Basic Local Alignment Search Tool (BLAST)

Stephen Altschul, Warren Gish, Webb Miller, Eugene Myers, David Lipman

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Brian Dunican
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The Problem

- Dynamic programming algorithms take too long when applied to large databases
- Also these algorithms maximize similarity
  - Insertions
  - Deletions
  - Replacements
- Example Needleman and Wunsch

BLAST

- Similarity measure is based on well defined mutation scores (PAM120)
  - Optimization of this measure approximates the results of dynamic programming algorithm

- "Detect weak but biologically significant sequence similarities, and is more than an order of magnitude faster"

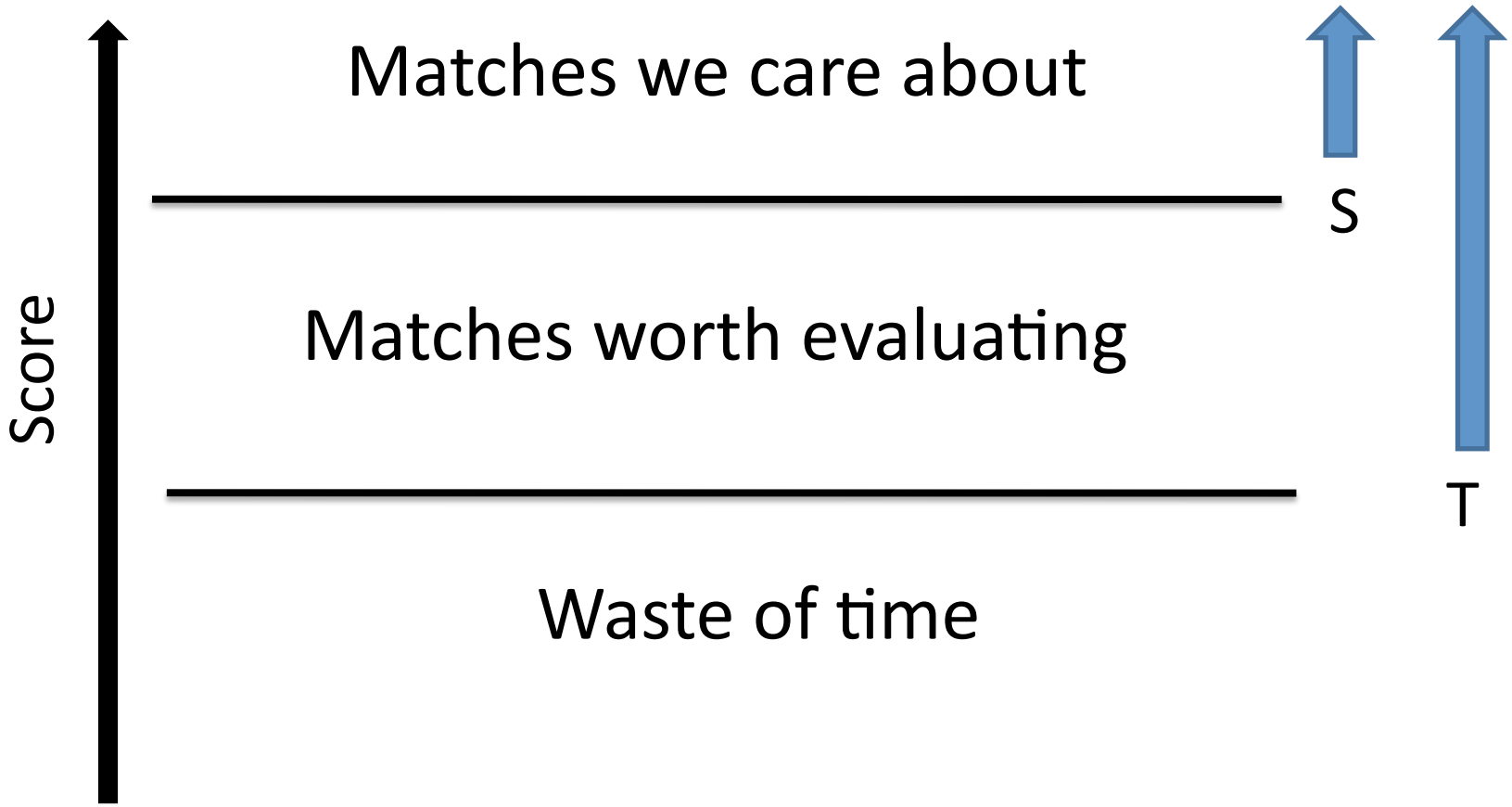
Methods

- Matrix of Similarity
  - Proteins: similar +, dissimilar – (PAM120)
  - DNA: identities +5, mismatches -4
- Units of Maximal Segment Pair (MSP)
  - Score can not be increased by shortening or lengthening the segment pair
- BLAST seeks the highest MSP score (>=S)

Method

- Computationally intensive to scan the database for all w-meres in search of S
- Define a threshold value, T , as the lower bound for further analysis.
- Database is searched for all words (w-meres) which can equal T.
  - Two steps
- From matches with score >= T, dynamic programming is used to determine MSP
  - Traces out from hit to maximize score

Method


Score
Matches we care about
S
Matches worth evaluating
T
Waste of time

Parameters

- The chance exists the a random sequence will exceed the S score

$$1 - e^{-y}, \qquad (1)$$

$$y = Kmn\ e^{-\lambda S}.$$

M and N are the length of the compared strings

S is the arbitrary score

K and lambda are coefficients

Parameters

- Used equation (1) to determine w and T parameters

w	T	Probability of a hit $\times 10^5$	Implied % of MSPs missed by BLAST when S equals						
			45	50	55	60	65	70	75
3	11	253	1	1	0	0	0	0	0
	12	147	4	3	2	1	1	0	0
	13	83	11	8	6	4	3	2	2
	14	48	20	16	12	10	8	6	5
	15	26	33	28	23	20	17	14	12
	16	14	46	41	36	32	29	26	23
	17	7	59	55	51	47	43	40	37
	18	4	70	67	63	60	57	54	51
4	13	127	2	1	1	0	0	0	0
	14	78	5	3	2	1	1	0	0
	15	47	10	7	5	4	3	2	1
	16	28	18	14	11	8	6	5	4
	17	16	28	23	19	16	13	11	9
	18	9	40	35	30	26	22	19	17
	19	5	51	46	41	37	33	30	27
	20	3	62	57	53	49	45	41	38
5	15	64	3	2	1	1	0	0	0
	16	40	6	4	3	2	1	1	0
	17	25	12	9	6	4	3	2	2
	18	15	20	15	12	9	7	5	4
	19	9	29	23	19	15	13	10	8
	20	5	38	32	28	23	20	17	14
	21	3	48	42	37	32	29	25	22
	22	2	57	52	47	42	38	35	31
Expected no. of random MSPs			50	9	2	0·3	0·06	0·01	0·002

Time Constraints

- Compile list of words that can score T from query
- Scan database for matches to T-scoring words
- Extend all hits to seek MSPs higher than S

- Increasing w decreases time spent on step 3.
- Make w too high and step one is limiting factor

Performance

- Against real proteins
  - Woolly monkey myoglobin (w=4, t=17)
    - Actual: missed 43 MSPs with a 50>S>80
    - Expected: miss 24 of 178
  - Mouse immunoglobulin precursor V region
    - Actual: missed 2 with a 45>S>65
    - Expected: miss 8 of 33
- Lost out in the monkey due to the uniform pattern of conservation
- Expect that on average Blast will outperform the random model.

Notes on Speed

- Proteins: 500,00 residues/s
- DNA: 2,000,000 bases/s