacgactcactatagagggac	37.4
3	cggttaatacgactcactataggagaac	34.4
4	gaagtaatacgactcagtatagggacaa	33.1
5	taattaattgaactcactaaagggagac	30.1
6	cgcttaatacgactcactaaaggagaca	29.1

Sequence Logo and Sequence Walker

Bacteriophage T7 RNA polymerase binding sites



Schneider & Stephens
Nucl. Acids Res.
18: 6097-6100
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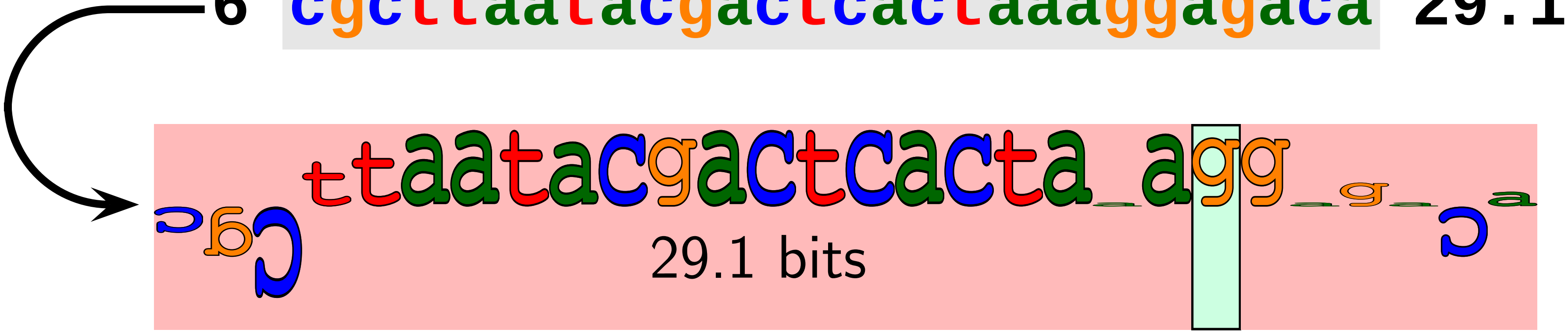
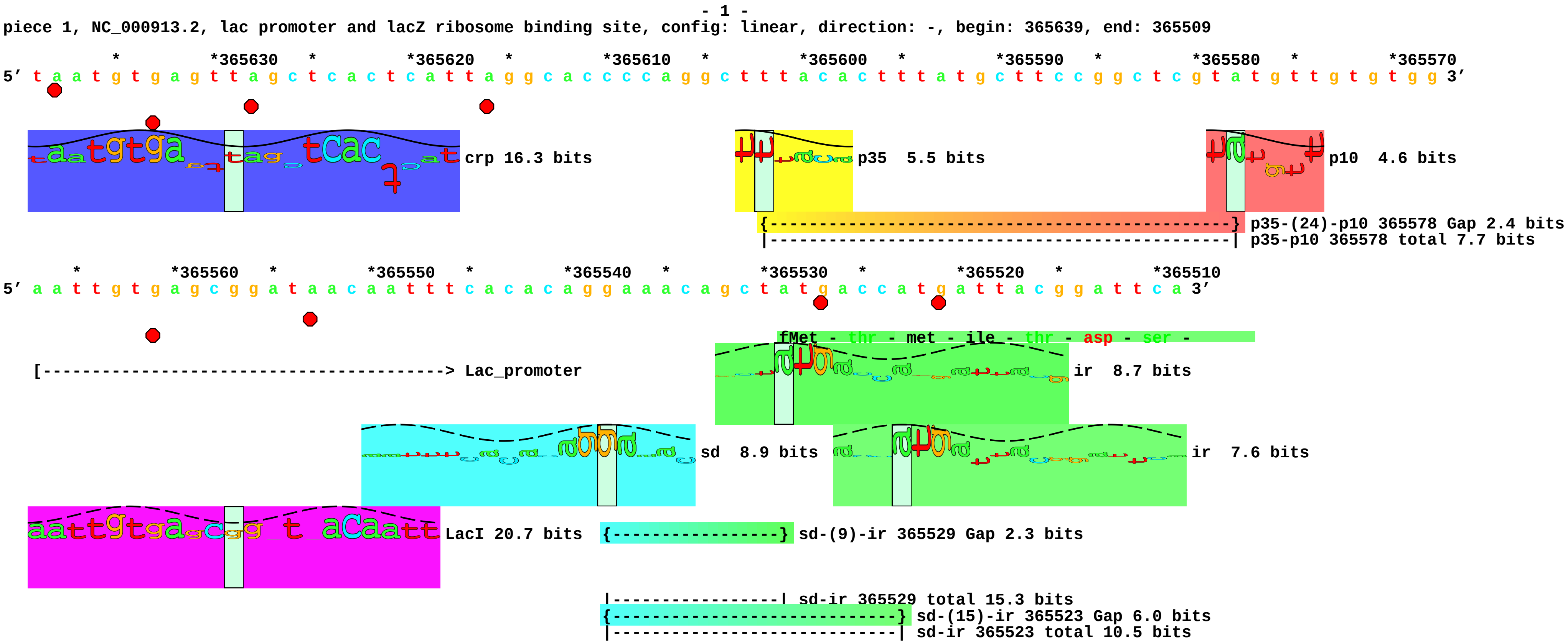
		Bits
1	ttattaatacaactcactataaggagag	33.3
2	aaatcaatacgactcactatagagggac	37.4
3	cggttaatacgactcactataggagaac	34.4
4	gaagtaatacgactcagtatagggacaa	33.1
5	taattaattgaactcactaaagggagac	30.1
6	cgcttaatacgactcactaaaggagaca	29.1



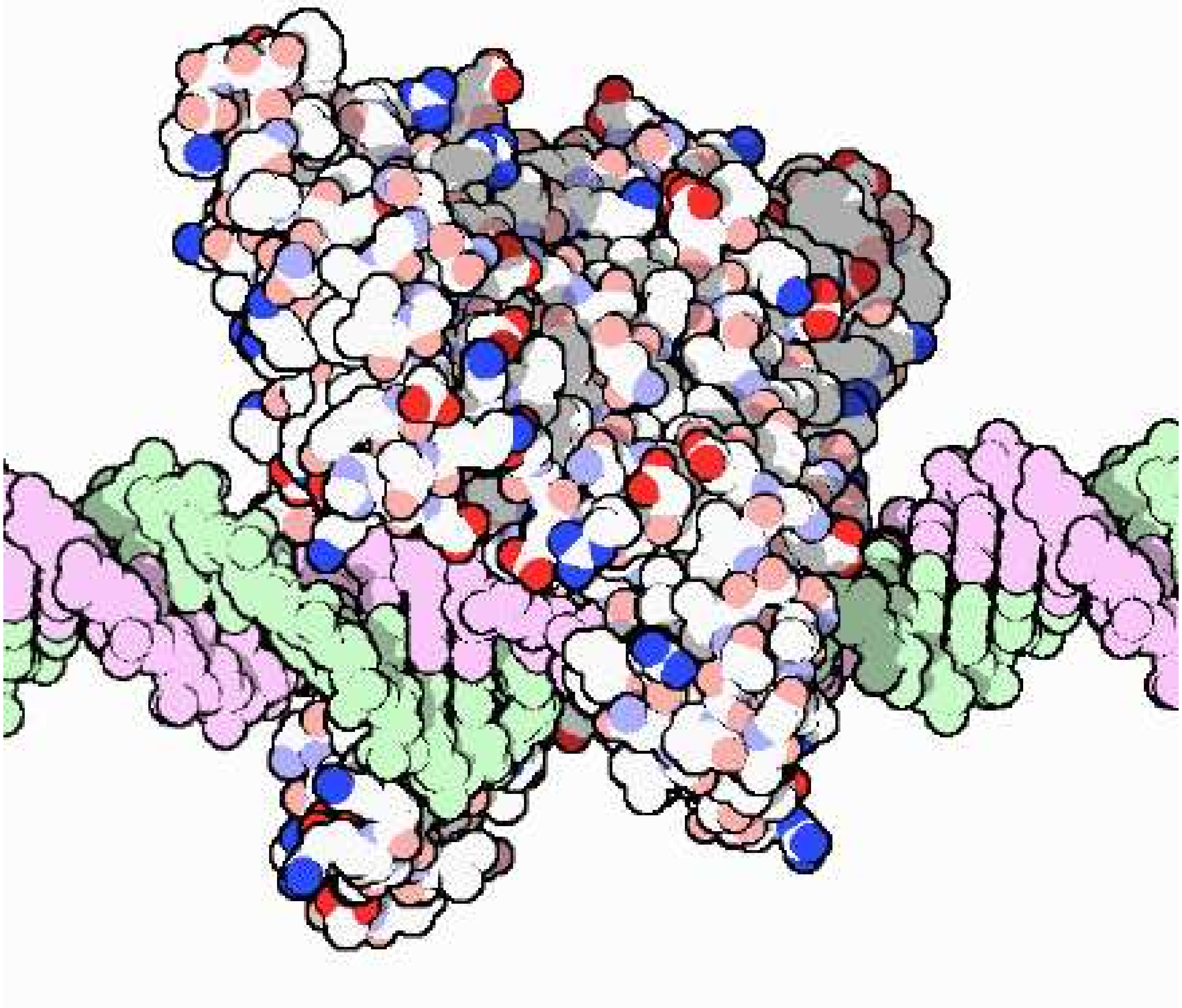
Sequence
Walker
Patent
5,867,402

Sequence Walkers in the Lac Promoter



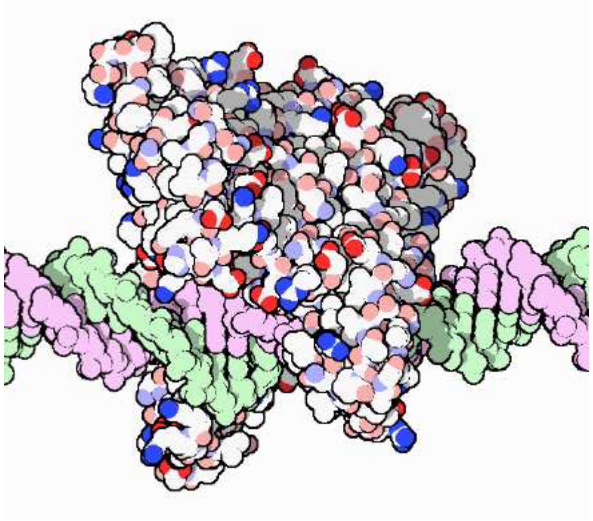
```
                                                    - 1 -
piece 1, NC_000913.2, lac promoter and lacZ ribosome binding site, config: linear, direction: -, begin: 365639, end: 365509

         *         *365630    *         *365620    *         *365610    *         *365600    *         *365590    *         *365580    *         *365570
5' 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 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 3'

crp 16.3 bits
p35   5.5 bits
p10   4.6 bits
{-----------------------------------------------} p35-(24)-p10 365578 Gap 2.4 bits
|-----------------------------------------------| p35-p10 365578 total 7.7 bits

     *         *365560    *         *365550    *         *365540    *         *365530    *         *365520    *         *365510
5' a a t t g t g a g c g g a t a 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
```

Information versus Energy



Information of EcoRI DNA Binding

- EcoRI - restriction enzyme



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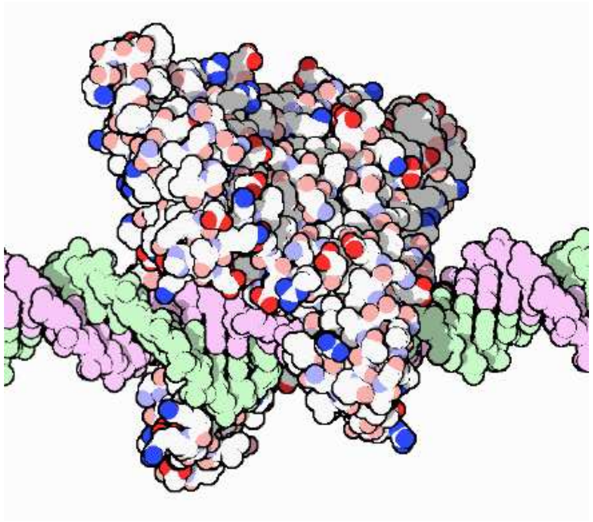

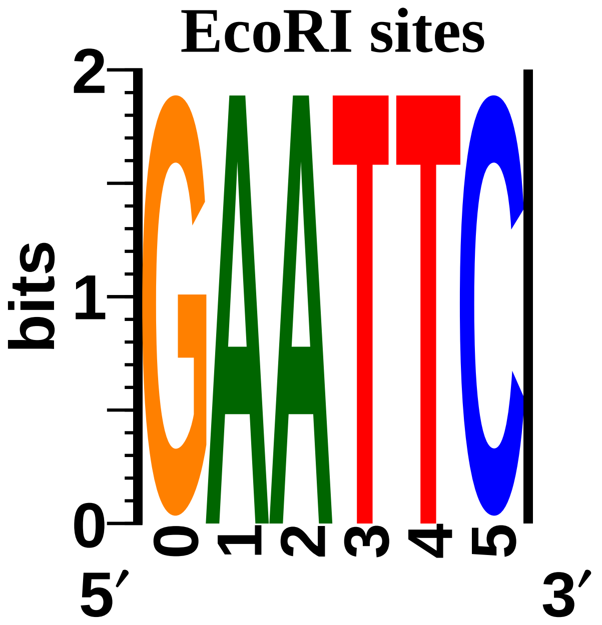

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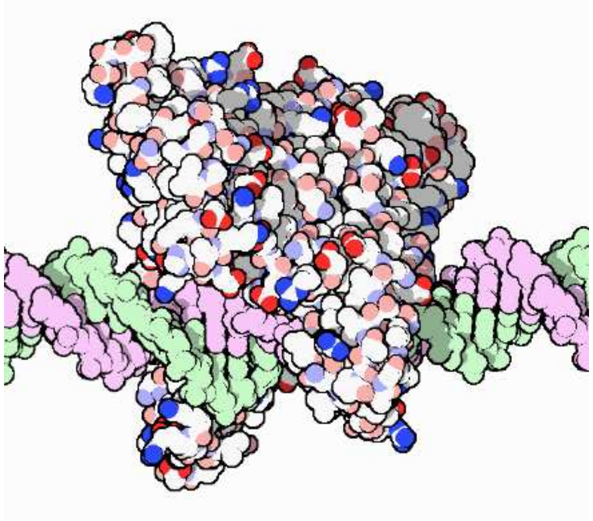
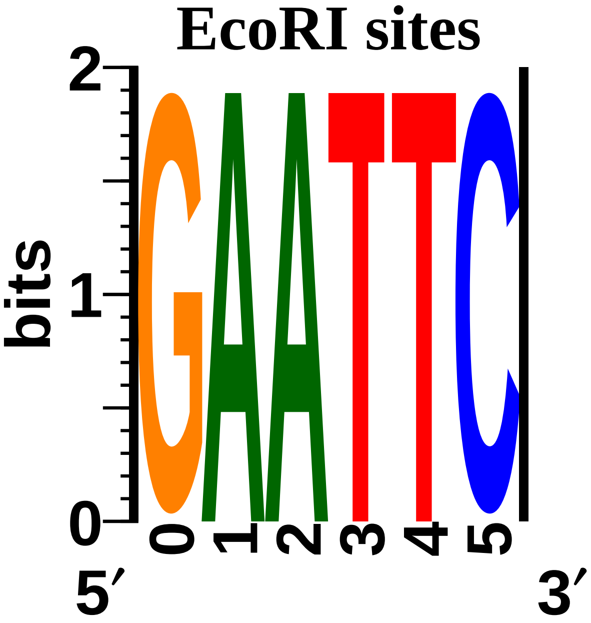
- $4^6 = 4096$ possible DNA hexamers





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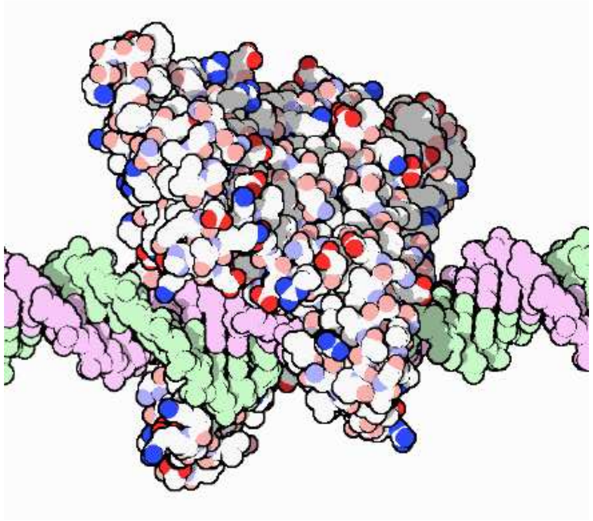
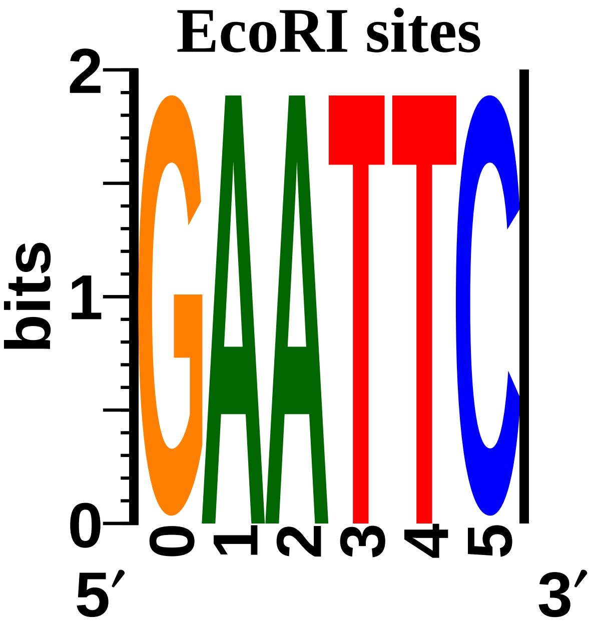


- EcoRI - restriction enzyme
- EcoRI binds DNA at $5'$ GAATTC $3'$
- $4^6 = 4096$ possible DNA hexamers
- information required:
  $\log_2 4096 = 12$ bits
  or
  6 bases $\times$ 2 bits per base $=$ $\boxed{\text{12 bits}}$



Energy Dissipation by EcoRI

- Measured specific binding constant:

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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

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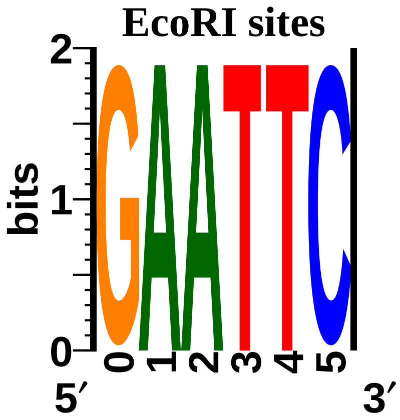
EcoRI could have made 17.3 binary choices
. . . but it only made 12 choices.



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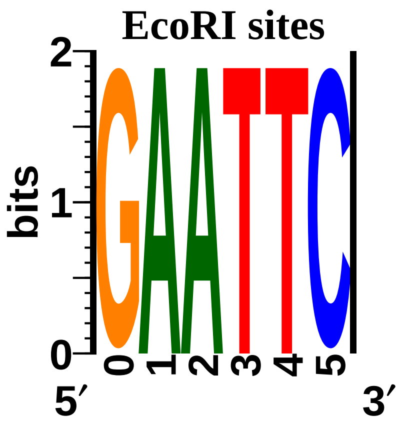
‘WORK’ DONE / ENERGY DISSIPATED



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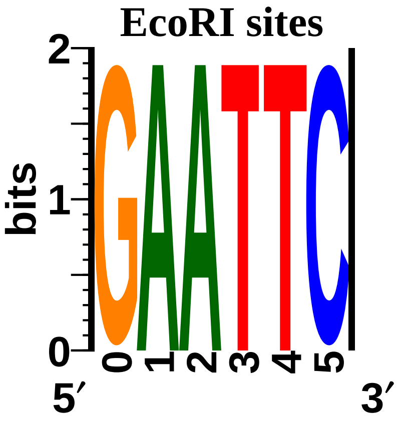

Efficiency is
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$$\frac{12 \text{ bits per binding}}{17.3 \text{ bits per binding}} = 0.7$$

Information/Energy = Efficiency of EcoRI = 70%

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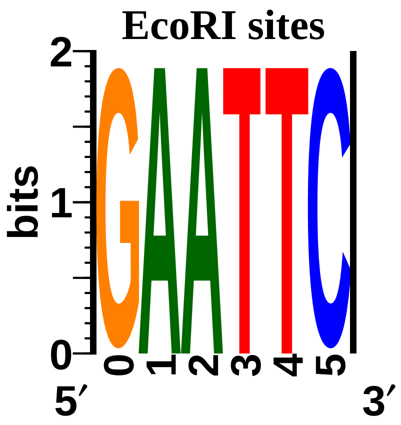

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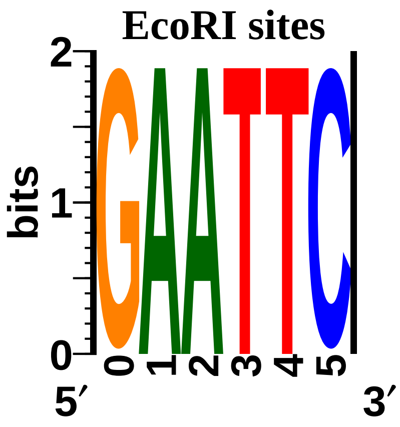

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18 out of 19 DNA binding proteins give ∼70% efficiency.

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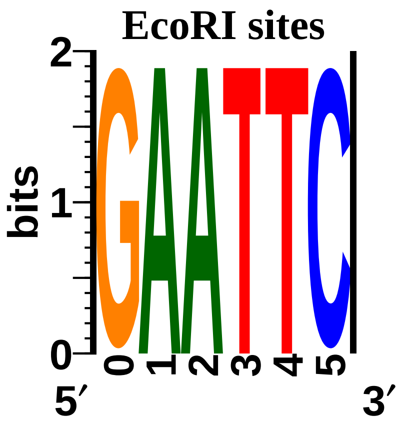

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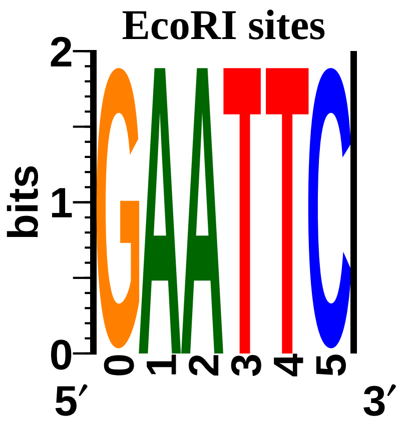

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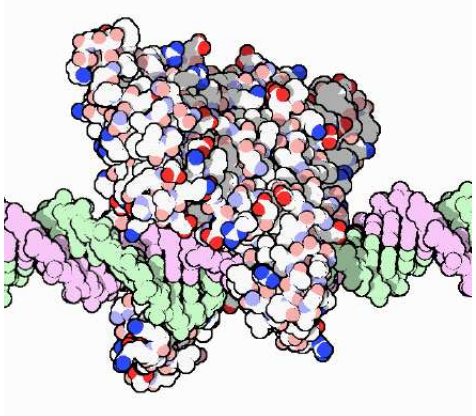
Why 70% efficiency?

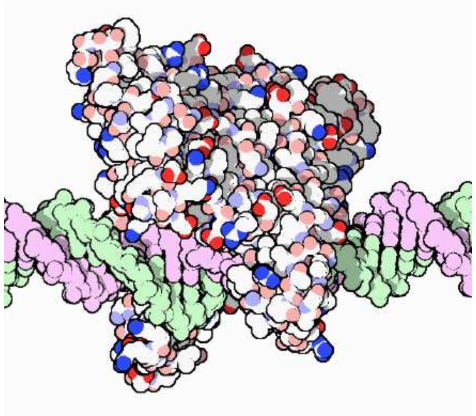
Theoretical Efficiency



- 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



- 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

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

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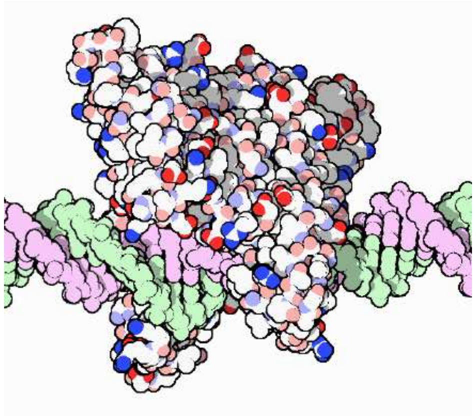

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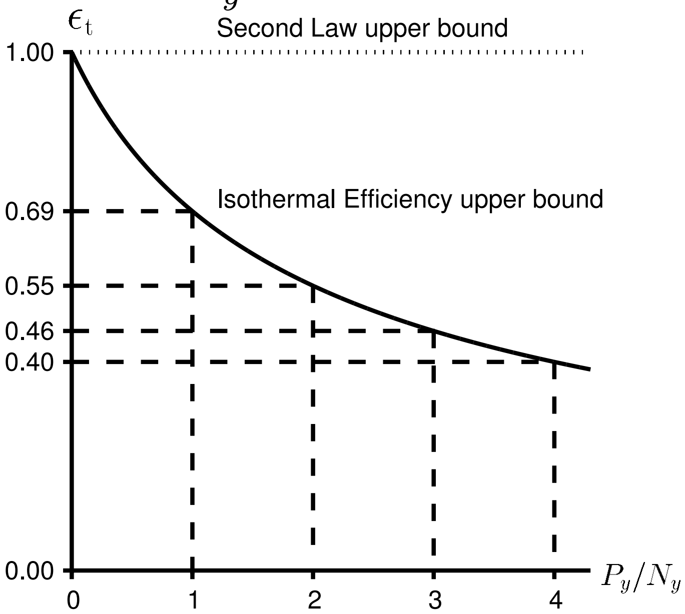
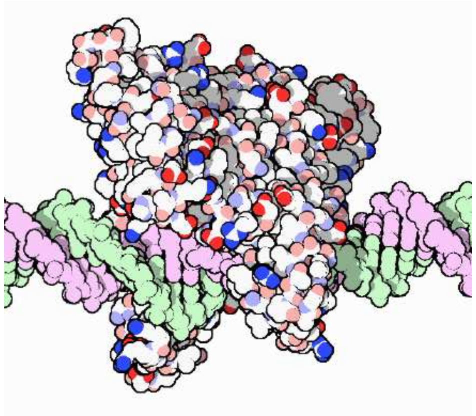


The curve is an upper bound

Theoretical Efficiency



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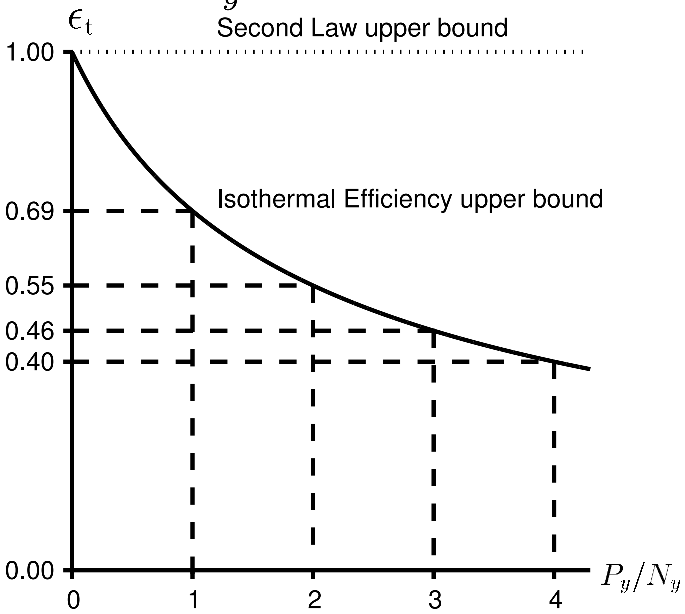
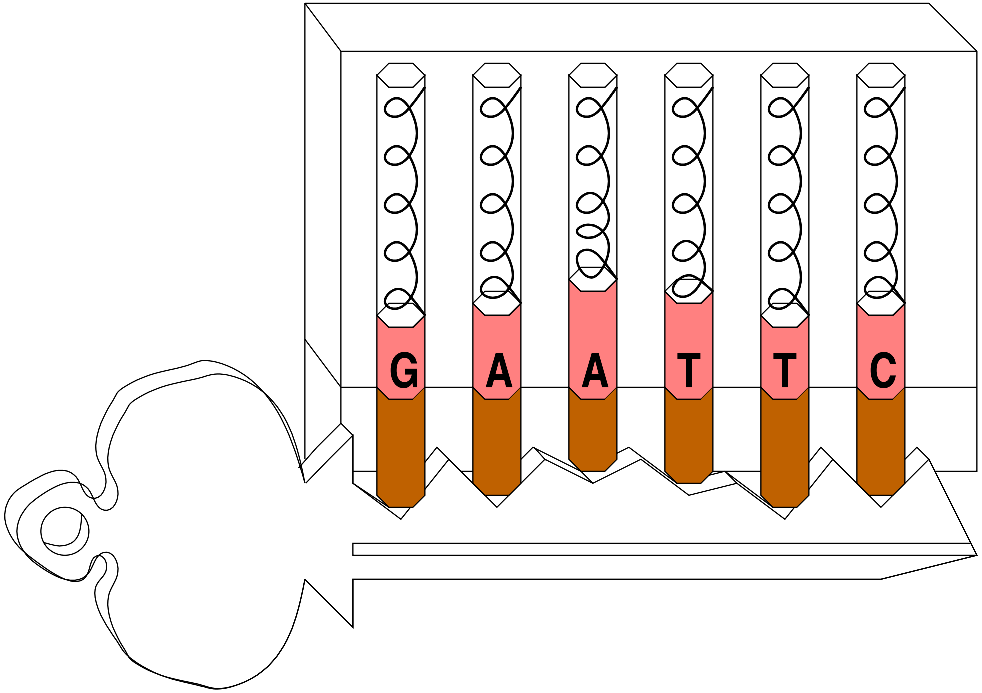


The curve is an upper bound

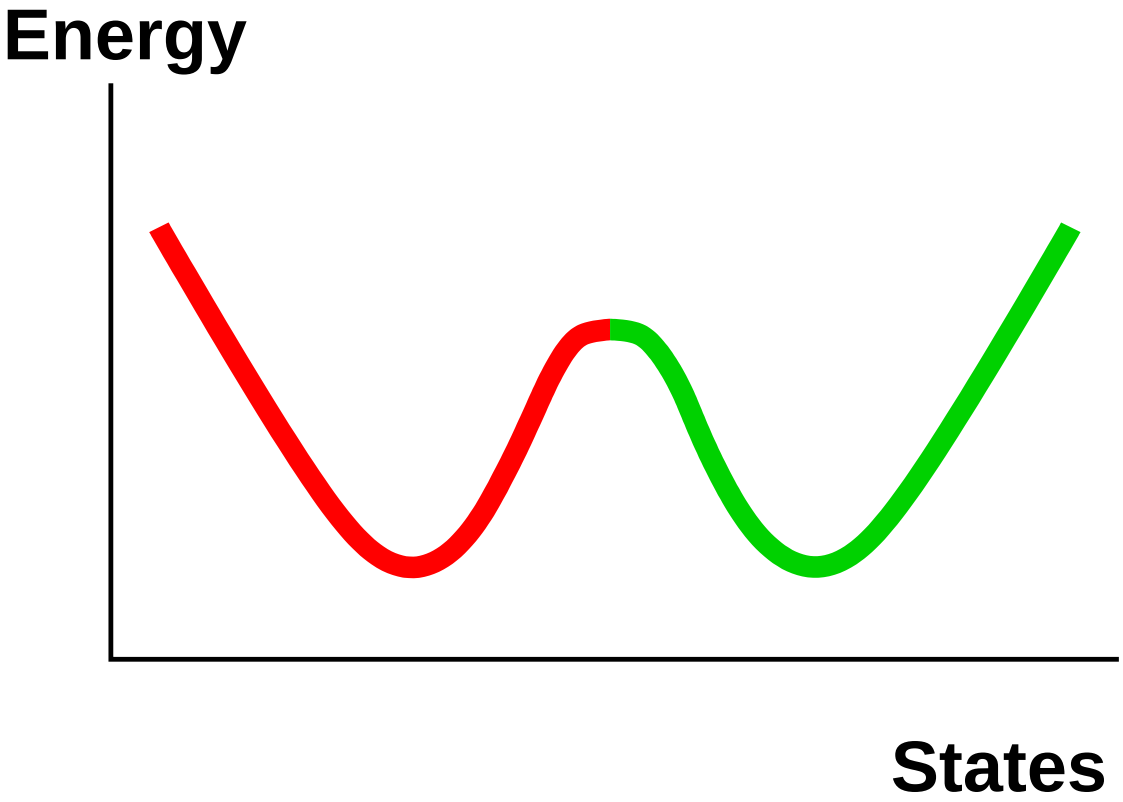
- $\boxed{\text{If } P_y/N_y = 1 \text{ the efficiency is 70\%!}}$

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

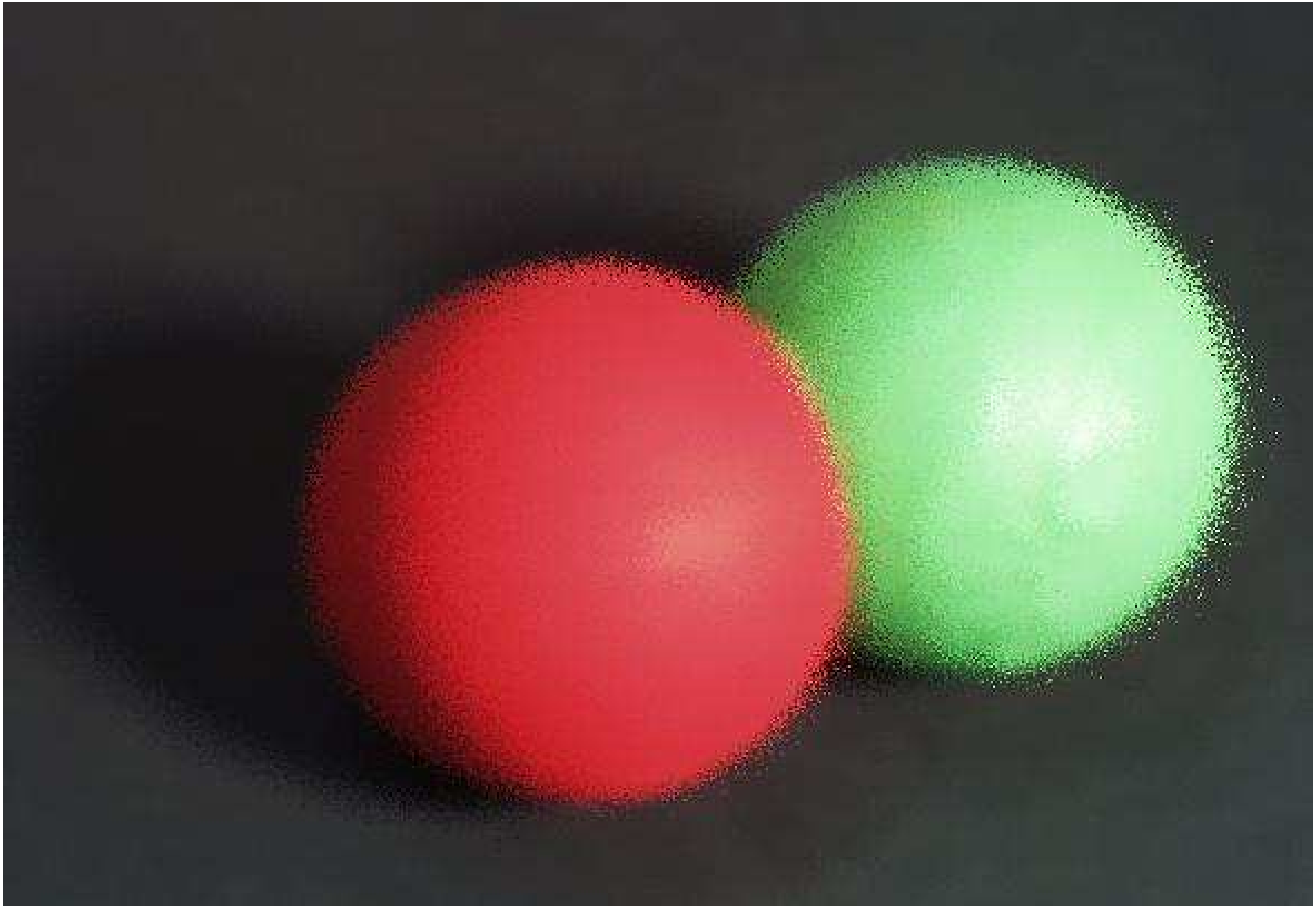
1 Dimension



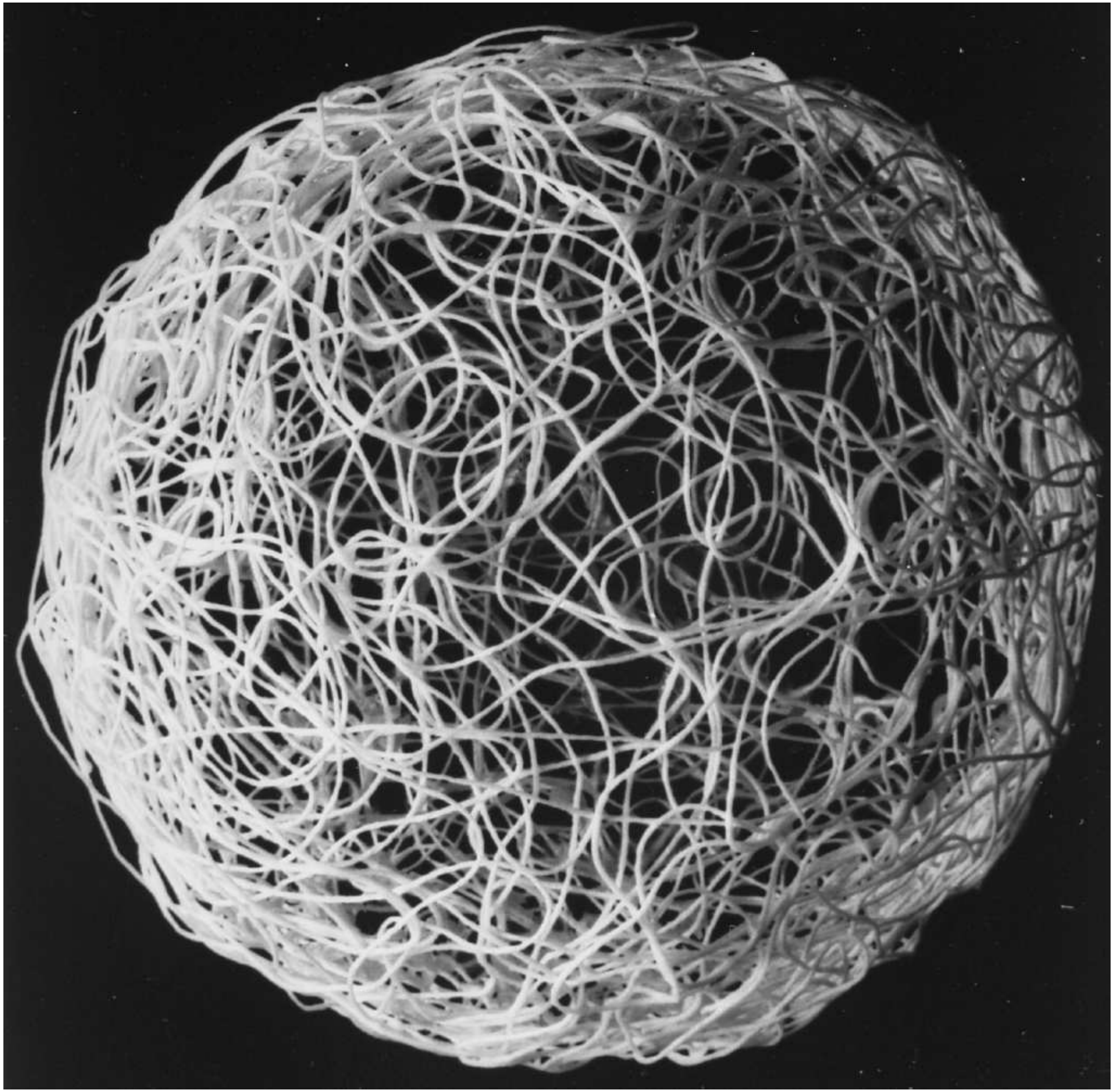
1 dimension is too simple!

Bowls in 2 Dimensions

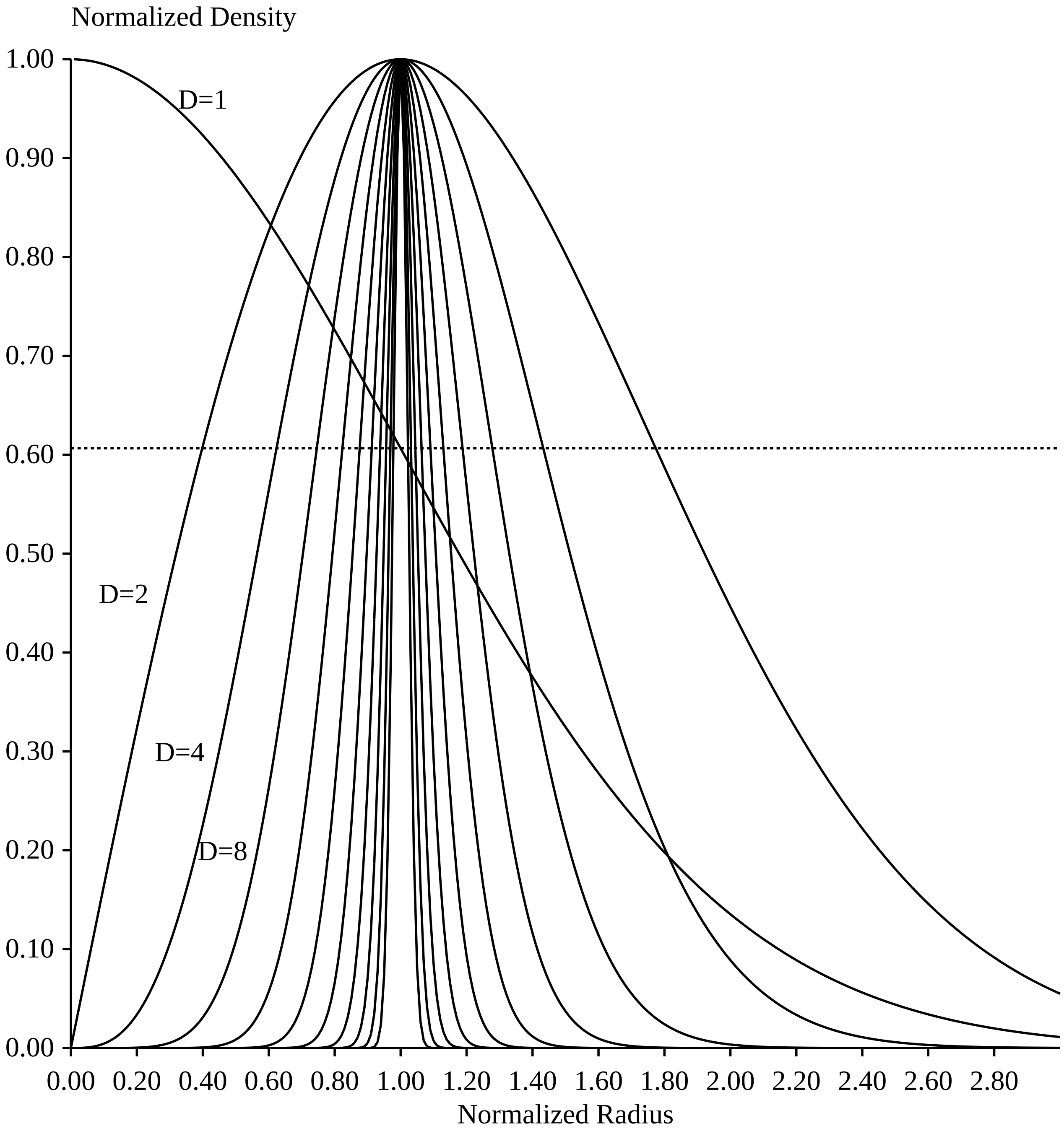
Spheres in 3 Dimensions



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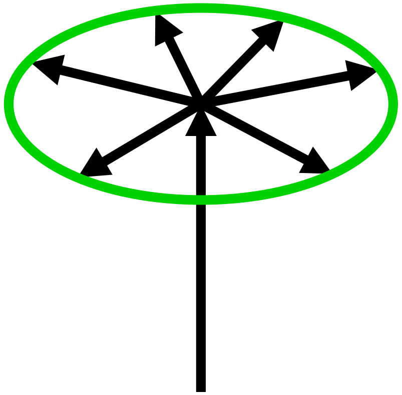
$$\text{maximum velocity} \propto \sqrt{\text{N}}$$

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

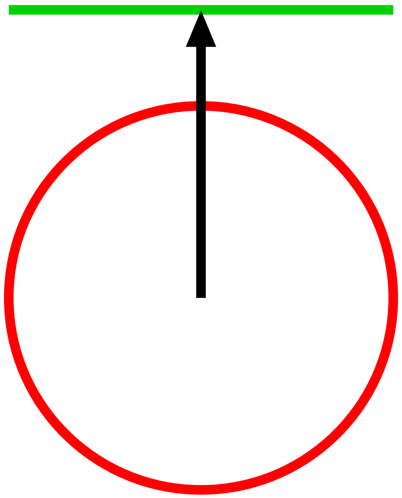
Sphere Packing

hyperdirection



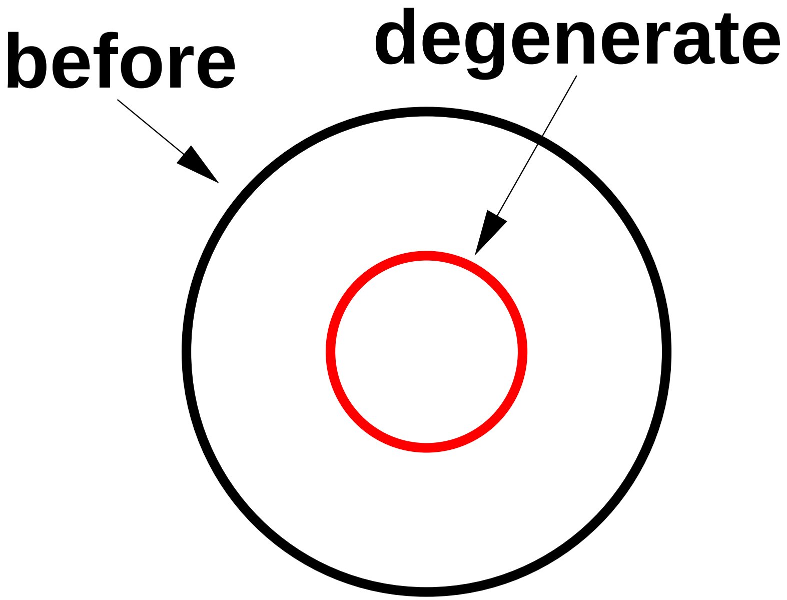
In 100 dimensions
99% of the thermal noise
is at right angles
to a given direction!

two



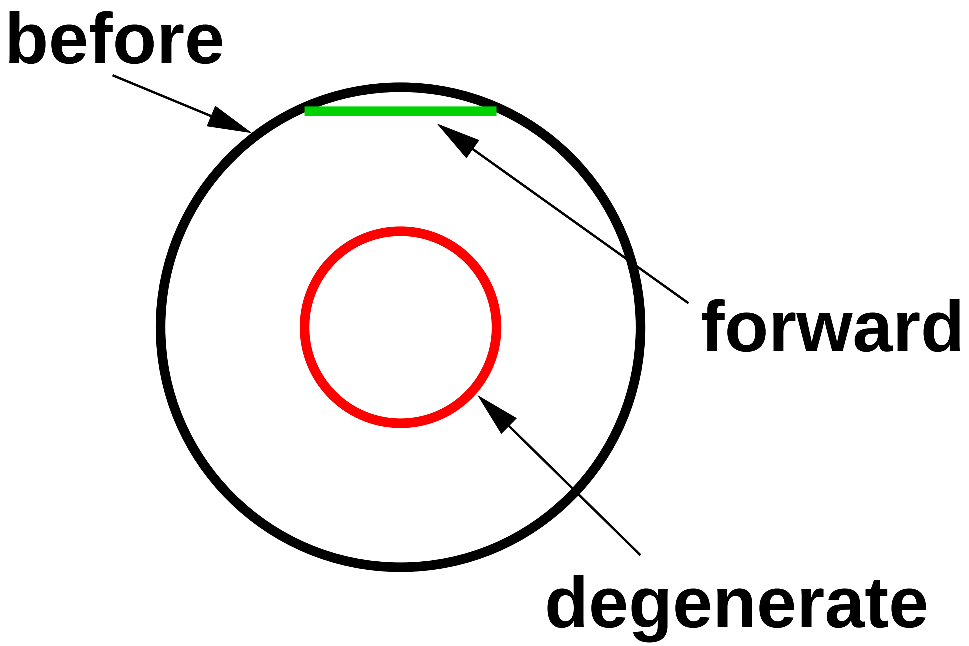
Two spheres in high dimensional space

degenerate



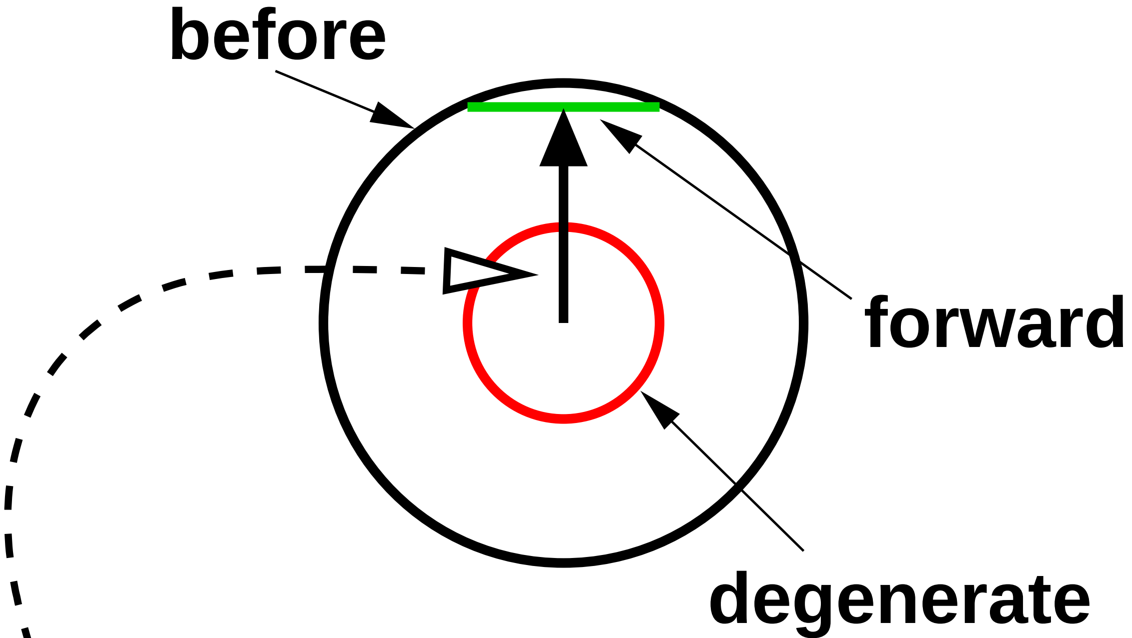
Hypothesis:
there is a sphere
in the middle
of the before sphere

forward



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

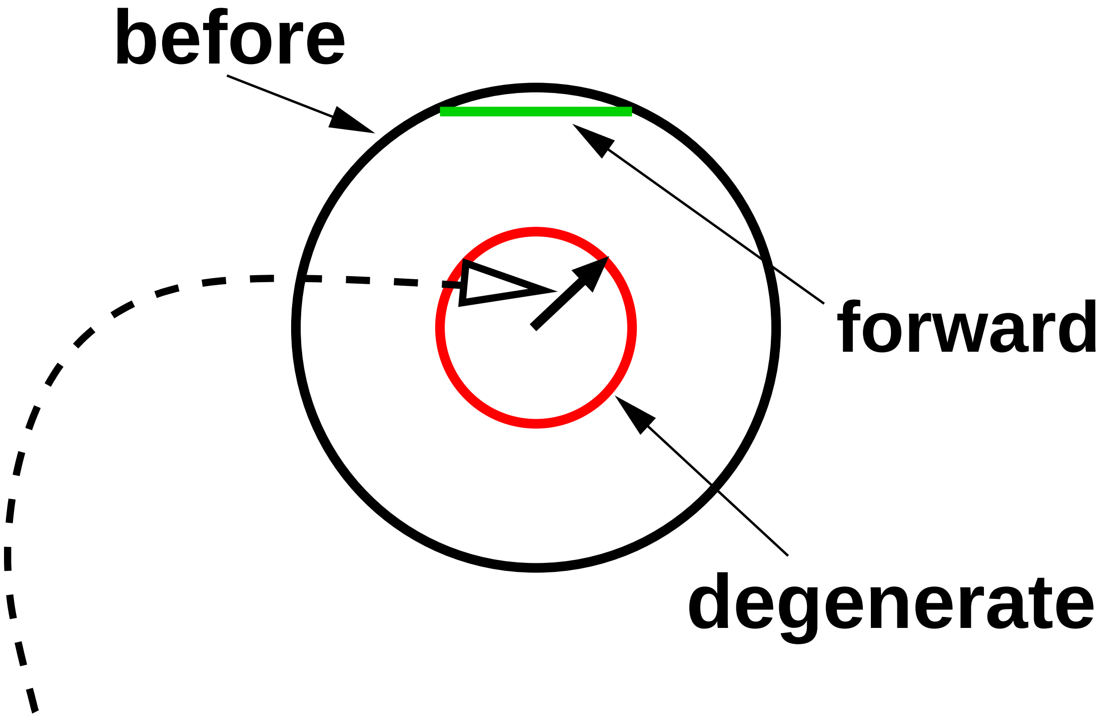
power



Power = energy dissipated = velocity^2

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

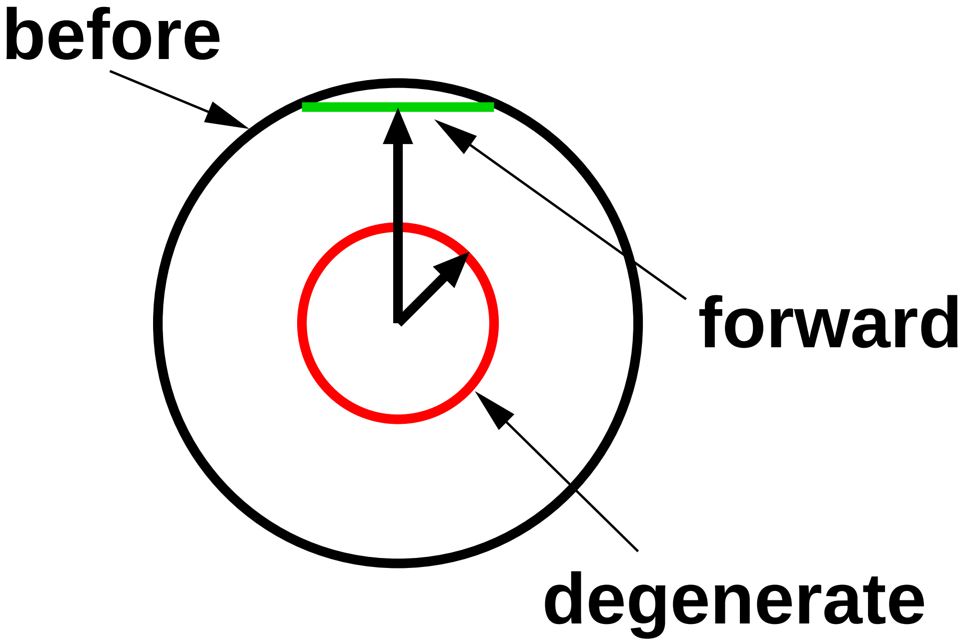
noise



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

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

criterion

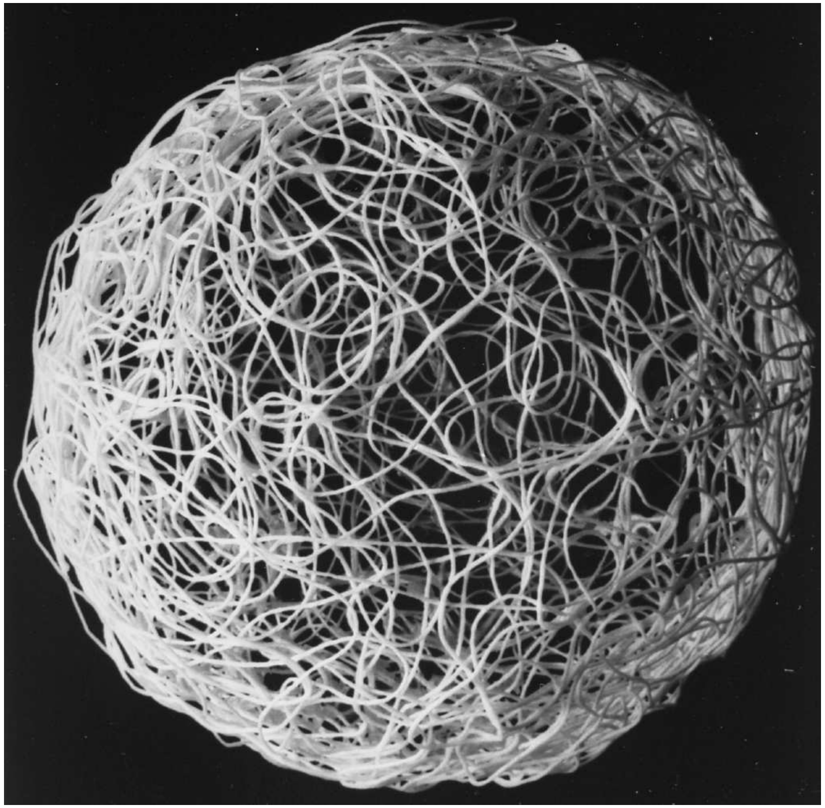


Criterion for distinct states:
forward does not touch degenerate

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

N Dimensional Sphere Separation

Degenerate Sphere



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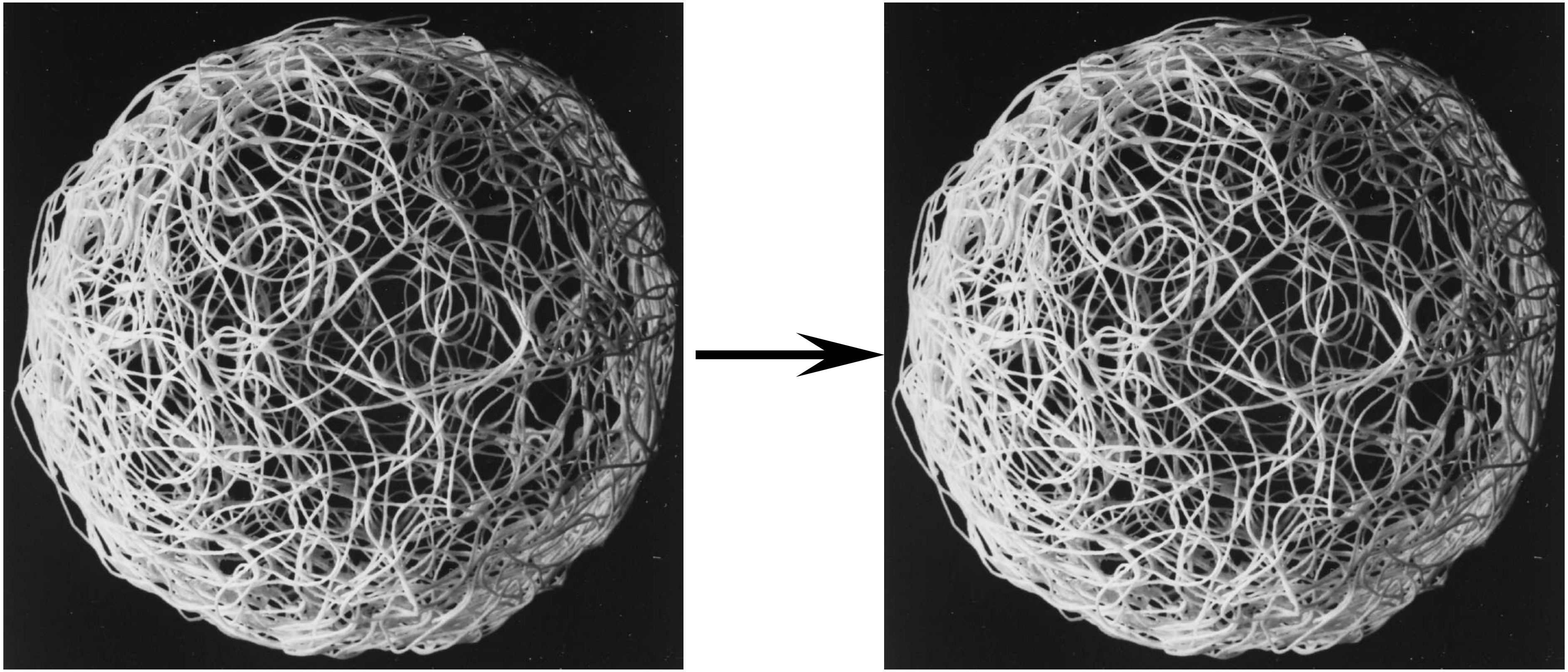

Degenerate Sphere

Forward Sphere

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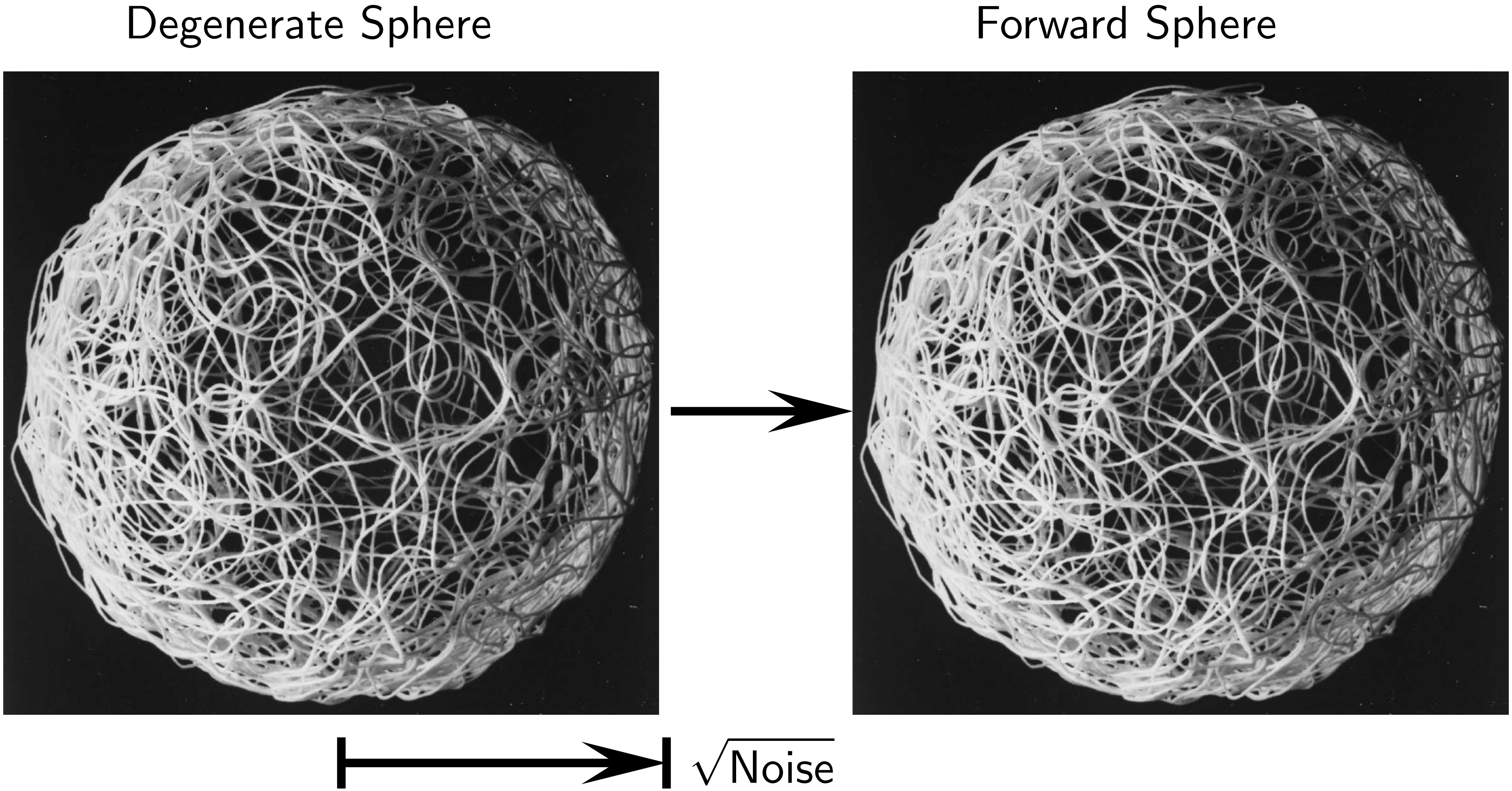

Degenerate Sphere

Forward Sphere

$\sqrt{\text{Noise}}$

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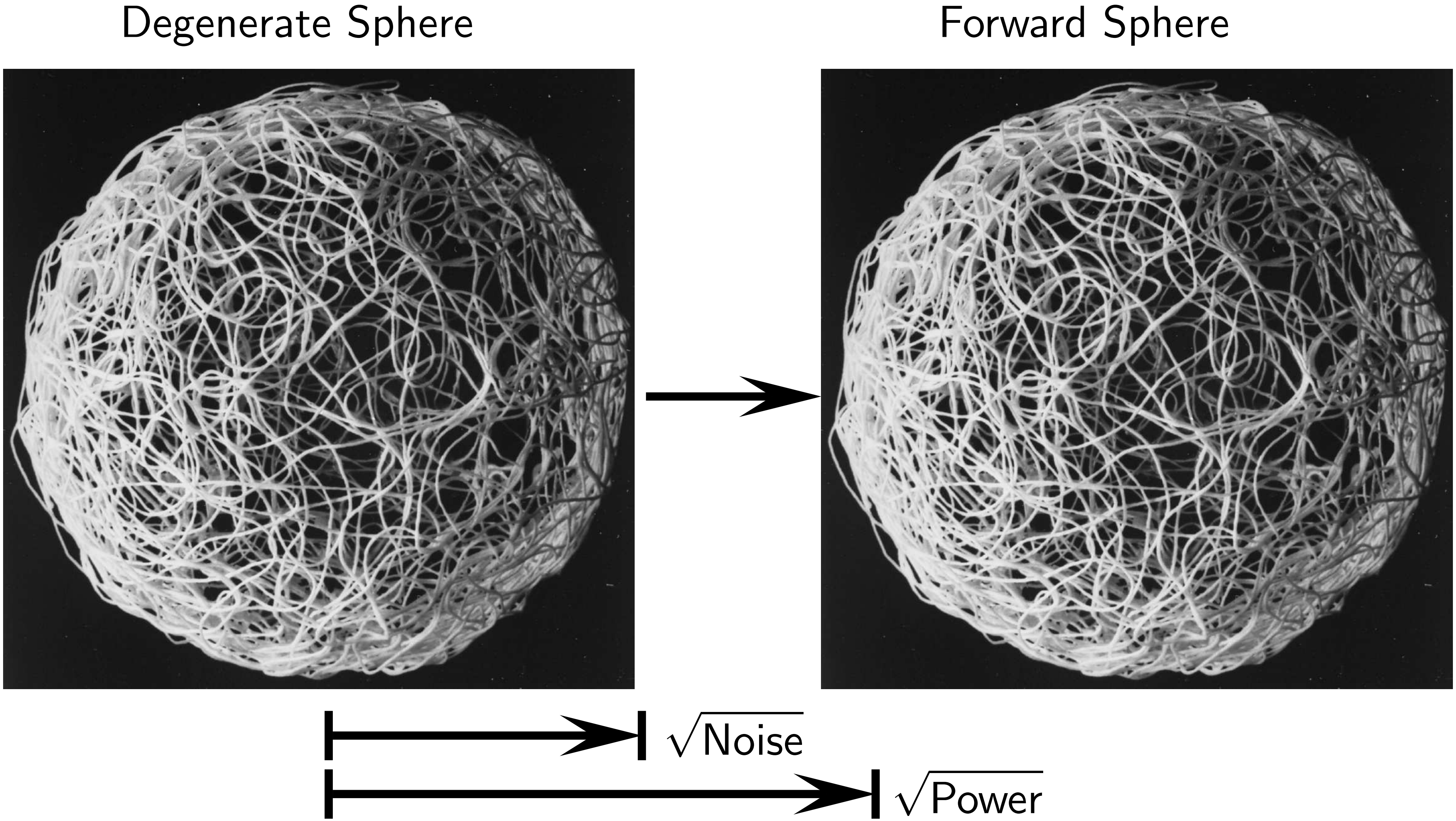

Degenerate Sphere

Forward Sphere

$\sqrt{\text{Noise}}$

$\sqrt{\text{Power}}$

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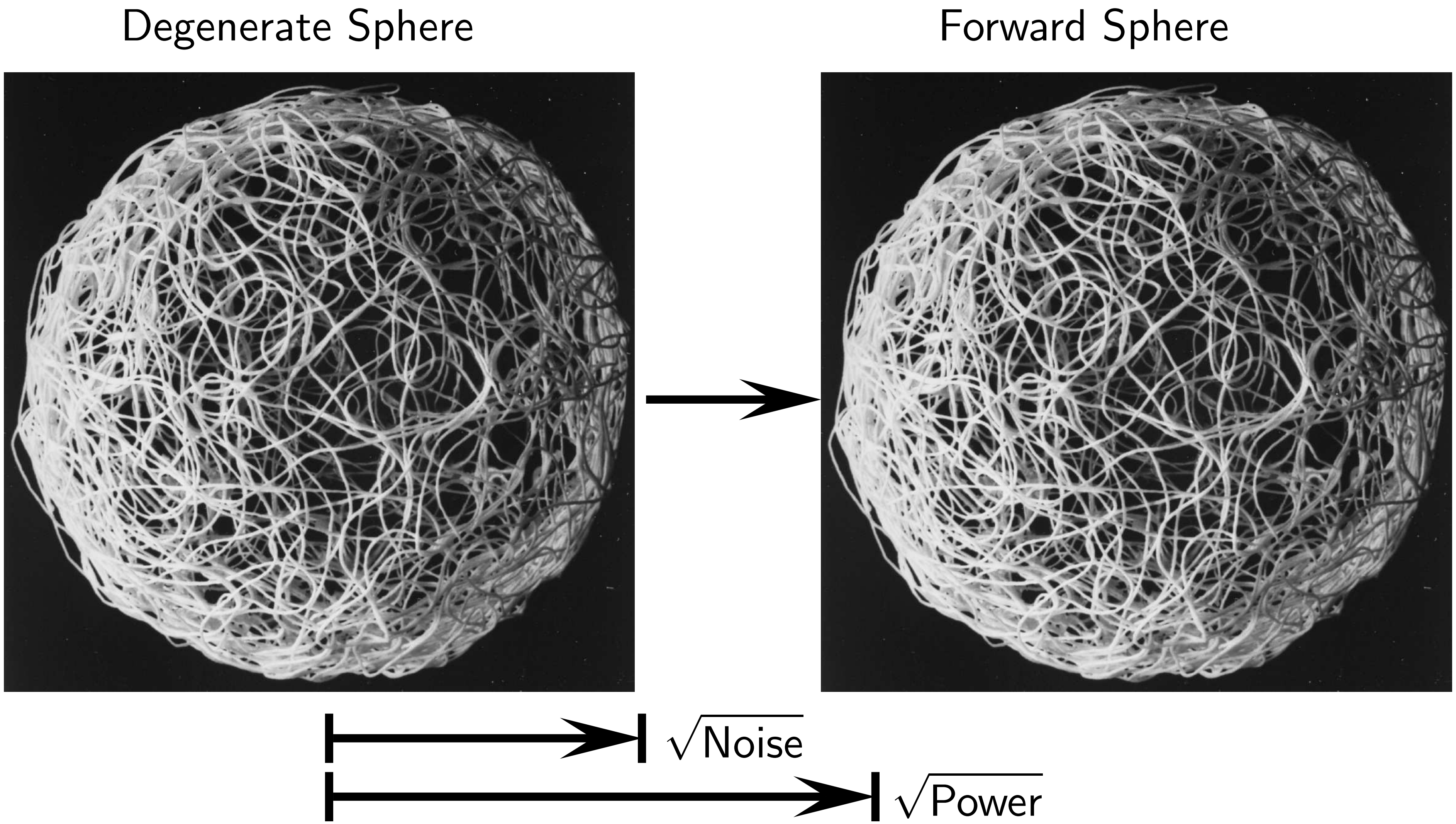

Degenerate Sphere

Forward Sphere

$\sqrt{\text{Noise}}$

$\sqrt{\text{Power}}$

Energy dissipated to escape the Degenerate Sphere must exceed the Noise

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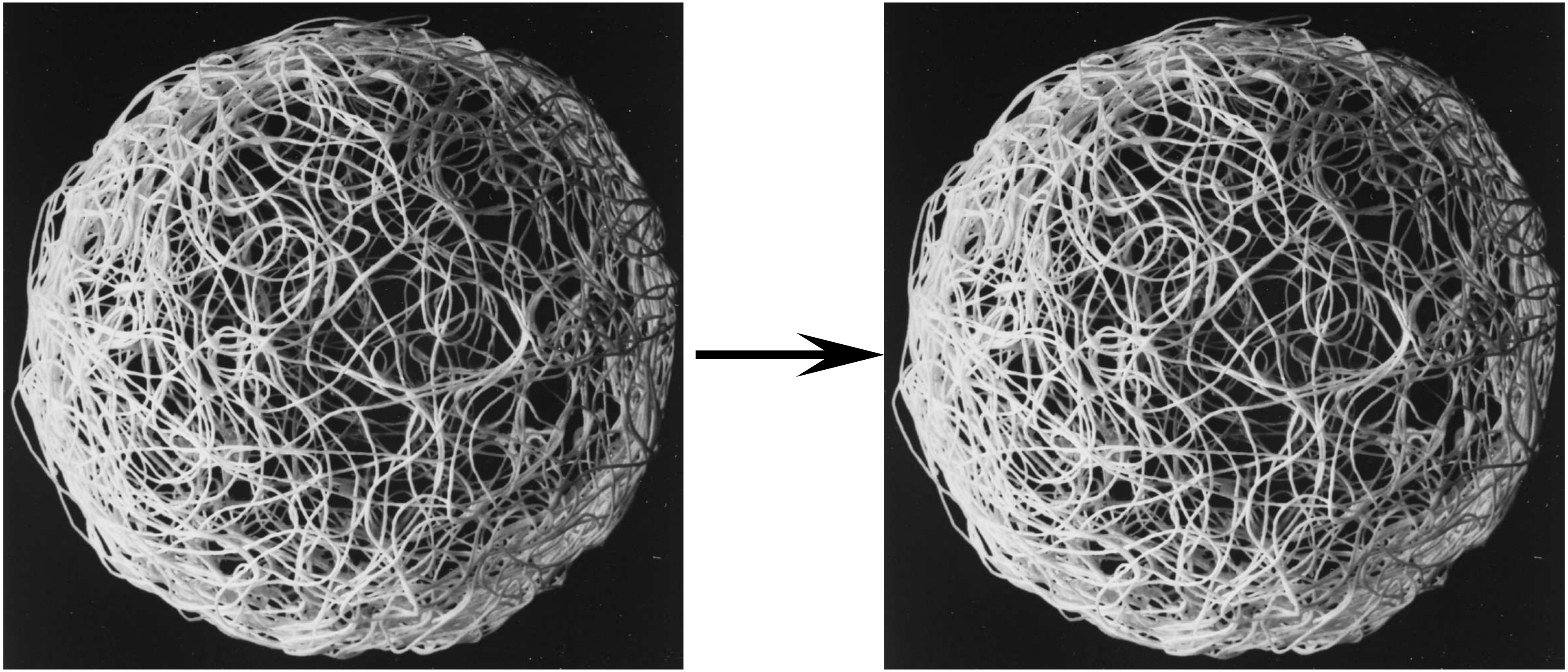

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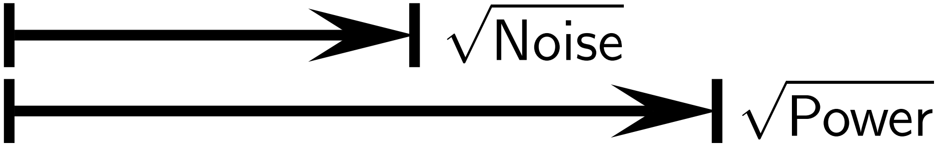

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$\sqrt{\text{Power}}$

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CONSEQUENCES OF THE DEGENERATE SPHERE HYPOTHESIS

The geometry gives:

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

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

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T. D. Schneider
Nucl. Acids Res. **2010**
doi: 10.1093/nar/gkq389

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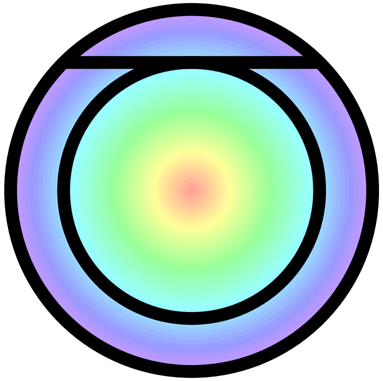

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Why is the Genetic Code Degenerate?

The Genetic Code

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

$\log_2 64 = 6$ bits/amino acid

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20 amino acids
$\log_2 20 = 4.3$ 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	91298299
C	15183770
D	59081152
E	67663968
F	42689961
G	72802737
H	23851938
I	61214309
K	57561410
L	104783181
M	24024396
N	46921121
O	5
P	53406141
Q	43463766
R	62295067
S	80237533
T	60736608
U	301
V	70111092
W	13441284
Y	32887204

Refine the Calculation

Obtain actual amino acid frequencies from the 50% sequence identity non-redundant Protein Information Resource (PIR) UniRef50 database, June 2010.

$n = 1{,}083{,}655{,}243 = 1.1 \times 10^9$ amino acids

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Compute the uncertainty:

$$\begin{aligned} H_{\text{aa}} &= -\sum_{\text{aa}\,=\,\text{A}}^{\text{Y}} P_{\text{aa}} \log_2 P_{\text{aa}} \quad \text{bits per amino acid} \\ &= 4.1706 \quad \text{bits per amino acid} \end{aligned}$$

That's what is actually accomplished by translation.

Translational Efficiency

Compute the efficiency:

$$\epsilon_r = \frac{4.1706}{6}$$

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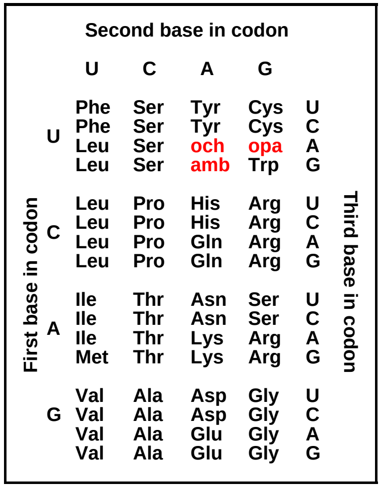

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Since this comes from > 1 billion amino acids, 0.2% excess is significant!

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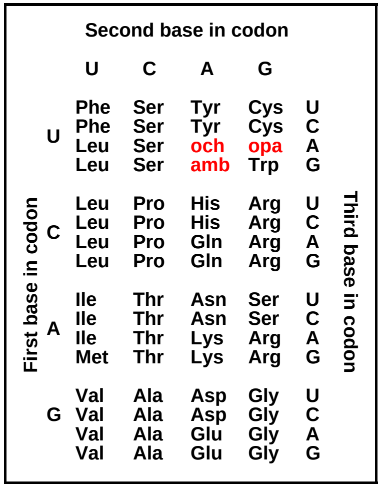

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	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
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Since this comes from > 1 billion amino acids, 0.2% excess is significant!

What's Missing?

- Rare amino acids don't contribute much.

Translational Efficiency

Compute the efficiency:

$$\begin{aligned}
\epsilon_r &= \frac{4.1706}{6} \\
&= 0.6951 \text{ Measured efficiency} \\
\epsilon_t &= 0.6931 \text{ Theoretical maximum} = \ln(2) \\
& \ 0.0020 \text{ difference}
\end{aligned}$$

	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
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- Removing the stop codons reduces the maximum from 6 bits to $\log_2 61 = 5.9307$ bits and the efficiency would be $4.1706/5.9307 = 0.7032$,
  so this makes the situation worse and does not explain the discrepancy.

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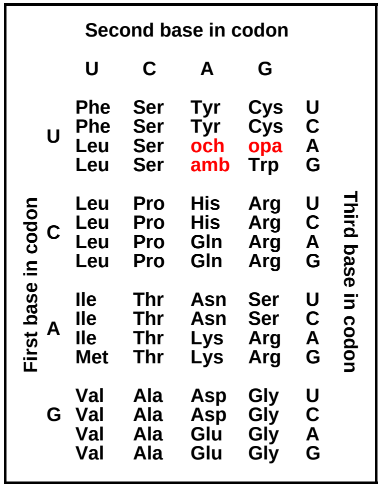

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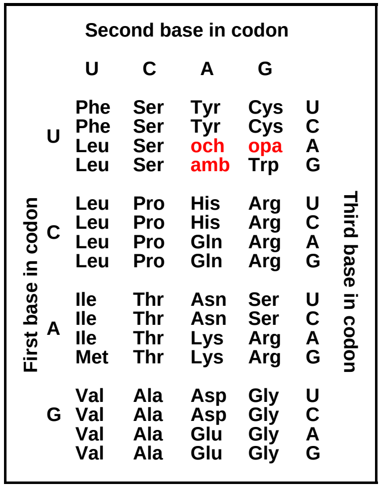
Efficiency of the Genetic Code

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



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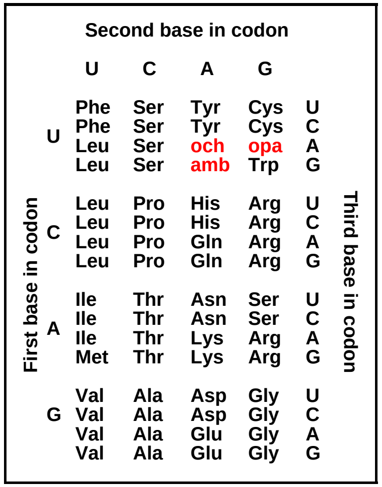

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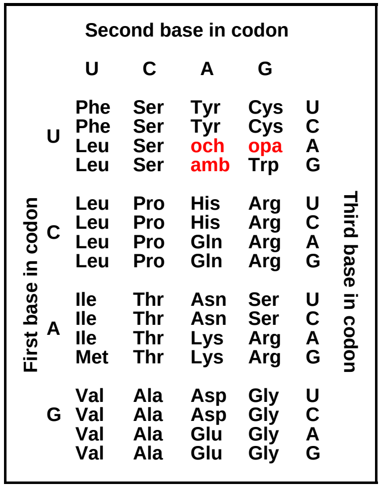

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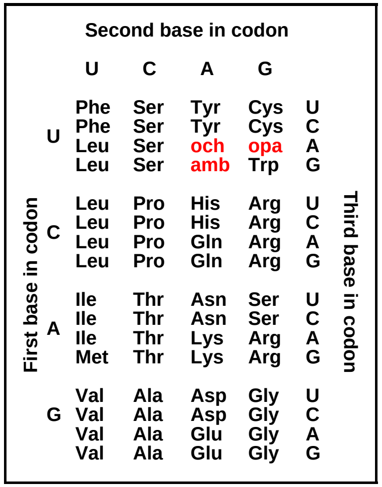

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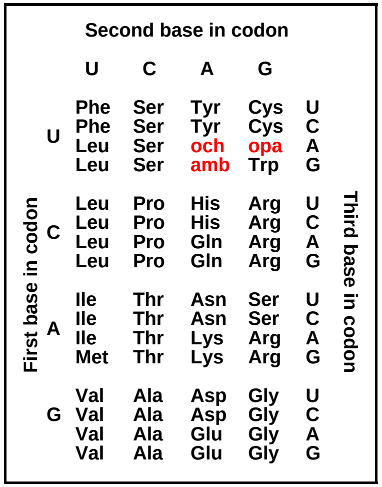

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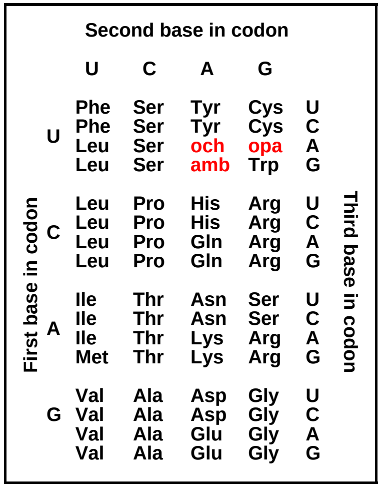

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The theory correctly predicts the error rate of translation

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Combine:
frequencies of 1 billion amino acids

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Efficiency of the Genetic Code

Combine:
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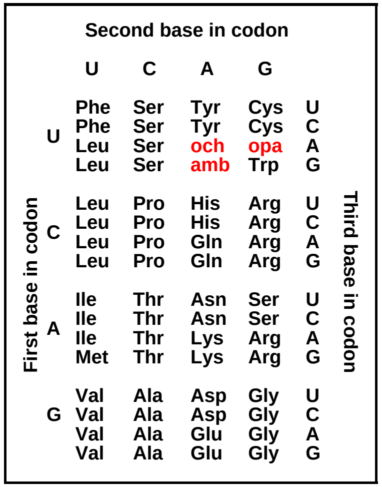

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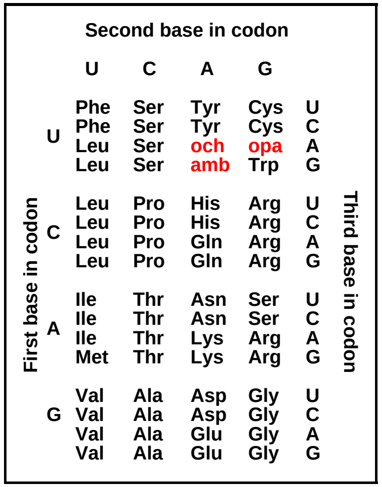

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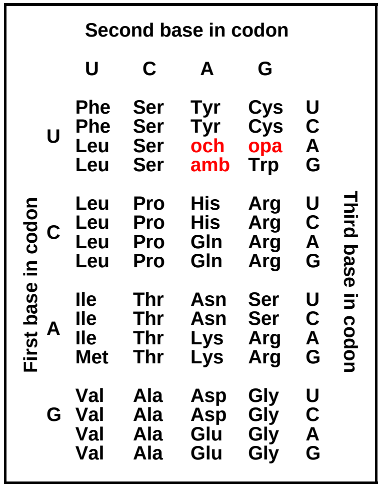
$$(H_{aa} - H(P_{\text{error}}))/6 \;=\; 0.69319588 = \text{ measured efficiency}$$

Efficiency of the Genetic Code



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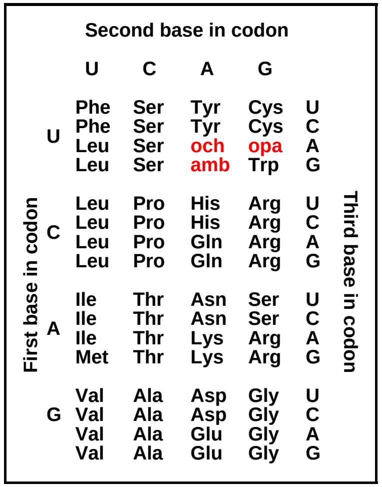
Efficiency of the Genetic Code



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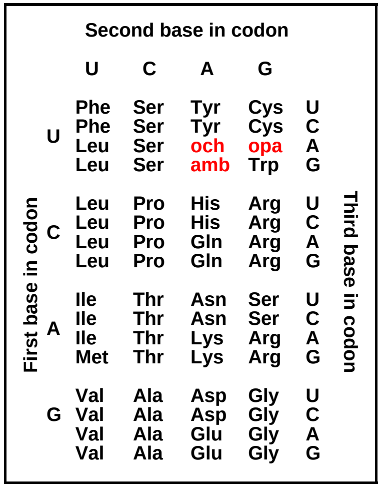
Efficiency of the Genetic Code



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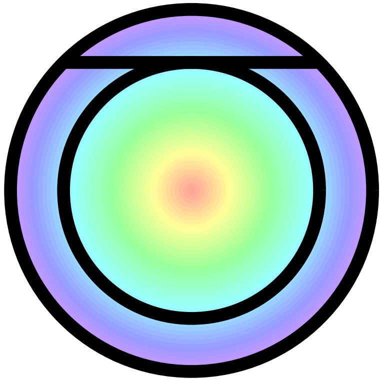
The theory matches the data to 4 decimal places!

Significance of 70% efficiency



- Establishes a novel mathematical field of biology

Significance of 70% efficiency

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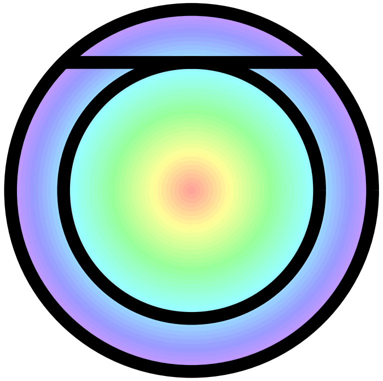
Significance of 70% efficiency



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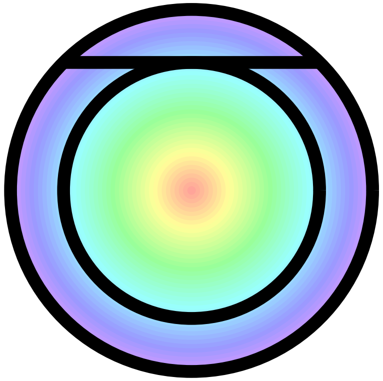

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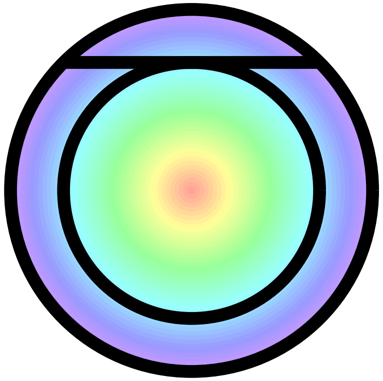

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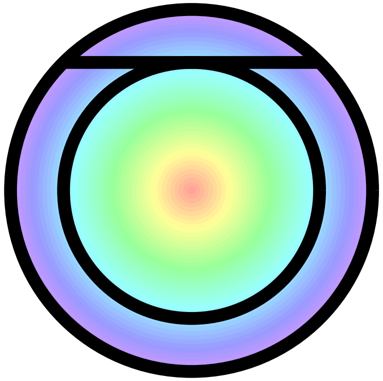

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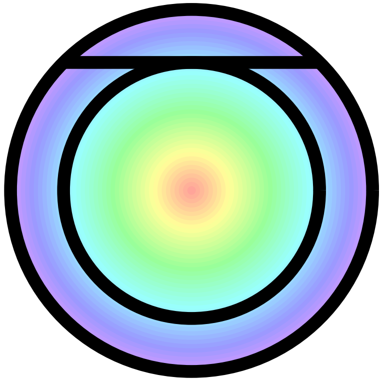

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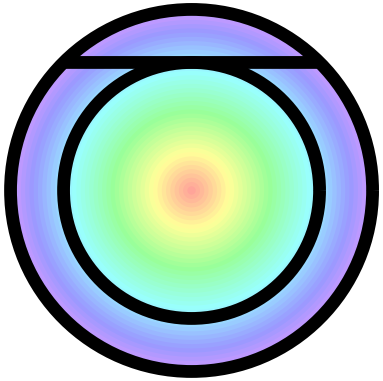

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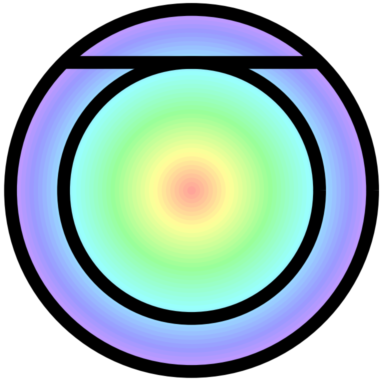

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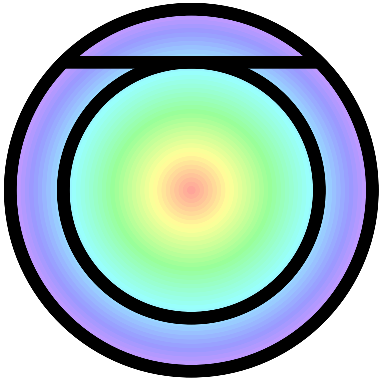
Significance of 70% efficiency



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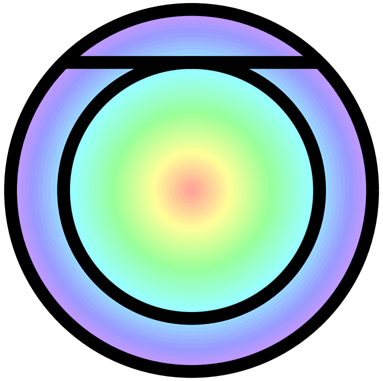

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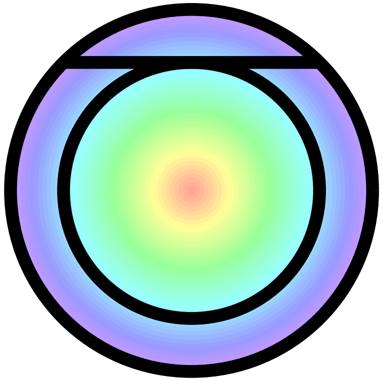

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Acknowledgments

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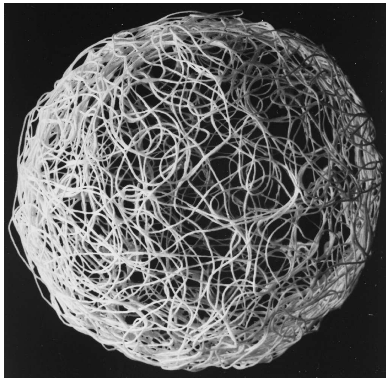
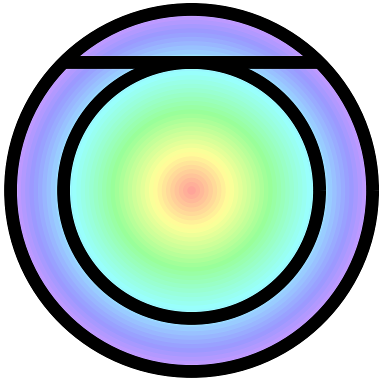
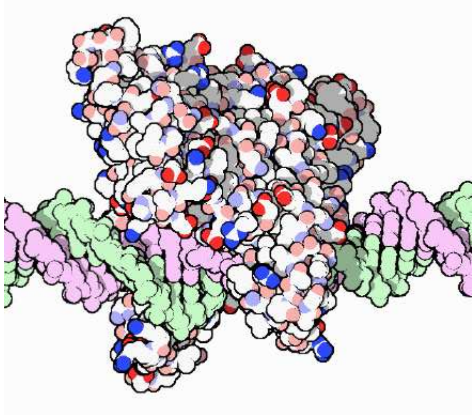
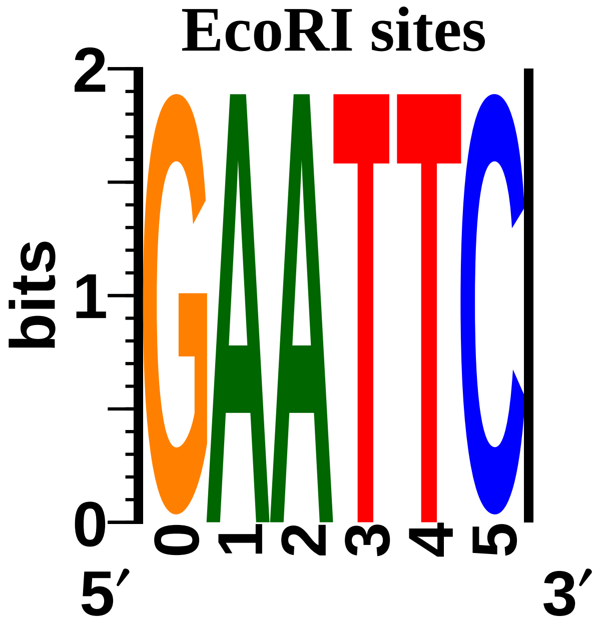
National Institutes of Health, National Cancer Institute

Web site:
TinyURL.com/tomschneider









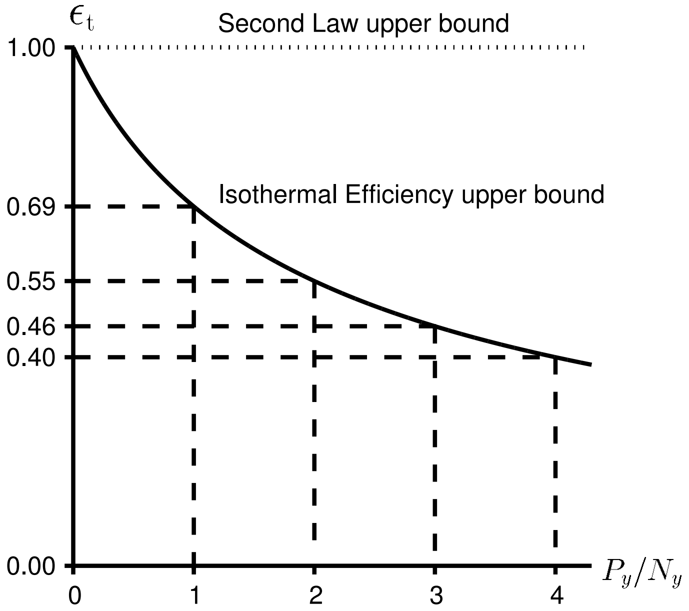
Second base in codon

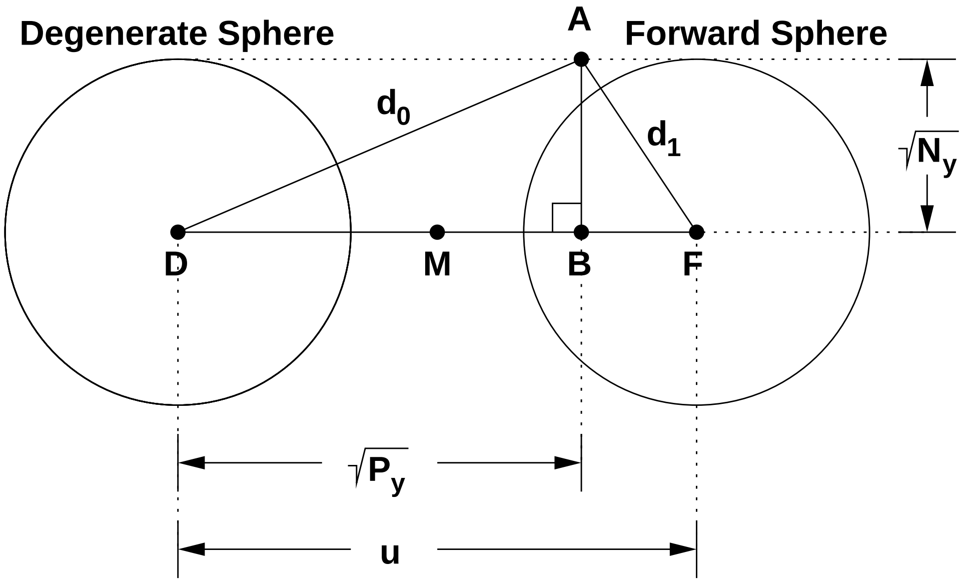
First base in codon	U	C	A	G	Third base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	och	opa	A
	Leu	Ser	amb	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val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

Version

version $=$ 1.37 of hidimtalk.tex 2010 Aug 05

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





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

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

distance^2 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:

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

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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

$\boxed{\text{EXAMPLE}}$

A phone rings once every 1024 seconds.

$$P_{\text{ring}} = 1/1024 \tag{8}$$

$$P_{\text{silent}} = 1023/1024 \tag{9}$$

More Information Theory - 2

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Information is a decrease in uncertainty

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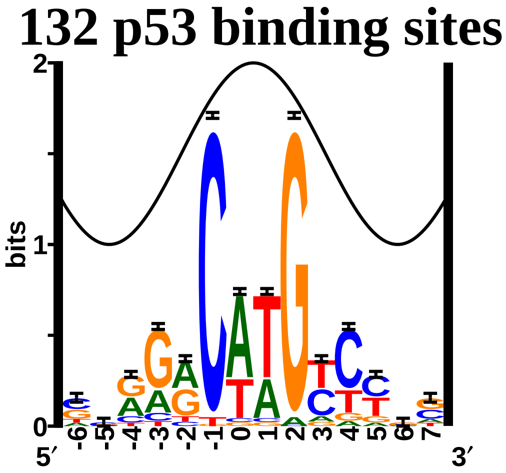
132 p53 binding sites

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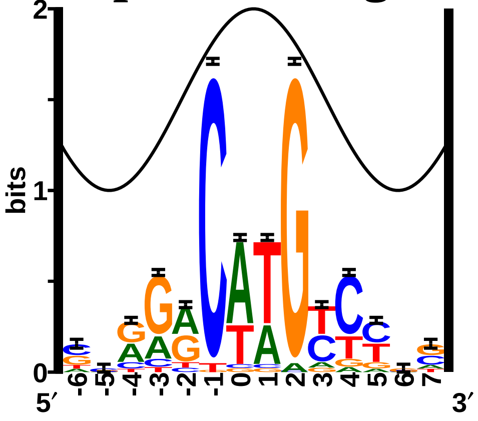

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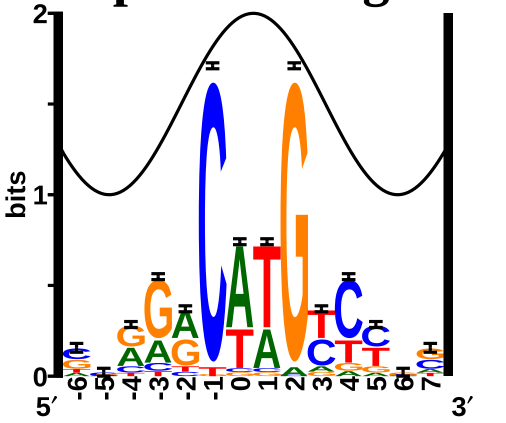
Note: with only one base, $H_{\textsf{after}} = 0$
so $R = 2$ bits/base.

132 p53 binding sites



Predicting splicing mutations using information theory

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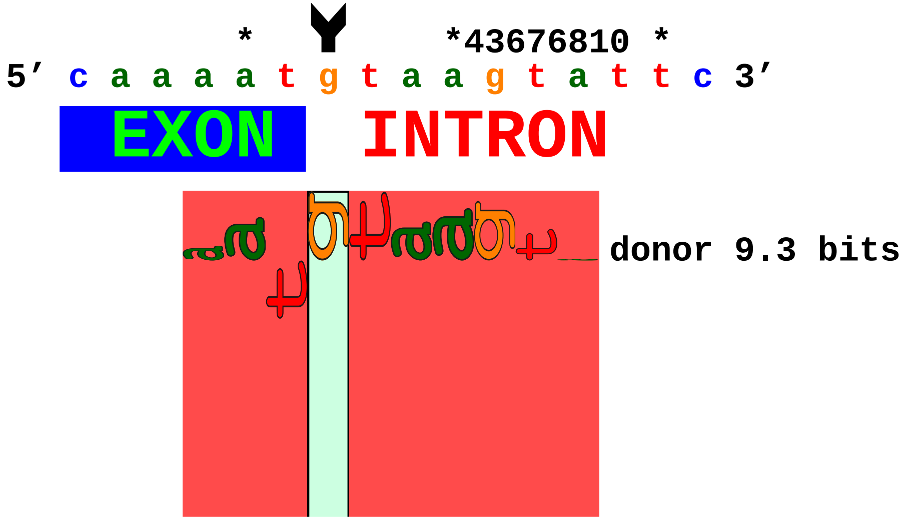

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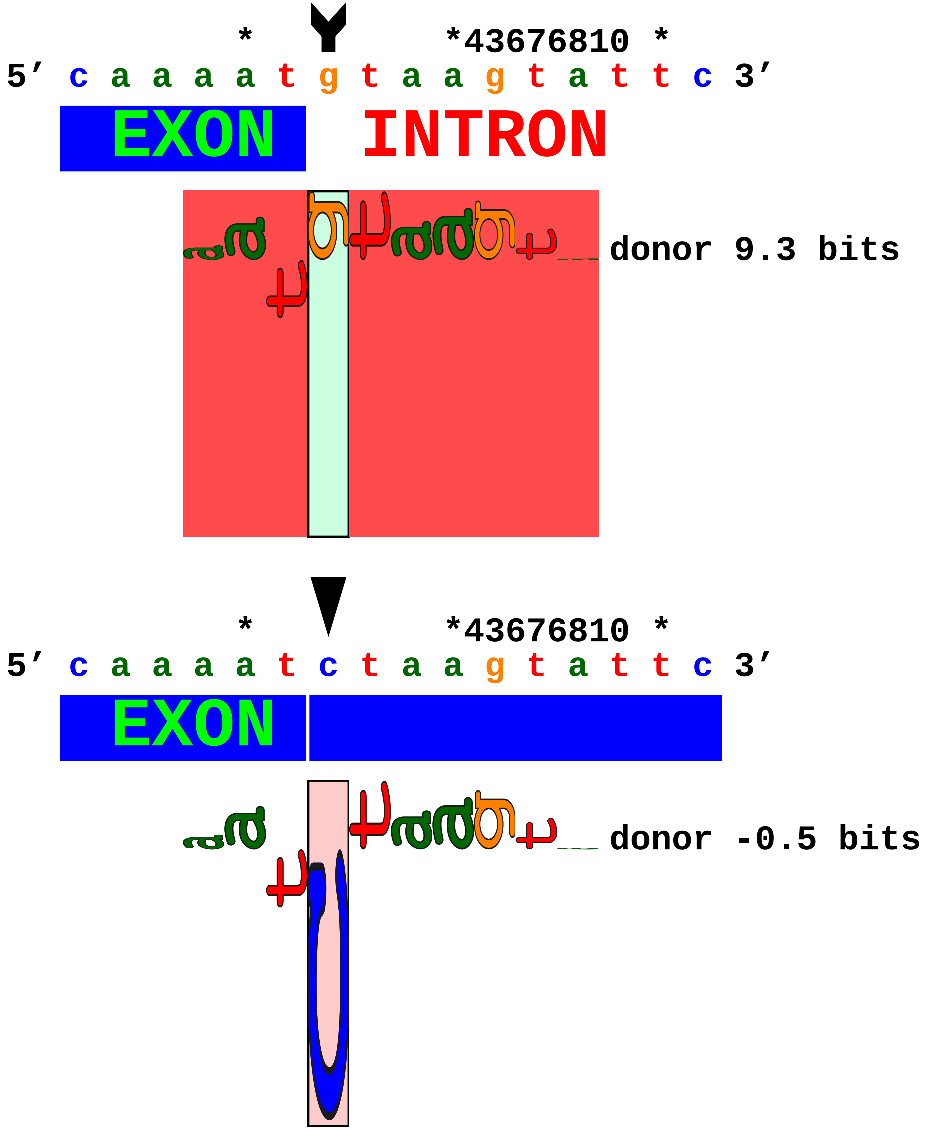

*
*43676810 *
5′ c a a a a t g t a a g t a t t c 3′
EXON
INTRON
donor 9.3 bits
*
*43676810 *
5′ c a a a a t c t a a g t a t t c 3′
EXON
donor -0.5 bits

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

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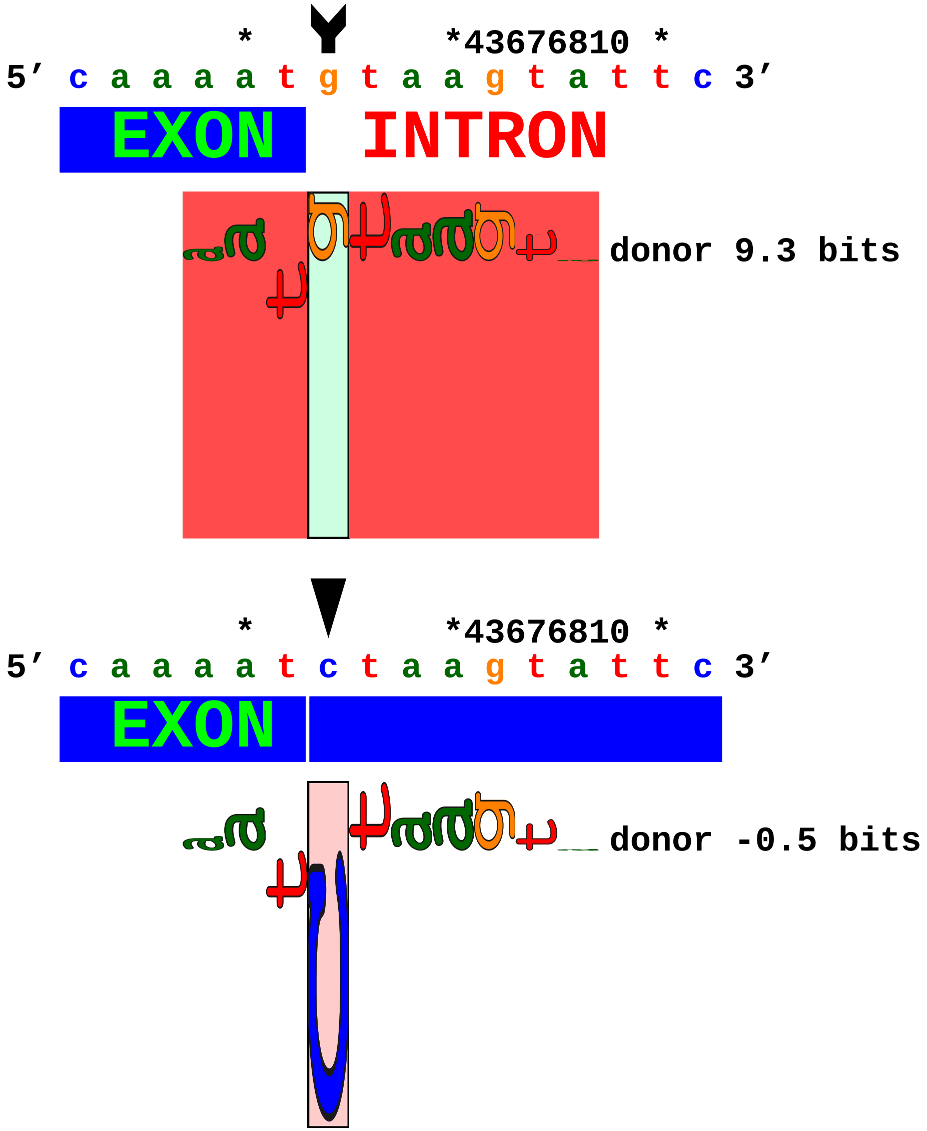
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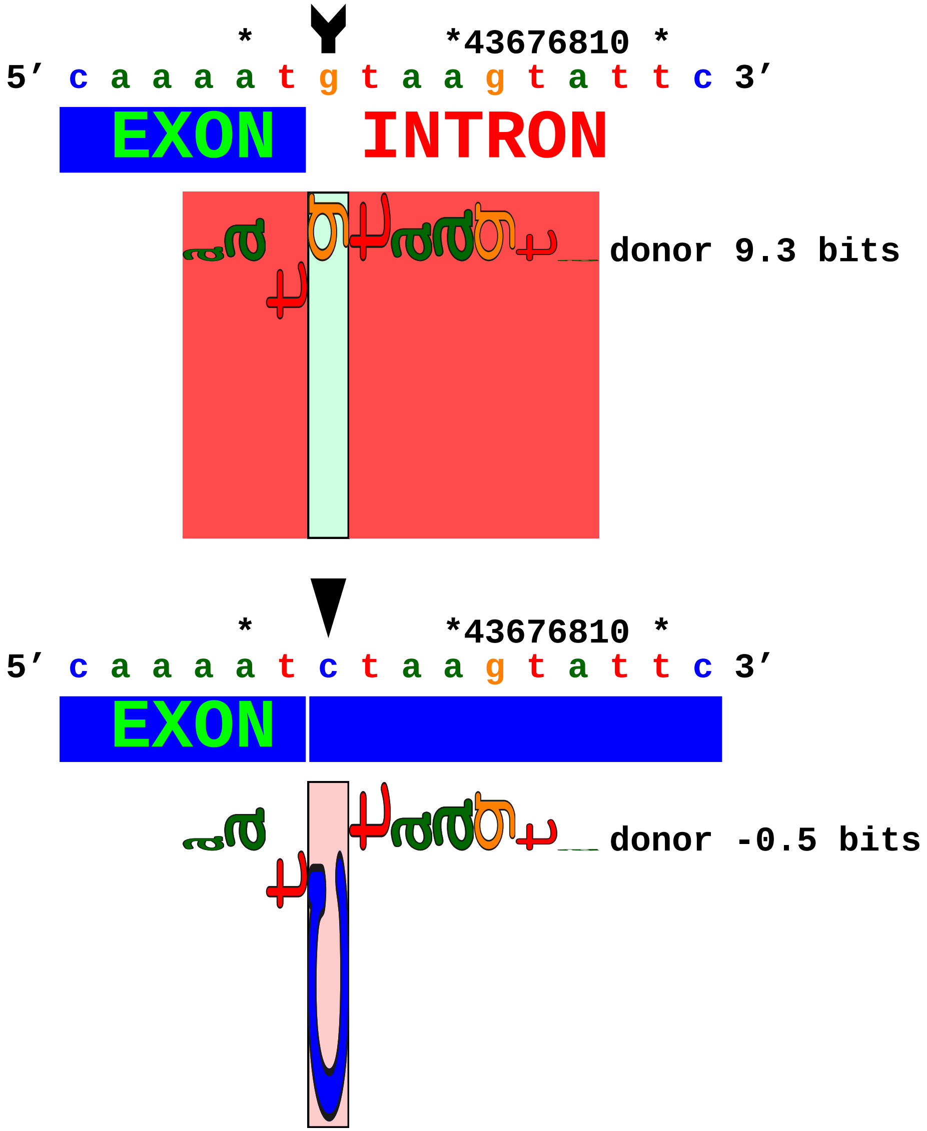
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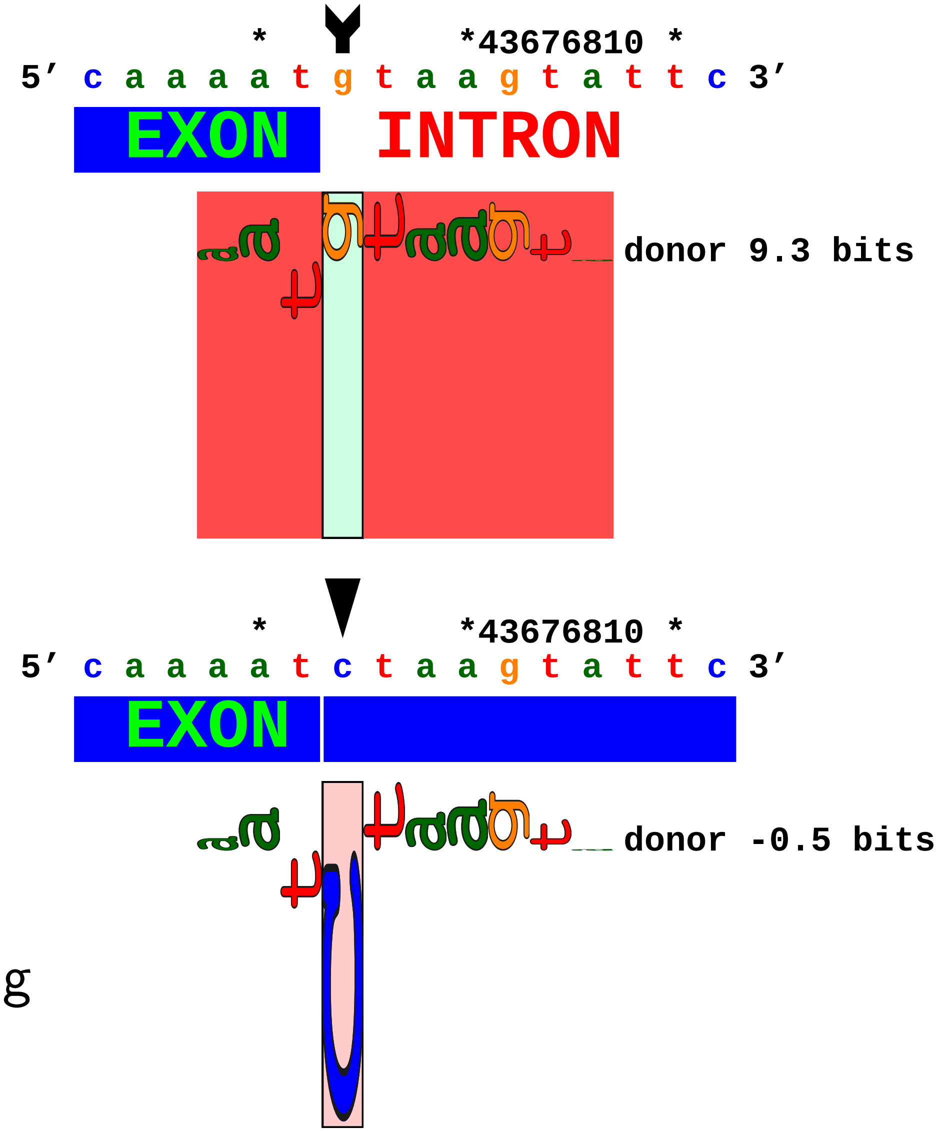
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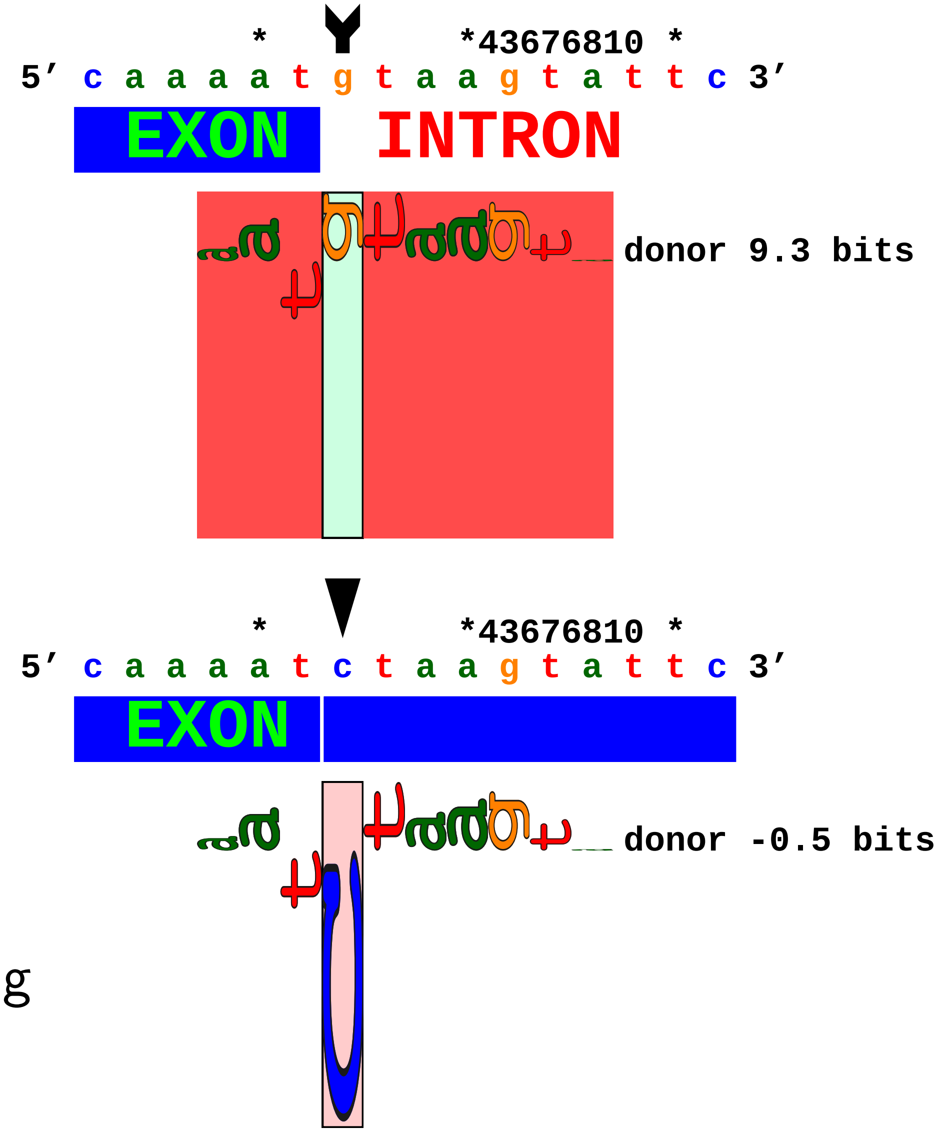

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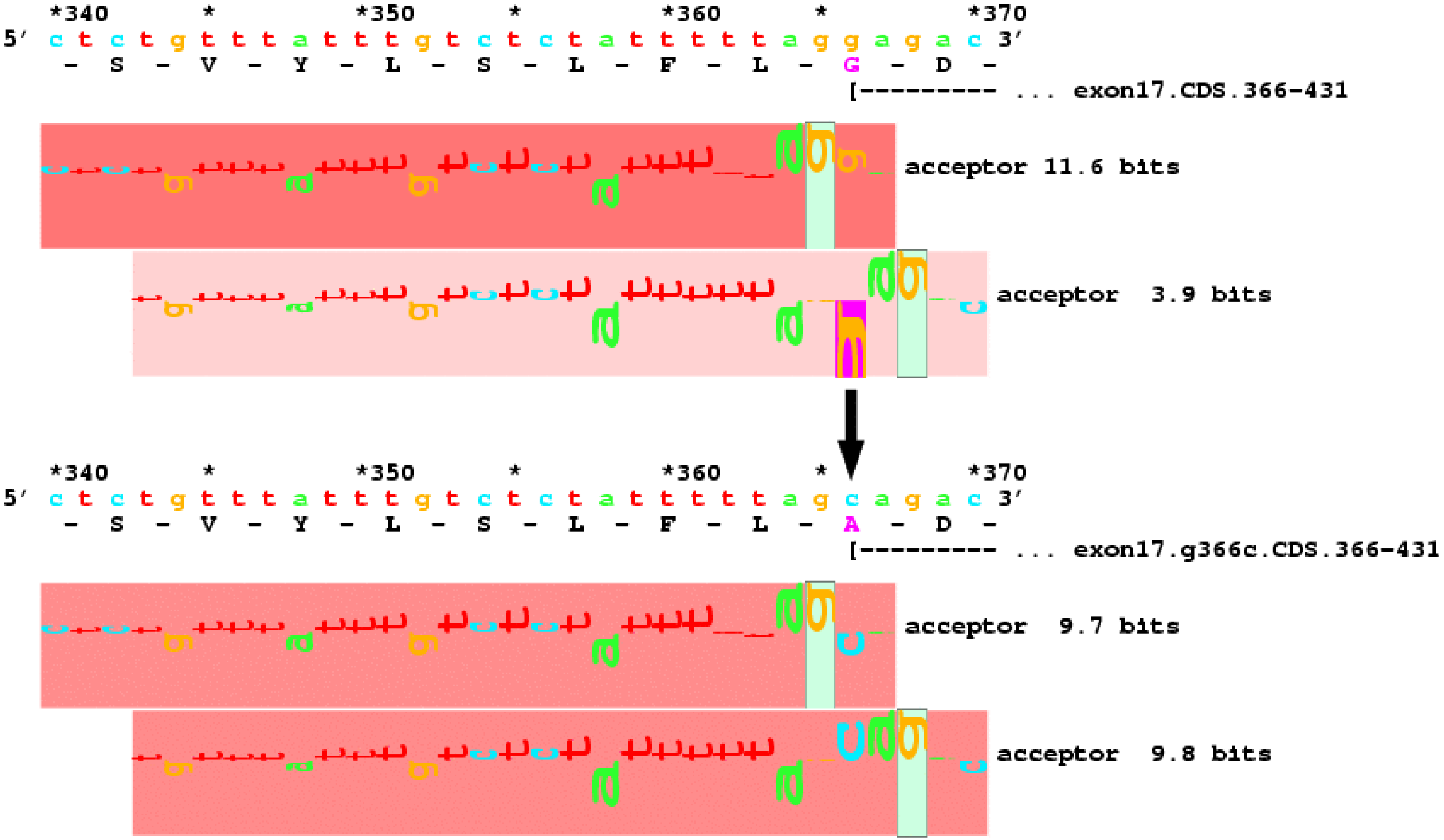
Medical Applications of Sequence Walkers


*340 * *350 * *360 * *370
5′ c t c t g t t t a t t t g t c t c t a t t t t t a g g a g a c 3′
- S - V - Y - L - S - L - F - L - G - D -
[--------- ... exon17.CDS.366-431
acceptor 11.6 bits
acceptor 3.9 bits
*340 * *350 * *360 * *370
5′ c t c t g t t t a t t t g t c t c t a t t t t t a g c a g a c 3′
- S - V - Y - L - S - L - F - L - A - D -
[--------- ... exon17.g366c.CDS.366-431
acceptor 9.7 bits
acceptor 9.8 bits

Mutation G863A: Stargardt disease = age-related macular degeneration

http://www.ccrnp.ncifcrf.gov/˜toms/g863a.html

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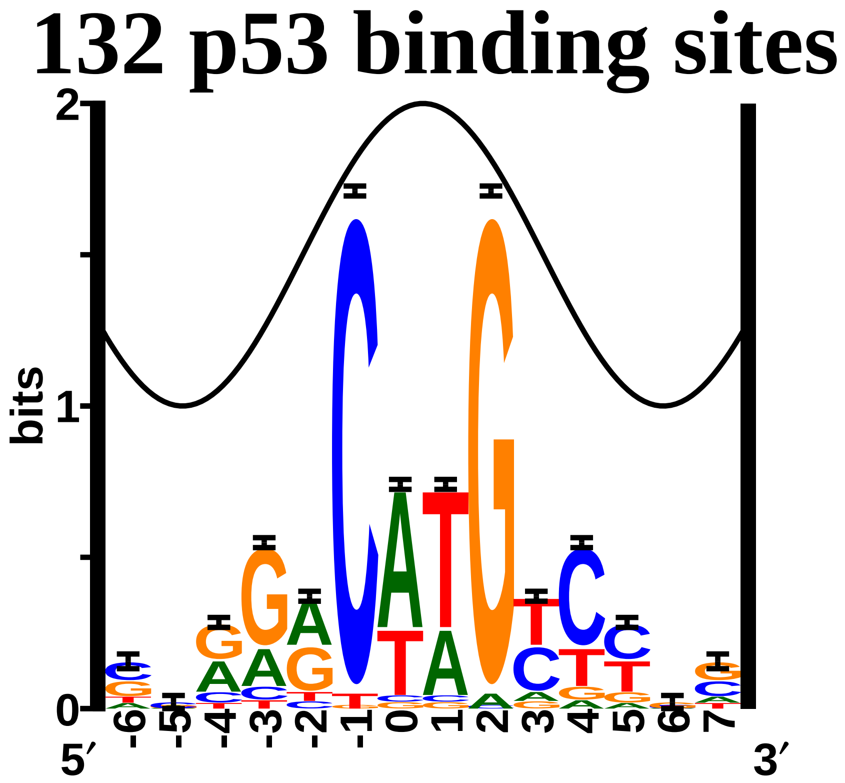

Lyakhov, Annangarachari and **Schneider**
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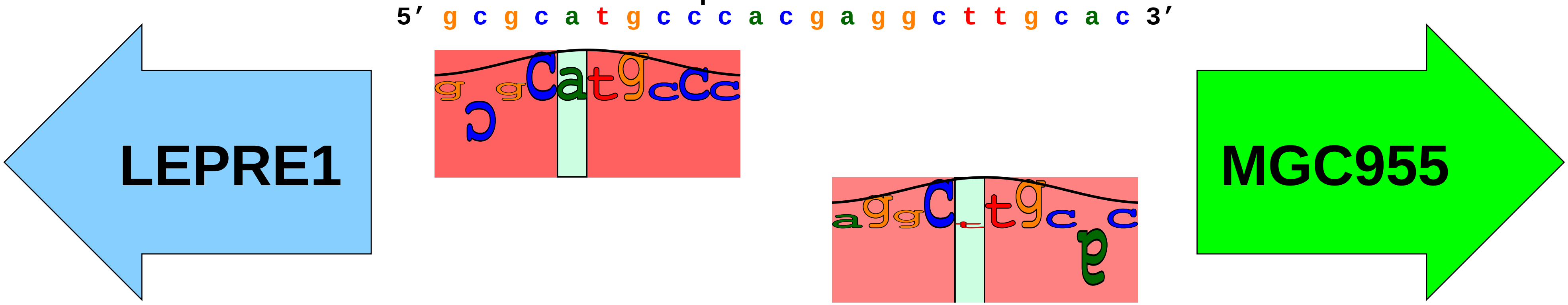

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Discovery of a 7^{th} Bacteriophage λ Operator

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

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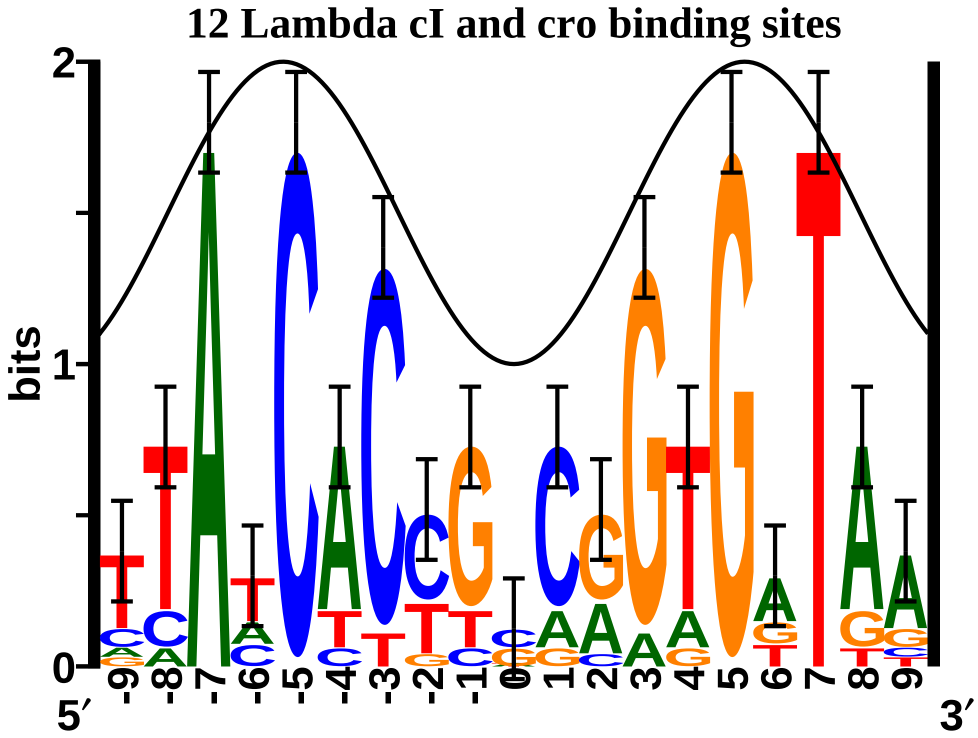

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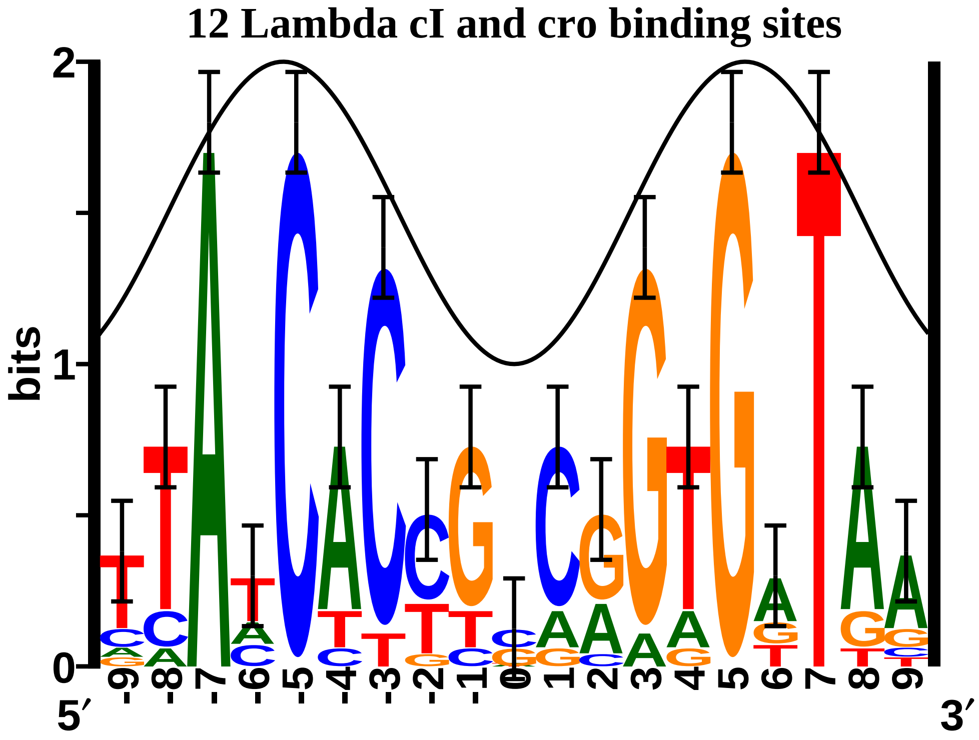

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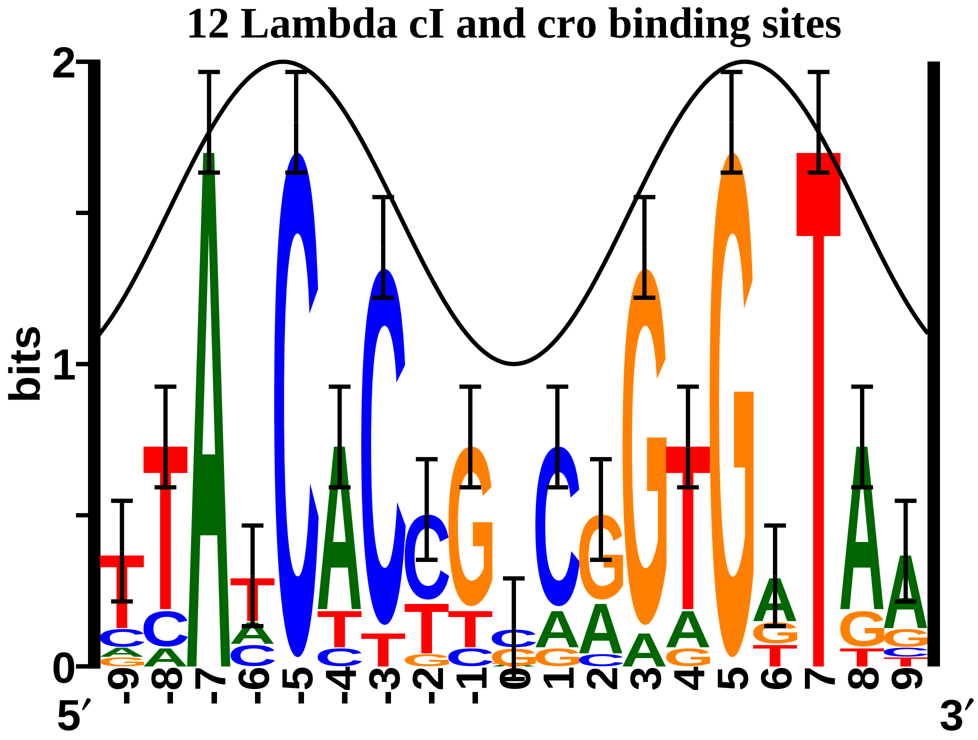

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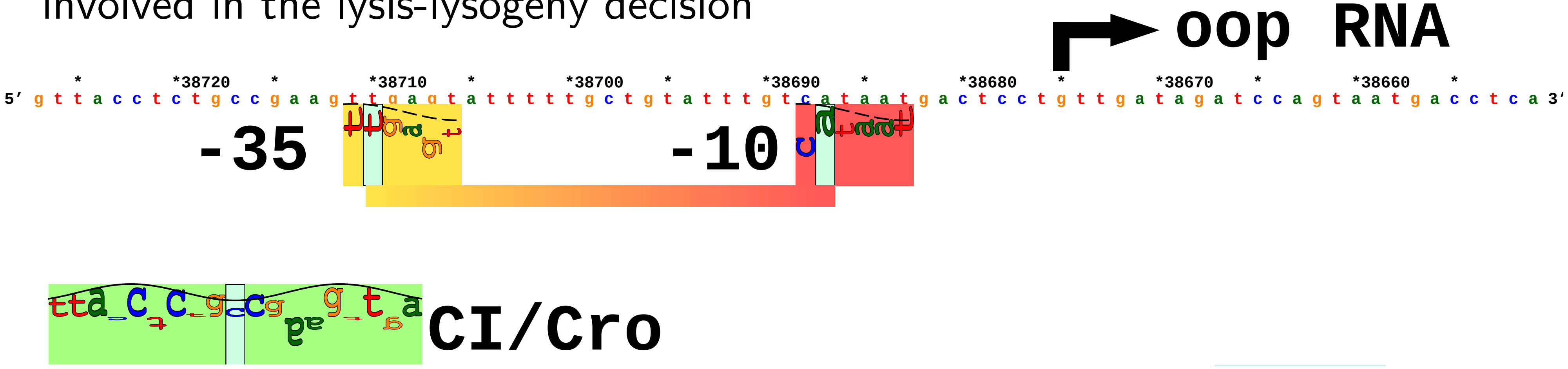

oop RNA

*　*38720　*　*38710　*　*38700　*　*38690　*　*38680　*　*38670　*　*38660　*

5′ g t t a c c t c t g c c g a a g t t g a g t a t t t t t g c t g t a t t t g t c a t a a t g a c t c c t g t t g a t a g a t c c a g t a a t g a c c t c a 3′

-35

-10

CI/Cro

CI/Cro	λ switch to lytic growth	predicted

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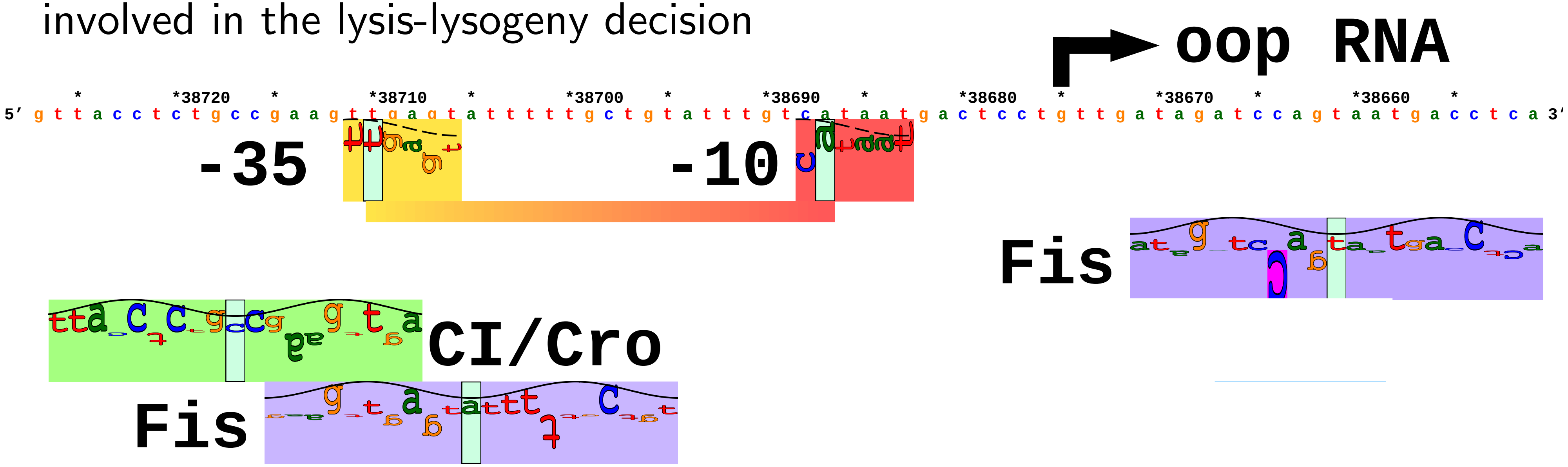
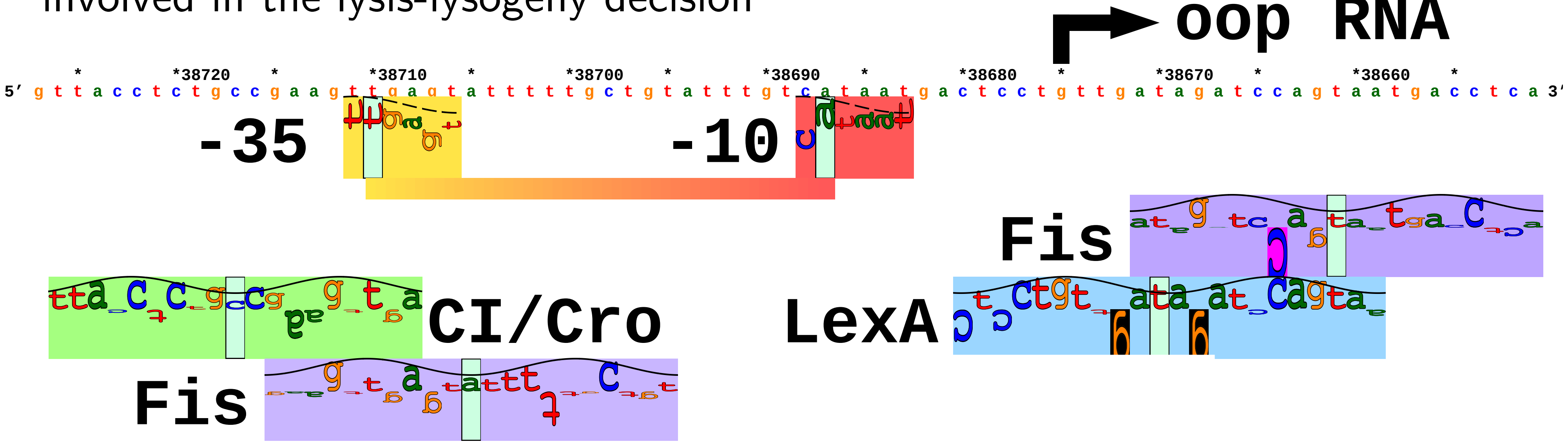


oop RNA
*38720
*38710
*38700
*38690
*38680
*38670
*38660
5′ gttacctctgccgaagtttgagtatttttgctgtatttgtcataatgactcctgttgatagatccagtaatgacctca 3′
-35
-10
Fis
CI/Cro
Fis

CI/Cro	λ switch to lytic growth	predicted
Fis	Nutrients	predicted

Bacteriophage λ Oop promoter: controlled by CI/Cro?

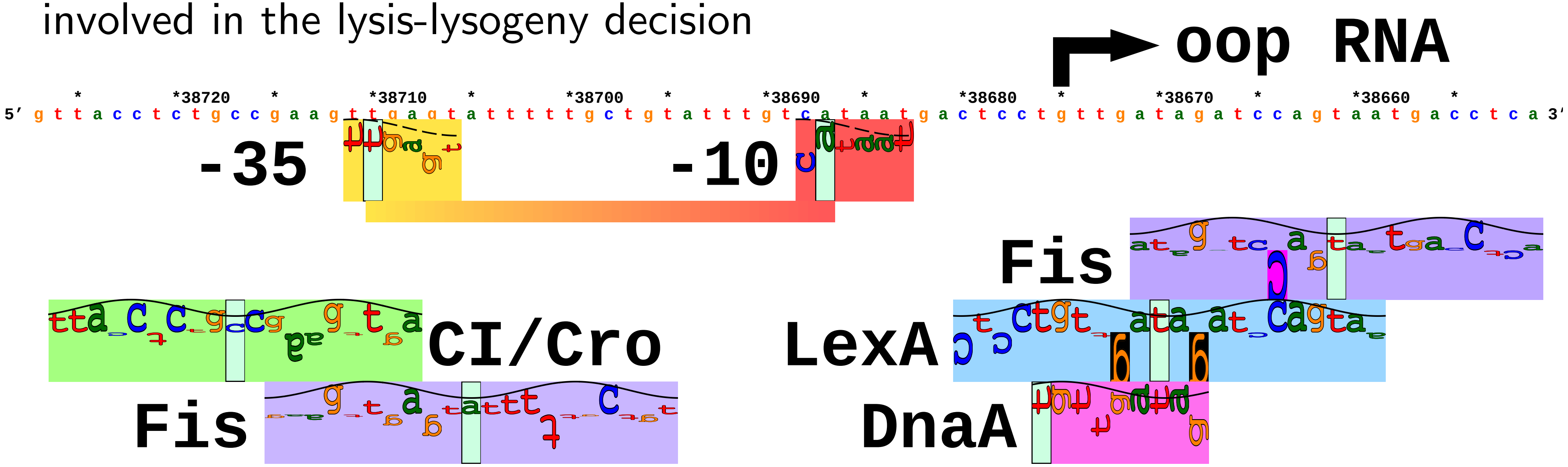
oop RNA is antisense to the $3'$ end of *cII* mRNA involved in the lysis-lysogeny decision


oop RNA
*38720
*38710
*38700
*38690
*38680
*38670
*38660
5′ g t t a c c t c t g c c g a a g t t g a g t a t t t t t g c t g t a t t t g t c a t a a t g a c t c c t g t t g a t a g a t c c a g t a a t g a c c t c a 3′
-35
-10
Fis
CI/Cro
LexA
Fis

CI/Cro	λ switch to lytic growth	predicted
Fis	Nutrients	predicted
LexA	DNA Damage	known

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

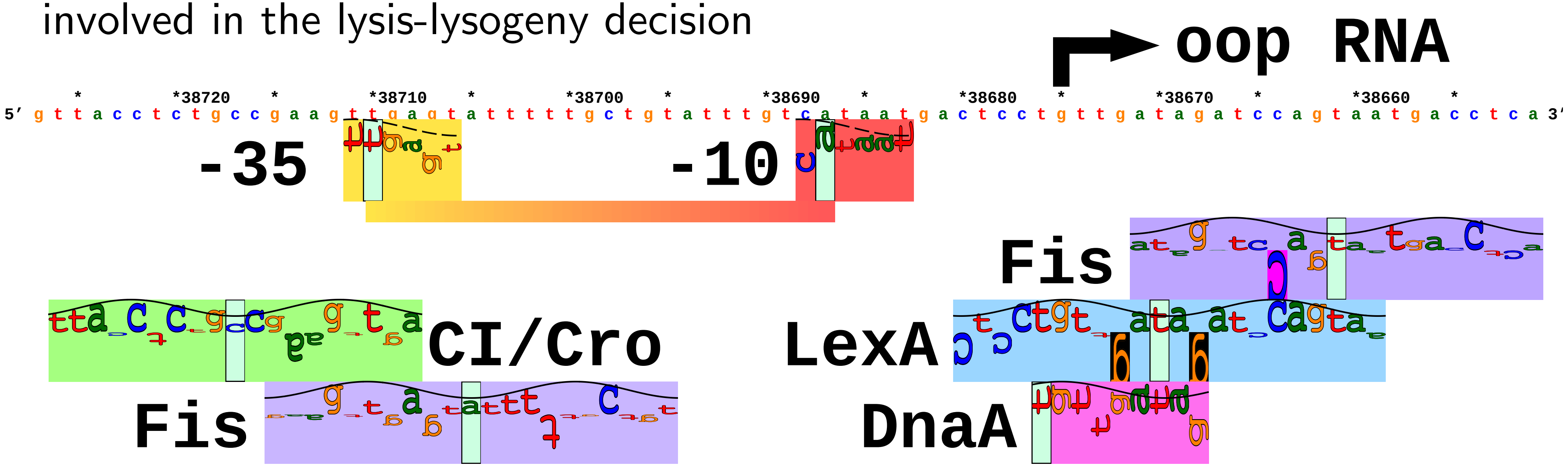

oop RNA
* *38720 * *38710 * *38700 * *38690 * *38680 * *38670 * *38660 *
5′ g t t a c c t c t g c c g a a g t t g a g t a t t t t t g c t g t a t t t g t c a t a a t g a c t c c t g t t g a t a g a t c c a g t a a t g a c c t c a 3′
-35
-10
Fis
CI/Cro
LexA
Fis
DnaA

CI/Cro	λ switch to lytic growth	predicted
Fis	Nutrients	predicted
LexA	DNA Damage	known
DnaA	Cell replication	predicted

- **4 new sites predicted by information theory**

Bacteriophage λ Oop promoter: controlled by CI/Cro?

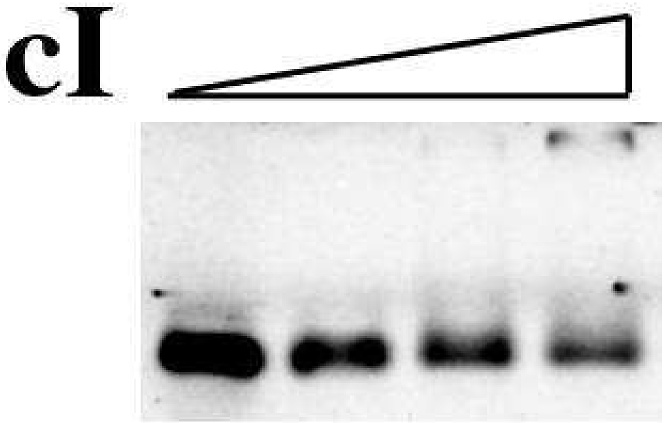
oop RNA is antisense to the $3'$ end of *cII* mRNA
involved in the lysis-lysogeny decision


oop RNA
* *38720 * *38710 * *38700 * *38690 * *38680 * *38670 * *38660 *
5′ g t t a c c t c t g c c g a a g t t g a g t a t t t t t g c t g t a t t t g t c a t a a t g a c t c c t g t t g a t a g a t c c a g t a a t g a c c t c a 3′
-35
-10
Fis
CI/Cro
LexA
Fis
DnaA

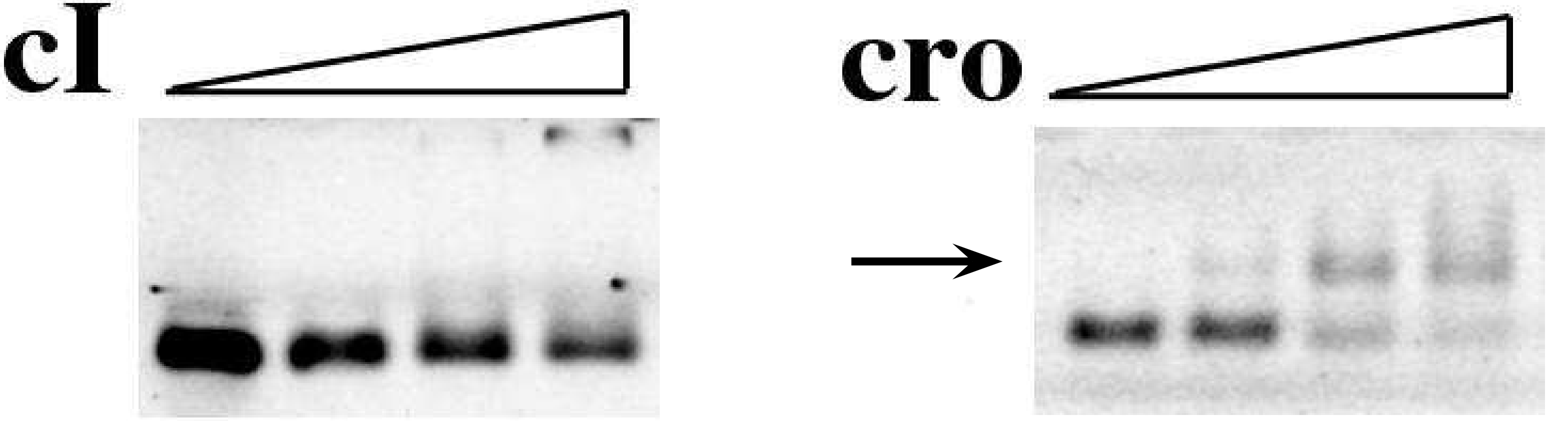
CI/Cro	λ switch to lytic growth	predicted
Fis	Nutrients	predicted
LexA	DNA Damage	known
DnaA	Cell replication	predicted

- **4 new sites predicted by information theory**
- **A cell-state detection/control center?**

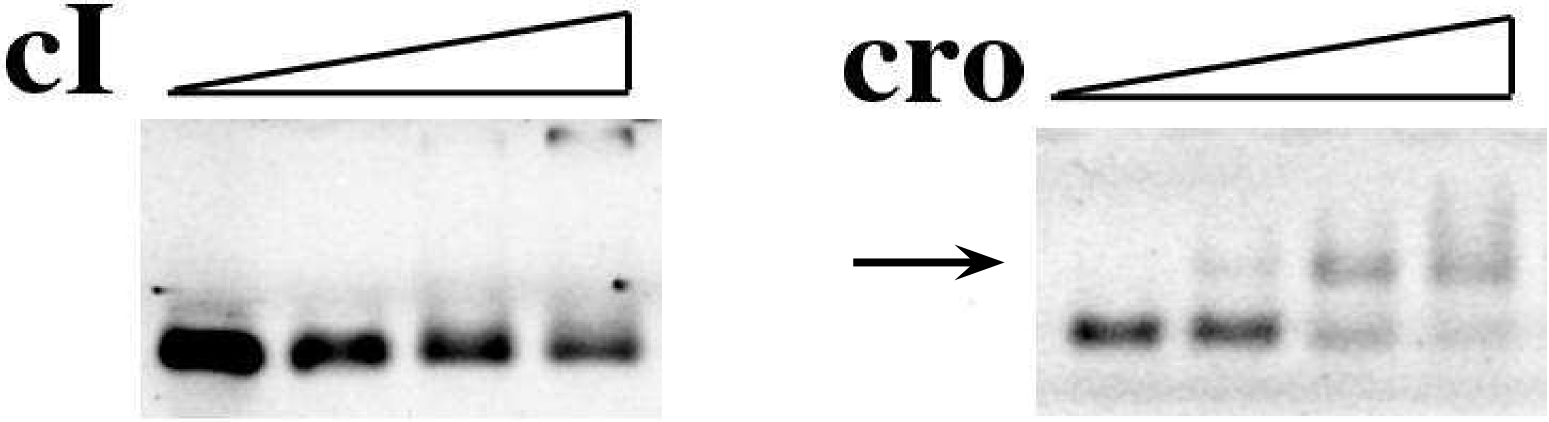
Bacteriophage λ Oop promoter Cro site



Bacteriophage λ Oop promoter Cro site

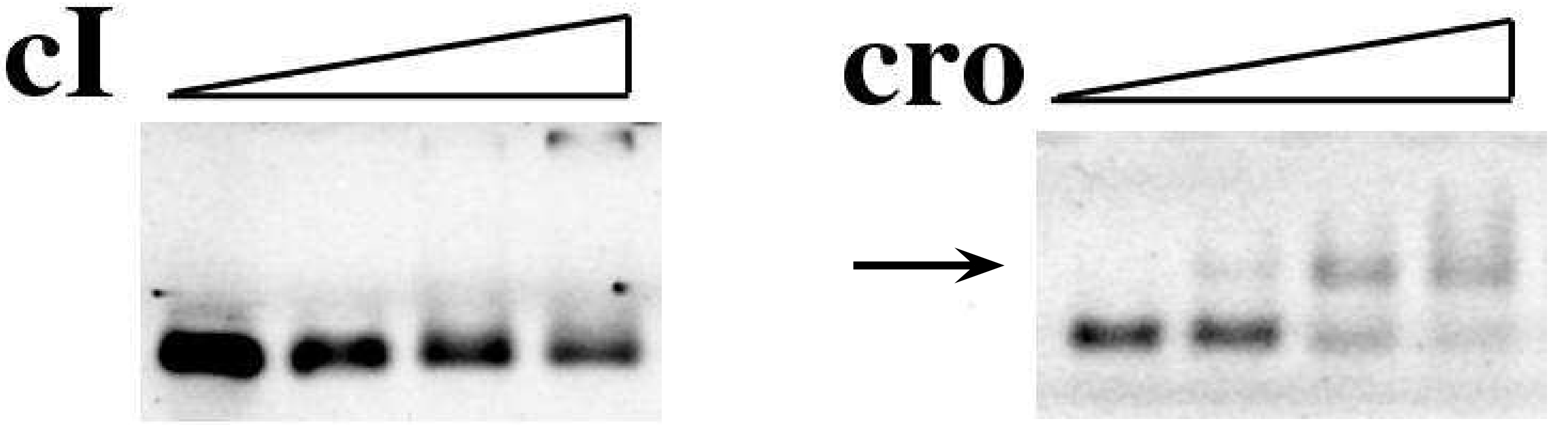


Bacteriophage λ Oop promoter Cro site



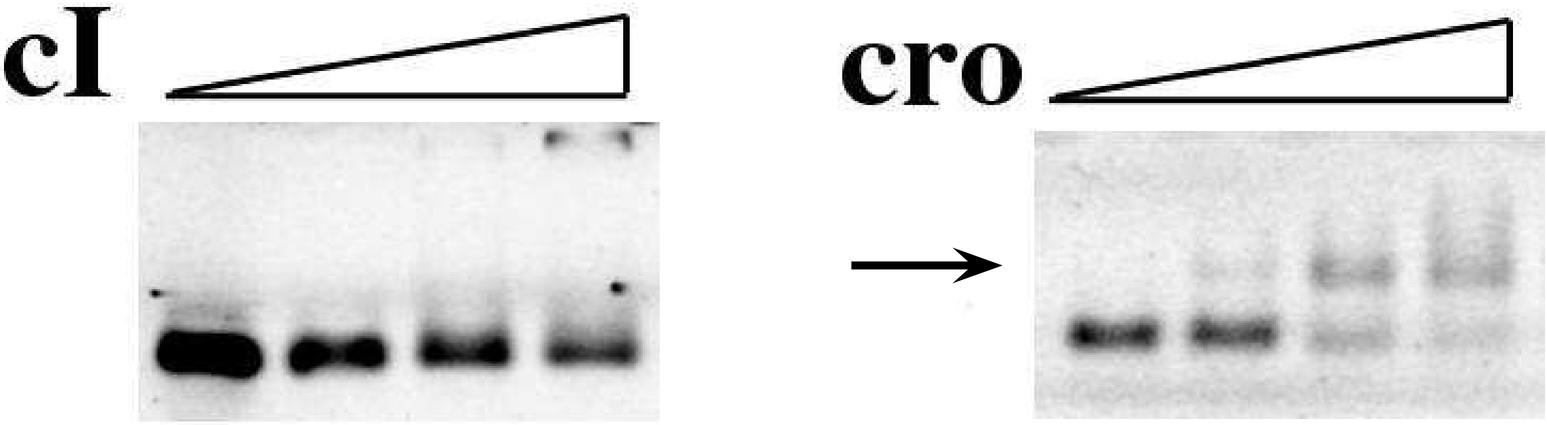
- The 7th λ Operator is a Cro site, NOT a CI site. Prediction confirmed

Bacteriophage λ Oop promoter Cro site



- The 7th λ Operator is a Cro site, NOT a CI site. Prediction confirmed
- Test information theory predictions to further confirm theory

Bacteriophage λ Oop promoter Cro site



- The 7th λ Operator is a Cro site, NOT a CI site. $\boxed{\text{Prediction confirmed}}$
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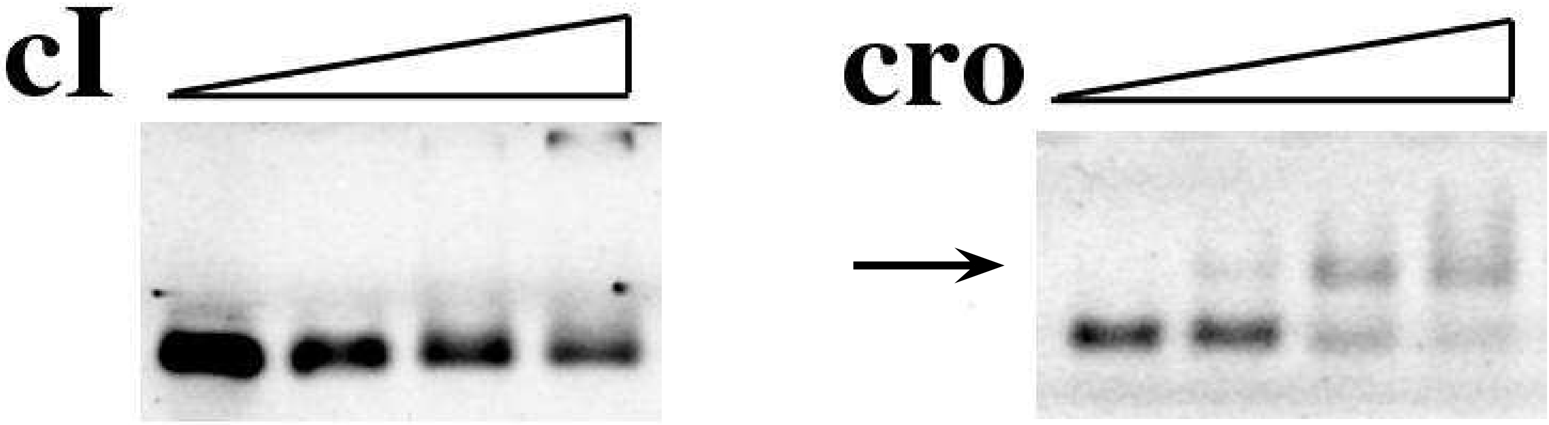
- *in vivo* experiments in progress: knock out Cro and Fis sites

Bacteriophage λ Oop promoter Cro site



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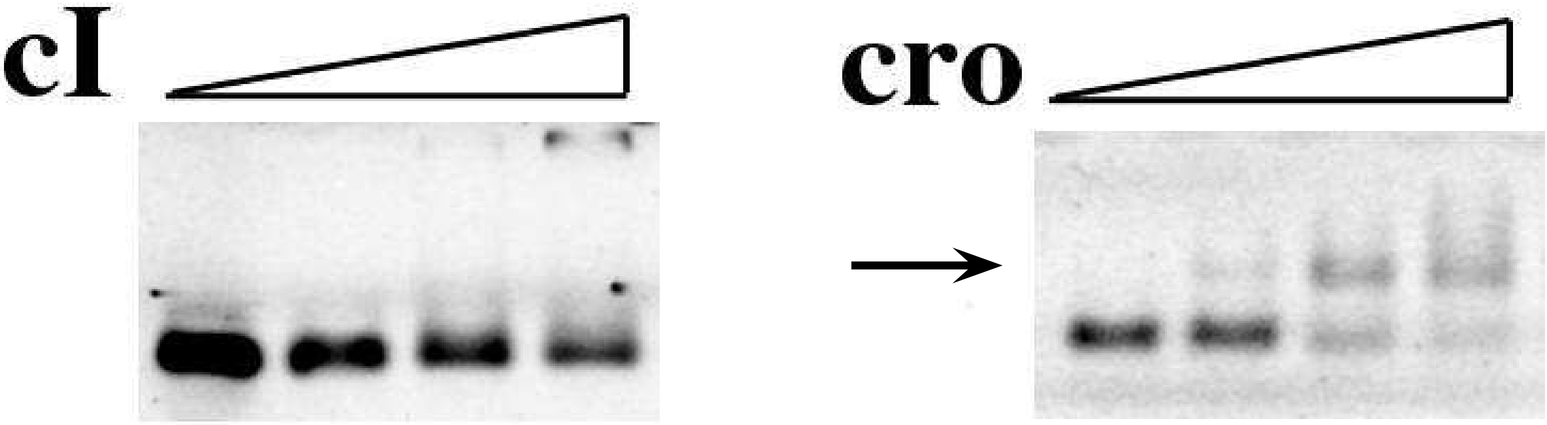
- live phage knockouts by recombineering planned: affects lysogeny?

Bacteriophage λ Oop promoter Cro site



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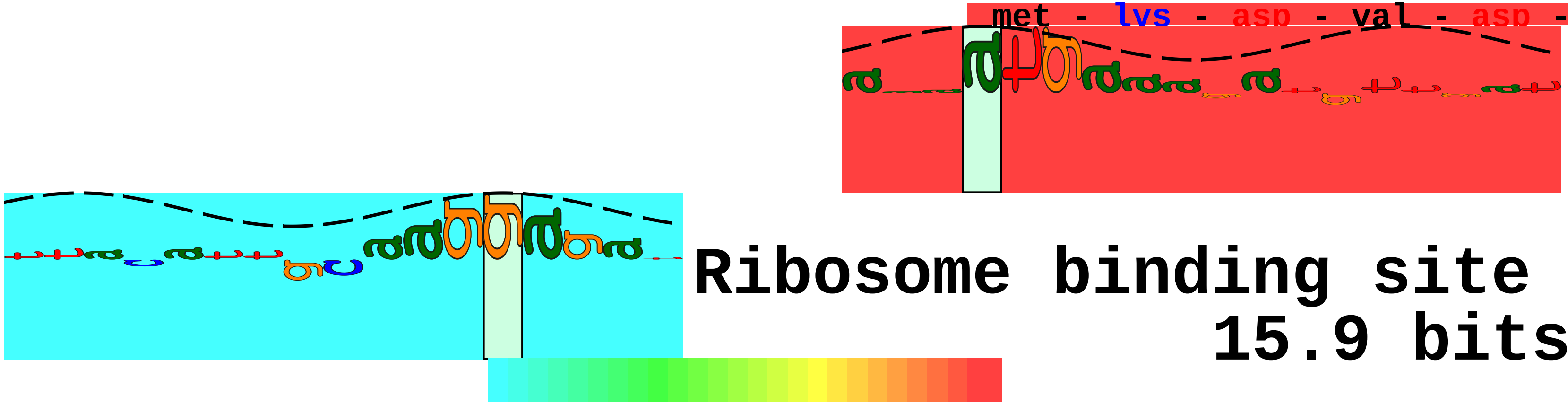
- Test information theory predictions to further confirm theory
- *in vivo* experiments in progress: knock out Cro and Fis sites
- live phage knockouts by recombineering planned: affects lysogeny?
- Collaborator: Dr. Don Court (NCI) - λ expert, invented recombineering

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 -
```

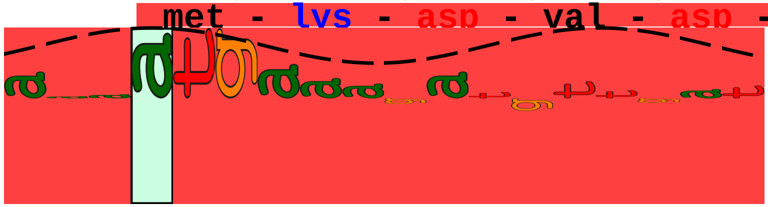
```
   *         *2987850   *         *2987840   *         *2987830   *         *2987820   *
5' t t g t t t t a t g a t t a a c g a g g t t c c a t c t t t t t g t t a t c t a t t t t a 3'
 - leu - phe - tyr - asp -
```

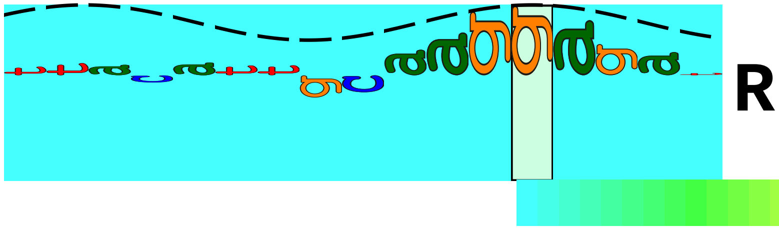
27 codon open reading frame

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

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 g t t a t c t a t t t t a 3′
 - leu - phe - tyr - asp -
```

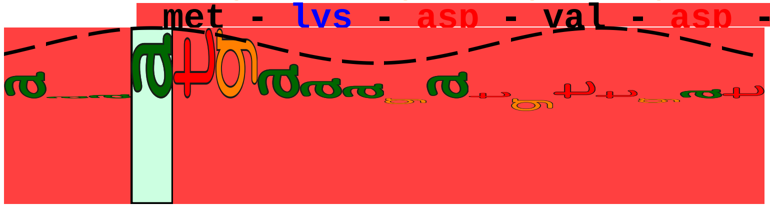
27 codon open reading frame

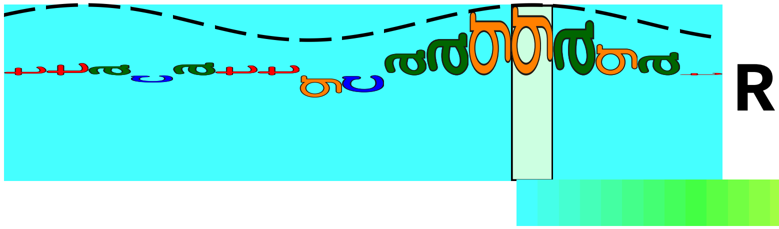
- > 2000 **information theory predictions; test 24**

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

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 g t t a t c t a t t t t a 3'
 - leu - phe - tyr - asp -
```

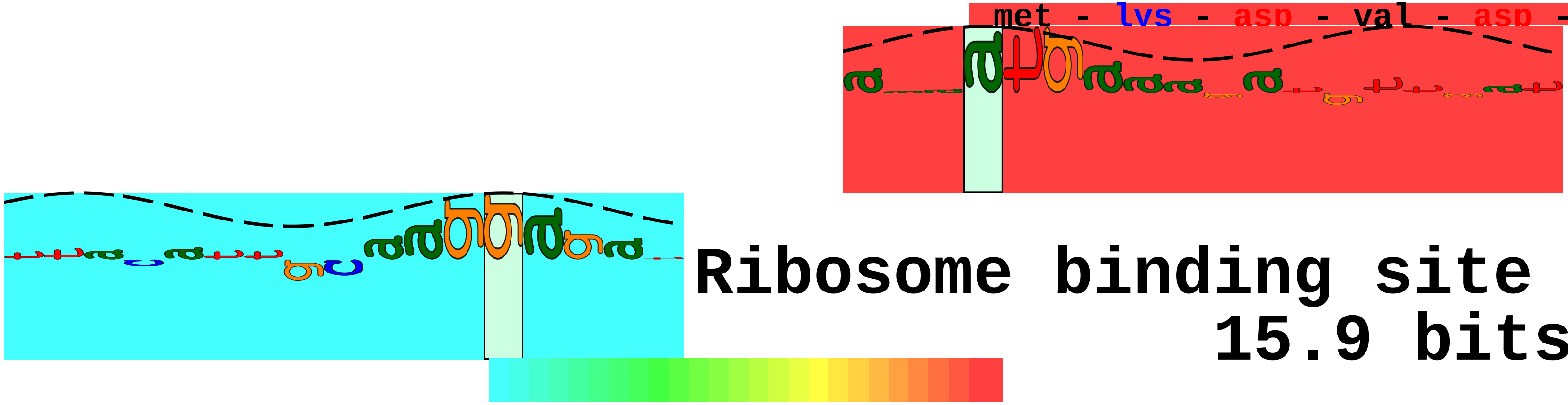
27 codon open reading frame

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

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

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 g t t a t c t a t t t t a 3′
- leu - phe - tyr - asp -

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) and
Dr. Kenneth Rudd (University of Miami School of Medicine, Miami, FL)