

## Patterns

Tore Samuelsson 2010

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### Patterns - comparison to method of aligning evolutionary related sequences

Dynamic programming algorithm.  
Designed to deal with closely as well as  
distantly related sequences, taking into  
account gaps (indel mutations) and  
substitution matrix information

		A	A	G
	0	-5	-10	-15
A	-5	2	-3	-8
G	-10	-3	-3	-1
C	-15	-8	-8	-6

Applications in:

- Sequence assembly
- Classification
- Prediction of function
- Comparative genomics
- Phylogeny / Evolutionary history

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## Patterns

### Regular expression

"Regexp"

"Regex"

Patterns / Regular expression matching

GR TKLPKLMKKWREKNR LYKMKWRAGGALKALK

Is there a match to **KWR** in this string?

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## Regular expressions and NFA / DFA

Regular expressions are related to theory of automata (*machines*):  
Regular expressions can be translated into :

*Non-deterministic Finite Automaton (NFA) &*

*Deterministic Finite Automaton (DFA)*

(and this is what happens in Perl and other utilities that make use of regexs)

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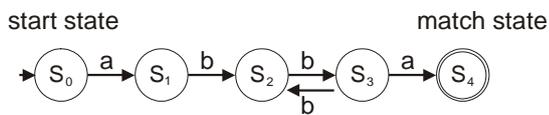
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## Regular expressions and finite state automata (state machines)

Regexp :  $a(bb)^+a$




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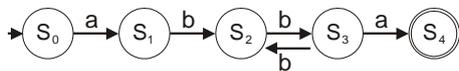
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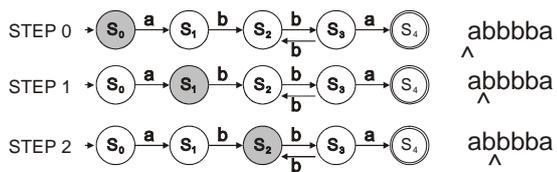
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start state match state



Regexp  $a(bb)^+a$  Testing the string "abbbba"




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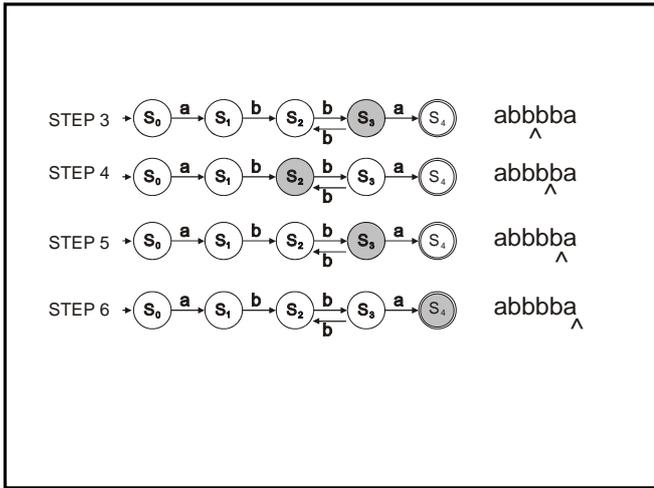
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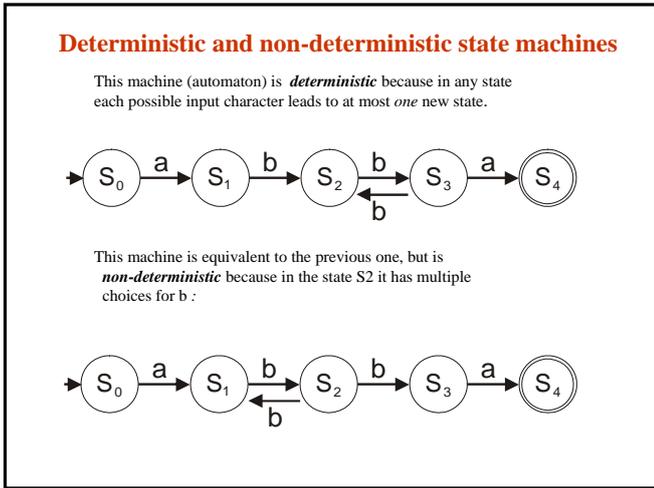
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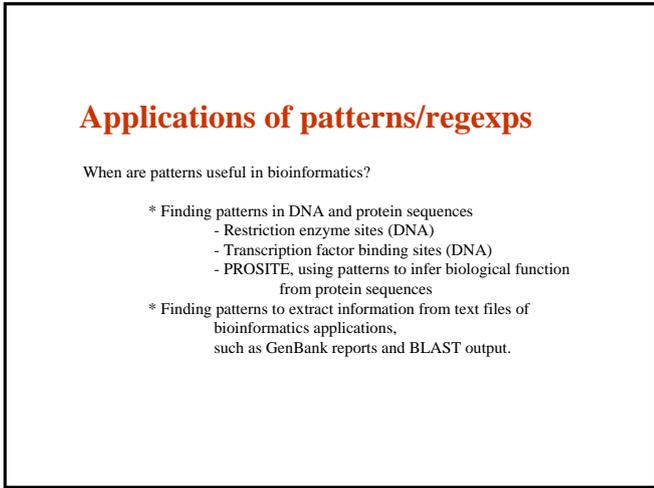
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### Recognition sites of restriction enzymes

EcoRI -GAATTC-  
-CTTAAG-

BamHI -GGATCC-  
-CCTAGG-

XhoII -RGATCY- R = A or G  
-YCTAGR- Y = C or T

PpuMI -RGWCCY- W = A or T  
-YCCWGR-

FokI -GGATGNNNNNNNNNNNNNNNN-  
-CCTACNNNNNNNNNNNNNNNN-

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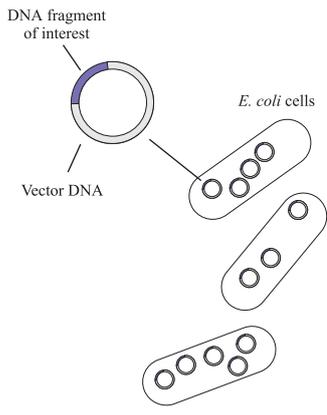
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### Cloning



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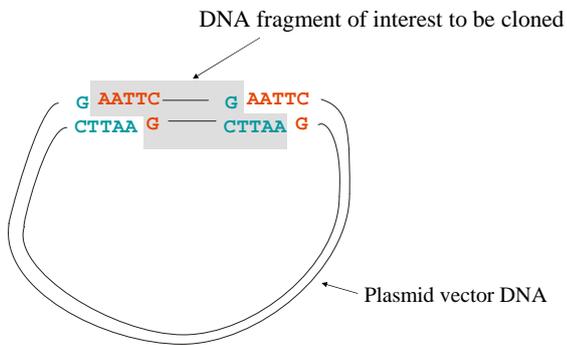
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### Restriction enzymes are used in cloning



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**Transcription factor databases contain information about DNA sequences recognized by transcription factors**

Name	Sequence	Trans. Factor
UAS(G)-pRH100	0 CCGAGTACTCTCTCCG	0 : GAL4
TFIIIC-Xla-58.1	0 TGGATGGGAG	0 : TFIIIC
HSE_CS_inverted_repeat	0 CTNGANNNTTNGAG	0 : HSTF
ZDNA_CS	0 GCGTGTGCA	0 : unknown
GCM4-his3-189	0 ATGACTCAT	0 : GCM4
Ad5_E1A_element_I	0 AAGAAAGTGA	0 : unknown
Ad5_E1A_element_II	0 GGGCCTAACCGAGTAAAGATTGGCCATTTTC	0 : unknown
BPV-E2_CS1	0 ACCNNNNKGGT	0 : (BPV-E2)
Alb_DEI	0 GATTTTUTAAATGG	0 : C/EBP
Alb_DEII	0 TTTTGGCAAAGAT	0 : CTF/NF-1
Alb_DEIII	0 GCAGGGATTAGTT	0 : unknown
Alb_FEI	0 TGTTTAATGATCTACAGT	0 : APF/HNF1
BPV-E2_CS2	0 ACCNNNNKGGT	0 : BPV-E2
CACA	0 CACACACACA	0 : unknown
dc_box	0 T8ATTTCAT	0 : unknown
GALV_F	0 AGAATAGATGATCAACAG	0 : unknown
GCRE	0 TGACTC	0 : GCM4
Pit-1_CS1	0 WTATTCAT	0 : Pit-1

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**Protein patterns and the PROSITE database**

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**Proteins that bind the nucleotides ATP or GTP share a short sequence motif**

The image shows the chemical structure of ATP (Adenosine Triphosphate) on the left, consisting of an adenine base, a ribose sugar, and three phosphate groups. On the right, a protein sequence alignment is shown with a vertical blue bar highlighting a conserved motif: **TAIVGPPSGSKRTLLRILAC**. A blue box highlights the sequence **IVILGPPSGSKRTLLNII** in the alignment, which is a variation of the conserved motif.

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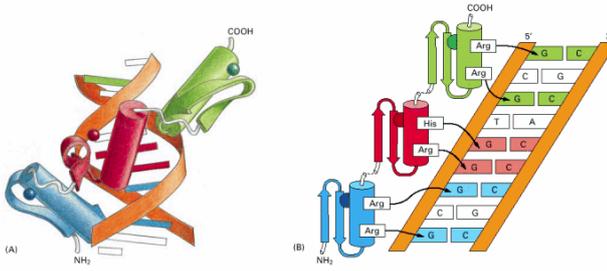
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## Recognition of DNA by zinc-finger binding protein



Zinc finger binding motifs are extremely common.  
Among 23000 human genes, 845 have C2H2 zinc finger domains !!

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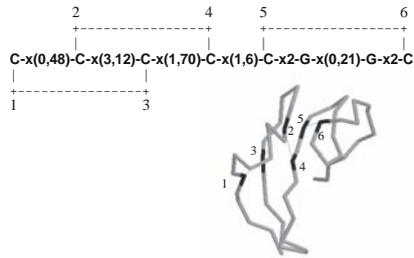
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## More PROSITE: Disulfide bonds in EGF domain

- First identified in epidermal growth factor, but present in many other proteins
- Function unclear, but found in extracellular part of membrane proteins
- Includes six cysteines involved in disulfide bonds




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## PROSITE



**prosite** PROSITE  
Database of protein families and domains

<http://www.expasy.org/prosite/> (Swiss Institute of Bioinformatics)

Release 20.67, of 05-Oct-2010 (contains  
1308 patterns and 909 profiles/matrices).

A - x(4,7) - G - x(5,6) - D

"Non-probabilistic"

A	10	0	0	10	5	4
K	0	0	0	0	0	0
G	0	0	0	0	1	4
L	0	10	10	0	4	2
...	etc.					

"Probabilistic"

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## PROSITE syntax

		Perl
D	matches D	
[AS]	matches A or S	
x	any symbol (amino acid)	.
x(3) or x3	any three symbols (amino acids)	.{3}
{AT}	matches any symbol <i>except</i> A and T	[^AT]
[AS]2	Matches two positions with either A or S (i.e. AA, AS, SS, or SA)	[AS]{2}
x(3,7)	a sequence of symbols between 3 and 7 in length (for instance GAT, GCRE, PPLKM, GTTREC or PPPPPPP)	.{3,7}

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## Variation in classification accuracy

**ZINC\_FINGER\_C2H2\_1, PS00028, Zinc finger C2H2 type domain signature (PATTERN)**

Consensus pattern: **C - x(2,4) - C - x(3) - [LIVMFYWC] - x(8) - H - x(3,5) - H**  
*The 2 C's and the 2 H's are zinc ligands*

Sequences known to belong to this class detected by the pattern: ALL

Other sequence(s) detected in Swiss-Prot: 42

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**ATP\_GTP\_A, PS00017, ATP/GTP-binding site motif A (P-loop) (PATTERN with a high probability of occurrence)**

Consensus pattern: **[AG] - x(4) - G - K - [ST]**

Sequences known to belong to this class detected by the pattern: a majority

Other sequence(s) detected in Swiss-Prot: in addition to the proteins listed above, the 'A' motif is also found in a number of other proteins. Most of these proteins probably bind a nucleotide, but others are definitively not ATP- or GTP-binding (as for example chymotrypsin, or human ferritin light chain).

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**ASN\_GLYCOSYLATION, PS00001, N-glycosylation site (PATTERN with a high probability of occurrence)**

Consensus pattern: **N - [P] - [ST] - [P]**  
*N is the glycosylation site*

- Scan Swiss-Prot/TrEMBL entries against PS00001
- view ligand binding statistics

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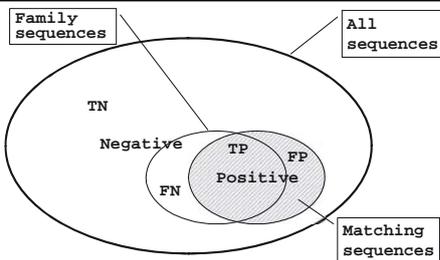
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- \* True positive - member of the protein family that is matched by the pattern
- \* False positive - a protein which is *not* a member of the protein family is matched by the pattern
- \* True negative - a protein which is *not* a member of the protein family is *not* matched by the pattern
- \* False negative - member of the protein family is *not* matched by pattern

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### Classification accuracy

$$\text{Specificity} : \frac{TP}{(TP+FP)}$$

$$\text{Sensitivity} : \frac{TP}{(TP+FN)}$$

- Ex: The flavodoxin family (PS00201)
 

True positives:	51	»	0.93
False positives:	4		

False negatives:	9	»	0.85

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### Important application of databases like PROSITE

*Biological information may be extracted from a protein sequence.*

A 'new' protein sequence has been identified using bioinformatics methods (like in a genome project). A scan of PROSITE using this sequence (regular expression matching) can give important clues as to the biological function of the protein.

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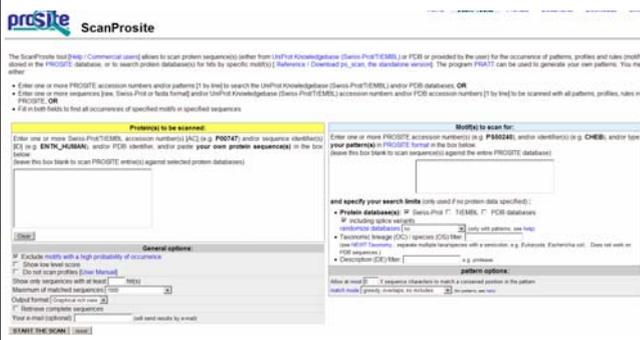
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### Common applications of PROSITE (ScanProsite/Motifscan)

- \* Search a sequence for all PROSITE patterns/profiles
- \* Search database with a pattern/profile




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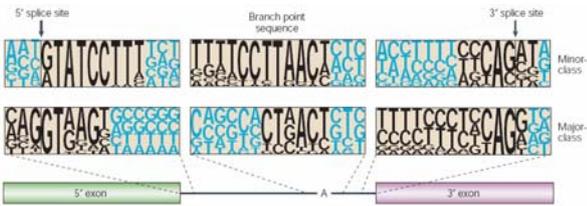
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**More applications of patterns ...**

**Finding minor introns**



A class of U12 (minor) introns are highly conserved in sequence:

RT|ATCCTYT.....TTCCTTTR.....AC|Y  
 exon | 5'                      intron                      3' | exon  
 [AG]TATCCT[CT]T.{30,1500}TTCCTT[AG].....AC[TC]

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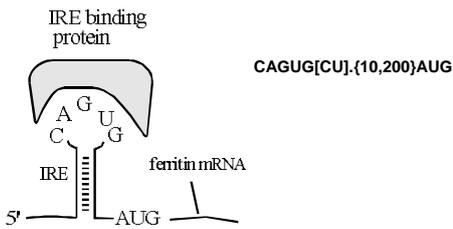
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**More applications of patterns ...**

**Finding the iron responsive element**



... and finding ORFs

AUG ( . . . ) { 0 , 200 } ? ( UAA | UAG | UGA )  
 match as few characters as possible

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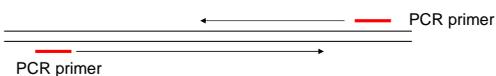
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**More applications of patterns ...**

**When BLAST will fail to identify regions of identity in a genome**

For instance: Find occurrences of 'AGCTGCAAAAA'

To find such short regions of identity BLAST is often difficult to use. There are however applications when you want to find such matches, like when searching for matches to oligonucleotides used in PCR or probes used in microarrays. Or you may want to search for matches to very short peptide sequences potentially encoded by the genome.




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## Sample session with 'fuzzpro'

```
% fuzzpro
Protein pattern search
Input sequence(s): tsw:*
Search pattern: [FY]-[LIV]-G-[DE]-E-A-Q-x-[RKQ](2)-G
Number of mismatches [0]:
Output report [100k_rat.fuzzpro]:
```

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## Perl

Example code that uses a regular expression:

```
variable
$str = 'GACACAGGGATCGGGGATC';
binding operator
if ( $str =~ /[AG][CT]CG/ ) {
  Is there a match
  of [AG][CT]CG in
  the variable $str?
  print "Found match!";
}
```

regex will match here  
GACACAGGGATCGGGGATC

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## The substitution and transliteration operators

*Transcribing DNA into RNA.*

```
$dna = 'GCAATGG';
print "The DNA sequence is $dna\n";
$rna = $dna;
$rna =~ s/T/U/g;
print "and the RNA sequence is $rna\n";
```

substitution operator  
s/T/U/g;  
REPLACEMENT; text to replace PATTERN  
PATTERN; regexp to be replaced by REPLACEMENT  
global modifier; do the substitution operation for all matches

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## The substitution and transliteration operators

Count the bases in a DNA sequence using *tr*

```
$dna = 'GCAATGNGATTACTTCG';  
  
$basecount = ($dna =~ tr/ACGT//);  
$nonbase = length($dna)-$basecount;  
print "There are $basecount As,Cs,Ts,and Gs \n";  
print "There is/are $nonbase other symbol(s) \n";
```

**tr/ACGT//;**  
operation does not change the string!

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## Metacharacters

. match any character  
^ match beginning of string  
\$ match end of string  
? optional match

### Quantifiers

\* Any number of characters, including zero  
+ One or more characters  
{m,n} minimum m , maximum n characters

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## Reading a file in PERL and checking for regular expressions

Program will read the file with the name 'myfile' and that has a sequence in EMBL format. The program will print to the screen all lines starting with 'FT', i.e lines with feature table information.

```
open IN, 'myfile';  
  
while (<IN>) {  
    if (/^FT/) {print ;}  
}  
close IN;
```

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## Example of how regexps may be used to parse the output from a BLAST search

'bl2seq' is a program to blast two sequences against each other. This is an output using two sequences seq1 and seq2:

```
Query= seq1
      (31 letters)
>seq2
      Length = 29
Score = 42.1 bits (21), Expect = 1e-10
Identities = 27/29 (93%)
Strand = Plus / Plus

Query: 3  acgacgtacacgactagtcaggcggagct 31
          ||| ||| ||| ||| ||| ||| ||| |||
Sbjct: 1  acgacgttcacgactagtcacgaggagct 29

.... (and some more text ) .....
```

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## Example of how regexps may be used to parse the output from a BLAST search

Let's say you have many output files like this and you want to make a script to present the names of the two sequences as well as the Expect value listed. Here's an example of code: ( we assume that the blast output is in a file called 'bl2seq.out')

```
open IN, 'bl2seq.out';
while (<IN>) { # we read one line at a time, each
              # line is stored in the default variable $_
  chomp; # remove the end of line character in $_
  if (/Query= (.*)/) {print "$1 "; }
  if (/^>(.*)/) {print "$1 ";}
  if (/Expect = (.*)/) {print "$1\n";}
}
close IN;
```

**.** **\*** means any number (including zero) of any characters;  
the regexp algorithm is **greedy** so it will try to find the longest substring that matches

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## Regular expression match basics

1. Quantifiers **\*** **+** **?** **{m,n}** are *greedy*

Perl example:

```
$str = "GGAAGG";
$str =~ s/(G.*G)//;
```

\$str is now empty

2. The match that begins earliest (leftmost) wins

Perl example:

```
$str = "GGAAGG";
$str =~ s/GG/XX/;
print $str;
```

\$str is now XXAAGG

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