ADVERTISING:

International School on Biomolecular and Biocellular Computing (ISBBC'17)

Valencia 28-30.06.2017

- **Travel expenses**
- **Accommodation**
- **Fee**
- **Meals**

COMPUTING WITH PEPTIDES

Victor Mitrana
victor.mitrana@upm.es

CONTENTS

Genera idea: Why unconventional computation?

Sources of inspiration (DNA as a computing tool)

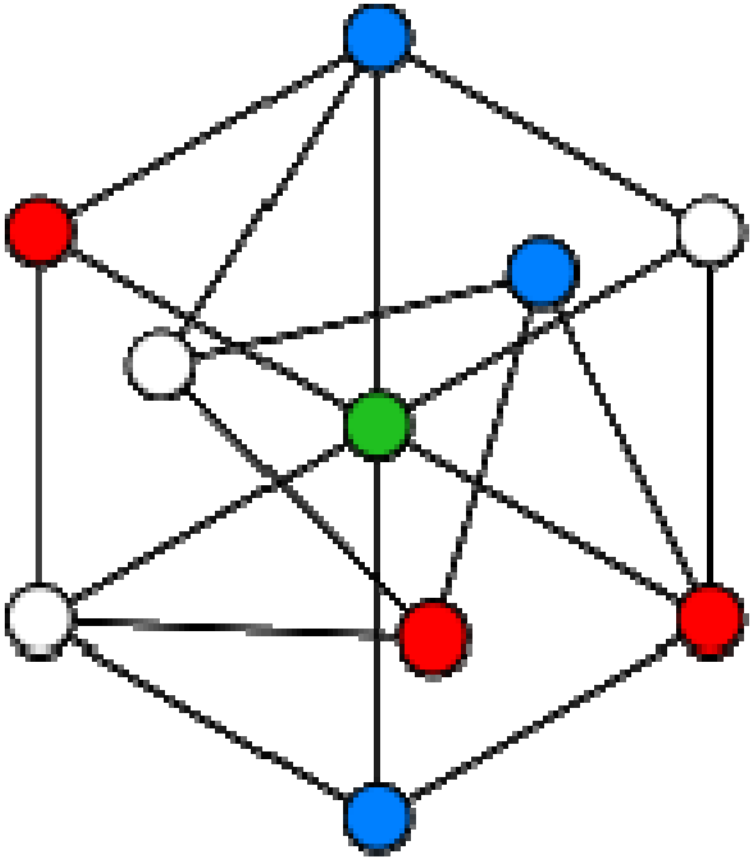
Description of the model

How the model computes

Advantages and drawbacks

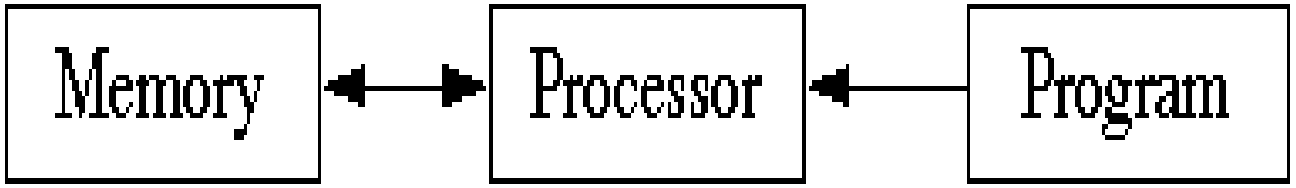
Discussions (questions, comments, suggestions, solutions, etc.)

3-COLORABILITY



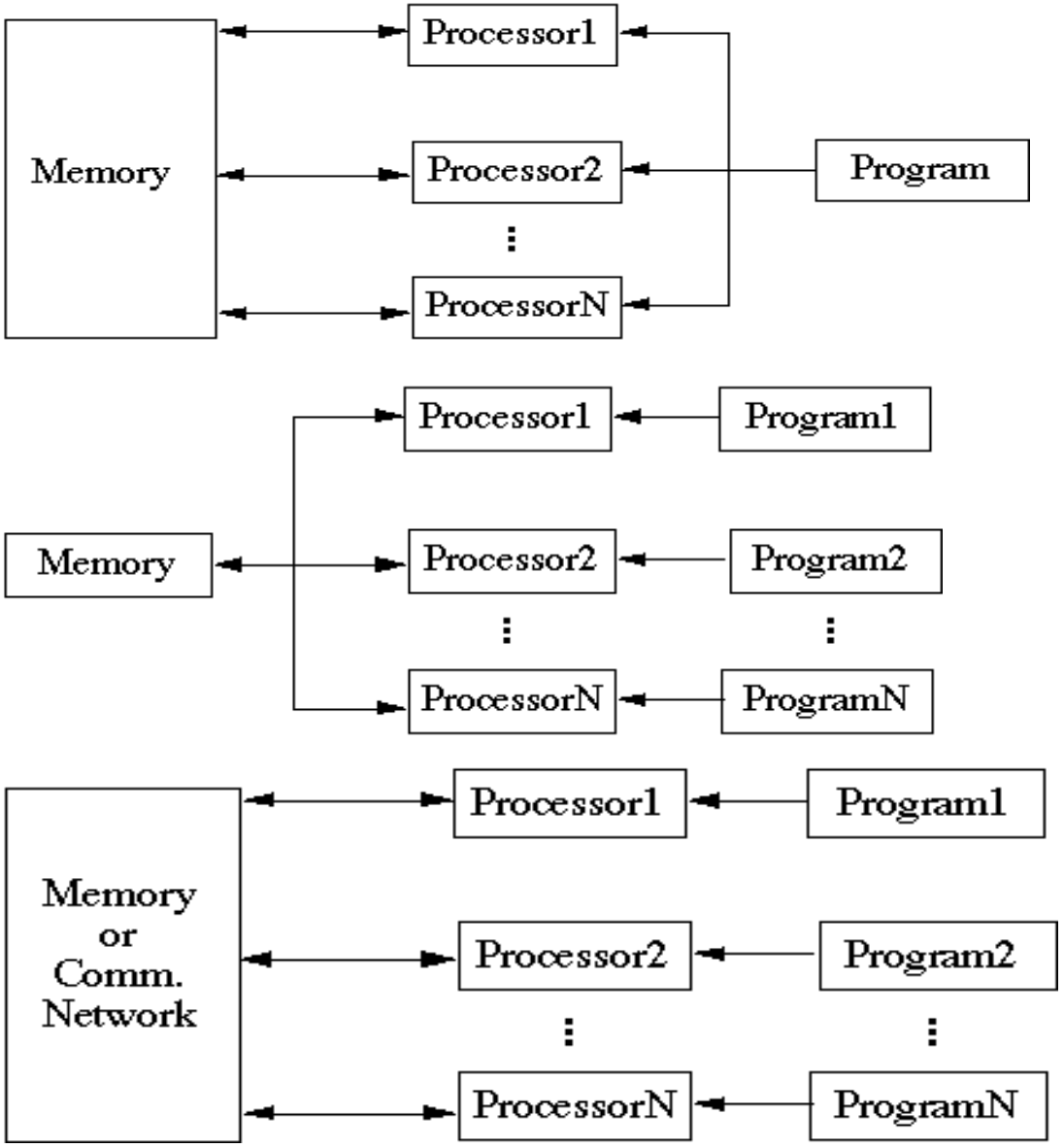
GENERAL IDEA

Is the classic architecture sufficient?



GENERAL IDEA

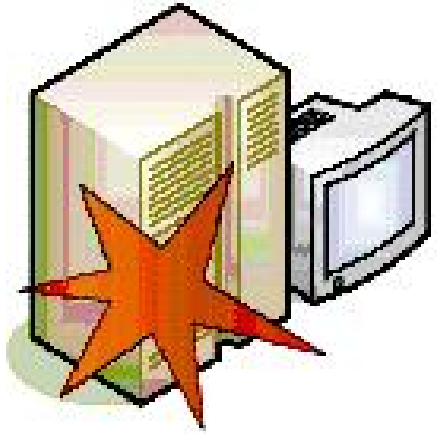
Make the computation in parallel



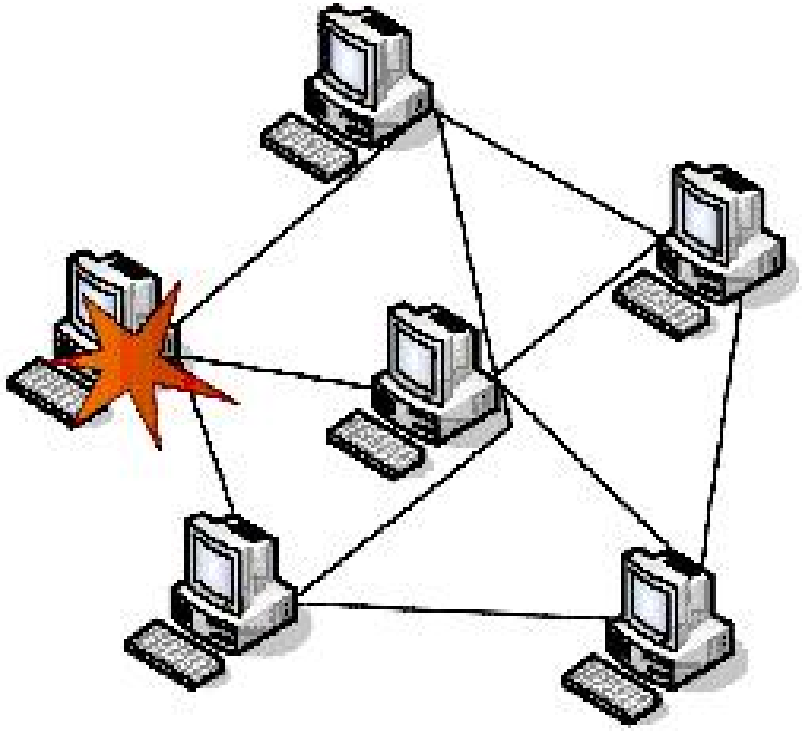
GENERAL IDEA

Distribute the computation

Distributed computing: networks of computer-like devices that can exchange large messages with their neighbors and perform arbitrary local computations.

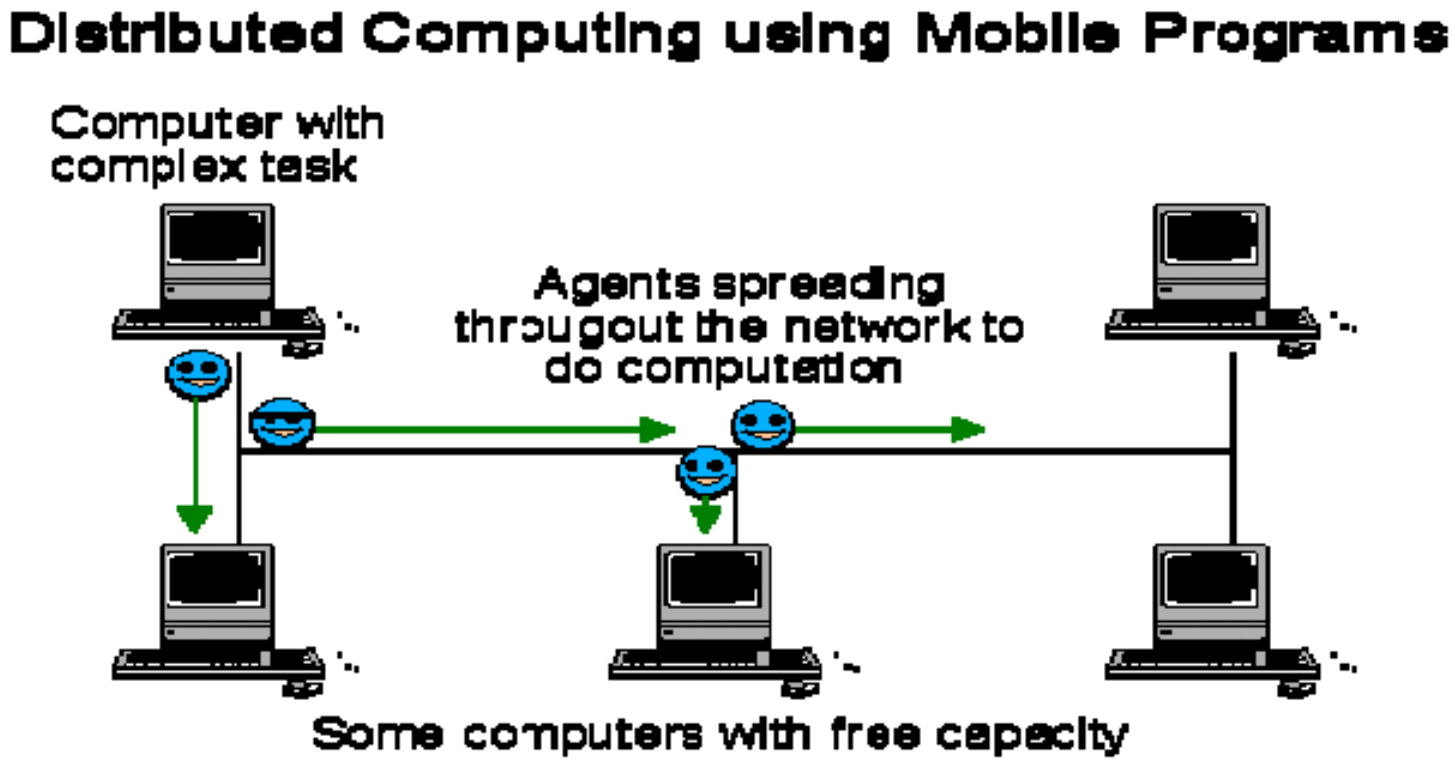


Supercomputers are more powerful, but errors or break downs are disastrous



Distributed computing systems are made up of many systems; so if one crashes, others are unaffected

GENERAL IDEA



-Processors having limited memory and computational abilities.
-Processors having no a priori knowledge of their location.
-Each processor has only a limited, incomplete view of the system.

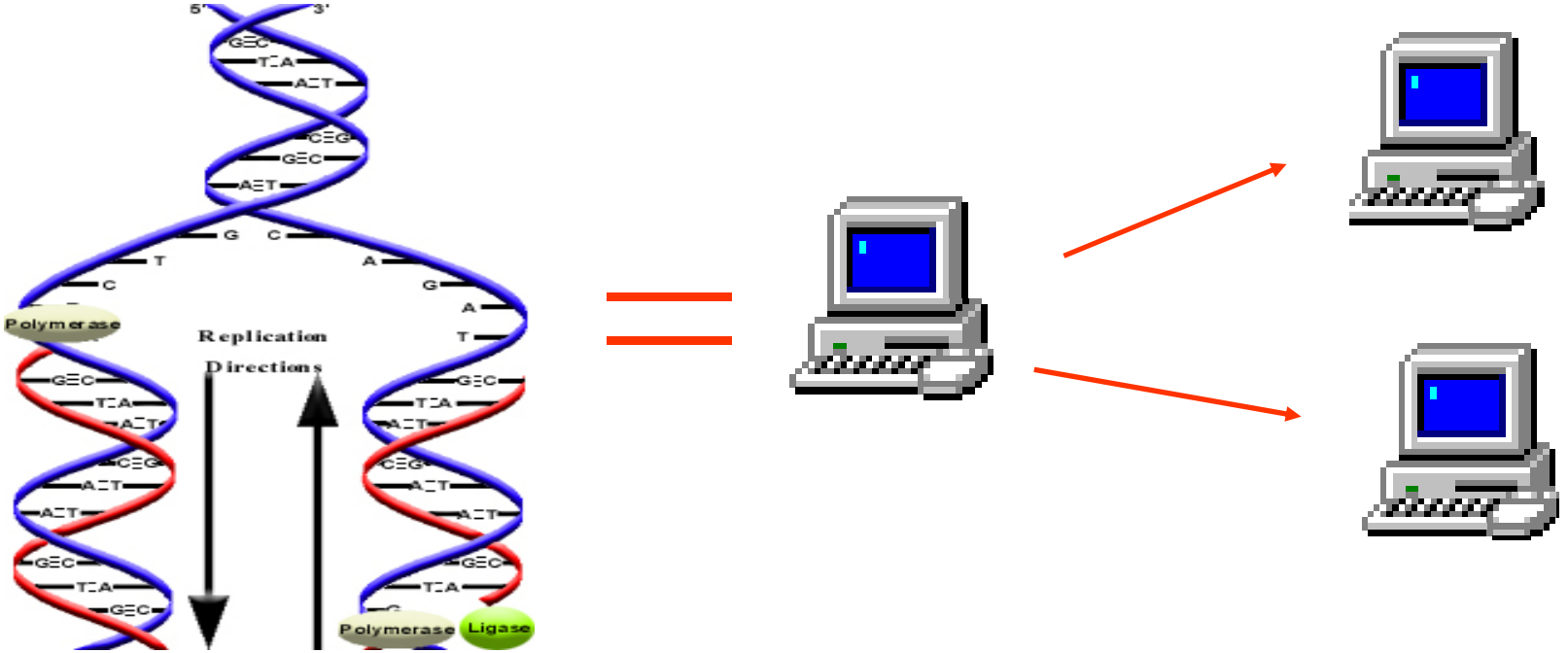
AMORPHOUS COMPUTING

GENERAL IDEA

Approximate the solution

Change the paradigm: natural computing
-Genetic algorithms, neural networks
-Quantum computing
-Molecular computing
and many others

DNA as a computing tool



Peptide

- A molecule consisting of 2 or more amino acids. Peptides are smaller than proteins, which are also chains of amino acids. The dividing line is at about 50 amino acids.
- Any number of amino acids can be joined together in chains of 50 amino acids called peptides, 50-100 amino acids called polypeptides, and over 100 amino acids called proteins. A number of hormones, antibiotics, antitumor agents and neurotransmitters are peptides.

Application of Synthetic Peptides

- **Diagnostic Peptides.** Peptides can be designed that change color under certain conditions, and these can be used for diagnostic purposes. For example, a chromogenic peptide substrate can readily detect the presence, absence and varying blood levels of enzymes that control blood pressure and blood clotting ability.
- **Peptide Drugs.** Peptide drugs are either naturally-occurring peptides or altered natural peptides. There are many naturally-occurring peptides that are biologically active. If a patient does not naturally produce a peptide that they need, this peptide can be synthesized and given to them.

A peptide computer ?

- **DNA** can be used to solve computational problems
  by **DNA** hybridization
- **Antibodies** can be similarly used for calculation
  by specific **peptide** sequence recognition
- **Peptide** computer : 20 different building blocks (amino acids)
- **DNA** computer : 4 different building blocks (nucleotides)

A peptide computer ? (II)

- With hybridization of **DNA** molecules only a yes or no decision (binary) is possible

  → can be applied to NP problems

- The epitopes of **peptides** are recognizable by one or more **antibodies** with different affinities

  → more efficient calculations become possible

- Under easily achievable conditions (temperature, pH value, salt concenration, tc.) each **antibody** binds reliably to its **peptide** (epitope)

A peptide computer ? (III)

- Under easily achievable conditions each **antibody** reliably dissociates from its **peptide** (epitope).
- Use a second **antibody** with a higher affinity for the same epitope
- Use an excess of free epitope
- Change the pH

  If necessary, all **antibodies** bound to the epitopes become covalently (sharing of pairs of electrons between atoms) attached to their epitopes.
- Under neither of the conditions above does any **antibody** bind to another **peptide** (epitope)

Problem 1.

Given two multiset of elements from a finite set (proteins or antibodies of a specific type) compare the number of a given element in the two set. Let G and H be the two sets and X be the element.

Solution (I)

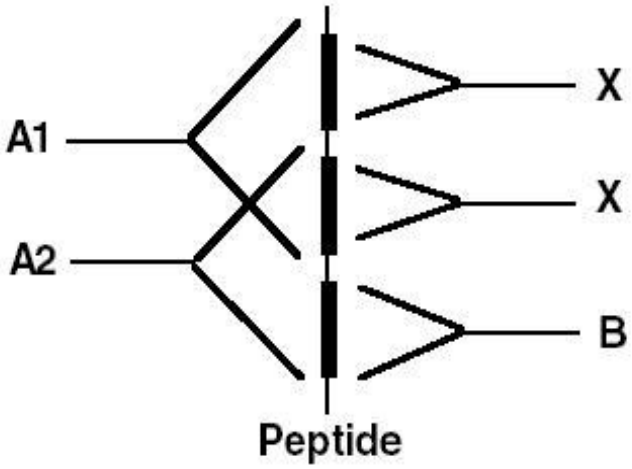


Fig. 1. Binding sites of the antibodies X, $A1$, $A2$ and B to the corresponding epitopes. The epitopes are shown by thick lines on the peptide (thin line). The length of an epitope is about ten amino acids. The whole length of the peptide is between 30 and 40 amino acids.

Affinity of **antibodies**

$B > A_2 > X > A_1$

1. Two disjoint epitopes for X
2. A1, A2, and B are not present in the two sets
3. The affinity of the upper epitope for X is higher that the lower one. This can be accomplished by replacing an amino acid with a similar one.

Solution (II)

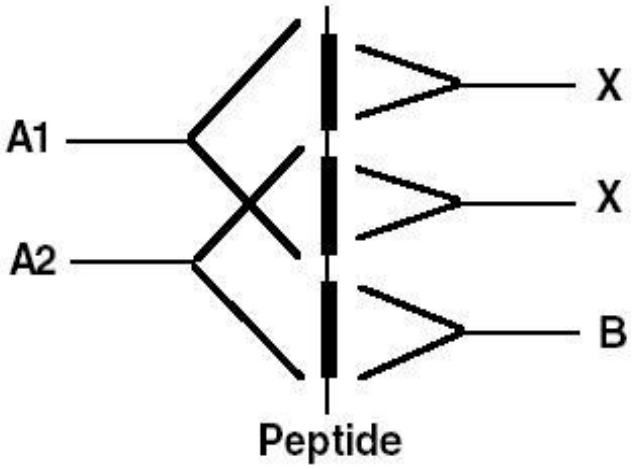


Fig. 1. Binding sites of the antibodies X, $A1$, $A2$ and B to the corresponding epitopes. The epitopes are shown by thick lines on the peptide (thin line). The length of an epitope is about ten amino acids. The whole length of the peptide is between 30 and 40 amino acids.

Affinity of **antibodies**

$B > A_2 > X > A_1$

1. The element X of the first set is bound to one of the possible binding sites for X on the peptide
2. The element X of the second set is bound to the other binding sites for X on the peptide
3. A set containing labelled element of X is used to detect any free binding site for X

Detection is by fluorescence

Solution (III)

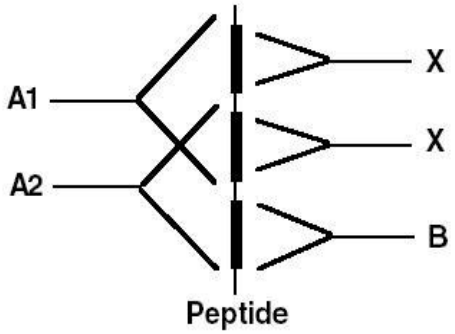


Fig. 1. Binding sites of the antibodies *X*, *A1*, *A2* and *B* to the corresponding epitopes. The epitopes are shown by thick lines on the peptide (thin line). The length of an epitope is about ten amino acids. The whole length of the peptide is between 30 and 40 amino acids.

Affinity of **antibodies**

$B > A_2 > X > A_1$

1. Antibody A_2 is added. It blocks the second epitope for X
2. Elements of G are added. X are bound to the first epitope.
3. B is added. It removes A_2.
4. A_1 is added. It binds to the peptides with two free epitopes.
5. A cross-linker is added. All bound antibodies are covalently attached.

Solution (IV)

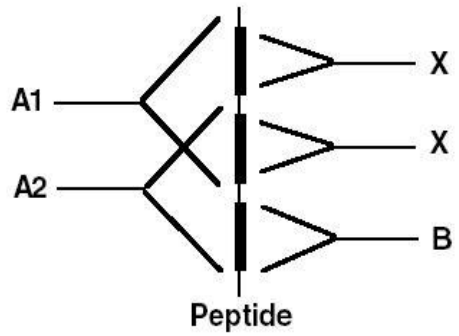


Fig. 1. Binding sites of the antibodies X, $A1$, $A2$ and B to the corresponding epitopes. The epitopes are shown by thick lines on the peptide (thin line). The length of an epitope is about ten amino acids. The whole length of the peptide is between 30 and 40 amino acids.

Affinity of **antibodies**

$$B > A_2 > X > A_1$$

6. H is added. X are bound on the second epitopes. They are covalently attached.
7. Labelled (fluorescent) X is added. It binds to free epitopes.
8. Detect fluorescence.

Problem 2.

Estimate the number of a given antibody in a multiset. Let X be the antibody and G be the set.

2^n : upper bound for the number of antibodies X in G

Solution (I)

- Prepare different peptides with different epitopes $E_1, E_2, \ldots, E_n$ in different amounts
- Each peptide contains an epitope for X and an overlapping epitope E_k
- Antibody A_k binds to E_k
- Number of peptides with E_k is approx. 2^k
- A labelled antibody Y that binds to the epitope for X
- $A_k > X > Y$

Solution (II)

1. Add G together with 2^n peptides E_n . X binds to its epitopes
2. Labelled Y is added. It binds to the remaining epitopes.
3. Detect Y. If Y is not detected, STOP.
4. k=n-1
5. Add A_{k+1} si 2^k peptides E_k . A_{k+1} removes X which will bind to its epitopes in E_k
6. Labelled Y is added. It binds to the remaining epitopes of E_k.
7. Detect Y. If Y is not detected, STOP.
8. k=k-1. If k > 0 goto 5.

Problem 3.

Satisfiability problem. $F = C_1 \wedge C_2 \wedge \ldots \wedge C_k$

Instance: $F = (v_1 \vee v'_2) \wedge v'_2 \wedge (v_1 \vee v_2)$

X_1=(false,false)
X_2=(false, true)
X_3=(true,false)
X_4=(true,true)

v_1=true
v_2=false

Solution (I)

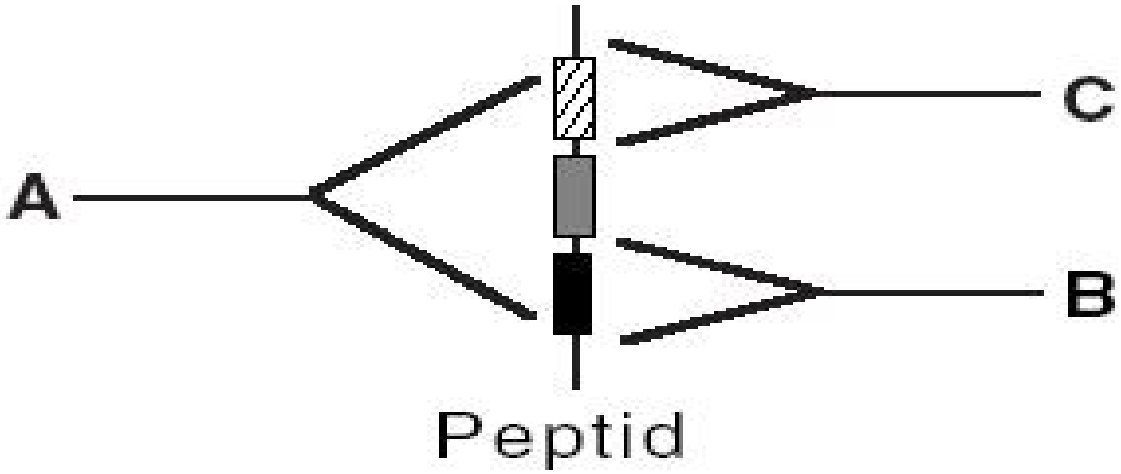


Fig. 2. Binding sites of the antibodies A, B and C to their corresponding epitopes. The antibody B and the antibody C are the same for each assignment. The antibody A is specific for each assignment. Antibodies A recognize an epitope which includes a specific part (gray) and the epitopes for B (black) and C (hatched). The binding affinities are $C > A > B$. The order of the epitopes on the peptide is arbitrary.

Solution (II)

We prepare $G_i = \{A \mid$ the corresponding assignment makes C_i true$\}$

Instance: $F = (v_1 \vee v'_2) \wedge v'_2 \wedge (v_1 \vee v_2)$

X_1=(false,false)
X_2=(false, true)
X_3=(true,false)
X_4=(true,true)

$G_1 = \{A_1, A_3, A_4\}$
$G_2 = \{A_1, A_3\}$
$G_3 = \{A_2, A_3, A_4\}$

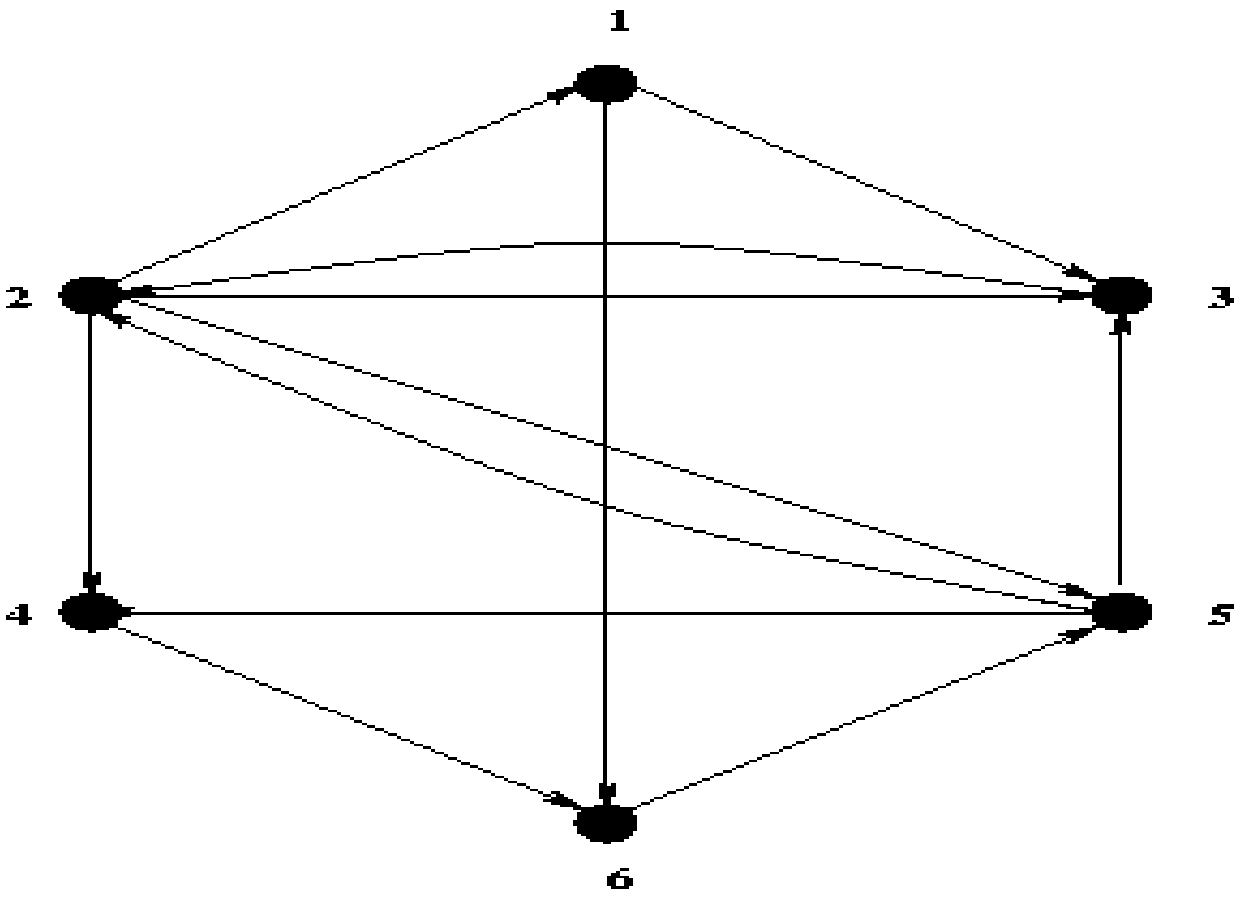
Solution (III)

1. G_k is added. Antibodies A of G_k bind to their epitopes. (All peptides corresponding to A_1 remain unbounded.)
2. Antibodies B are added. (B bind to all peptides corresponding to A_1)
3. Antibodies C are added. All antibodies A are removed while B remain bounded.
4. Antibodies C are removed by adding epitope C in excess.
5. All remaining antibodies are covalently attached.
6. k=k-1 If k > 0 goto 1
7. Add labelled antibodies A or B
8. Detect fluorescence.

Hamiltonian Path Problem

- $G = (V,E)$ is a directed graph
- $V = \{v_1, v_2, \ldots, v_n\}$ is the vertex set
- $E = \{e_{ij} \mid v_i$ is adjacent to $v_j\}$ is the edge set
- v_1 - source vertex, v_n – end vertex
- **Problem** – Test whether there exists a Hamiltonian path between v_1 and v_n

Graph *G*



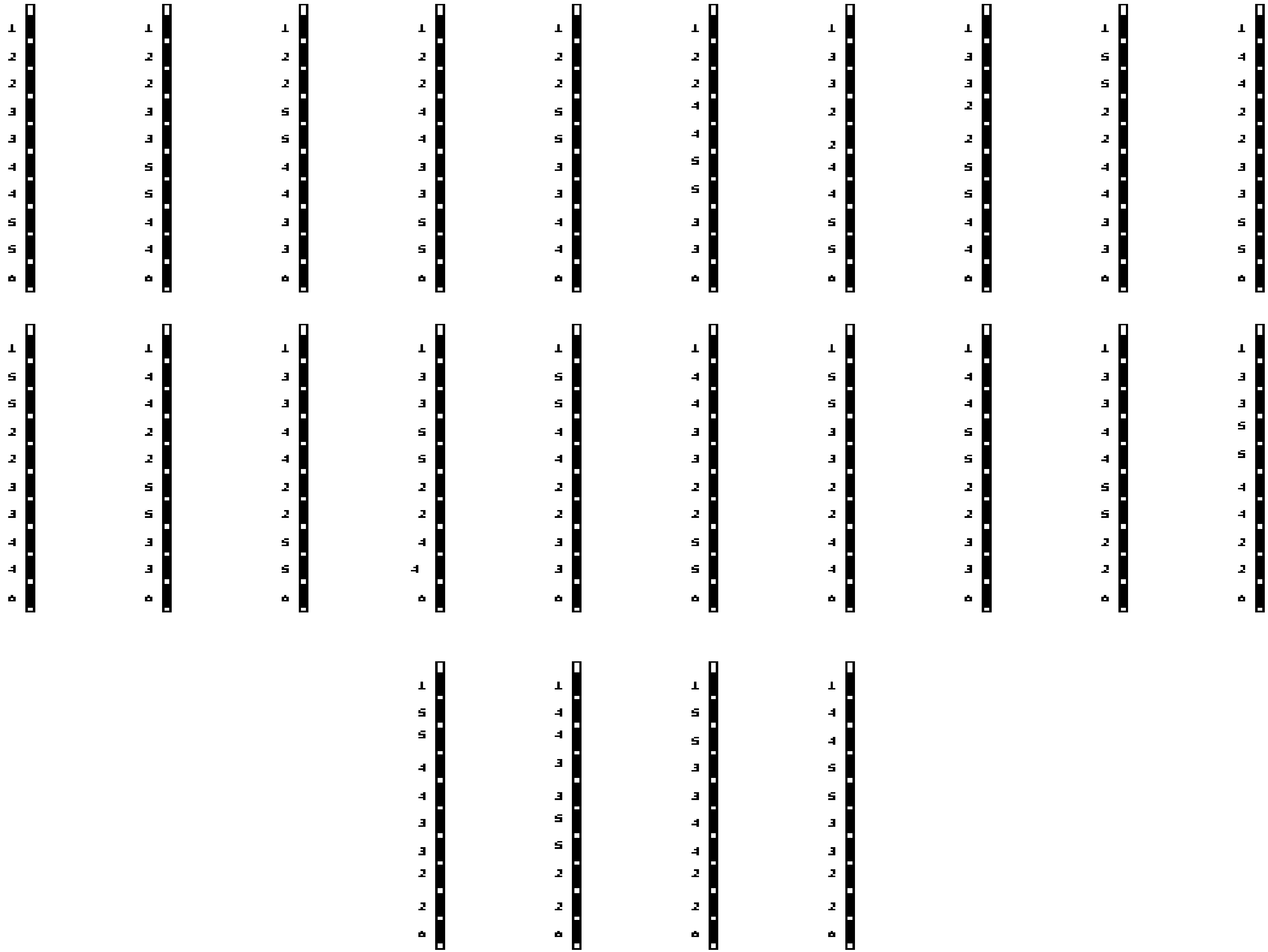
Peptides Formation

- Each vertex v_i has a corresponding epitope ep_i
- Each peptide has ep_1 on one extreme and ep_n on the other extreme
- All doubly duplicated permutations of

  $\{ep_2, \ldots, ep_{n-1}\}$ are formed in each of the peptide in between ep_1 and ep_n

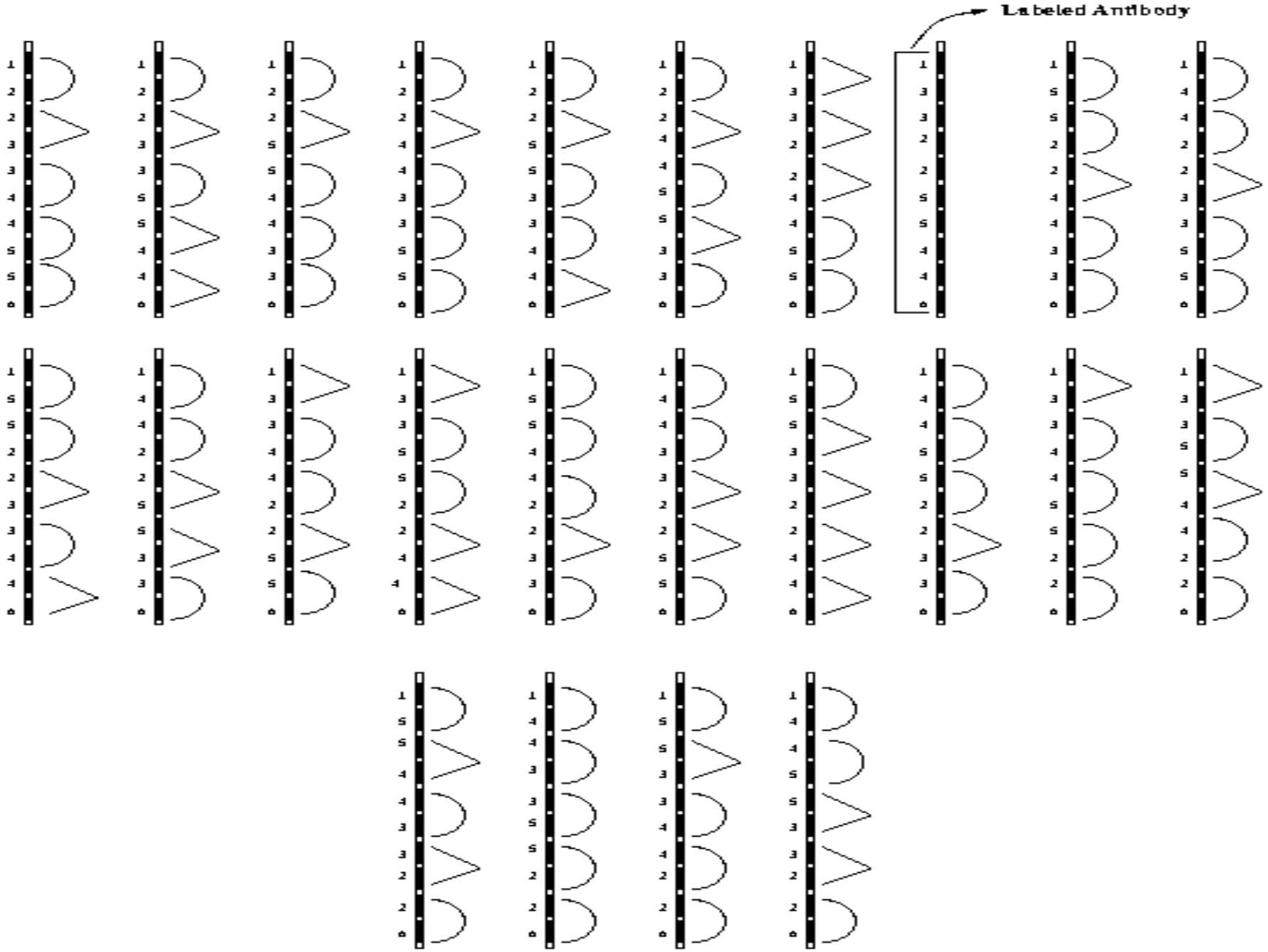
Antibody Formation

- Form antibodies A_{ij} – site = $ep_i ep_j$ s.t. v_j is adj. to v_i
- Form antibodies B_{ij} – site = $ep_i ep_j$ s.t. v_j is not adj. to v_i
- Form antibody C – site is whole of peptide
- Affinity(B_{ij}) > Affinity(C)
- Affinity(C) > Affinity(A_{ij})

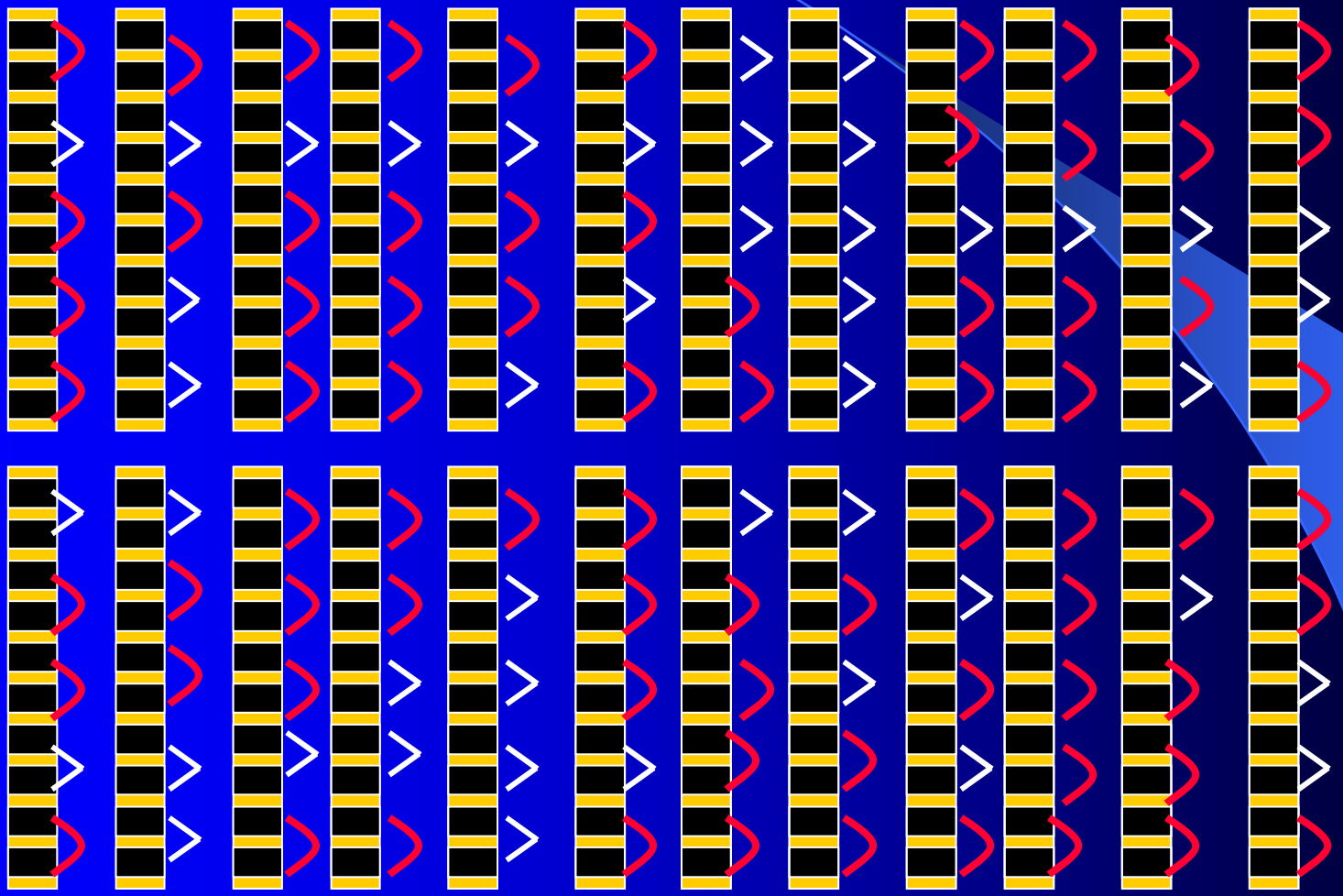


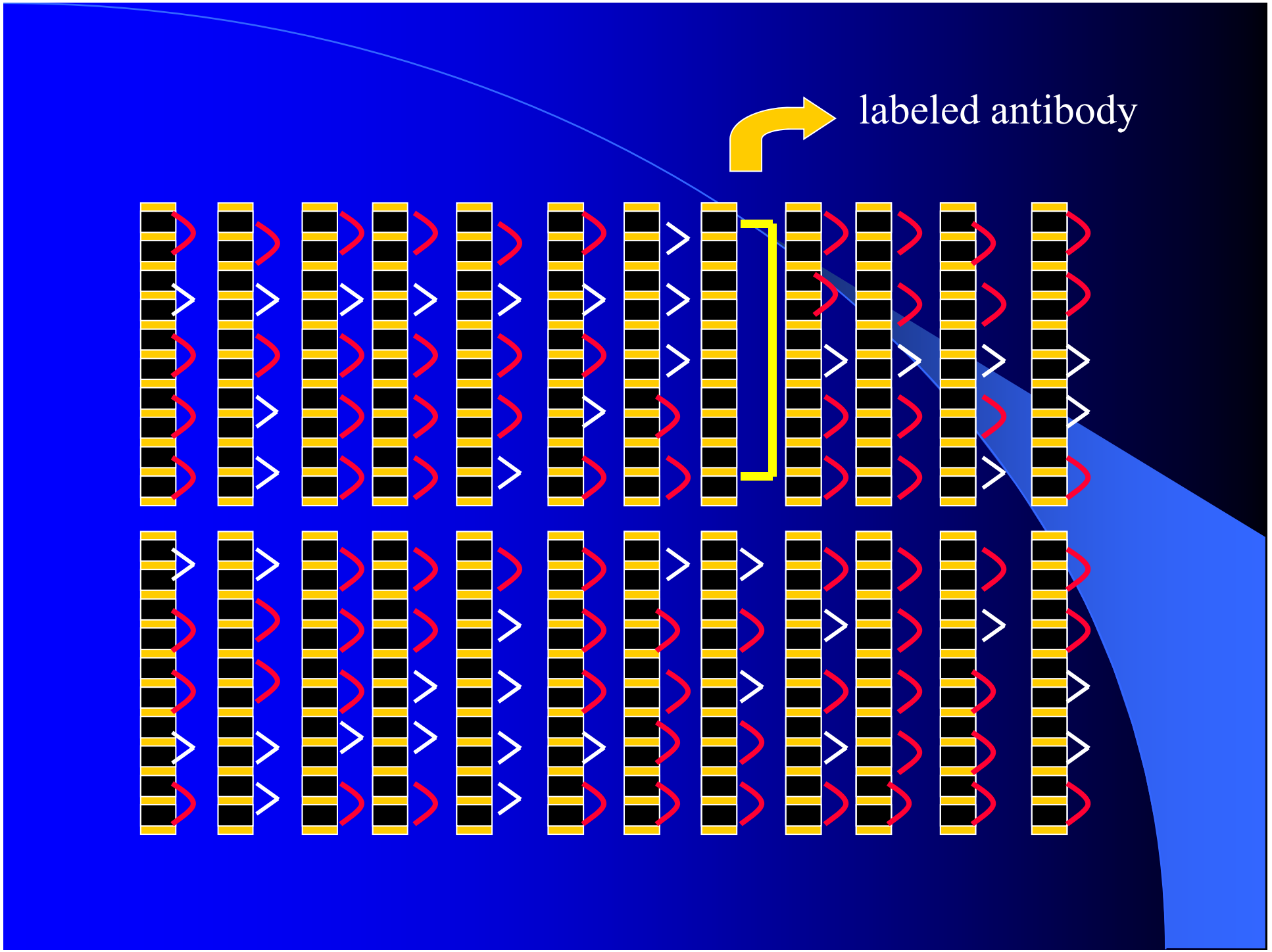
Algorithm

1. Take all the peptides in an aqueous solution
2. Add antibodies A_{ij}
3. Add antibodies B_{ij}
4. Add labeled antibody C
5. If fluorescence is detected answer is *yes* or else the answer is *no*


Labeled Antibody

Peptide with Antibodies




labeled antibody