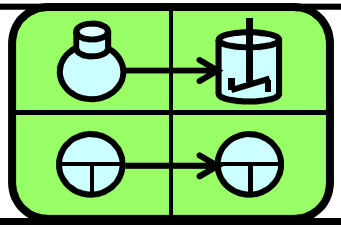
R&D Project Management in the Chemical Industry



The following collection of PowerPoint® Charts is intended to further clarify and supplement the relevant specialist publications on the subject matters dealt with. This collection in no way is used for any commercial purposes, but as learning material for students.

Selected sources for in-depth studies of the respective subject matters are given in some lists of references.

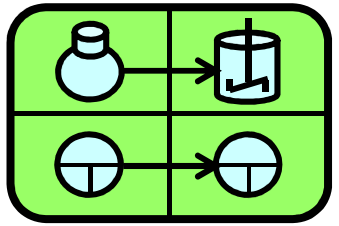
The chemical-technical target components listed in the case study tasks, the formulas, deadlines, economic and technical data as well as the data in the "profile boxes" are widely with a practical orientation, but purely fictitious.

They are solely used for a vivid depiction of the methods and as exercise materials.

Congruence with target sets of third parties would be purely coincidental.

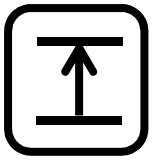
Rainer Buerstinghaus

R&D Project Management
in the Chemical Industry



Supplementary Module 02 for (Bio) Chemists (m/f/d)

Information Material *for the subject matter:*
Innovation, jump of the technical progress.



Insecticidal "Sodium Channel Activators".

Insecticidal "AChE Inhibitors".

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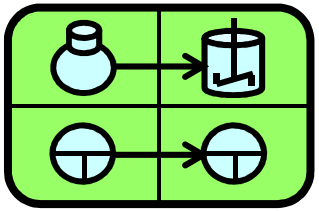
R&D Project Management in the Chemical Industry



Subject Matter

Jump of Technical Progress

Chemical-Biological Basics: Insecticidal "AChE Inhibitors".

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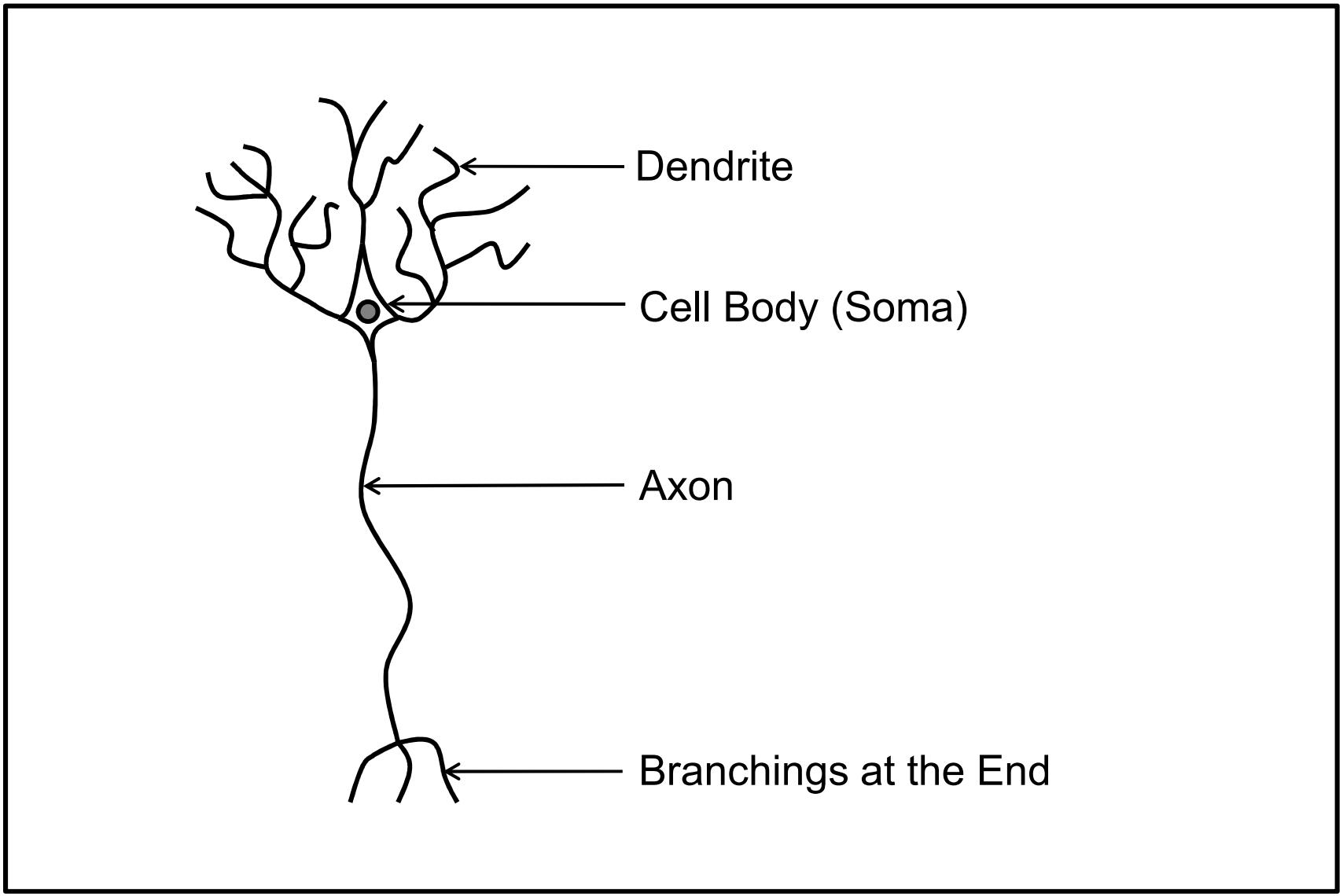
General Structure of a Single Nerve Cell (Neuron)



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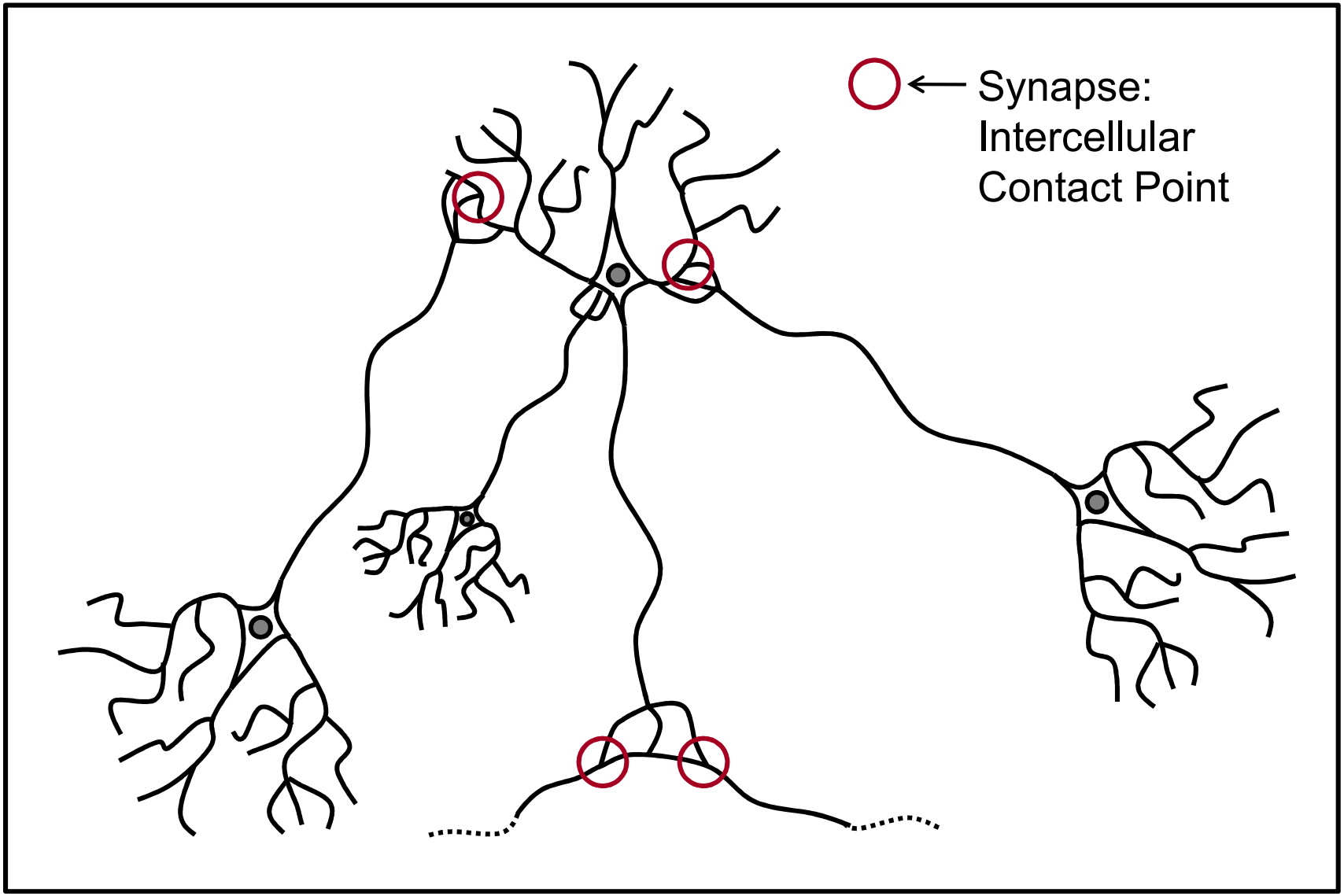
Nerve Cells (Neurons), Connections via Synapses



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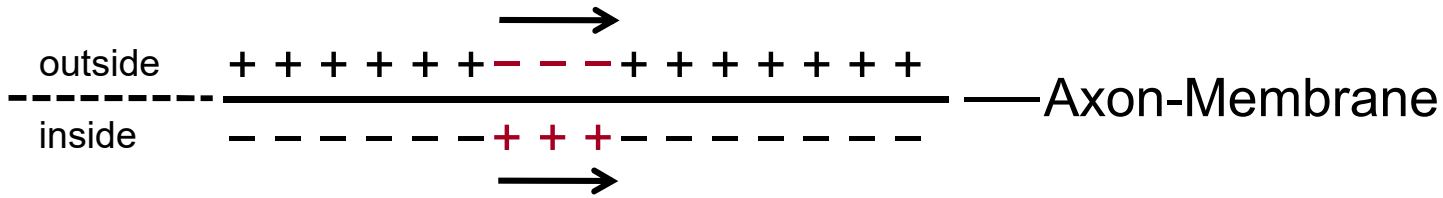
Nervous System, Principles of Impulse Transmission

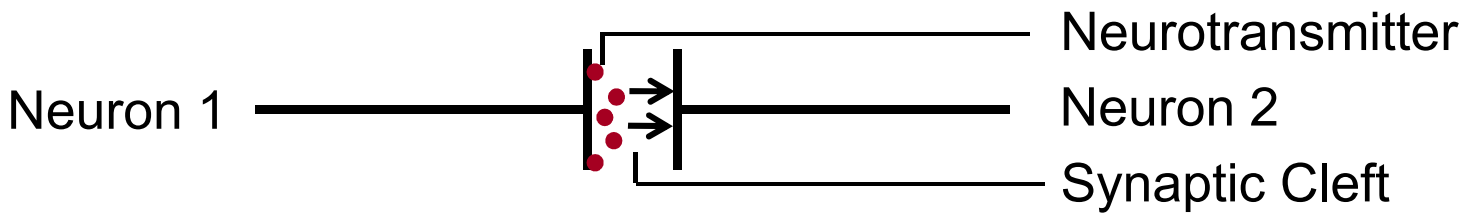
Inside the Cell:

- In an electrical way.
- Continuous changes in membrane potential.



From one nerve cell to the next:

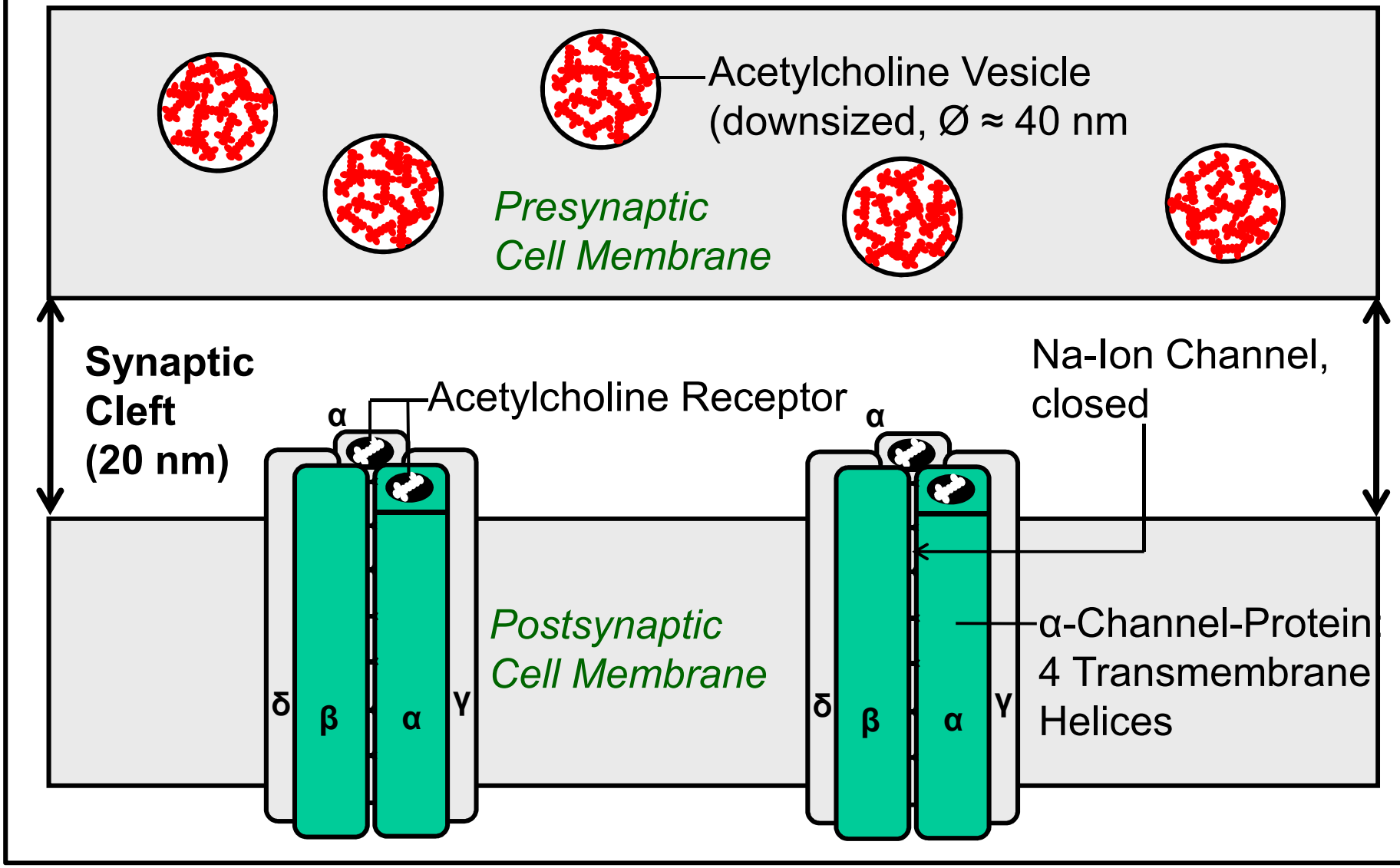
- By chemical means.
- Diffusion of neurotransmitters.



Rainer Buerstinghaus

Synaptic Cleft (20 nm) between two Nerve Cells

ACh-Receptor with the 5 Subunits (α, β, α, γ, δ):



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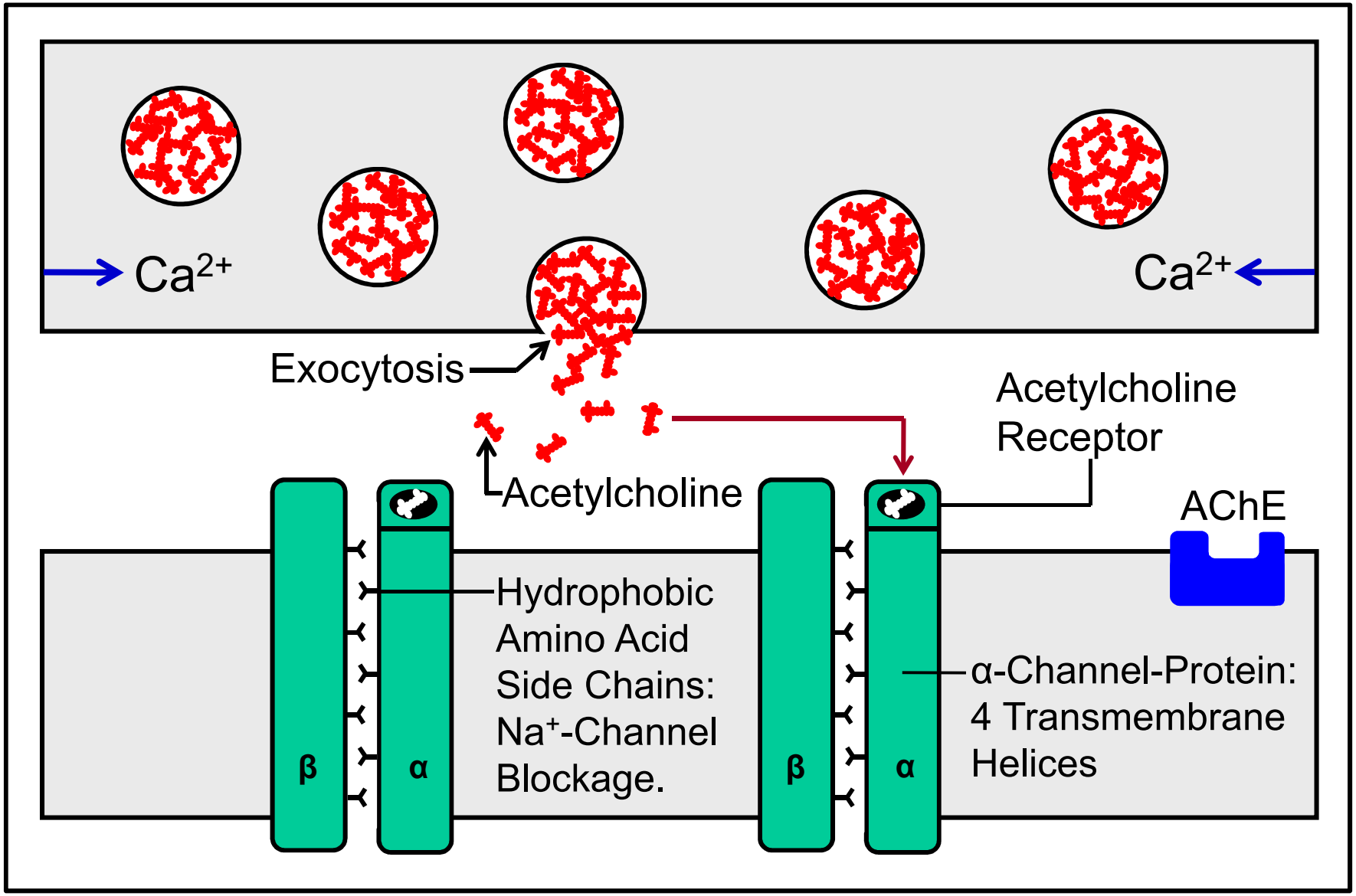
Synaptic Cleft (20 nm) between two Nerve Cells



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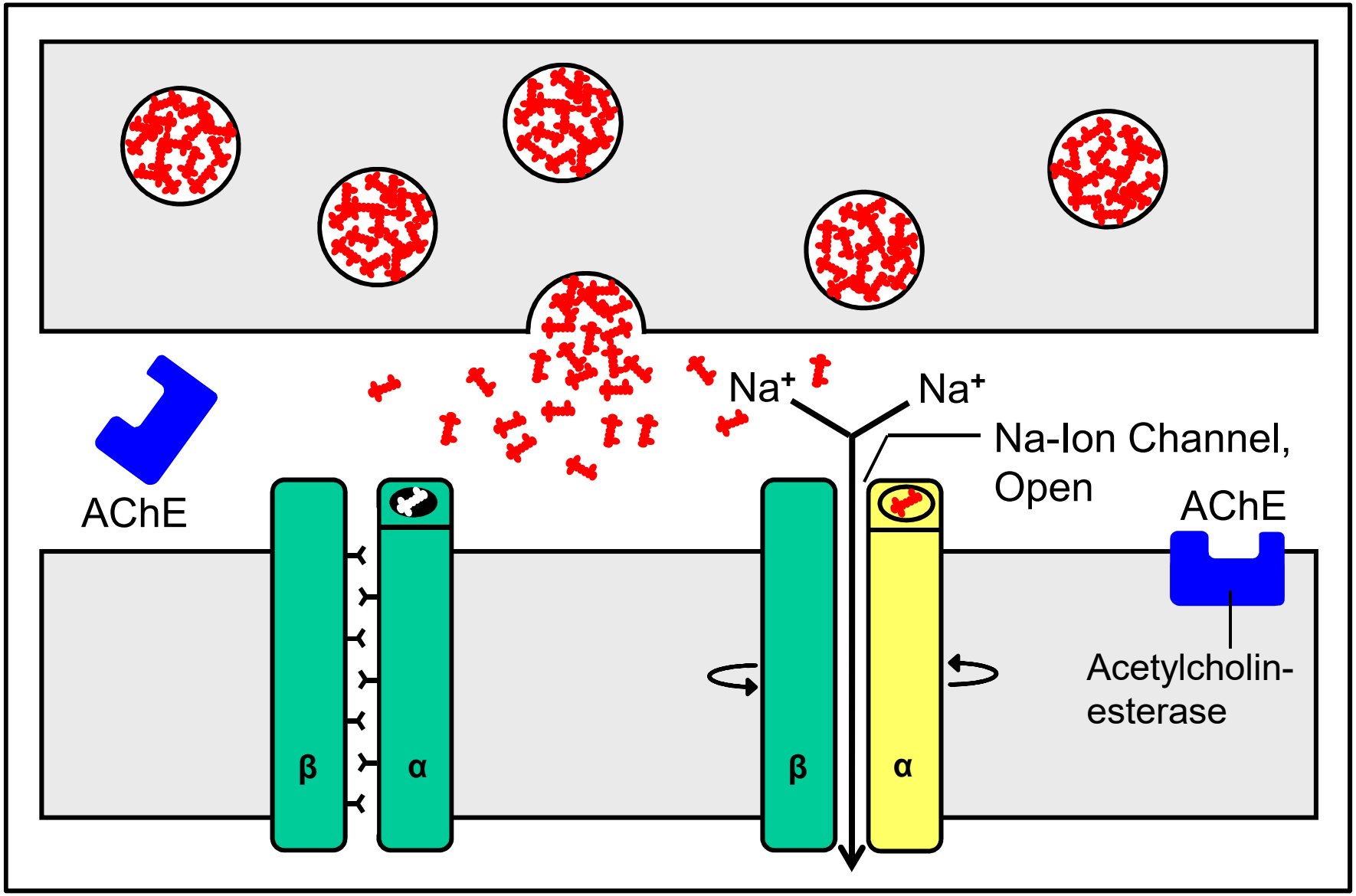
Synaptic Cleft (20 nm) between two Nerve Cells



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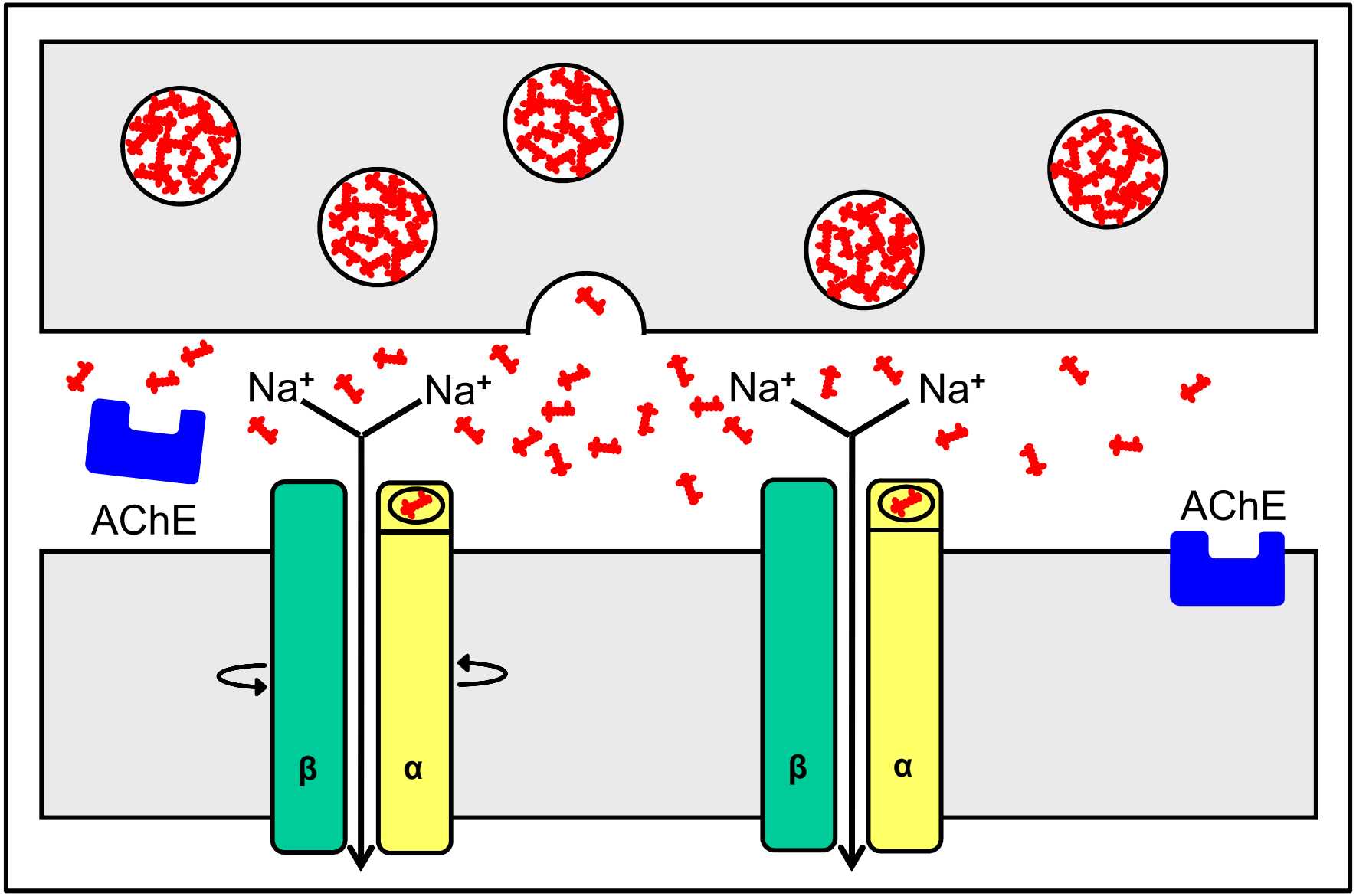
Synaptic Cleft (20 nm) between two Nerve Cells



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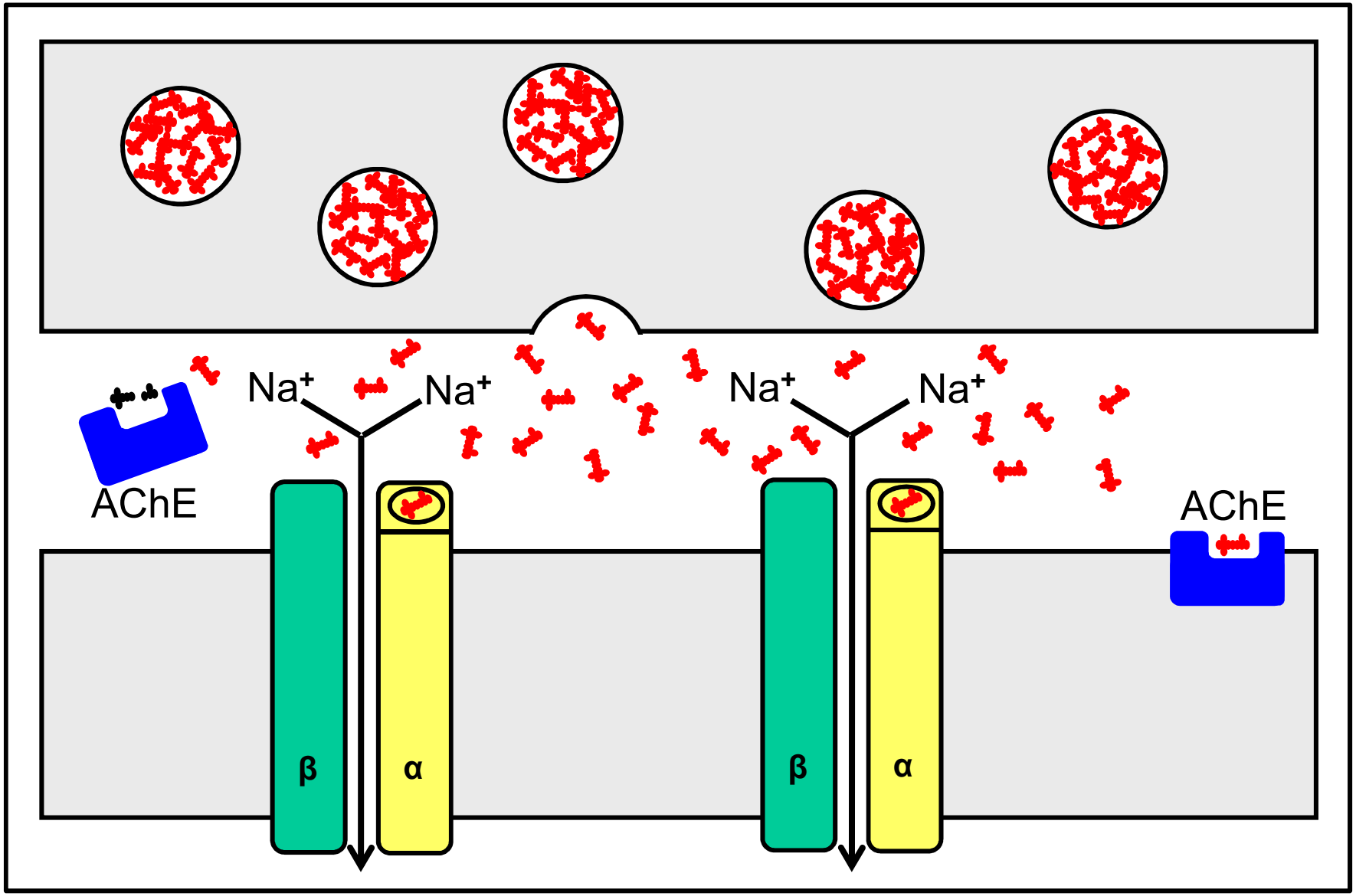
Synaptic Cleft (20 nm) between two Nerve Cells



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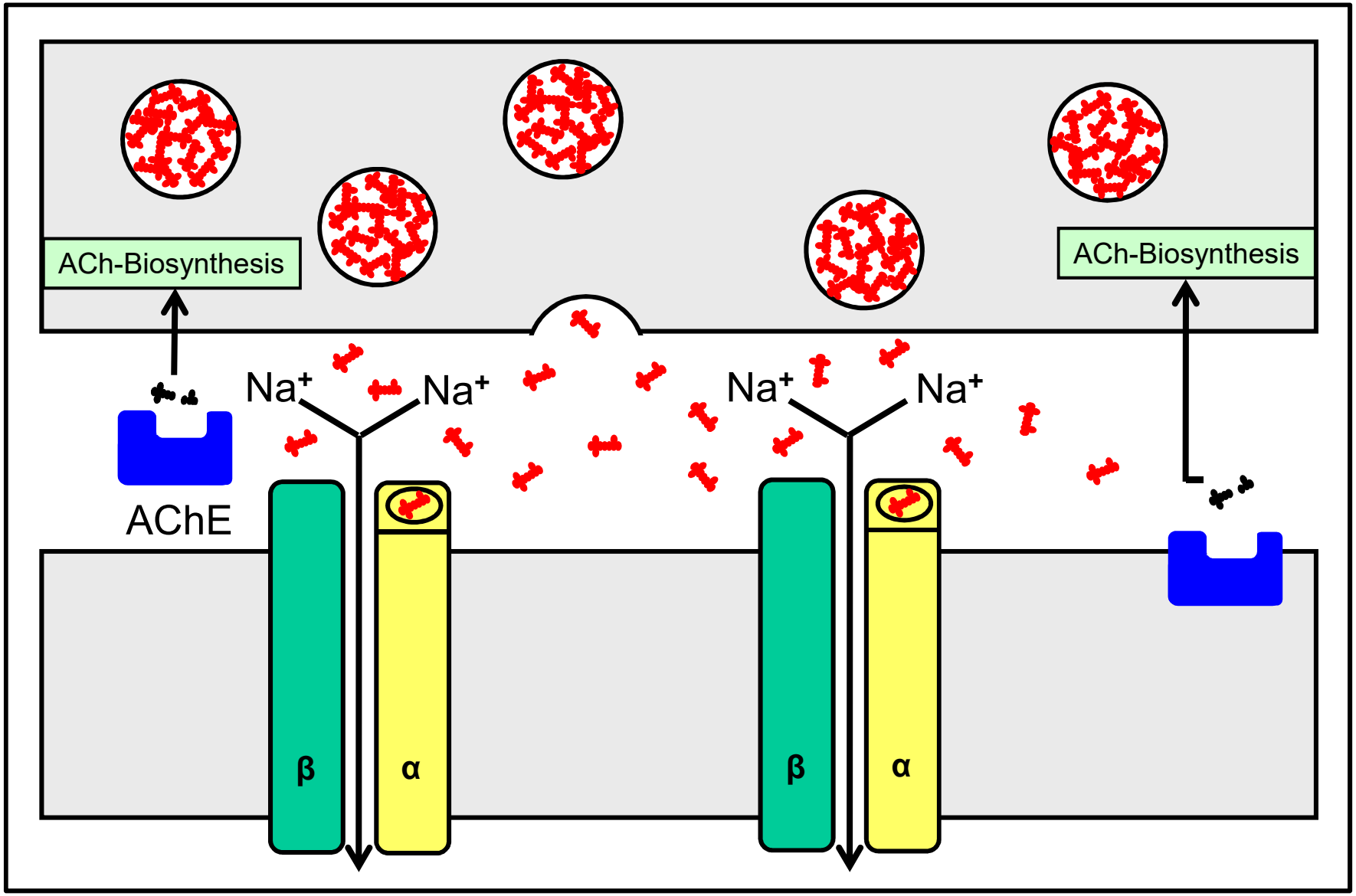
Synaptic Cleft (20 nm) between two Nerve Cells



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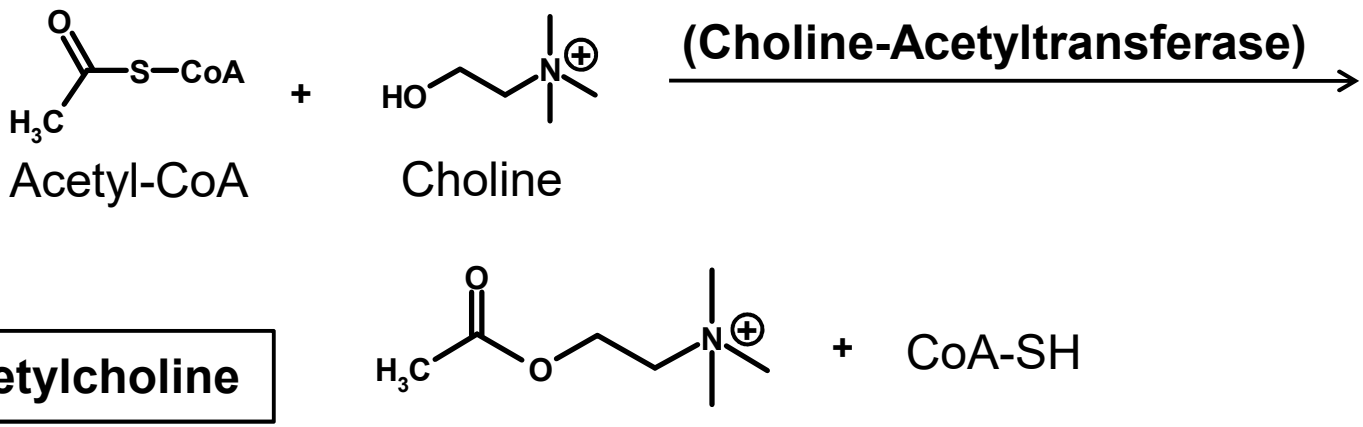
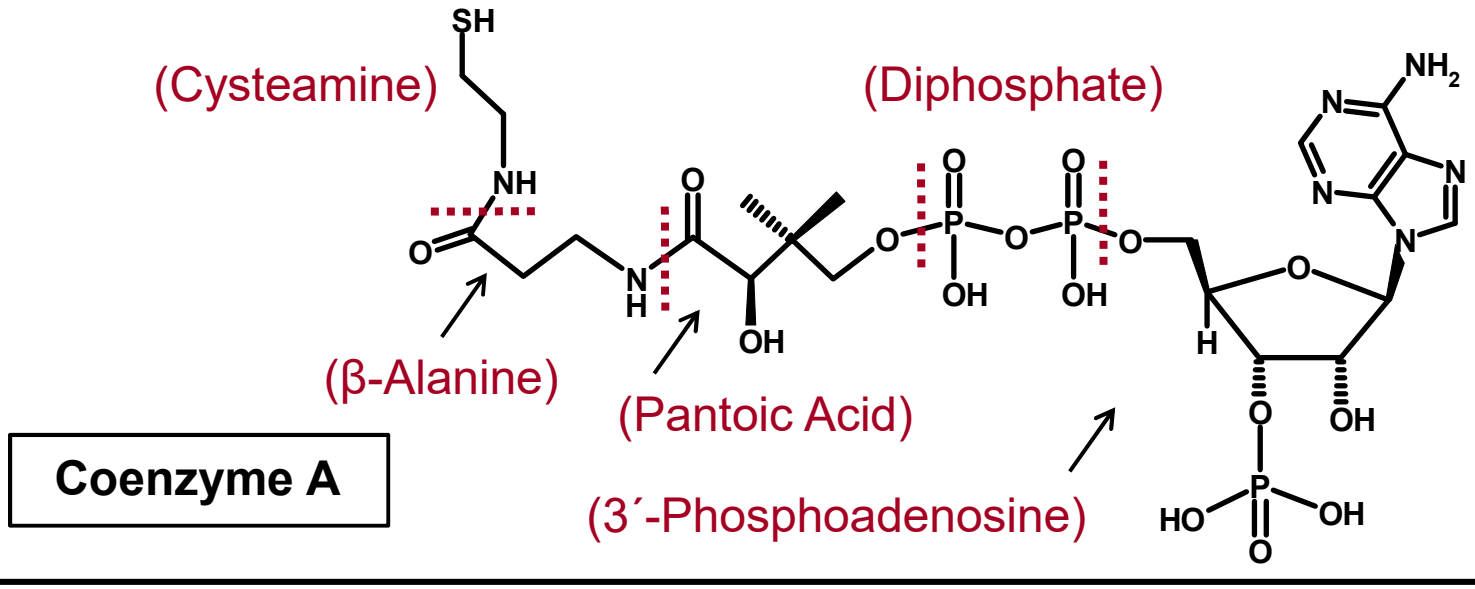
Biosynthesis of Acetylcholine from Choline; Acetyl-CoA





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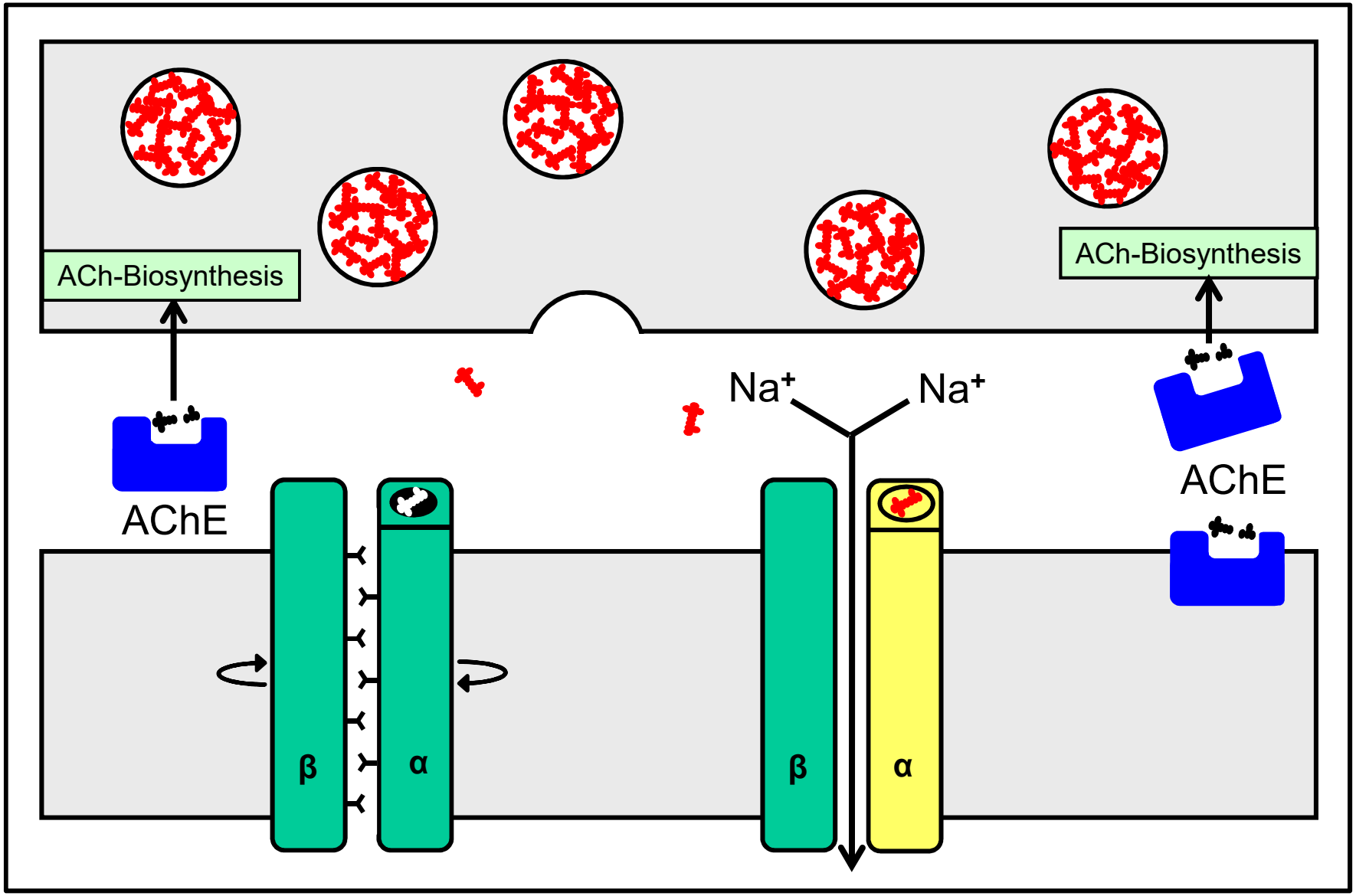
Synaptic Cleft (20 nm) between two Nerve Cells



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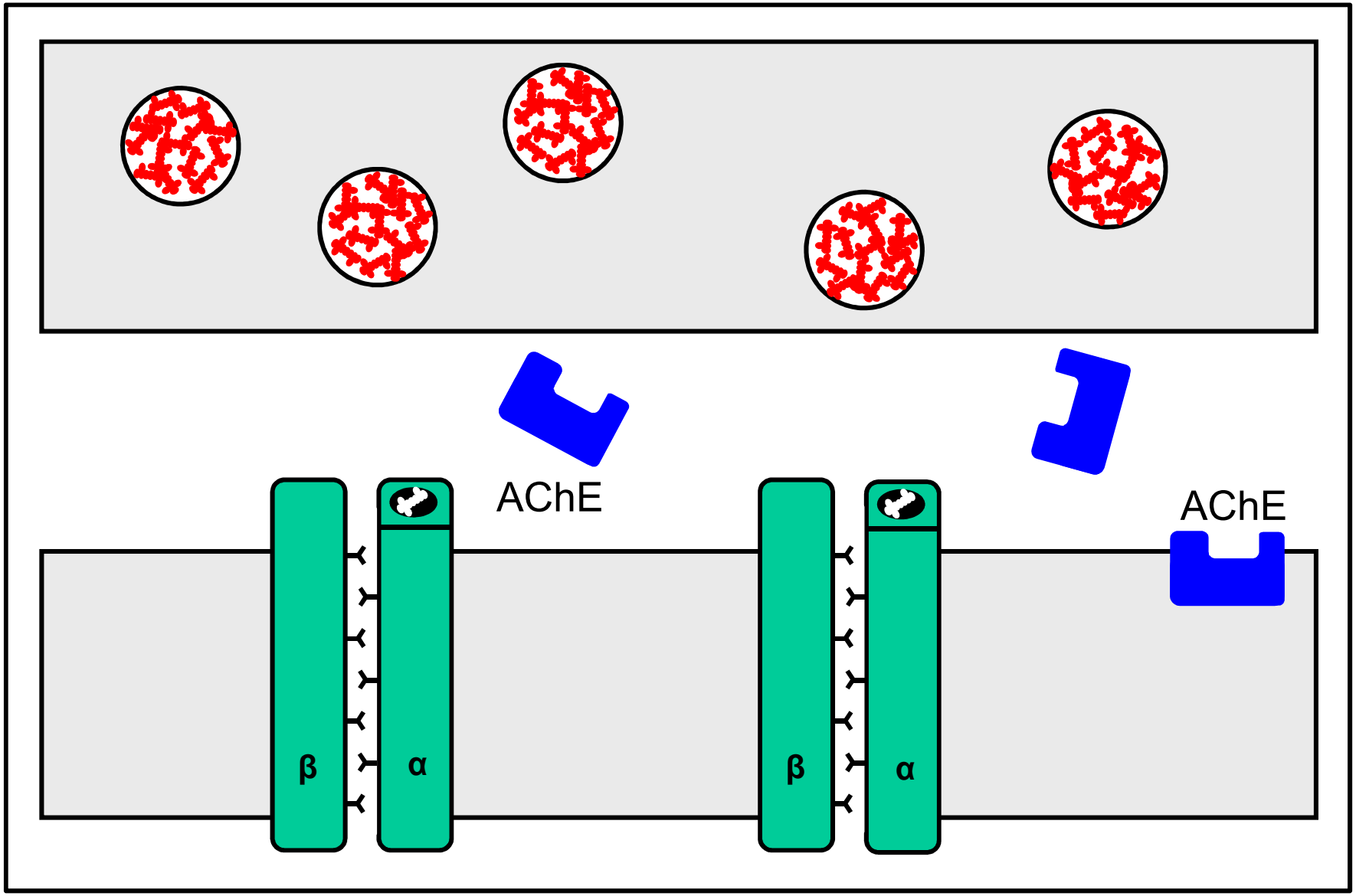
Synaptic Cleft (20 nm) between two Nerve Cells



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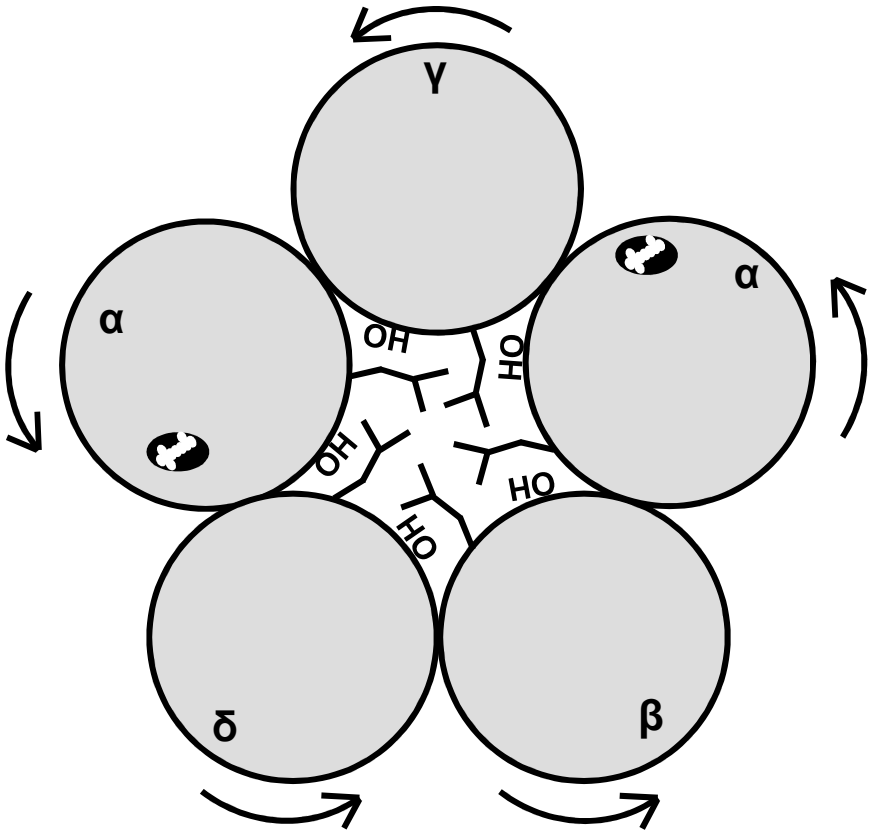
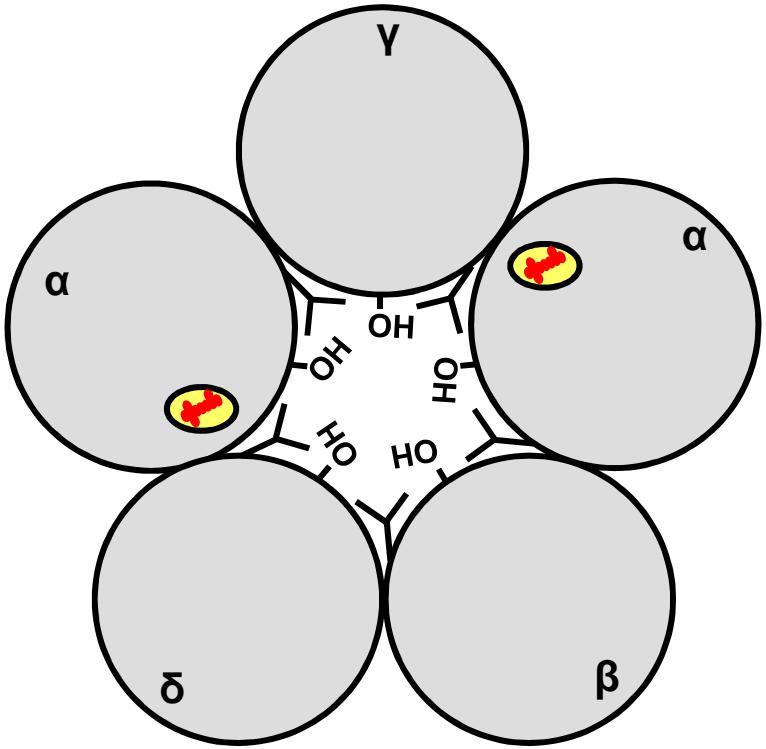
Subunits of the Nicotinic ACh-Receptor

α, δ, β, α, γ: 5 Channel Helices, Their Rolling Sliding Motion:





OH: From Serine

: Acetylcholine-Receptor

: From Leucine

: Acetylcholine

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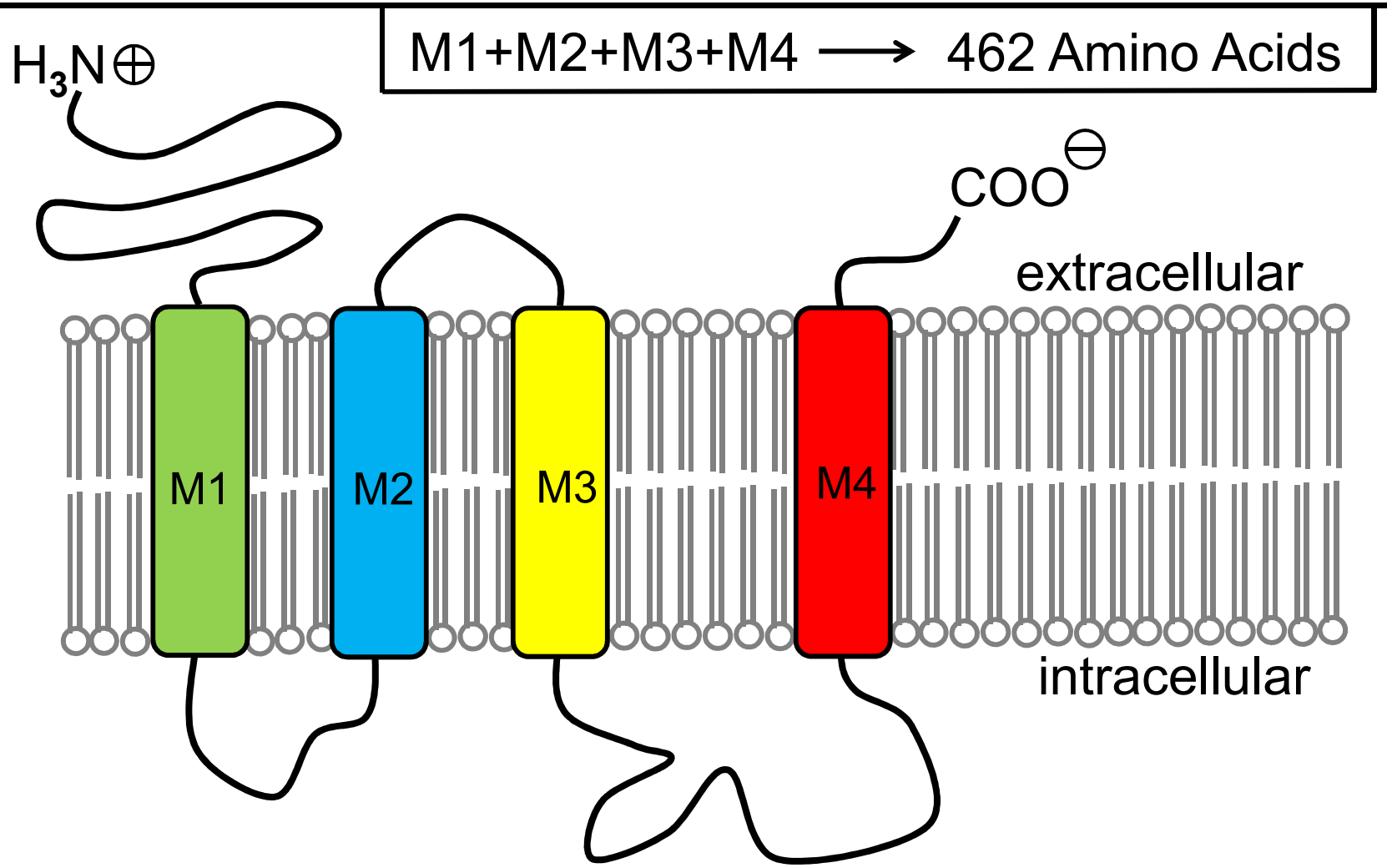
α-Subunit of the Nicotinic ACh Receptor

Loop-Forming Protein with Four Helical Transmembrane Segments M1, M2, M3 and M4:



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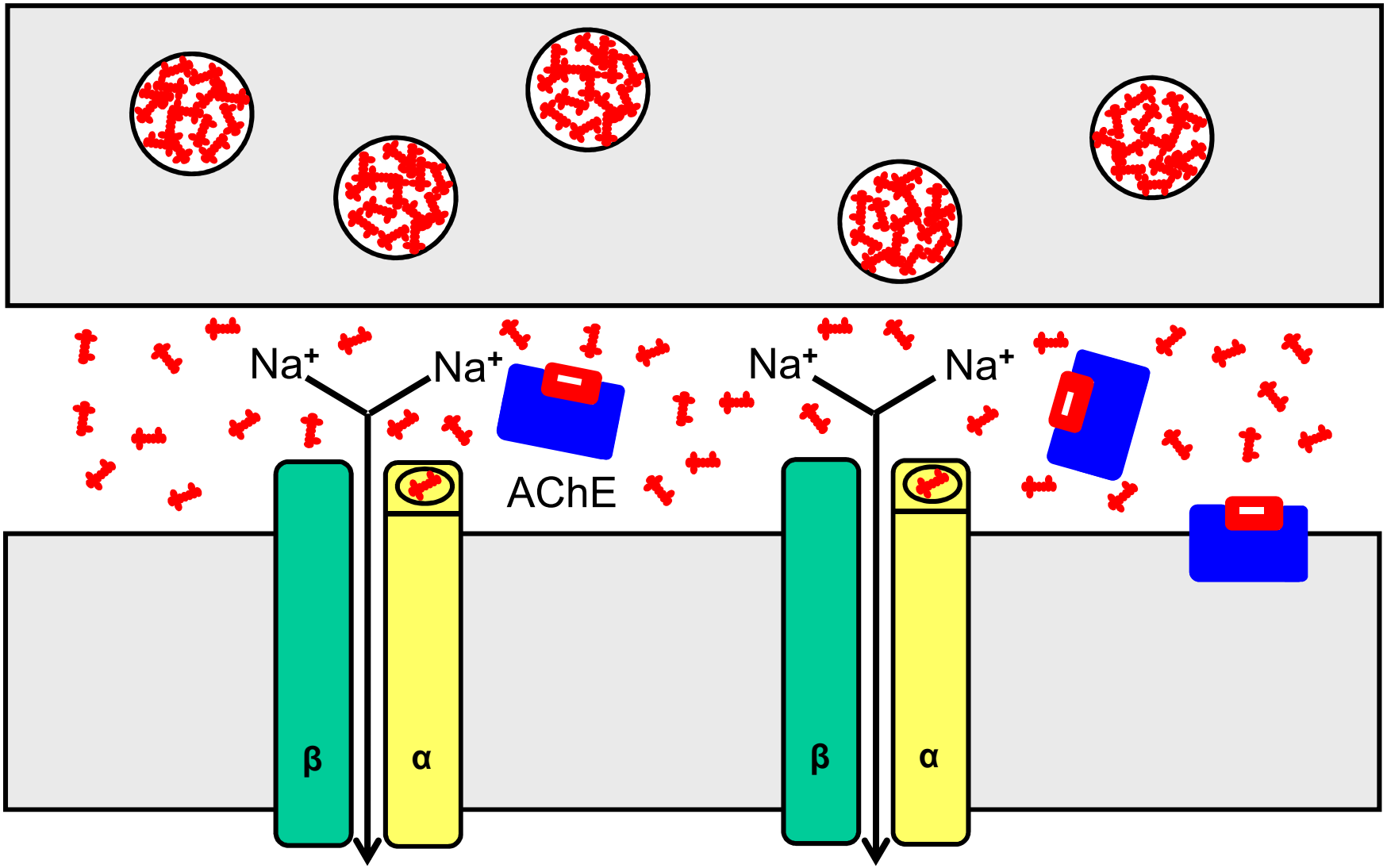
Synaptic Cleft (20 nm) between two Nerve Cells

Blocked Acetylcholinesterase, Permanent Excitation:



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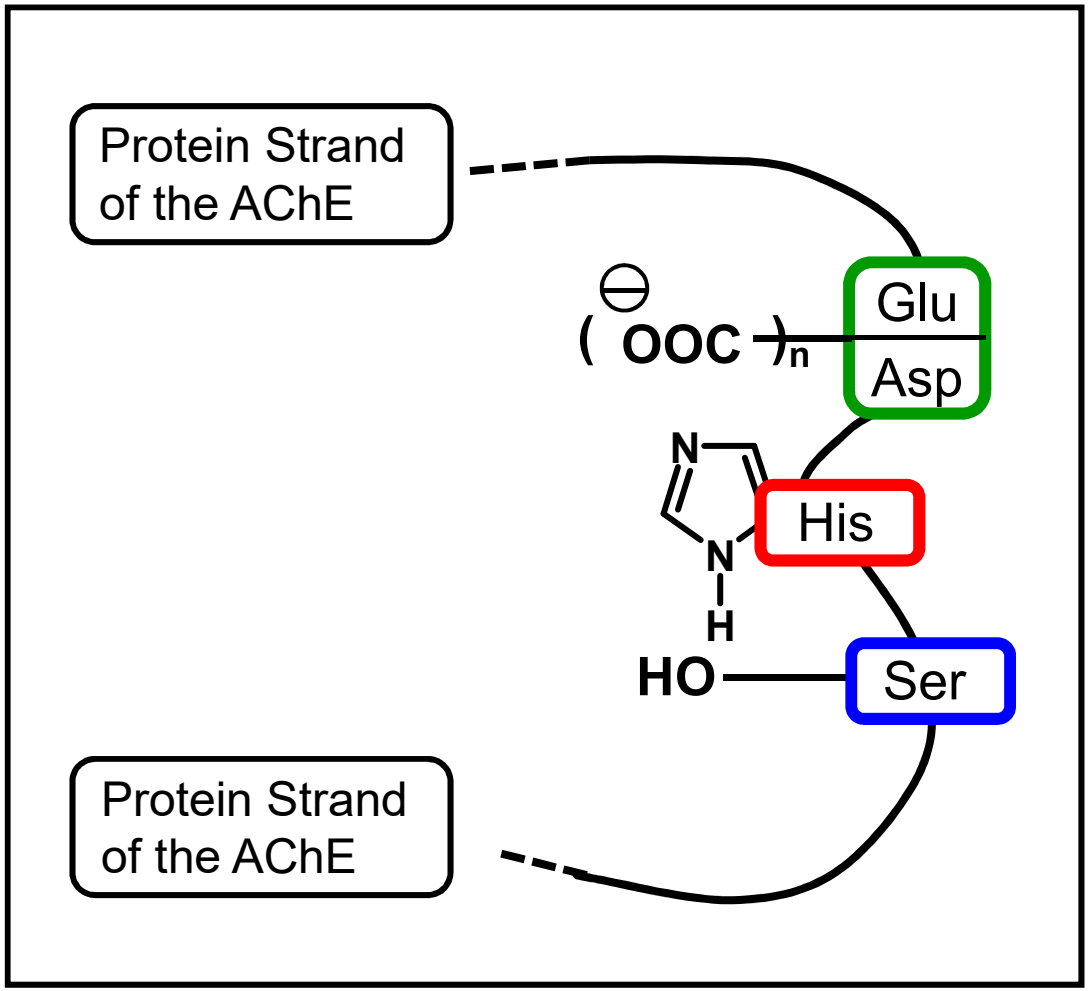
Acetylcholinesterase (AChE), Active Centers (Simplified)

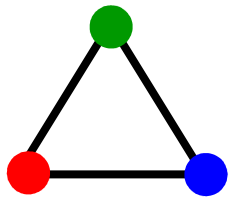
"Preserved" Amino Acids, "Catalytic Triad":



Glutamic Acid/
Aspartic Acid

Histidine

Serine



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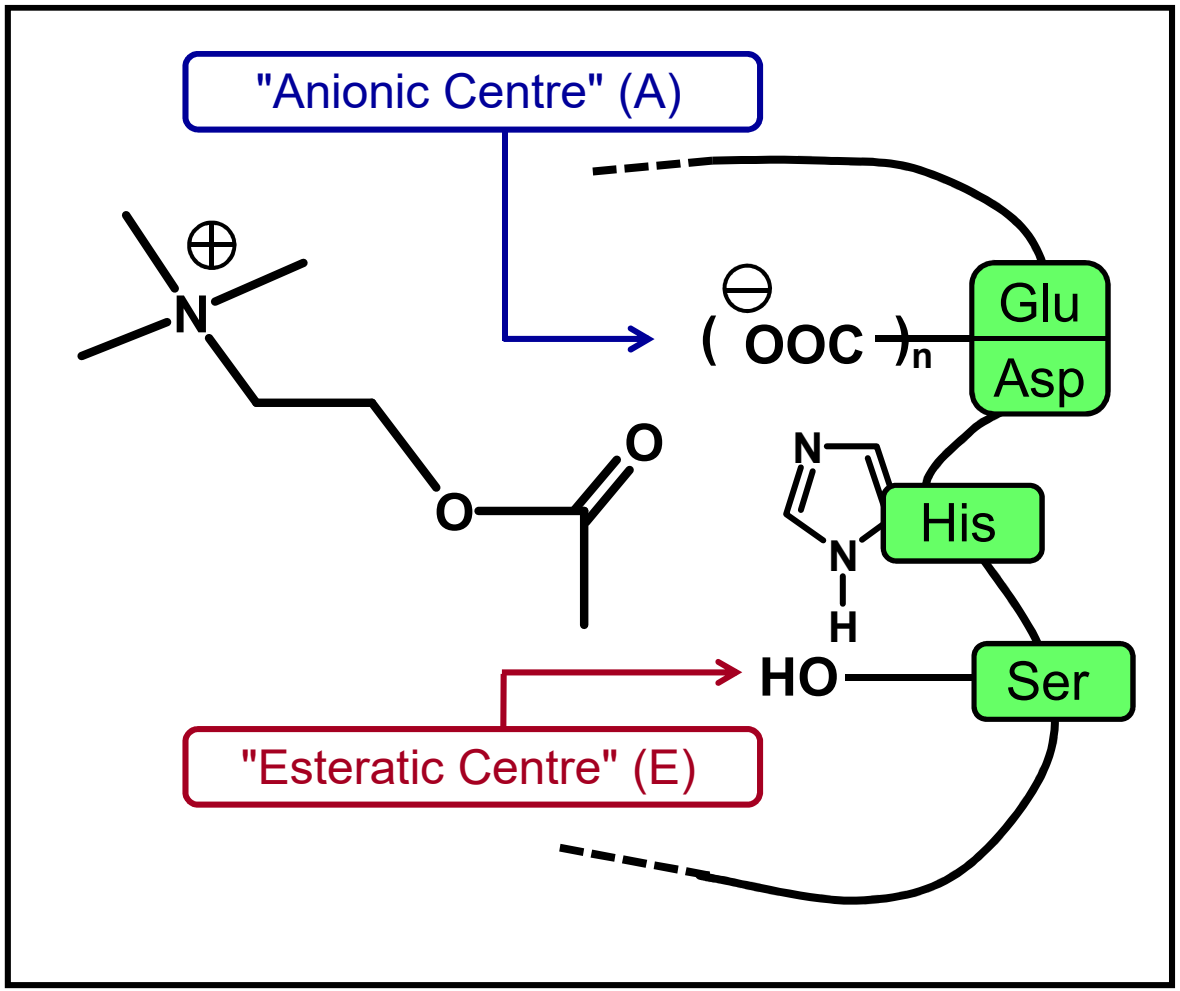
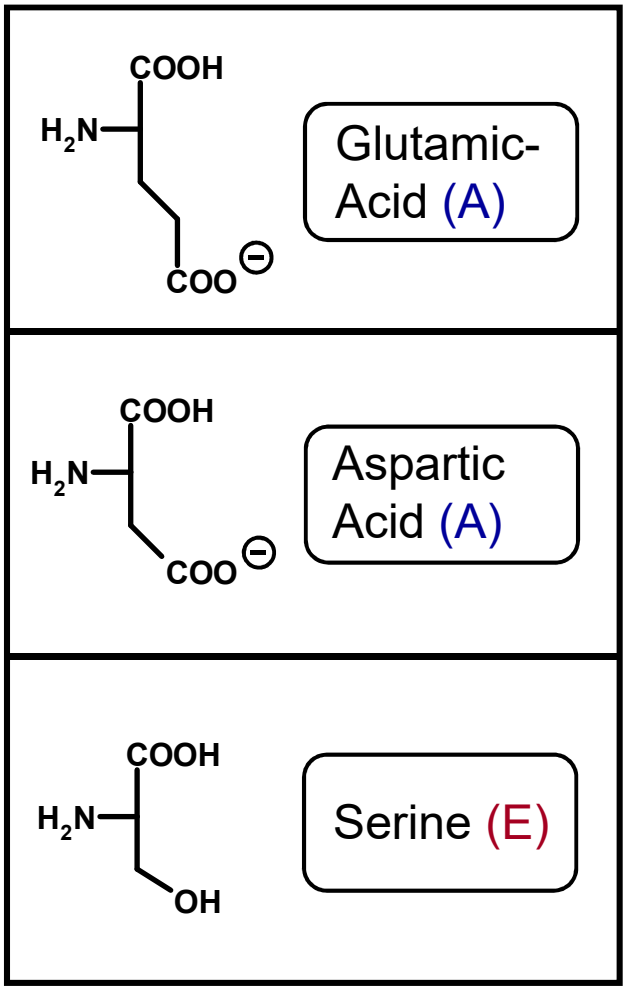
Acetylcholinesterase (AChE), Active Centers (Simplified)

Mechanism of Action, Centers of Interaction:





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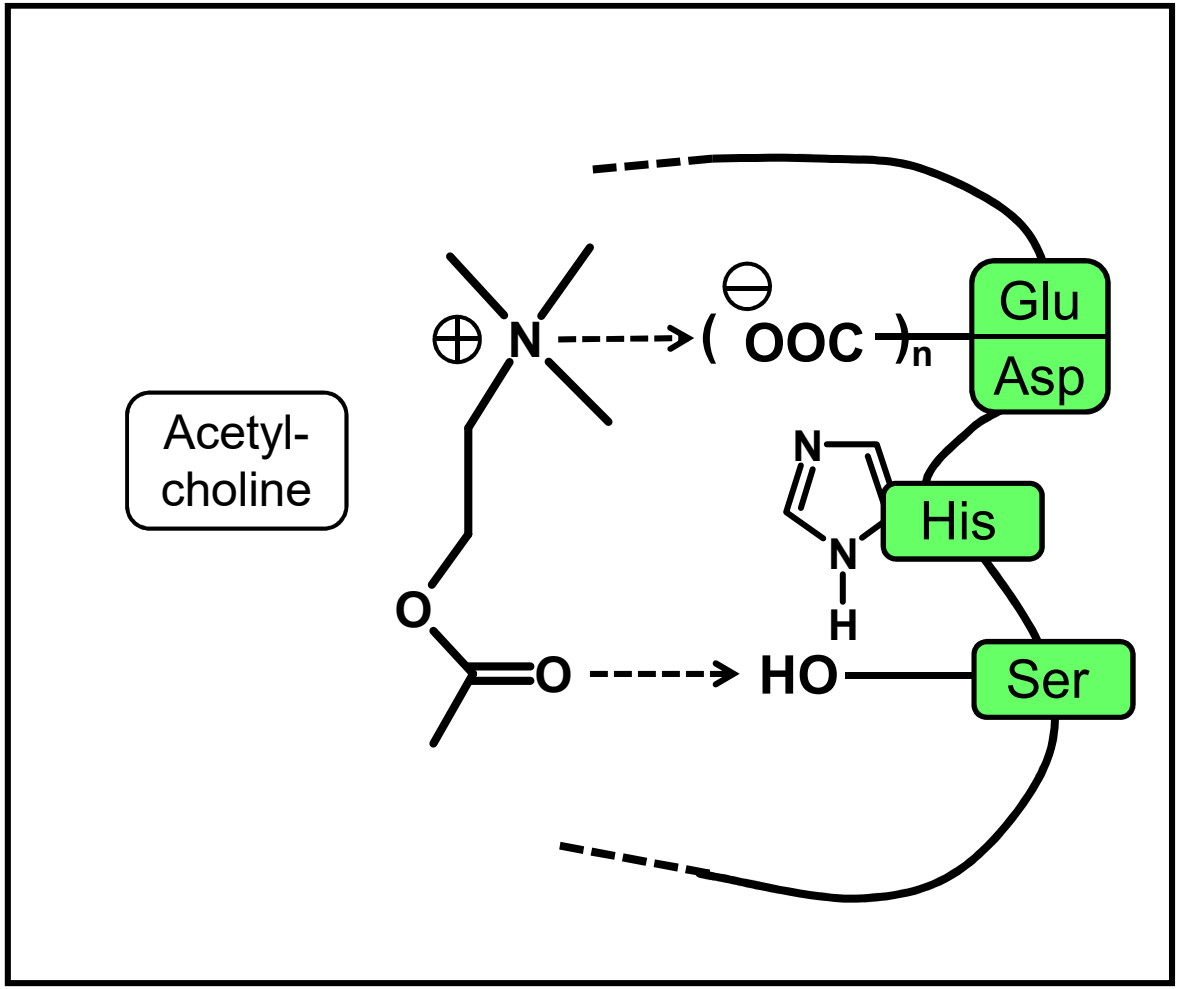
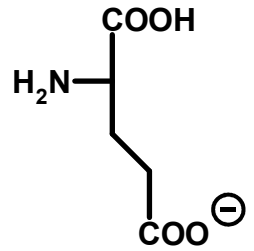
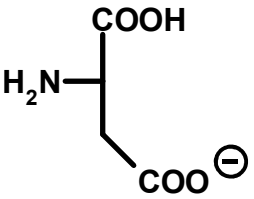
Acetylcholinesterase (AChE), Active Centers (Simplified)

Mechanism of Action, Electrostatic Attraction:

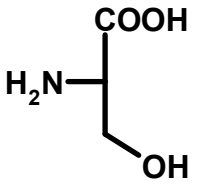




Glutamic-
Acid (A)



Aspartic
Acid (A)



Serine (E)

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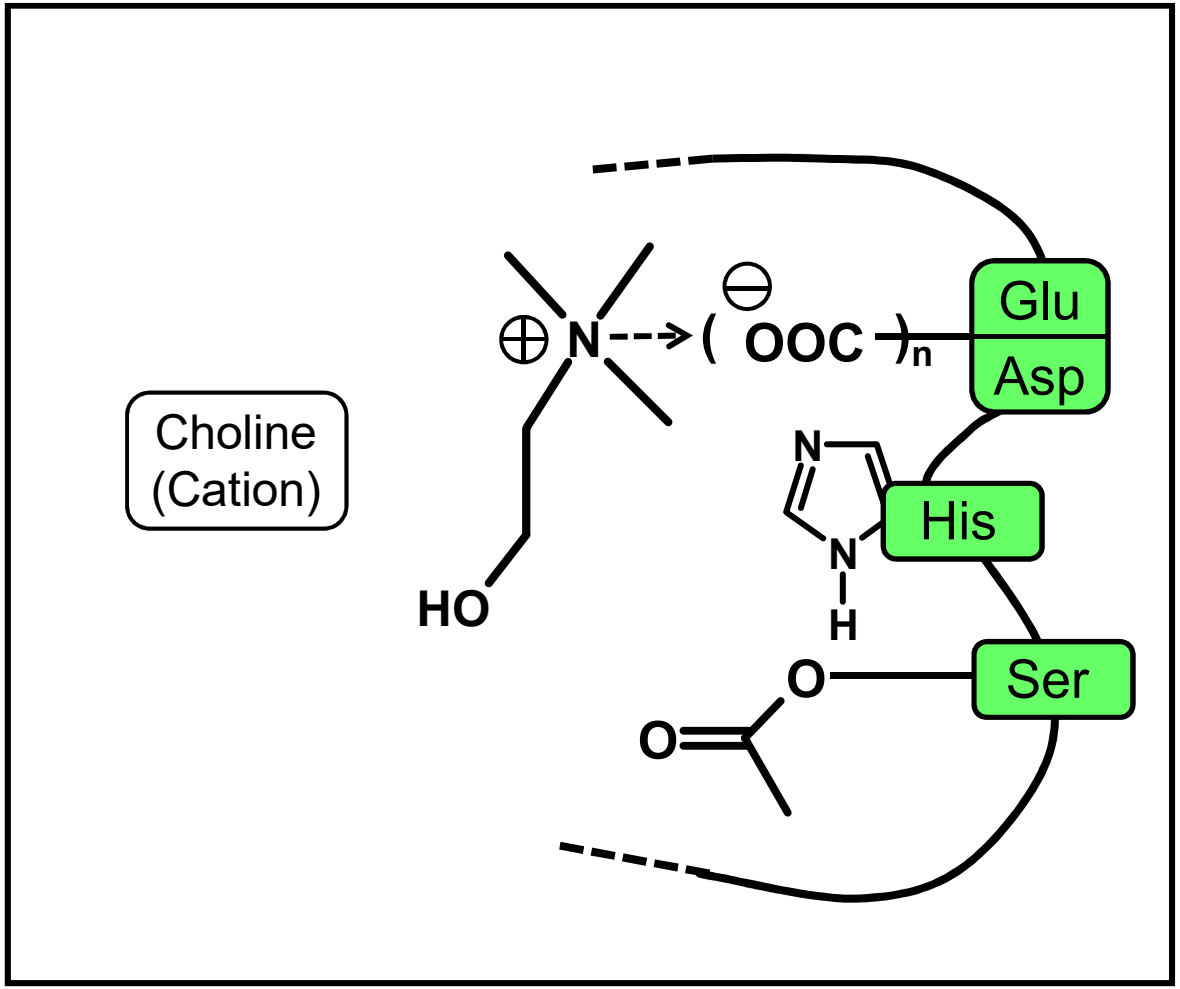
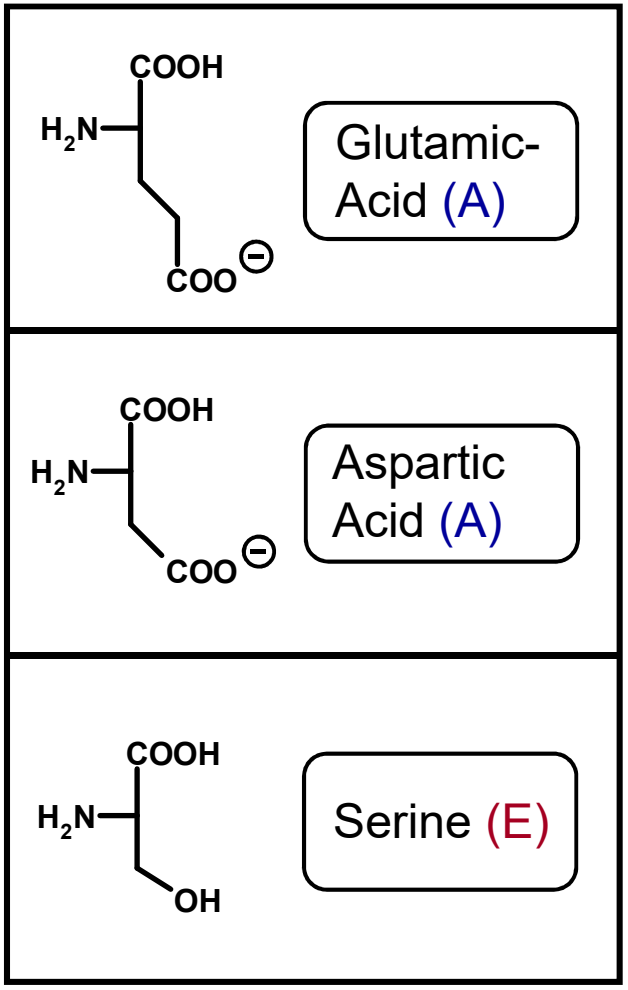
Acetylcholinesterase (AChE), Active Centers (Simplified)

Mechanism of Action, Acetylation of the Serine-OH-Group:





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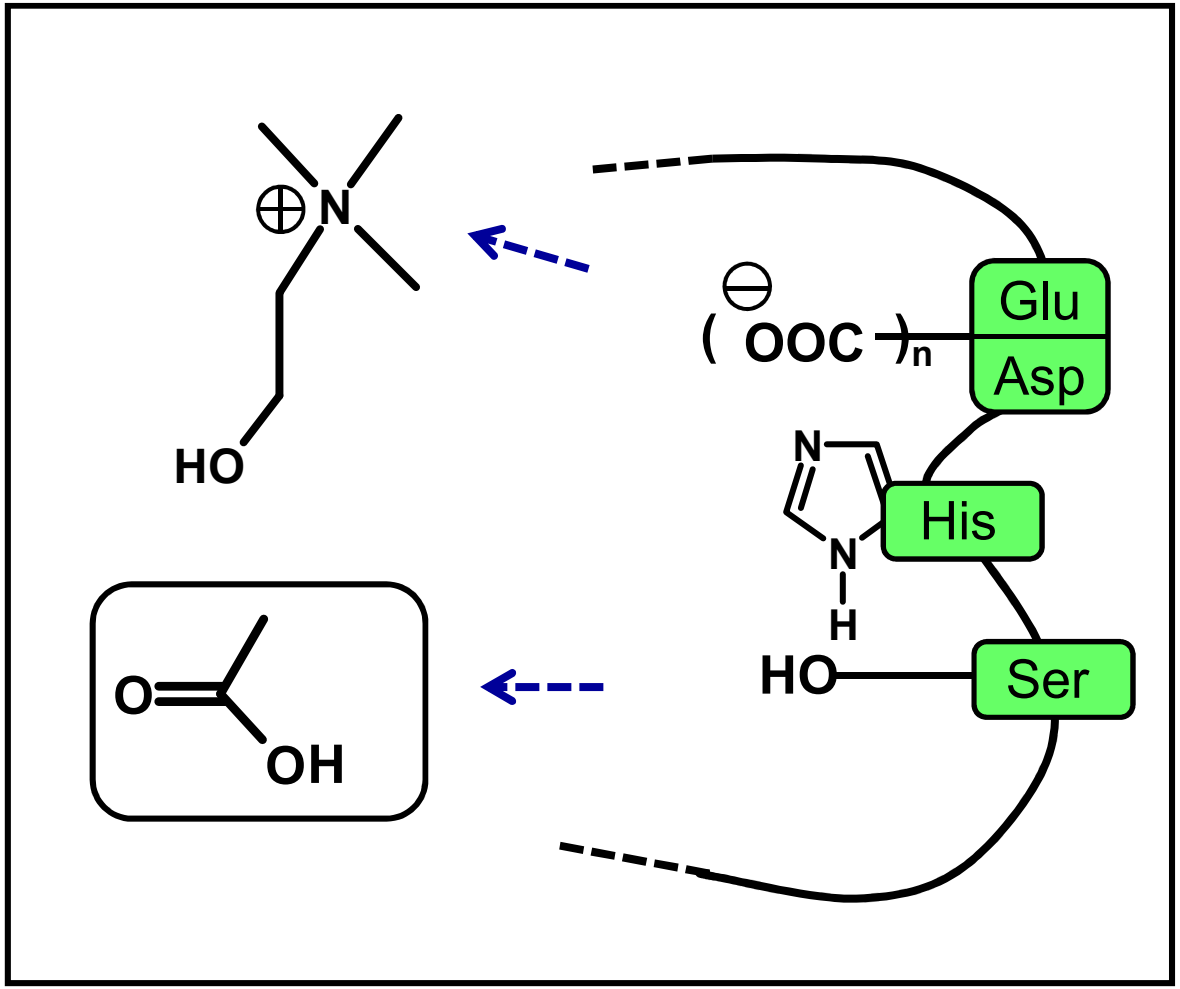
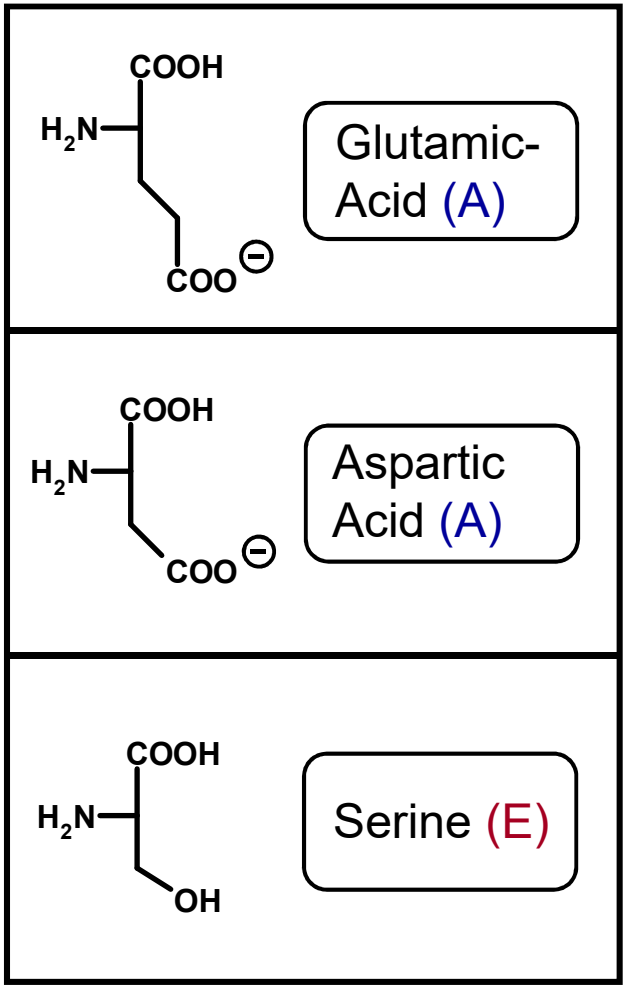
Acetylcholine Esterase (AChE), Active Centers (Simplified)

Mechanism of Action, Rapid Hydrolysis to Acetic Acid:





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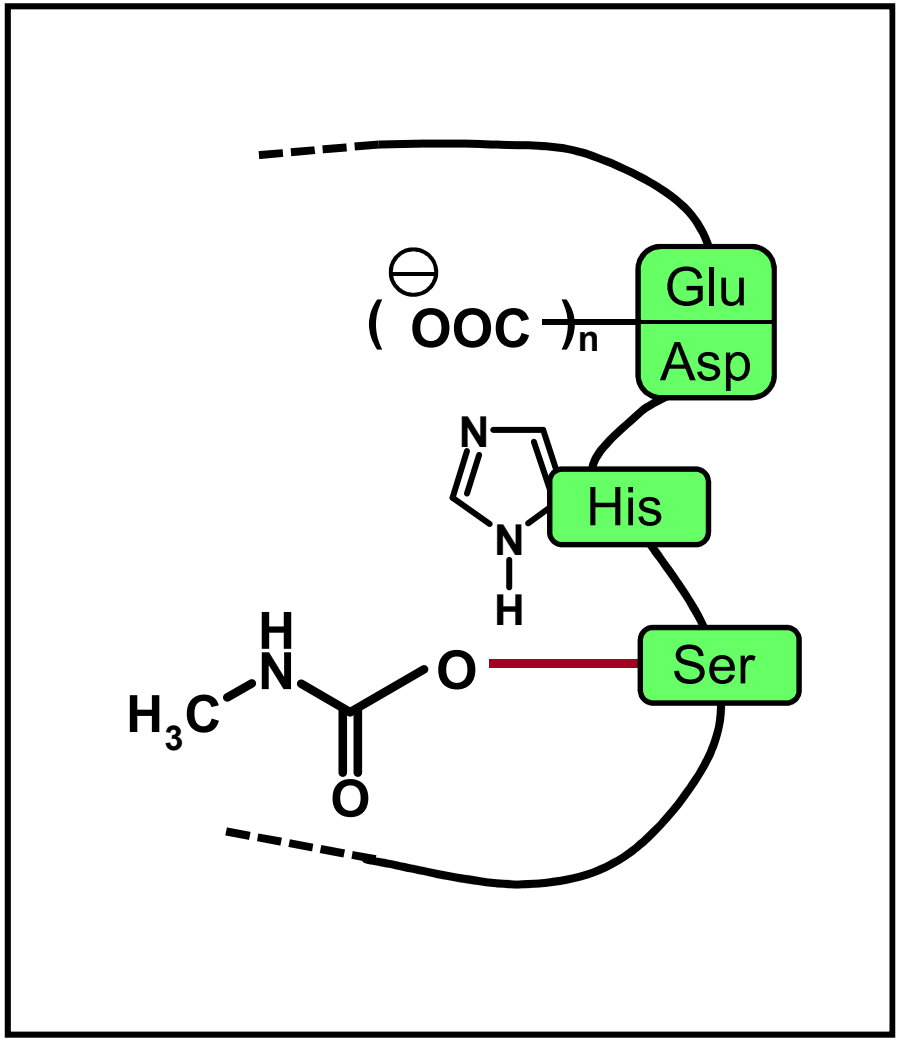
AChE, Active Center, Permanent Blockade

Irreversible Carbamoylation or Phosphorylation:



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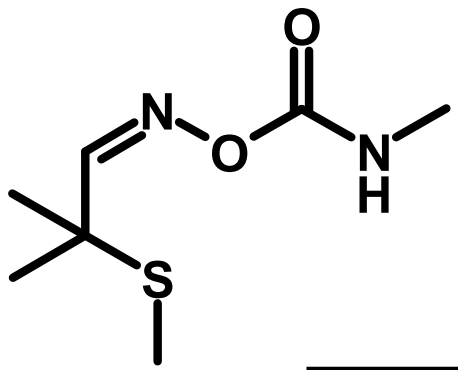
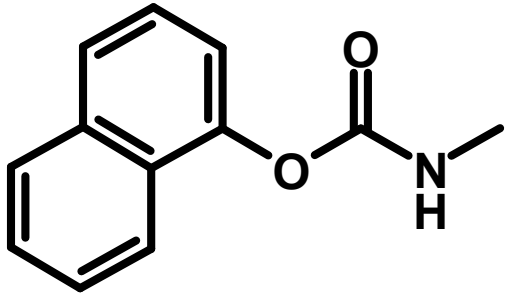
Acetylcholinesterase(AChE) Inhibitors

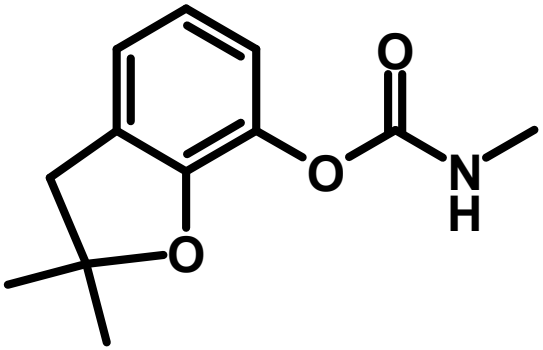
Insecticidal N-Methylcarbamates ("Common Names"):



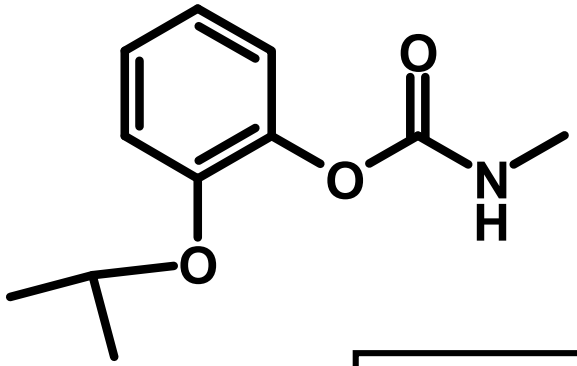
Aldicarb



Carbaryl



Carbofuran



Propoxur

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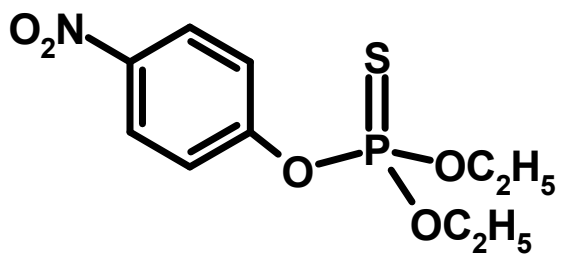
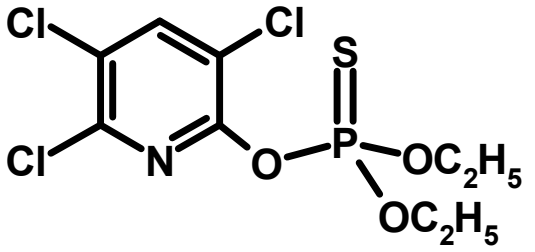
Acetylcholinesterase(AChE) Inhibitors

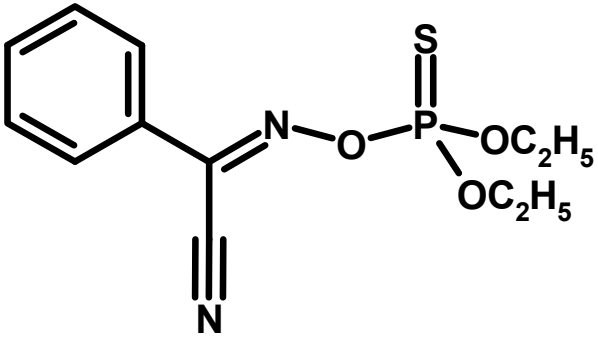
Insecticidal Phosphoric Acid Esters ("Common Names"):



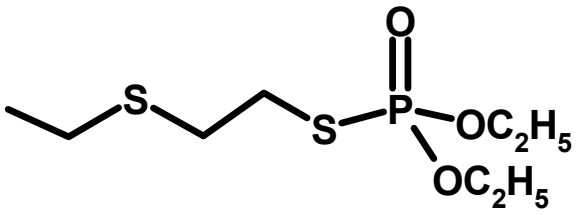
Parathion



Chlorpyrifos



Phoxim



Demeton-O

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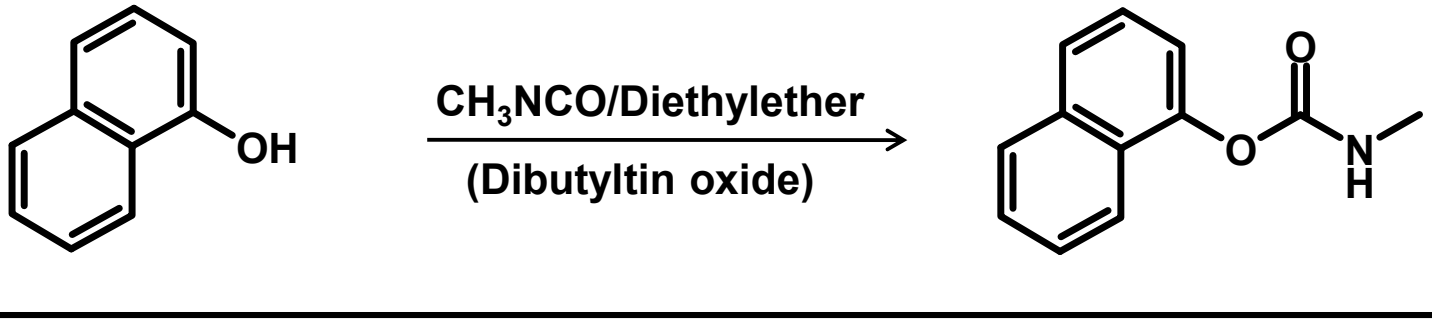
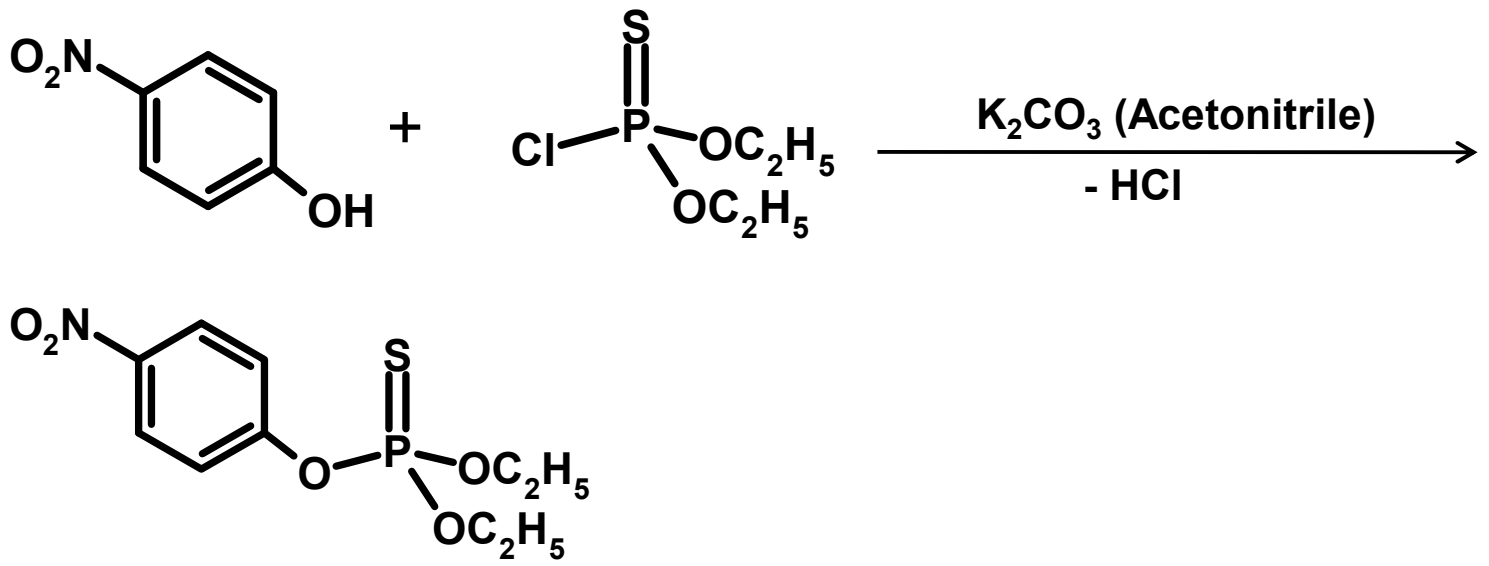
Acetylcholinesterase(AChE) Inhibitors

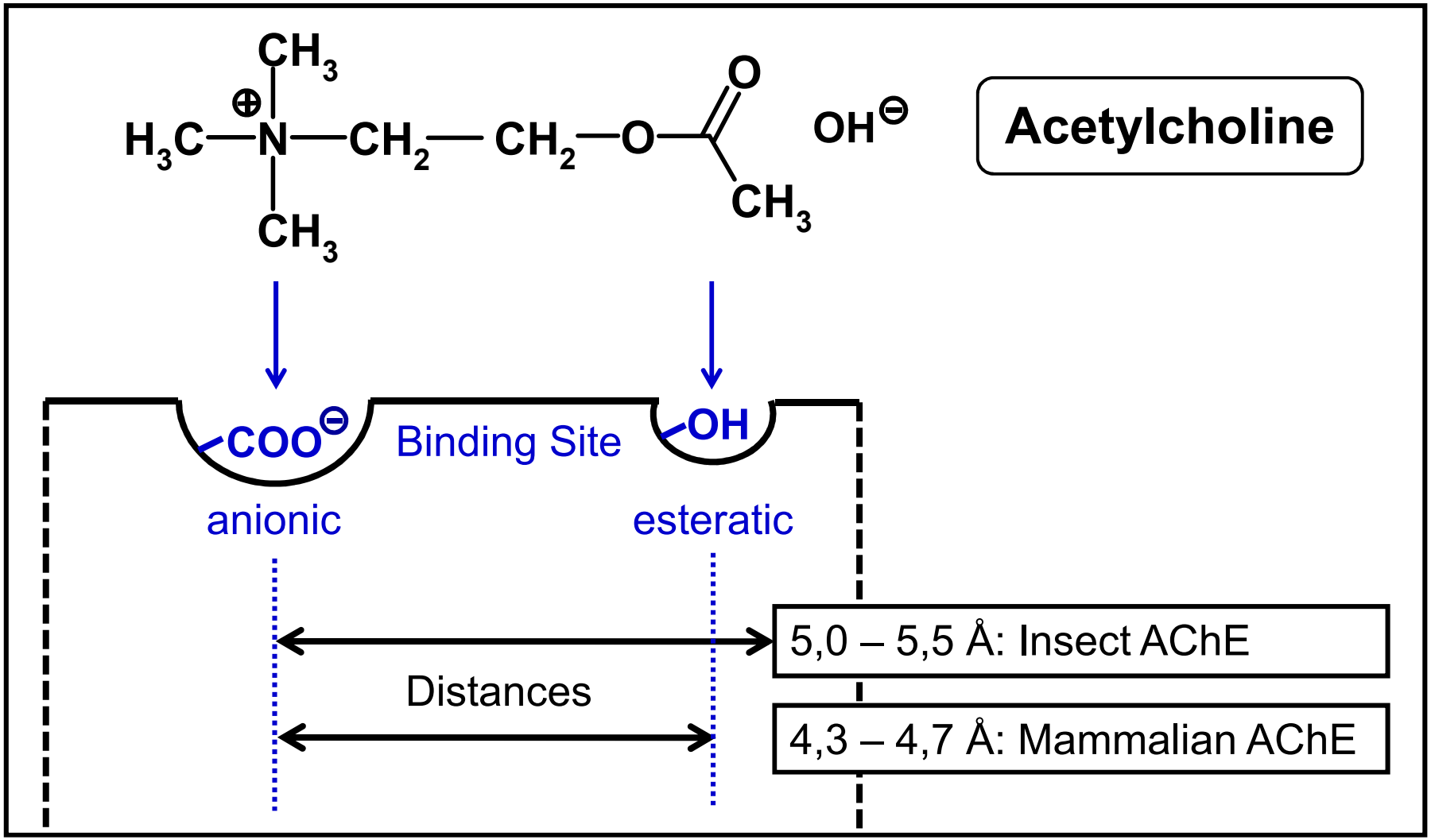
N-Methylcarbamate, Phosphoric Acid Ester, Syntheses:





Acetylcholine Esterase (AChE), Active Centers (Simplified)

Different Acetylcholinesterases in Insects/Mammals:



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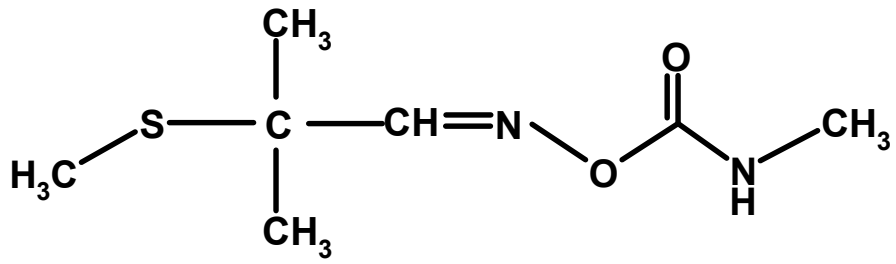
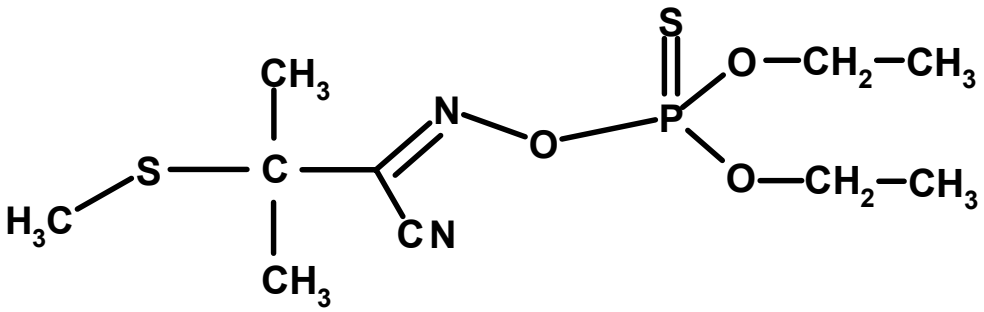
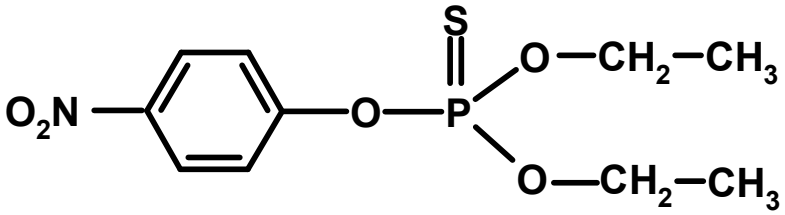
Acetylcholinesterase(AChE) Inhibitors (Examples)

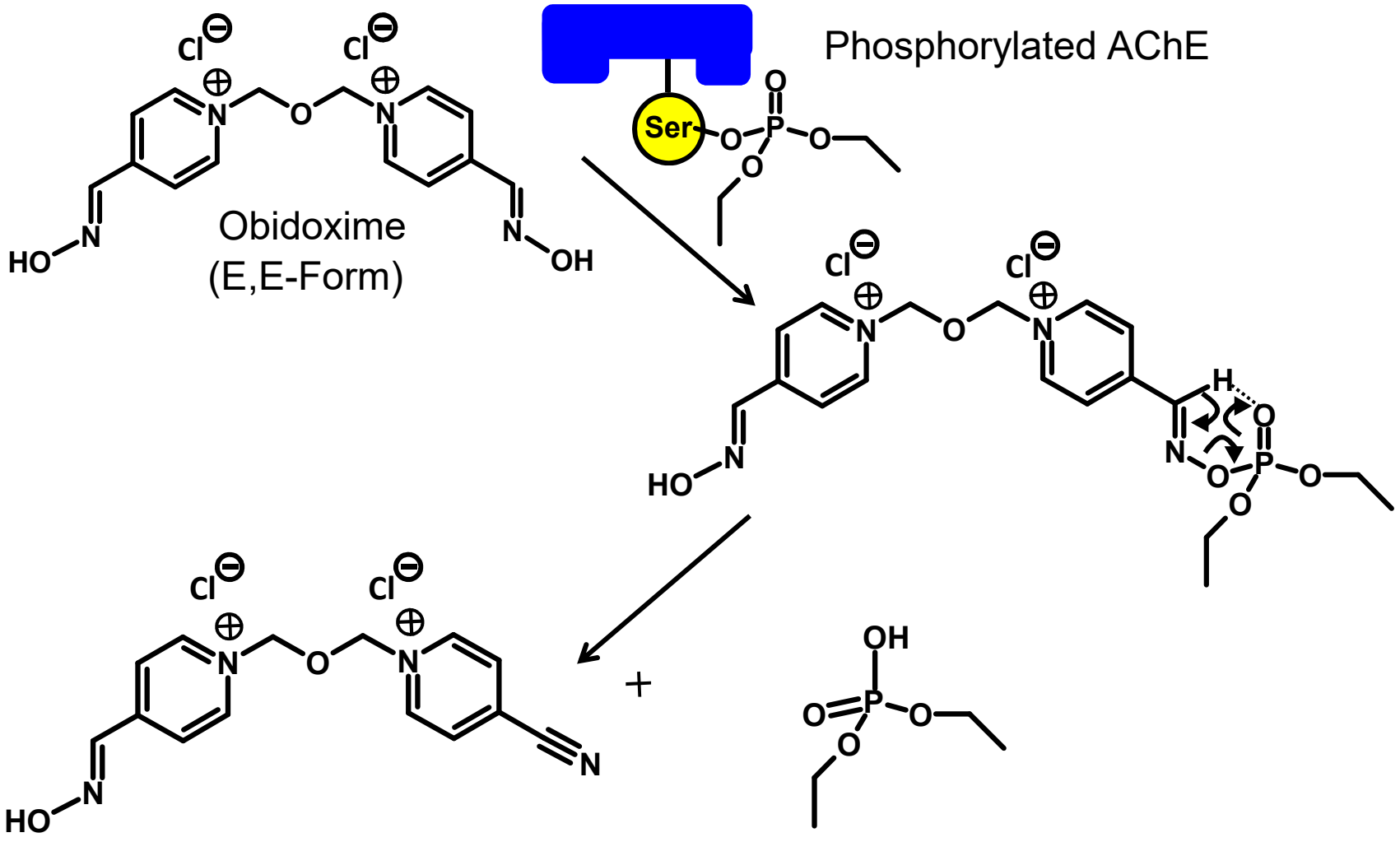
Sales Products/Laboratory Product:

	Aldicarb (Temik®), UCC
	EP 0150822A2, BASF SE
	Parathion (E 605®), Bayer

Rainer Buerstinghaus

Acetylcholinesterase Inhibitor, AChE Reactivation

Obidoxime Chloride, Antidote by "Ligand Displacement":



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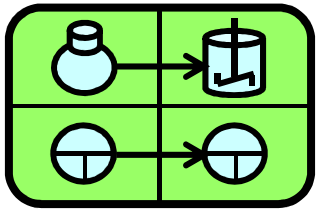
R&D Project Management in the Chemical Industry



Subject Matter

Jump of Technical Progress

Chemical-Biological Basics:
Insecticidal "Sodium Channel Activators".

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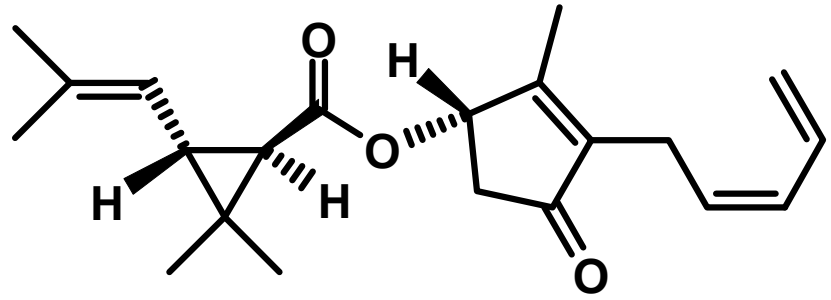
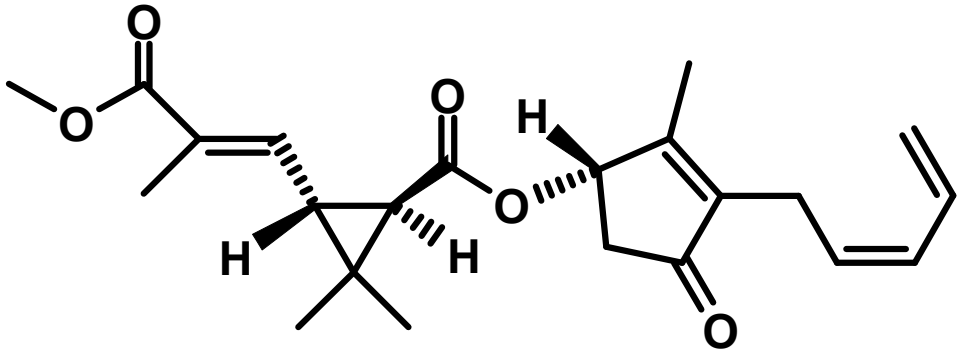
Sodium Ion Channel Activators: Plant Substances from Chrysanthemum Cinerariifolium (Feverfew).

	Pyrethrin I
	Pyrethrin II

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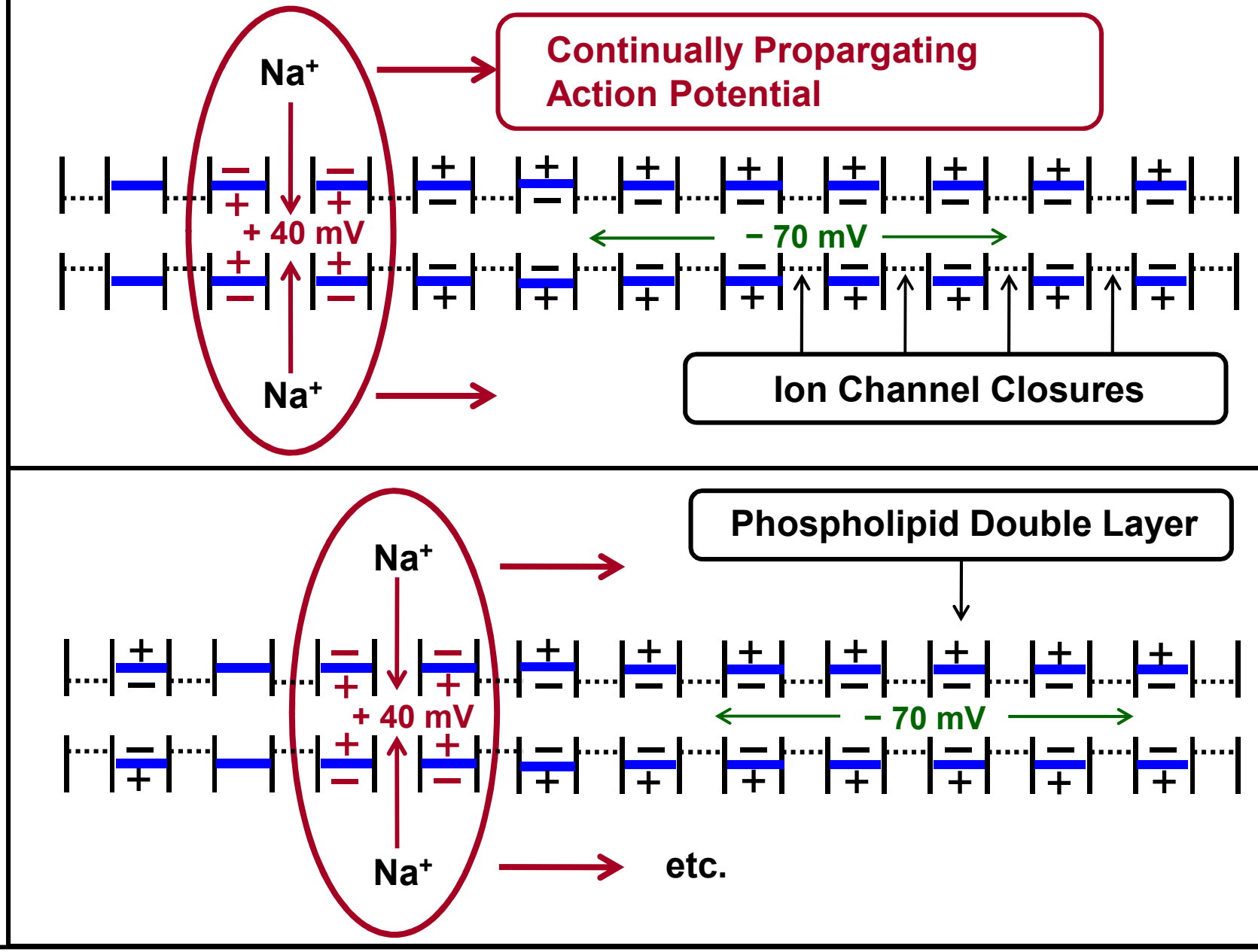
Continuous Transmitting Stimuli at the Axon of the Neuron.



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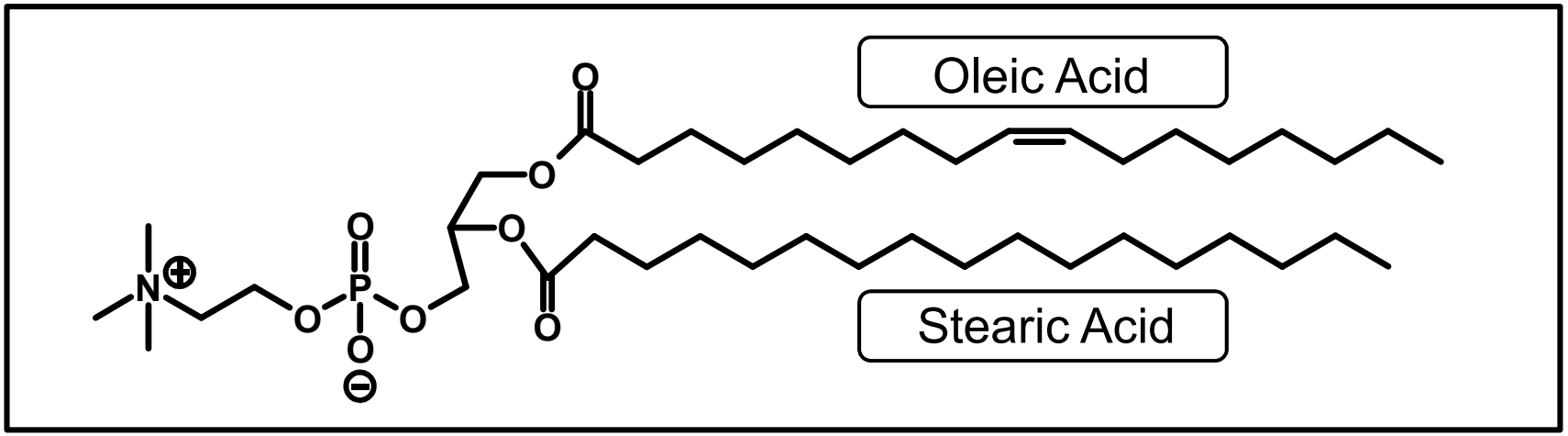
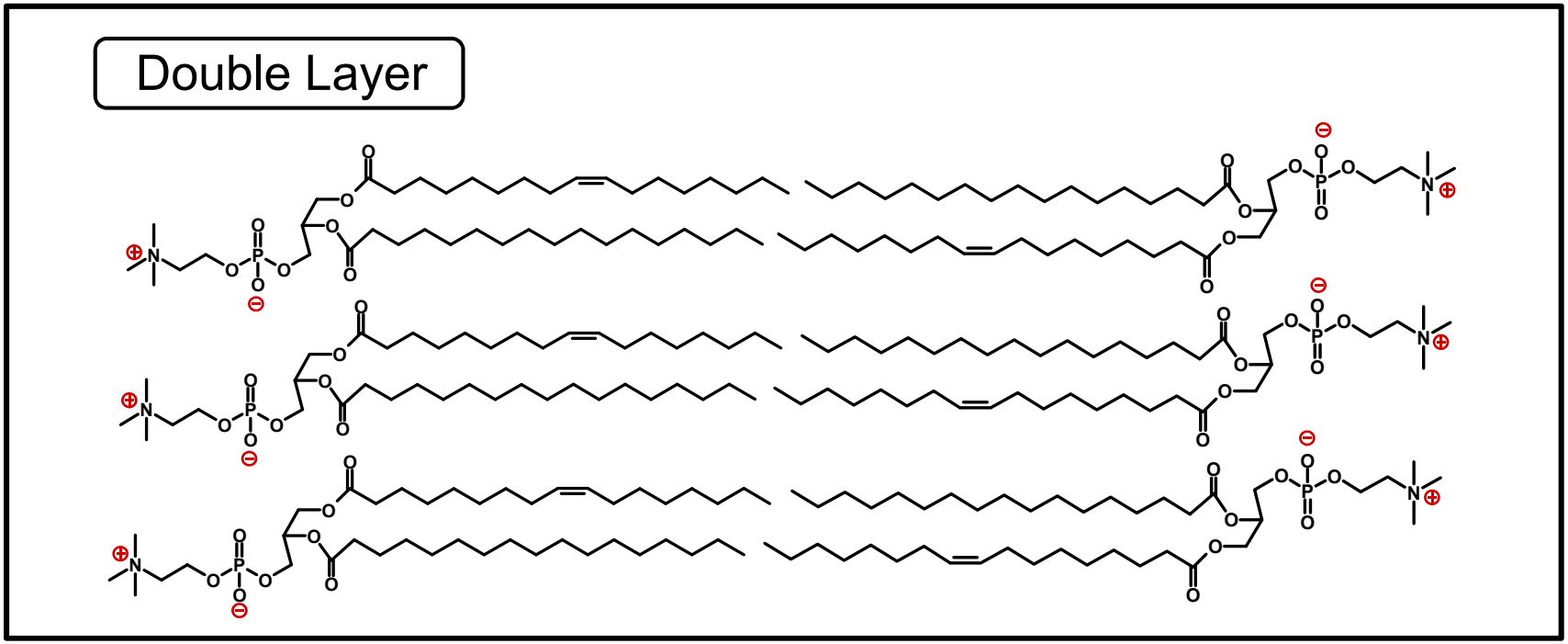
Phospholipid, Structural Formula (Example), Double Layer.





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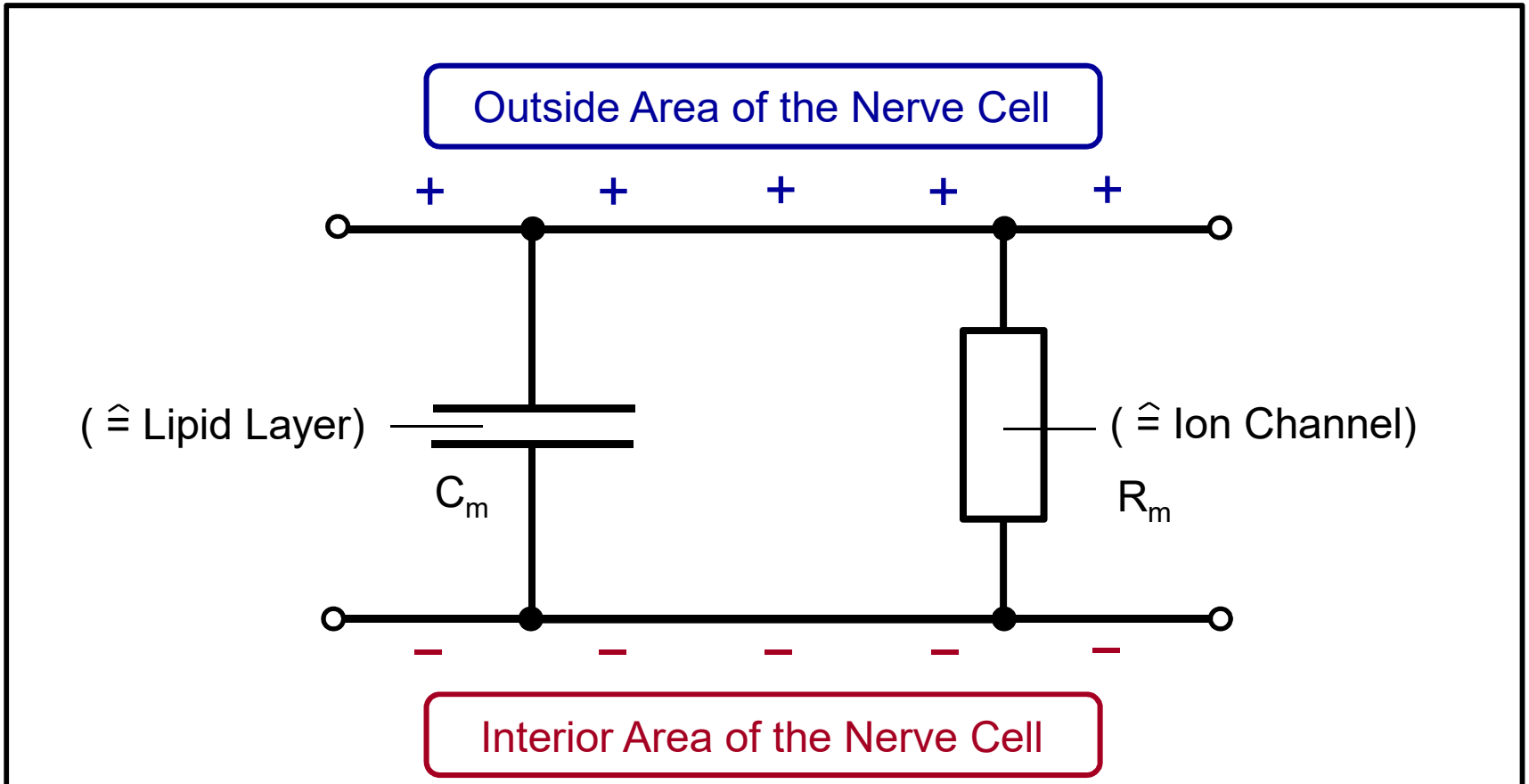
Section of a Neuron: Electrical "Analogy Circuit".

"RC Element" as a Model of a Membrane Section:



C_m : Membrane Capacity	R_m : Membrane Resistor

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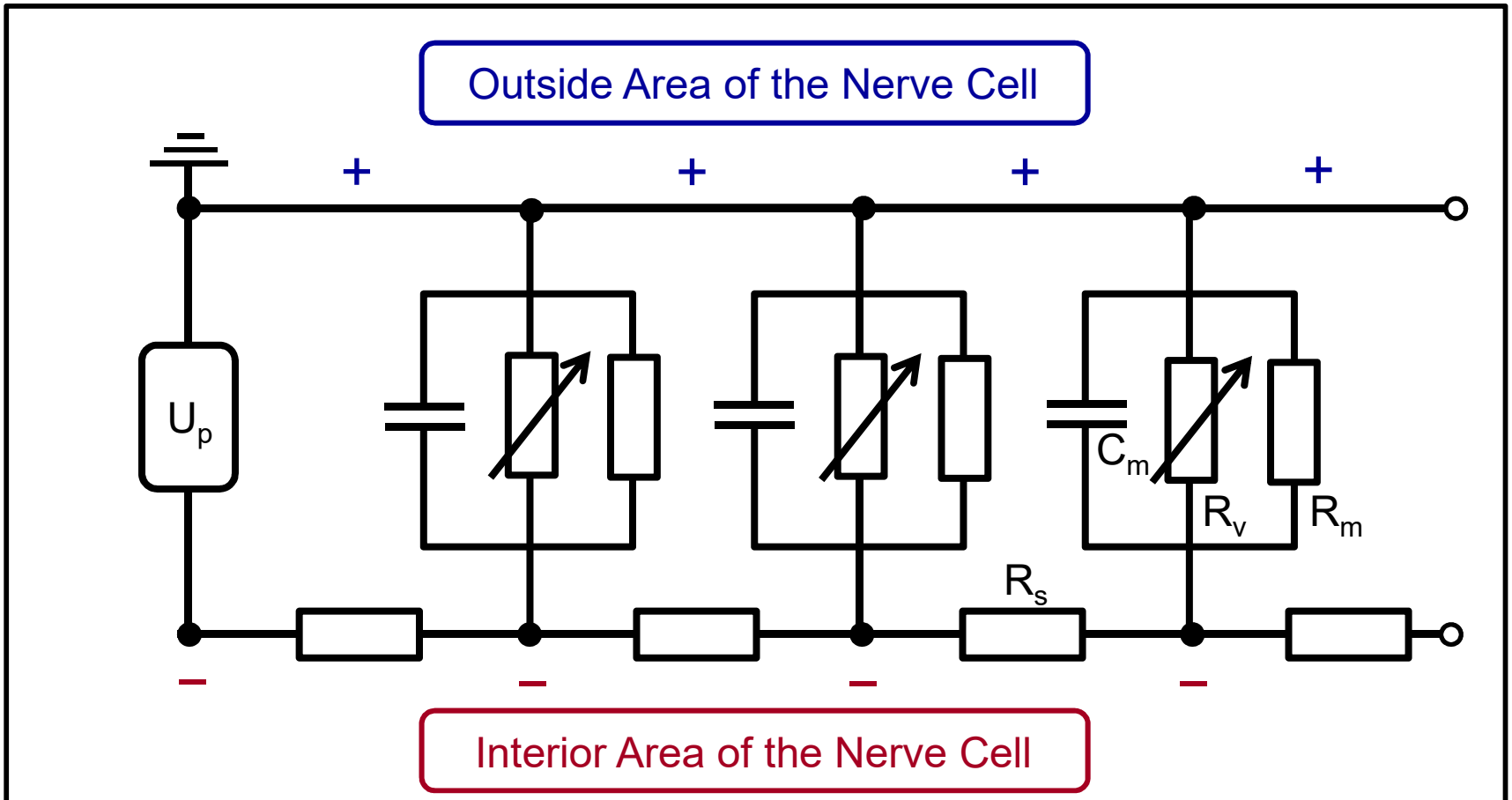
Section of a Neuron: Electrical "Analogy Circuit".

"RC Network" as a Model of a Membrane Segment:



U_p: Voltage Pulse Generator. R_s: Series Resistance.	R_v: Variable Resistor (Activatable Ion Channel).

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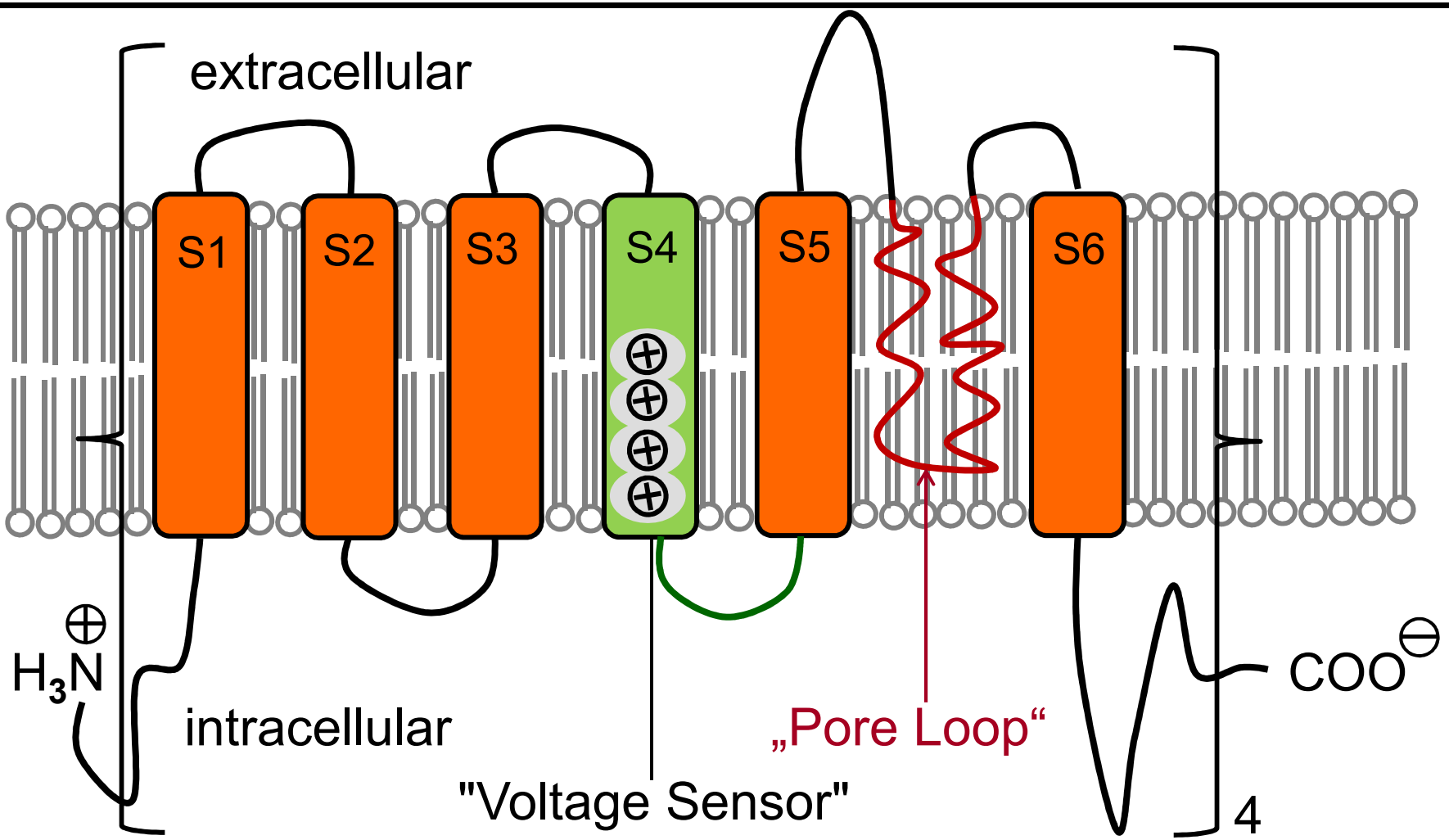
Structure of a Voltage-Gated Na^+-Channel

Loop-Forming Protein with 4 x 6 = 24 Helical Transmembrane Segments S1, S2, S3, S4, S5, S6:



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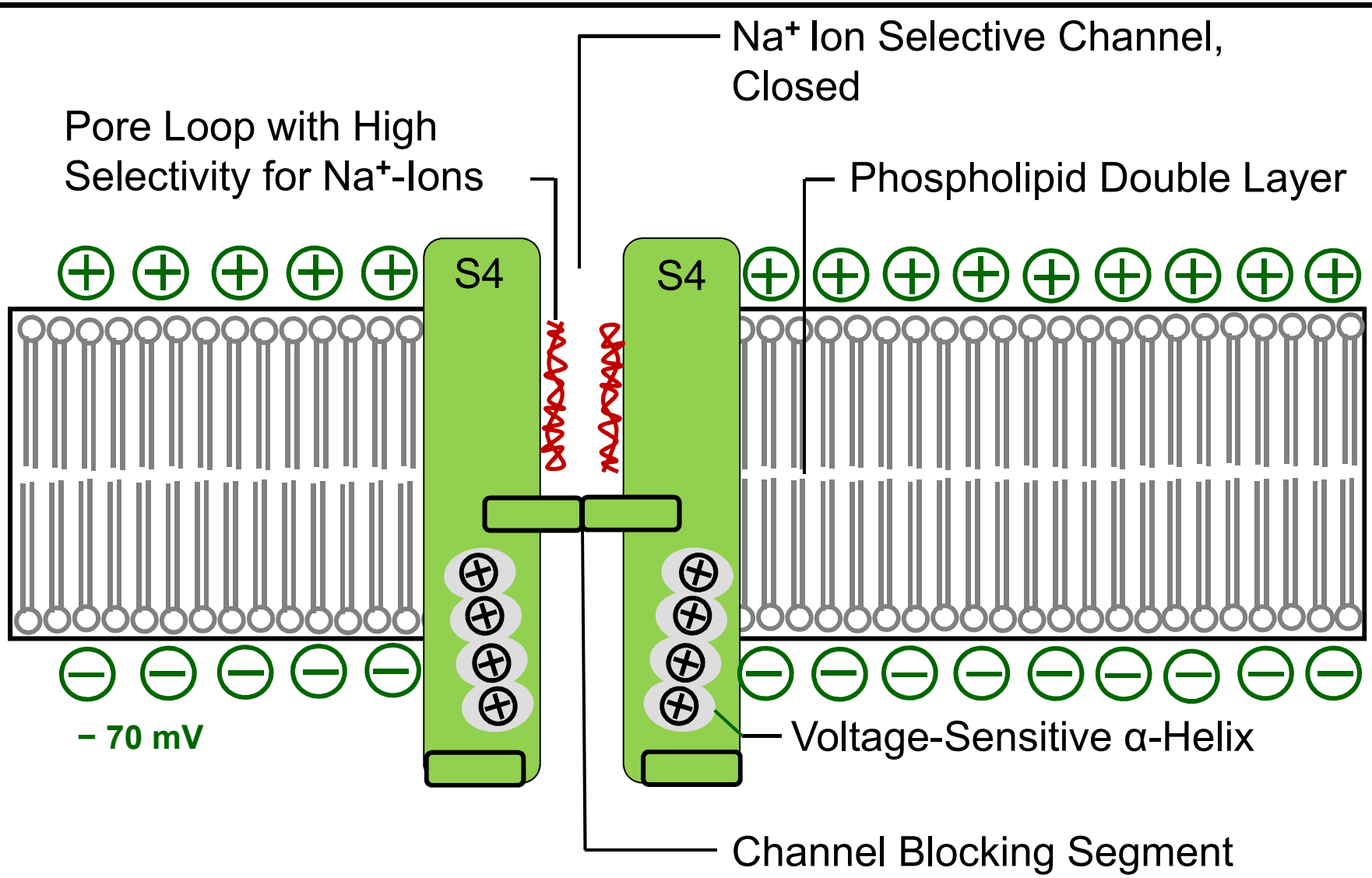
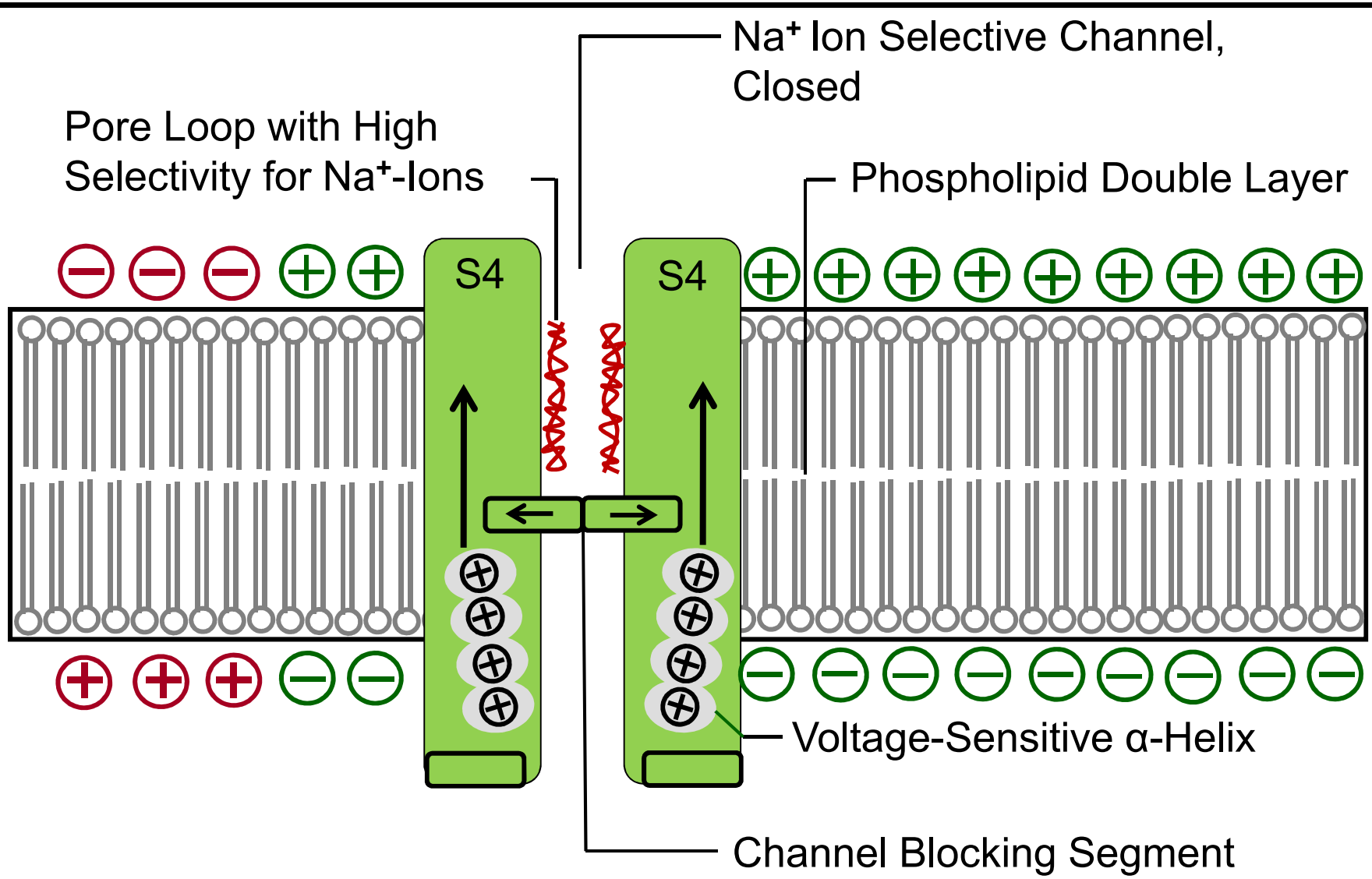
Continuous Excitation Conduction on the Axon (Simplified)

State of Rest:



Continuous Excitation Conduction on the Axon (Simplified)

Beginning Depolarization:



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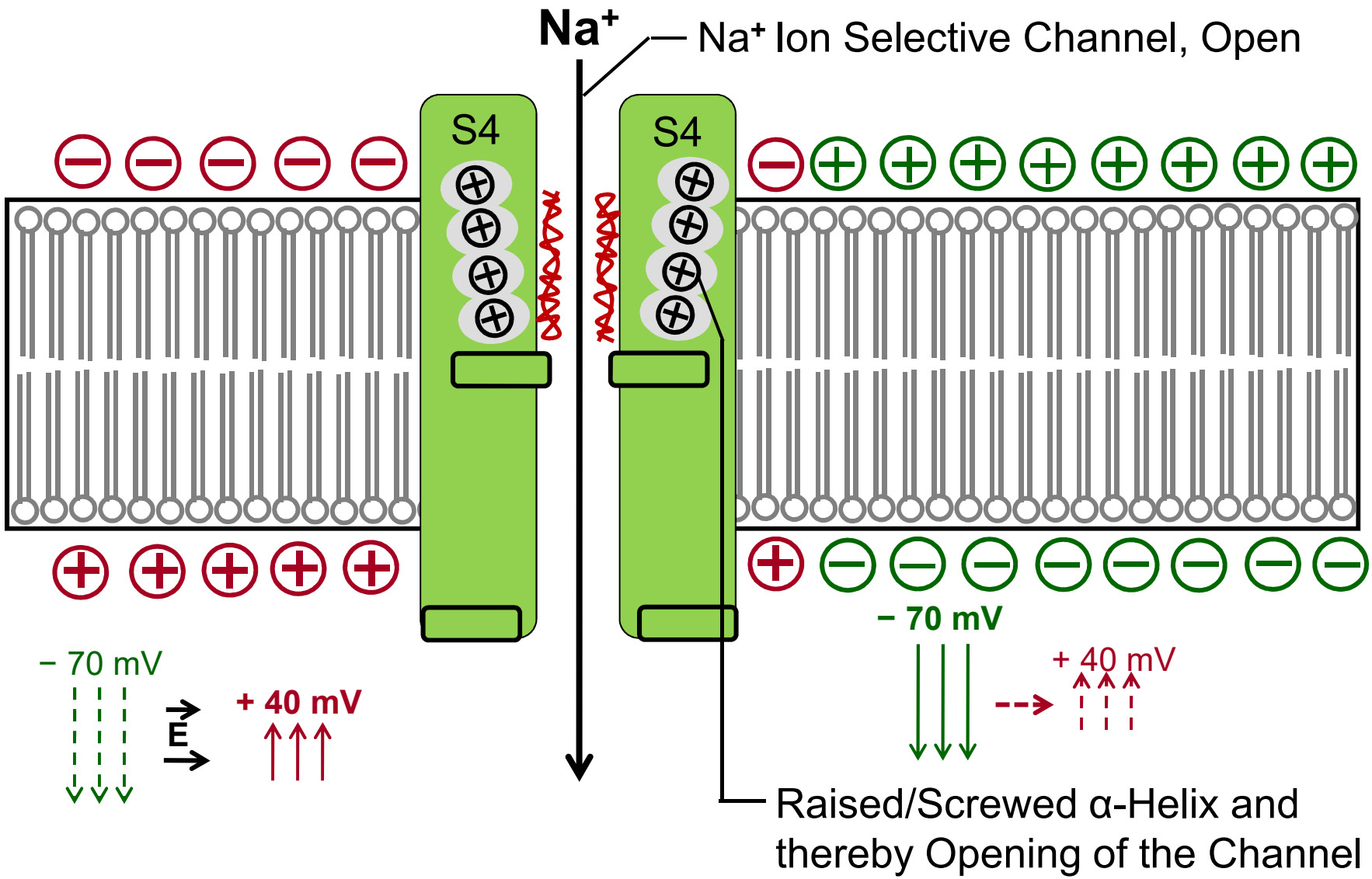
Continuous Excitation Conduction on the Axon (Simplified)

Progressive, Channel Comprehensive Depolarization:



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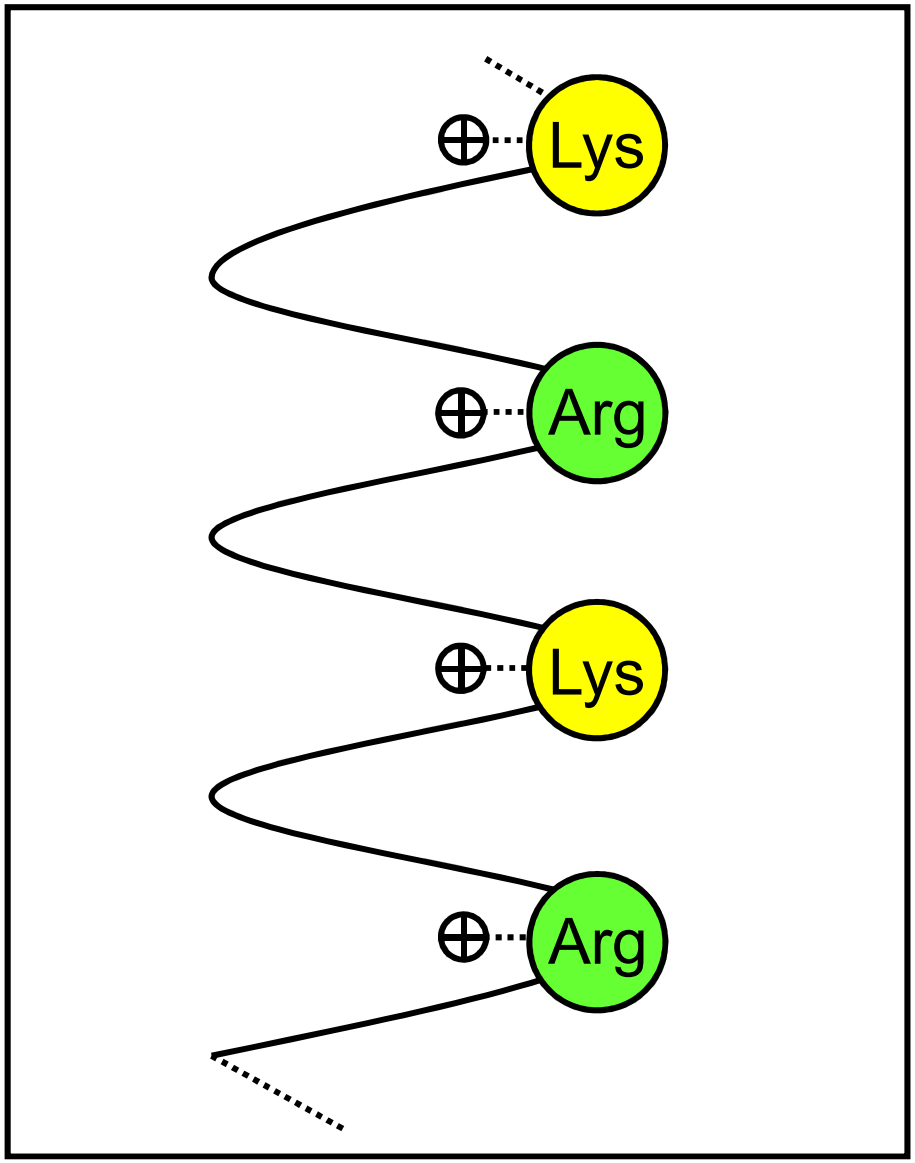
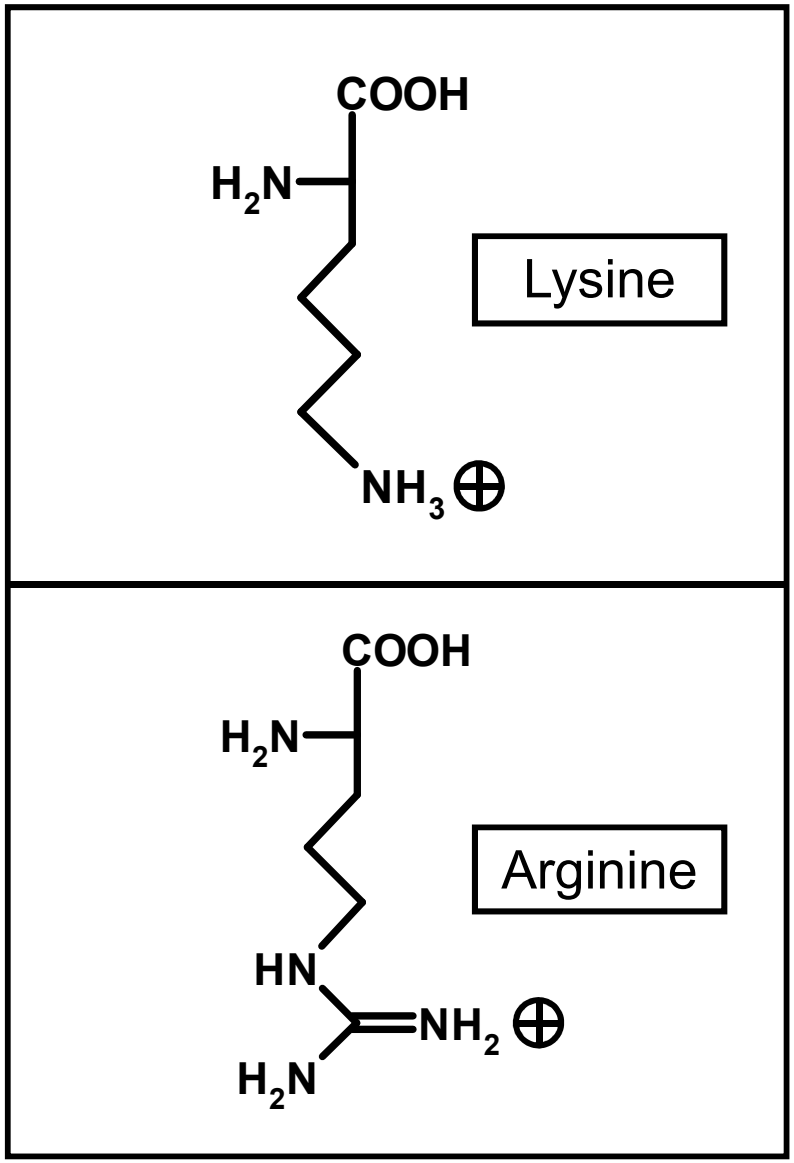
Voltage-Sensitive α-Helix in S4, Construction Principle.





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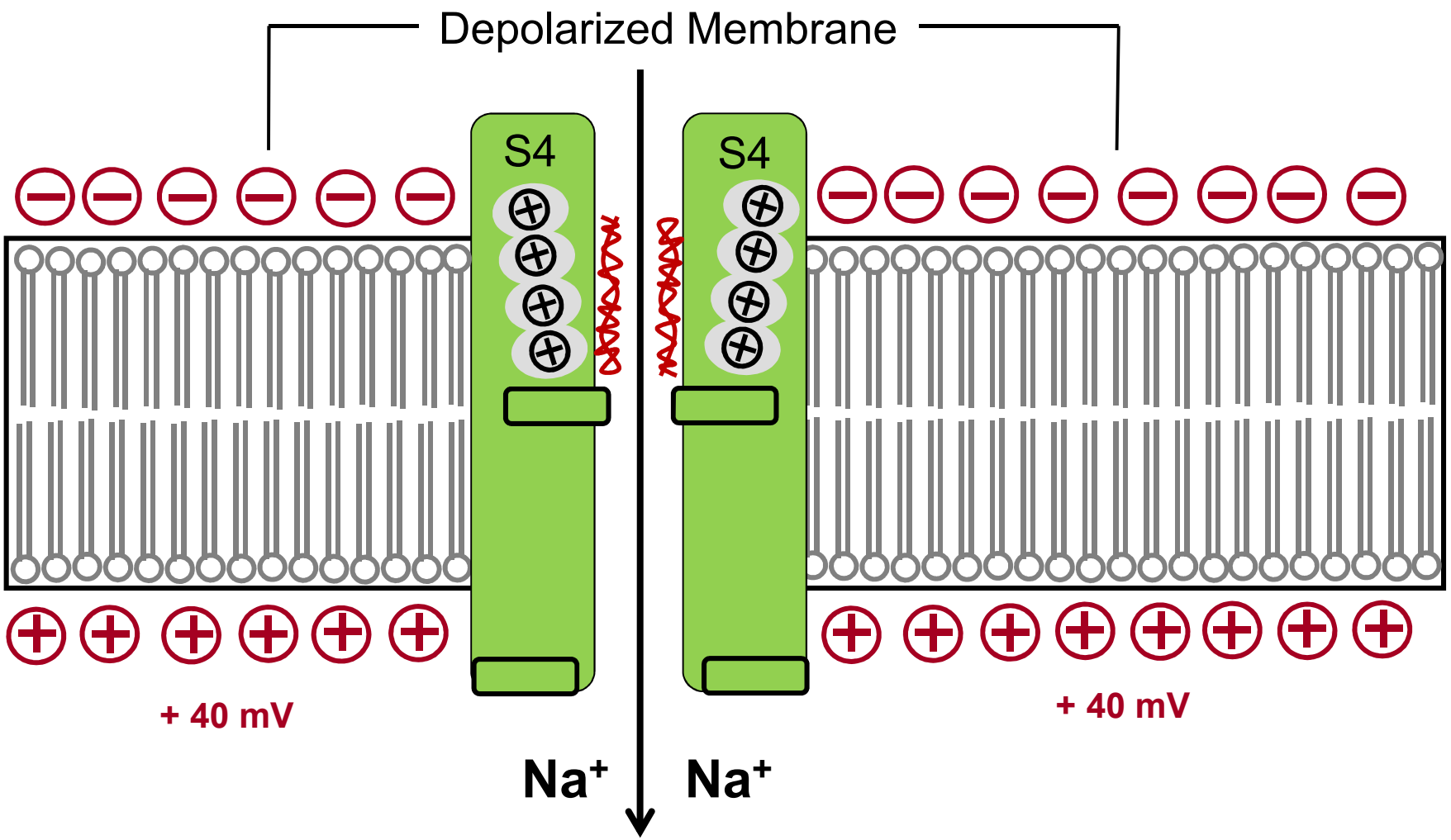
Continuous Excitation Conduction on the Axon (Simplified)

Complete Depolarization, Open Channel, Na^+-Influx:



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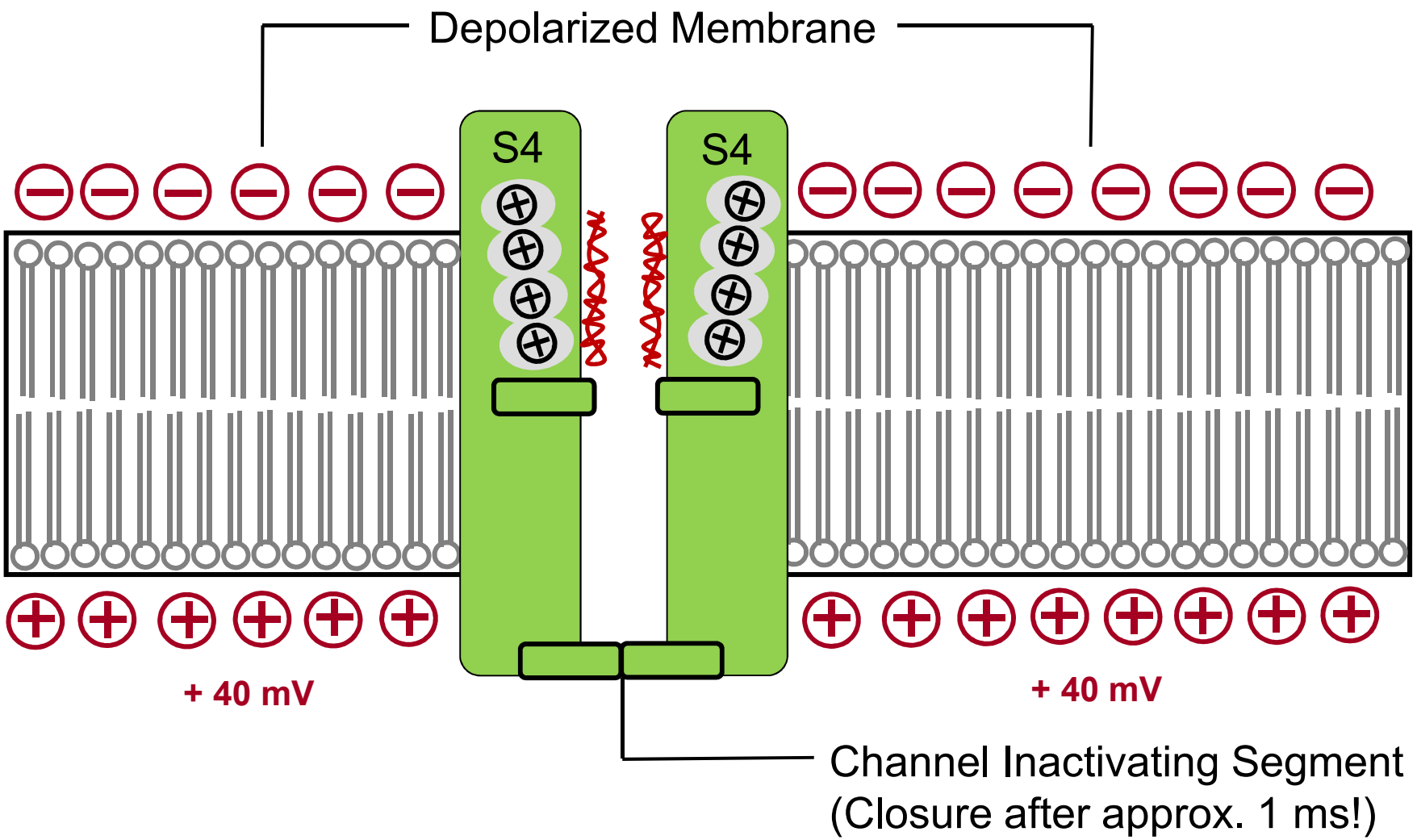
Continuous Excitation Conduction on the Axon (Simplified)

Complete Depolarization, Channel Inactivation:



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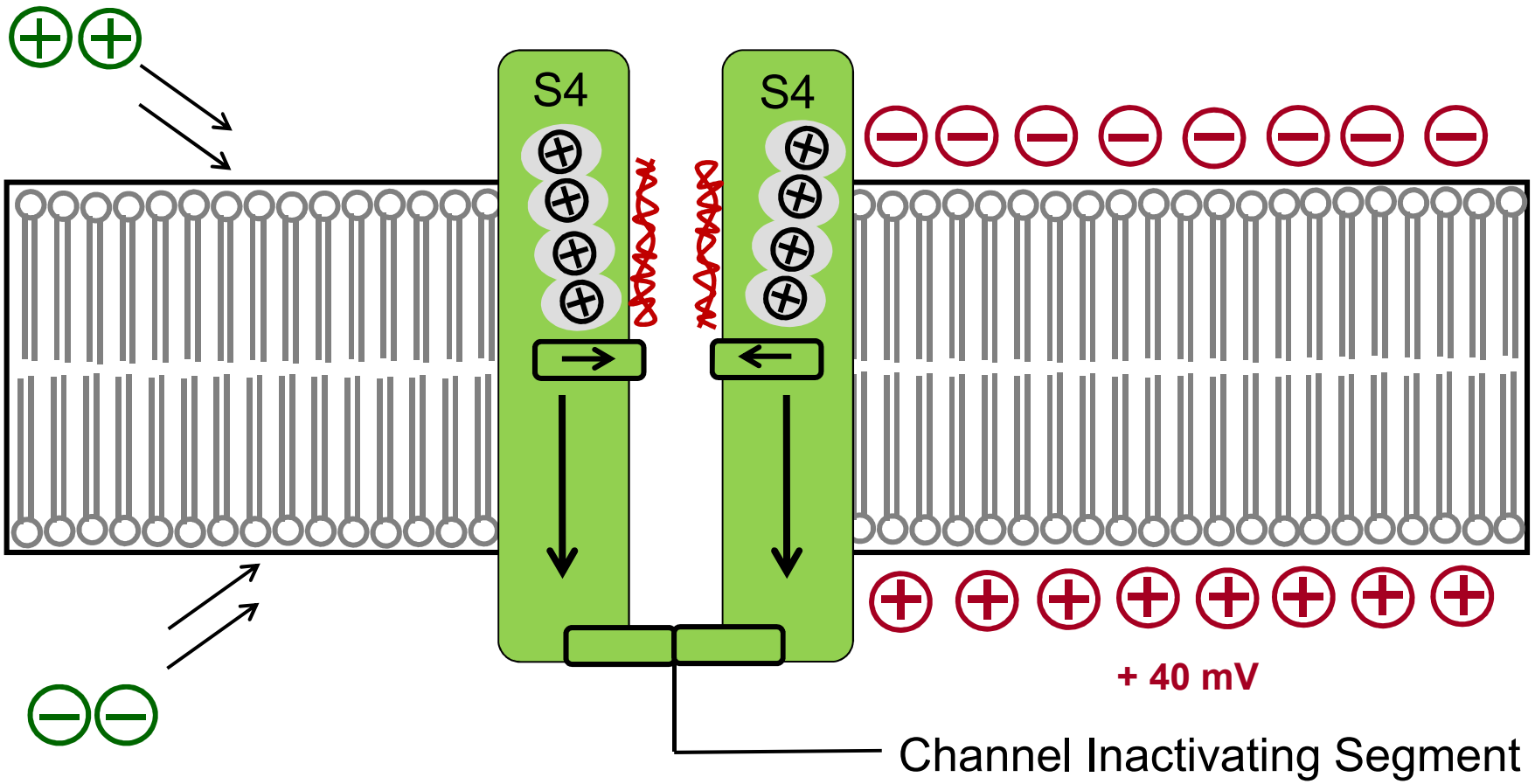
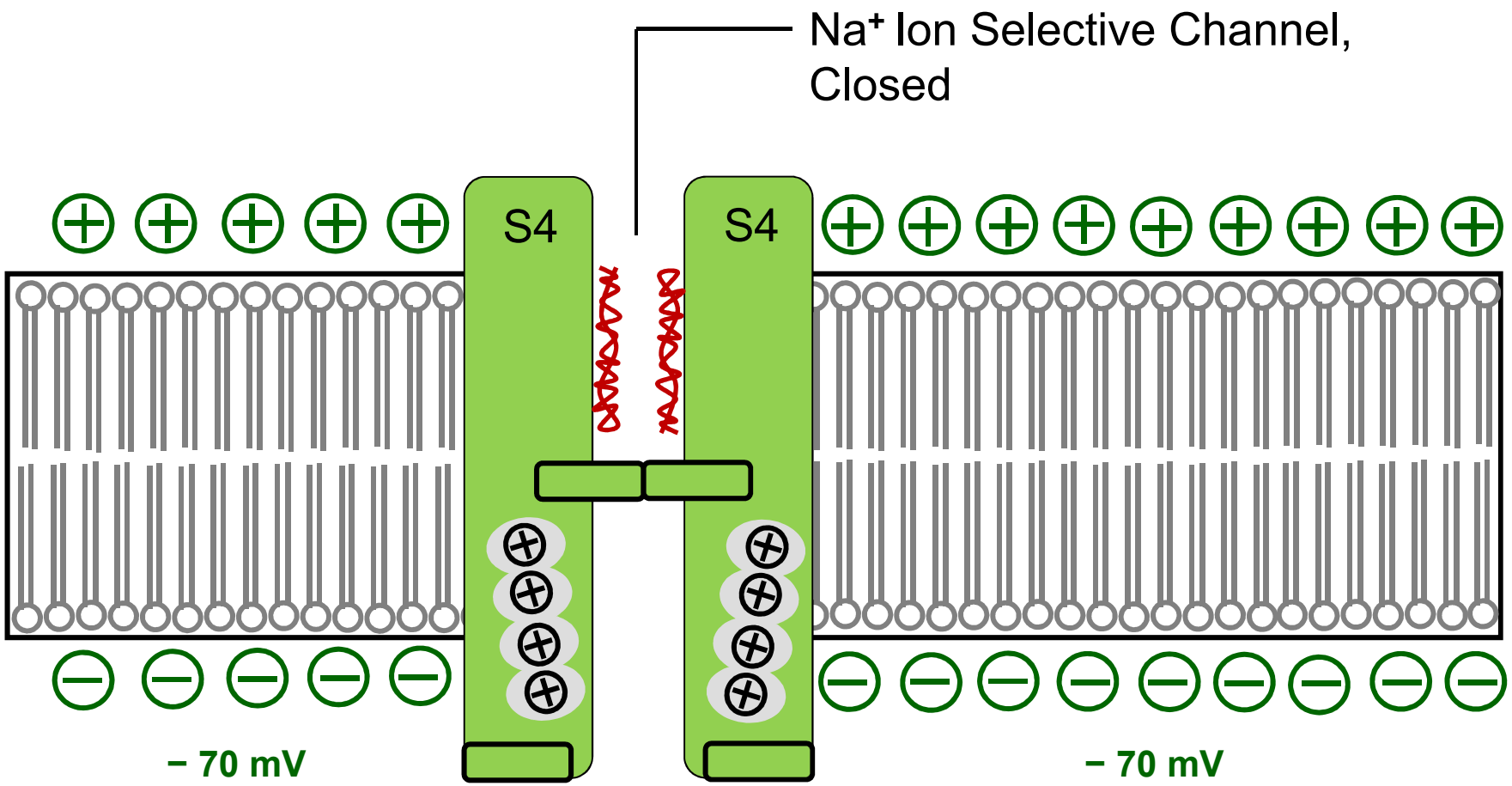
Continuous Excitation Conduction on the Axon (Simplified)

Refractory State, Temporarily Unpolarized Sections:



Continuous Excitation Conduction on the Axon (Simplified)

State of Rest:



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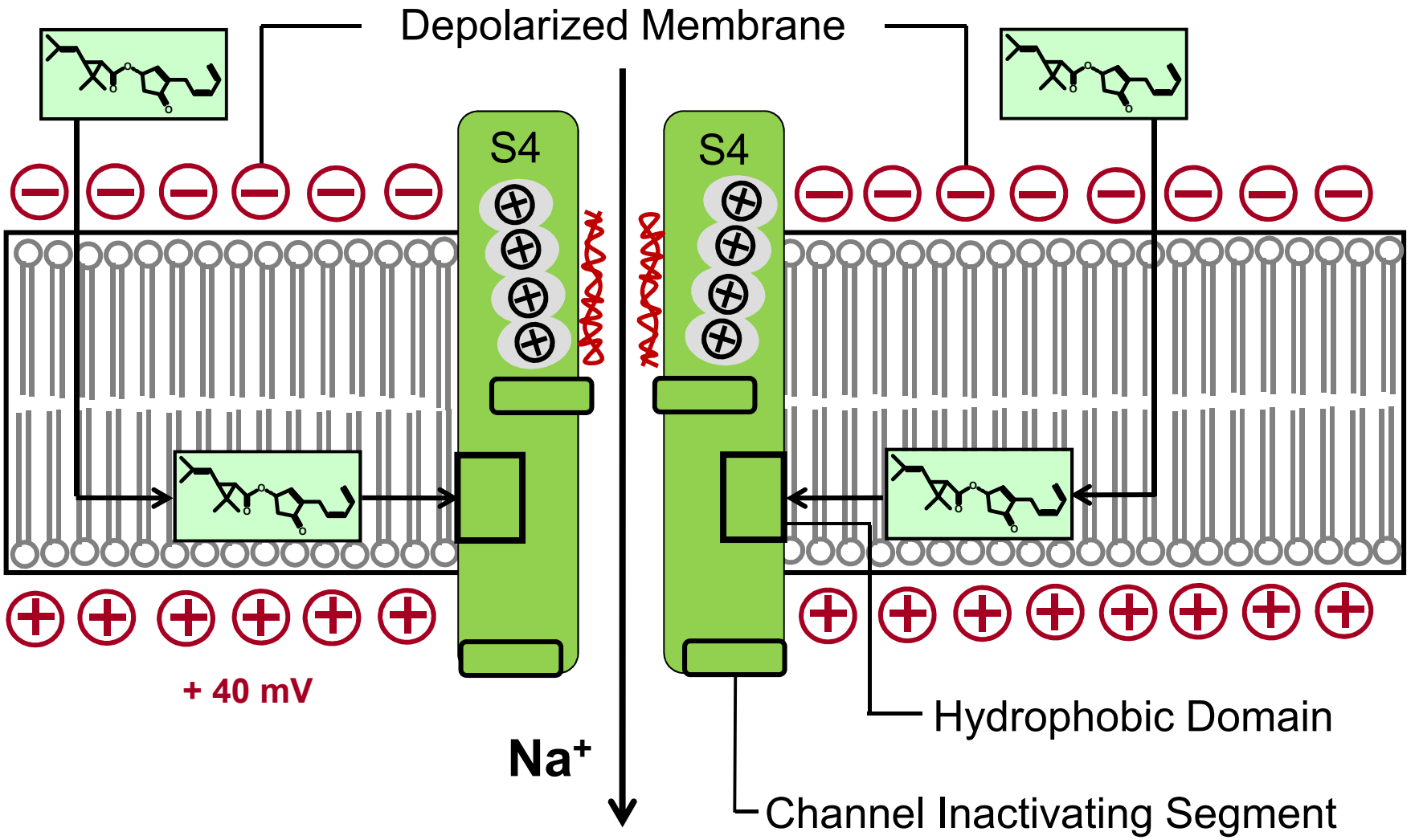
Effect of a Pyrethroid on the Axon (A. O. O'Reilly, 2006)

Diffusion of the Active Ingredient into the Phospholipid Layer:



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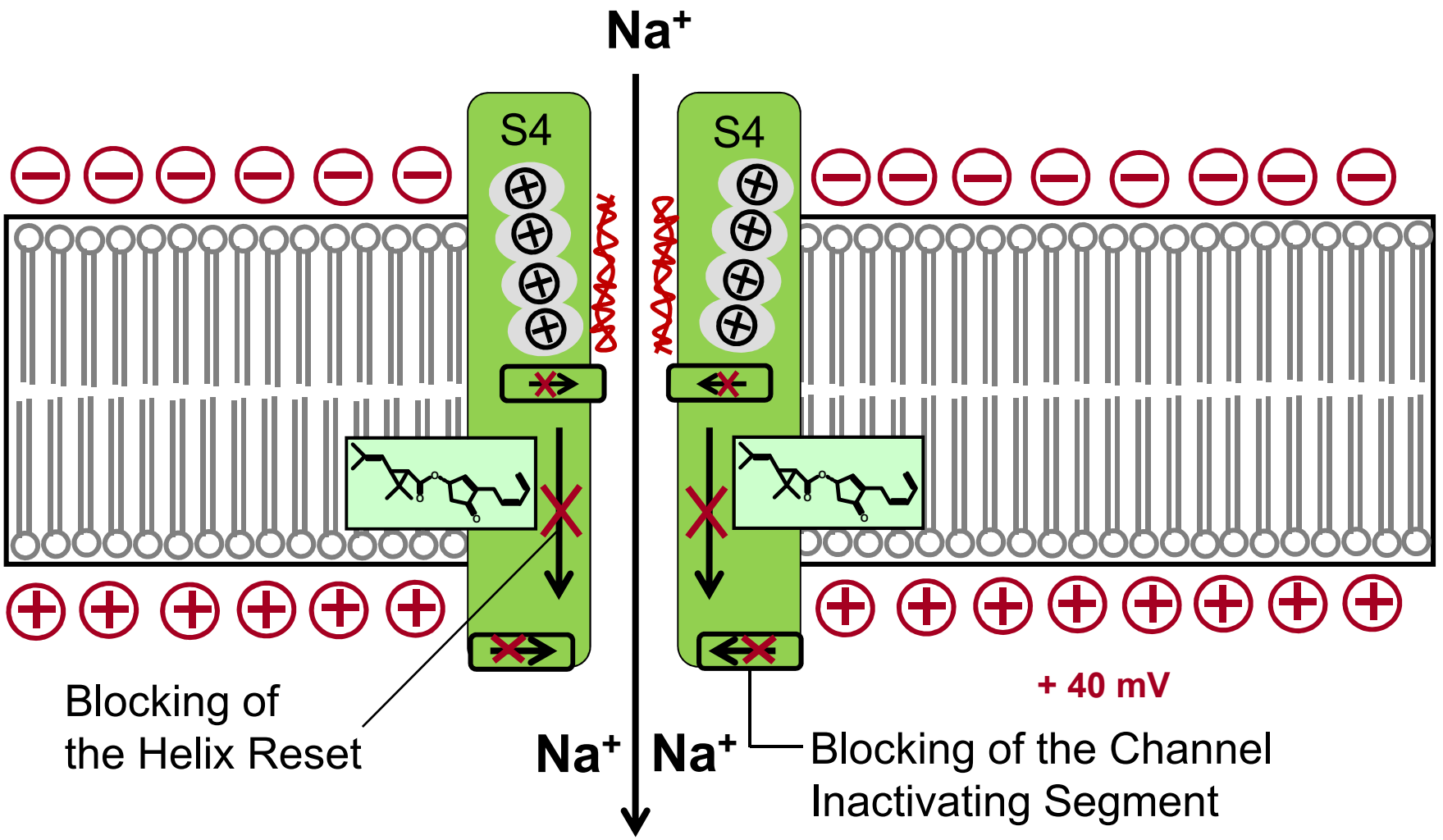
Effect of a Pyrethroid on the Axon (A. O. O'Reilly, 2006)

Binding of the Active Ingredient in the Hydrophobic Domains of the Channel Protein: Permanent Opening Permanent Excitation.



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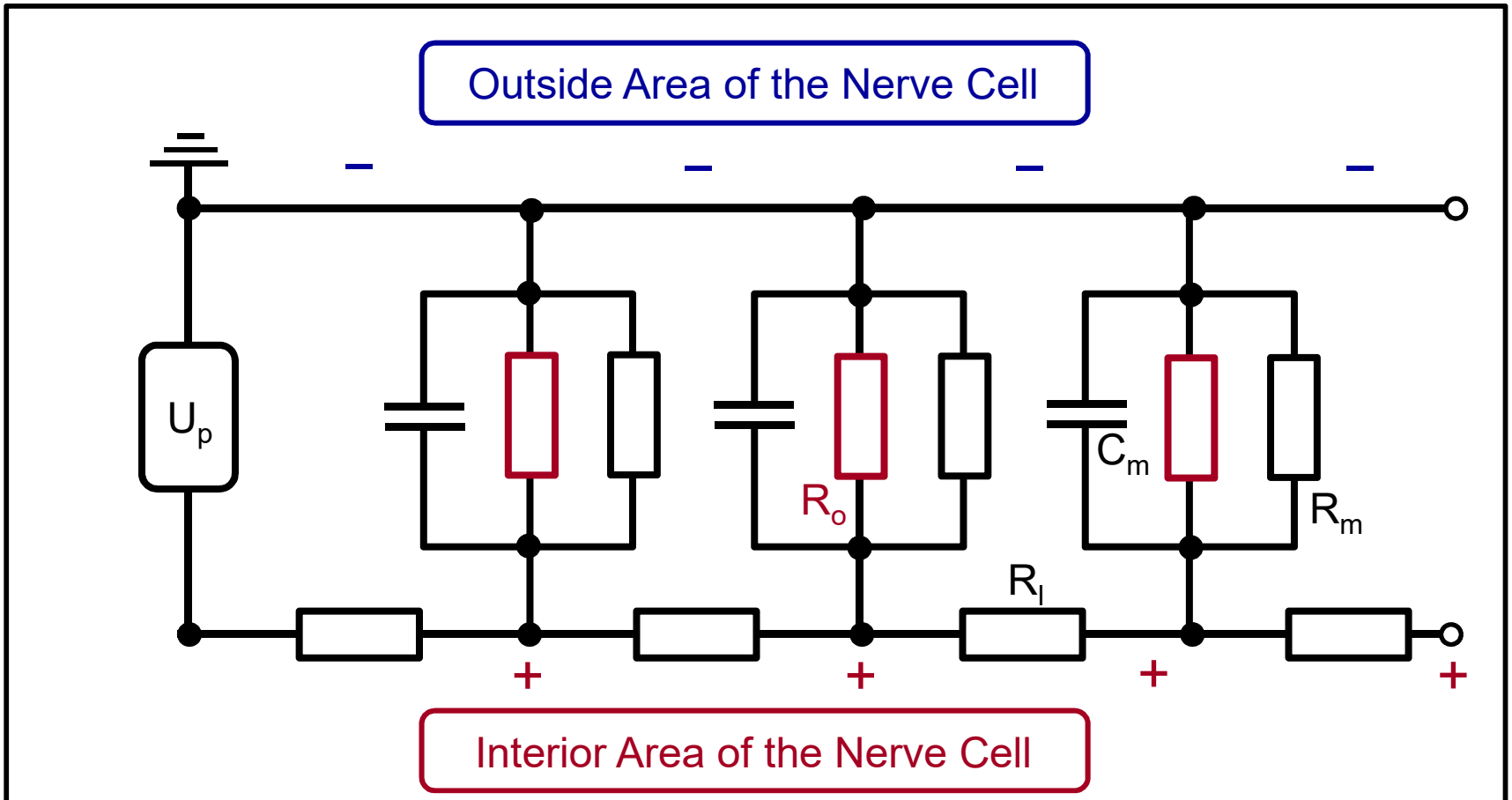
Section of a Neuron: Electrical "Analogy Circuit".

"RC Net", Membrane Segment in Continuous Excitation:



U_p: Voltage Pulse Generator. R_s: Series Resistance.	R_o: (Low) resistance of the permanently open ion channel.

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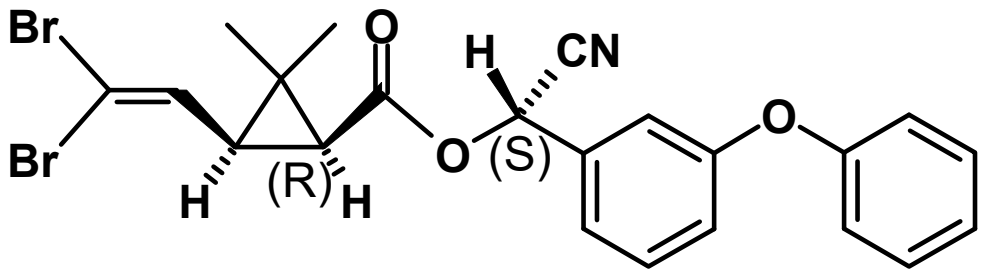
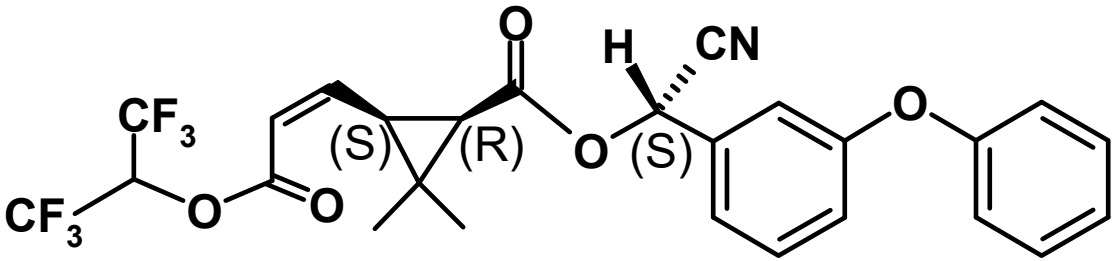
Sodium Channel Activators, Pyrethroids

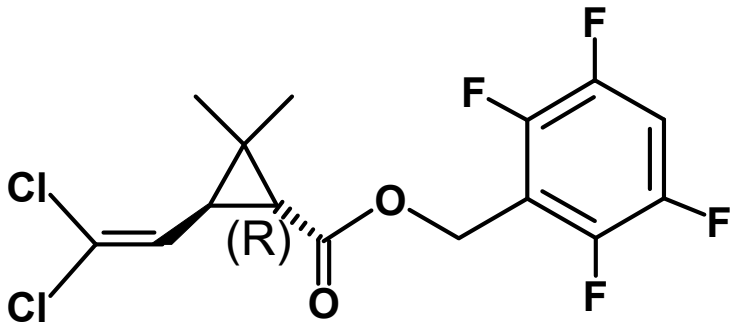
Commercial Active Ingredients, Chemical Structures:



Deltamethrin



Acrinathrin



Transfluthrin

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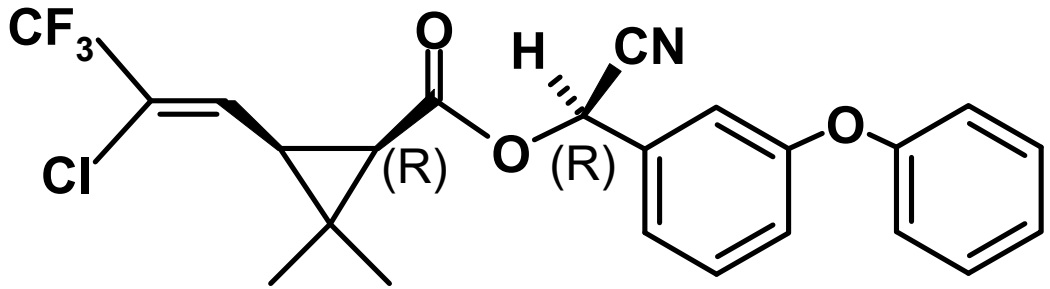
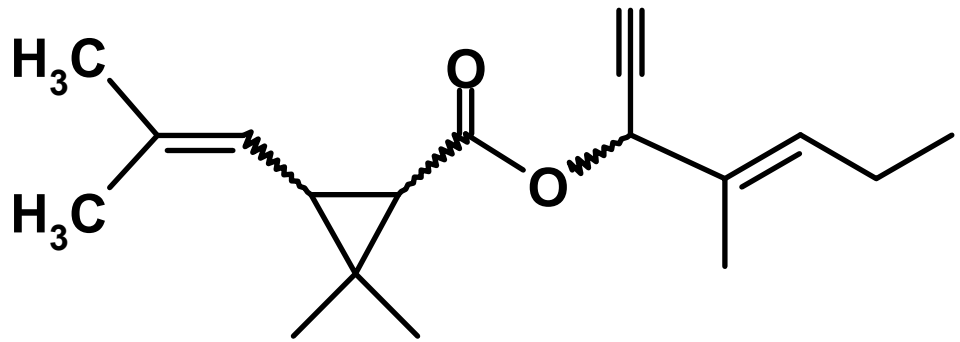
Sodium Channel Activators, Pyrethroids

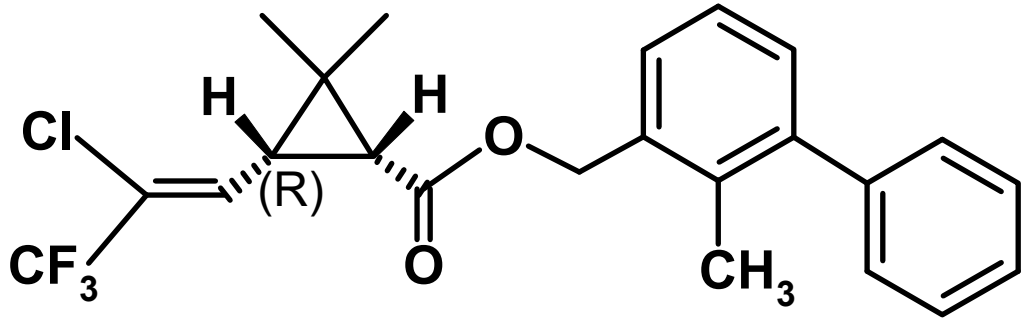
Newer Active Ingredients, Chemical Structures:



λ-Cyhalothrin



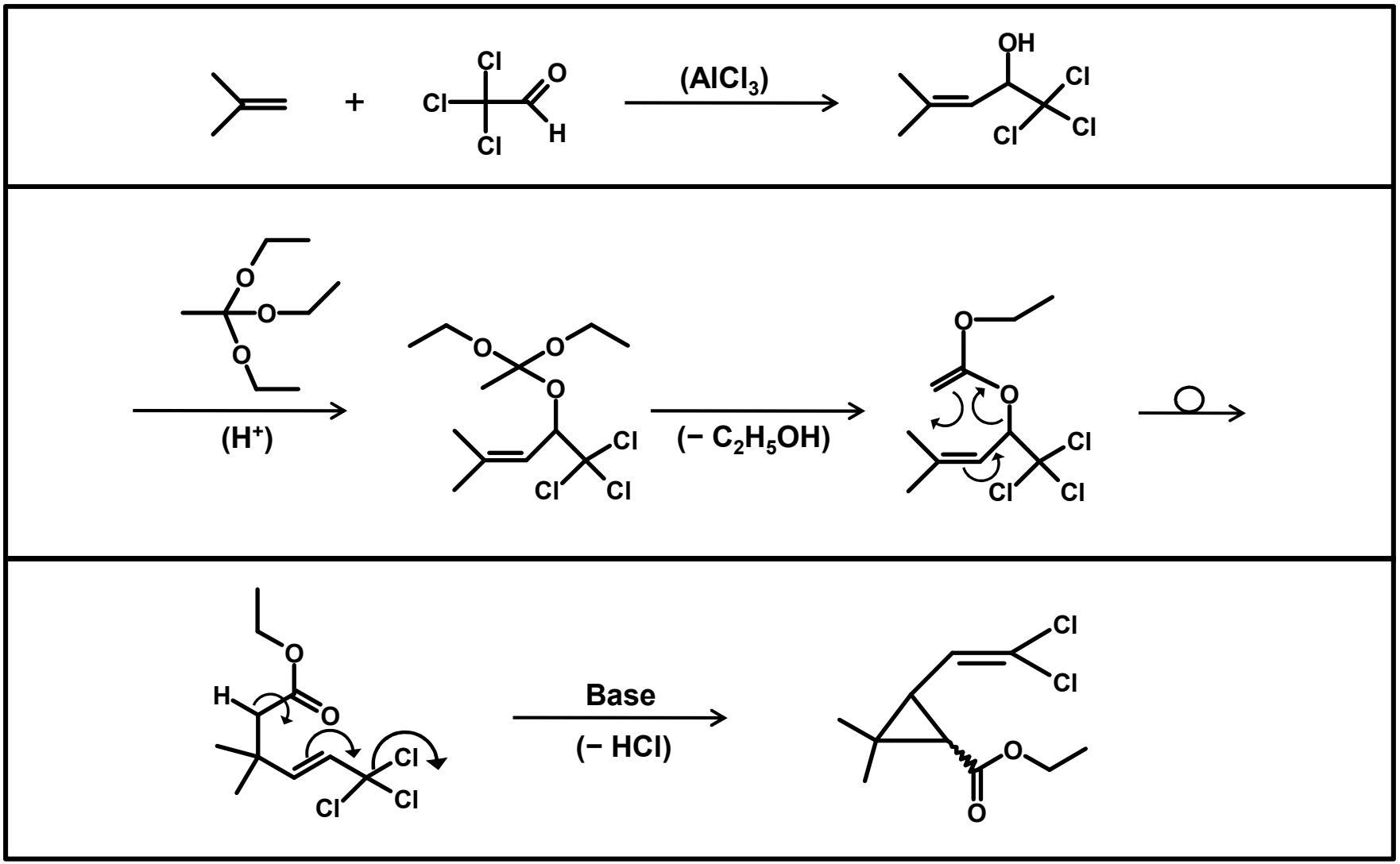
Empenthrin



Bifenthrin

Sodium Channel Activators, Pyrethroids

Dichloro-Chrysanthemic Acid Ester; Technical Synthesis:



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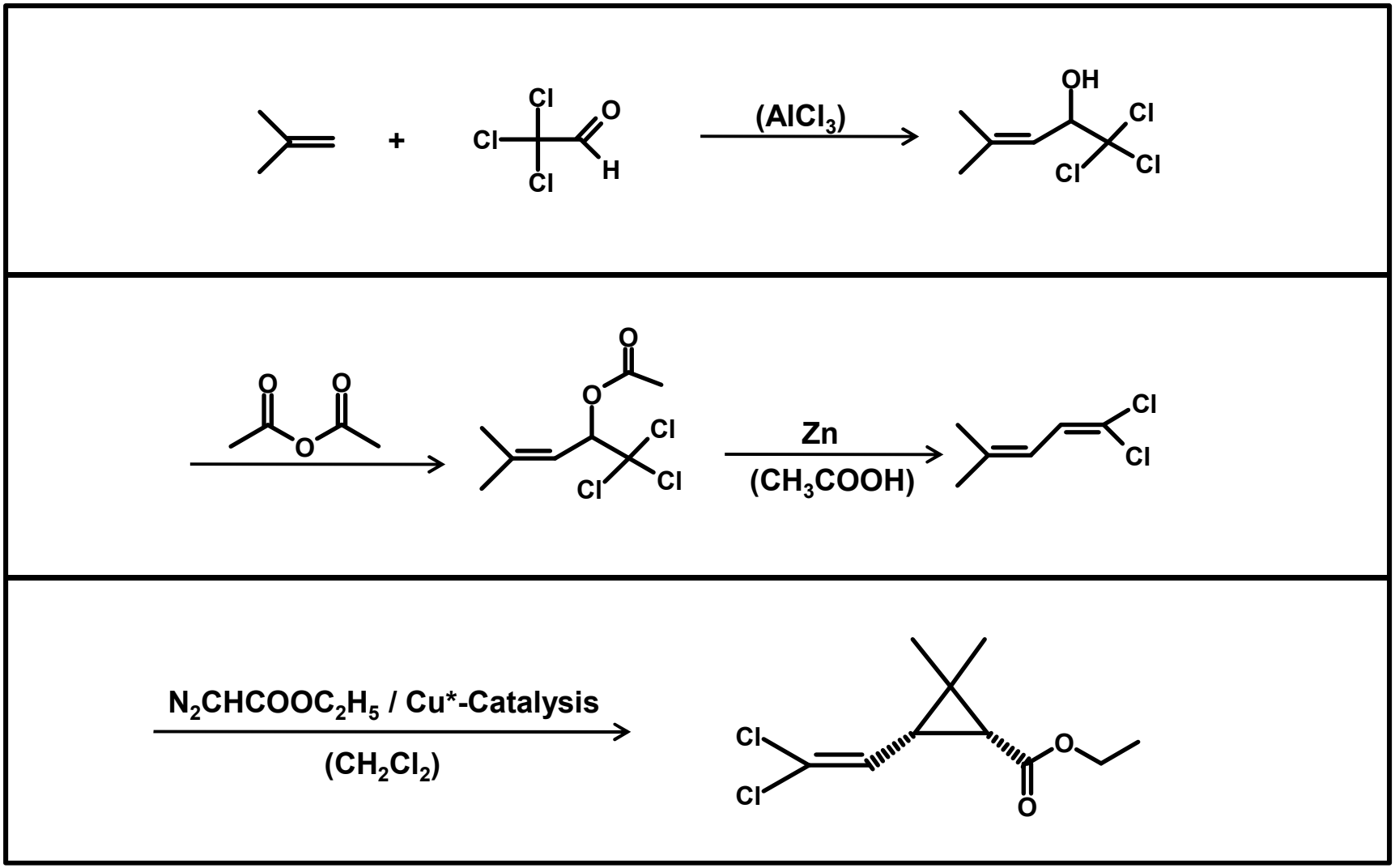
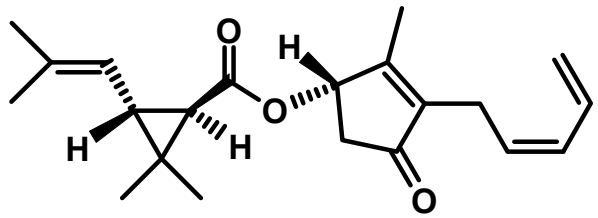
Sodium Channel Activators, Pyrethroids

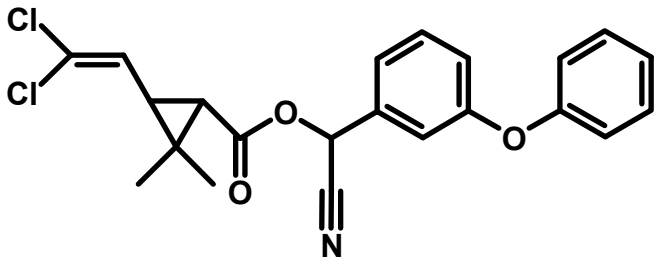
Dichloro-Chrysanthemic Acid Ester; Technical Synthesis:



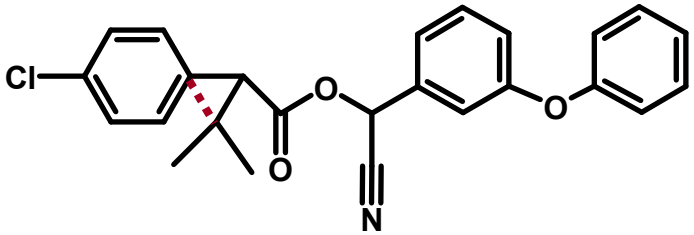
Sodium Channel Activators, **Pyrethroid Variants:**



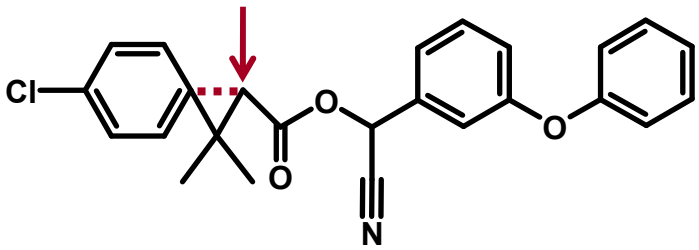
Pyrethrin I, (Chrysanthe-mum, Natural Product)



Cypermethrin (Shell plc)
(Mixture of Stereoisomers)



Fenvalerate (Sumitomo, J)
(Mixture of Stereoisomers)



Inactive laboratory product.
Oxidative functionalization in the insect organism (?)

Important Types of Formulation for Crop Protection Agents.

EC	**Emulsifiable Concentrate**	Solution of the solid or liquid active ingredient and emulsifier in an organic solvent.
EW	**Emulsion of Oil in Water**	Solution of the active ingredient in oil, which forms a stable emulsion with water and emulsifier.
SL	**Water Soluble Concentrate**	Concentrated solution of the active ingredient in water or water-miscible solvents.
SC	**Suspension Concentrate**	Stabilized suspension of finely dispersed, solid active ingredient in water.
WP	**Wettable Powder**	Solid active ingredients in combination with carrier materials, dispersing and wetting agents, finely ground.
WG	**Water Dispersible Granules**	Solid substance in the granulate, which itself forms a stable suspension after being dispersed in water.

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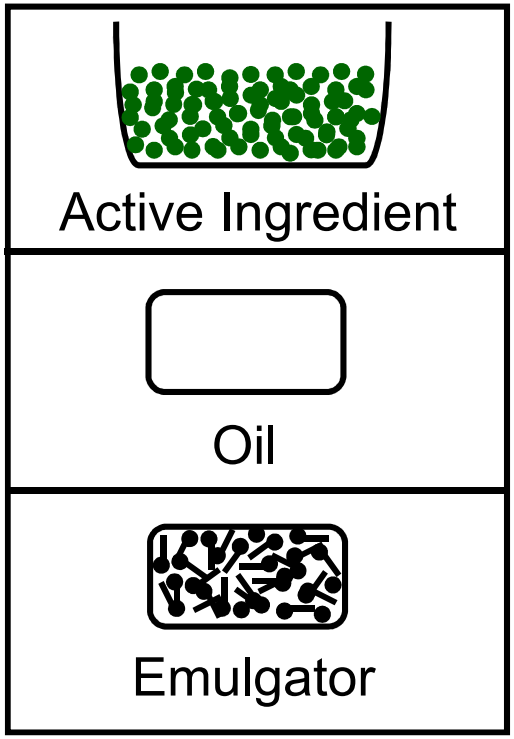
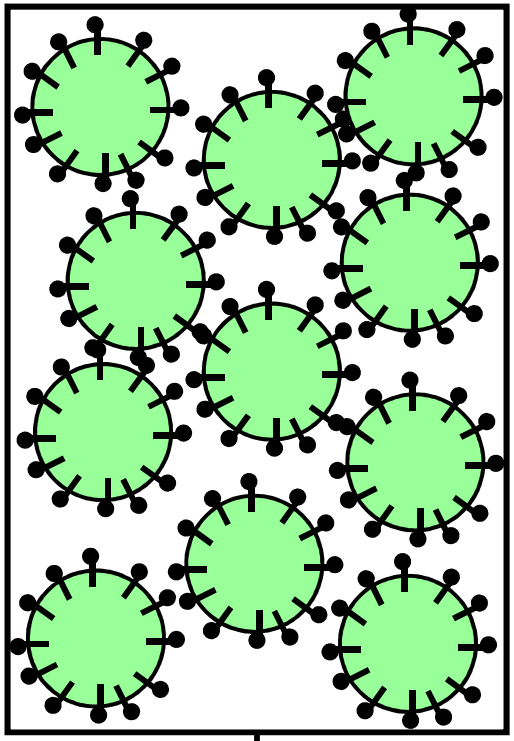
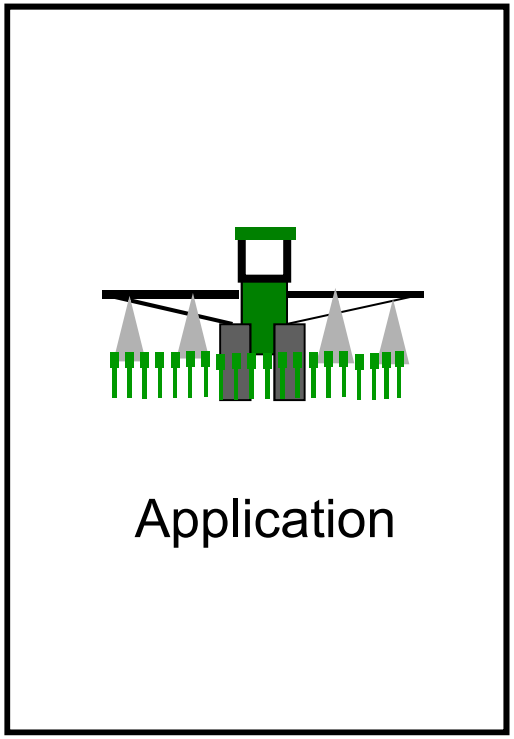
Formulation and Application of Crop Protection Agents







Formulation of the insecticidal active ingredient, for example as a solution in oil (light green), which is then emulsified in water (EW).

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Further literature (specialist books, specialist articles) on the topics: "Insecticidal sodium channel activators" / "Insecticidal AChE inhibitors".

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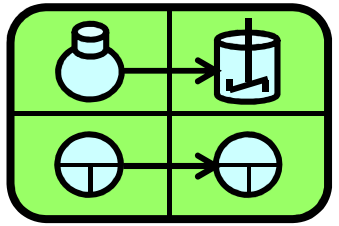

Supplementary Module for (Bio) Chemists (m/f/d)

Information Material *for the subject matter:*
Strategic Invention / Selection Invention.

"DNA Computer for Massive Parallel Data Processing".

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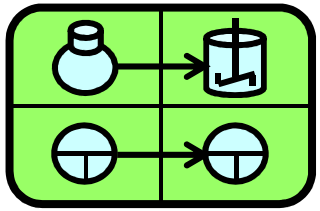
R&D Project Management in the Chemical Industry

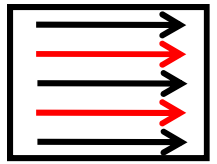


Subject Matter	***Strategic Invention Selection Invention***

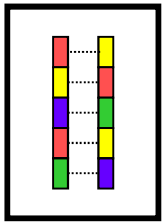
Chemical-Biological Basics: "DNA Computer for Massive Parallel Data Processing".

DNA Computer for Massive Parallel Data Processing

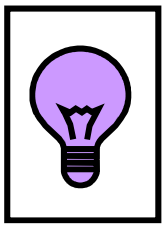
Problem (Need for Action in the IT Sector):
Powerful computers that can use massive parallel data processing.



Biochemical Approach:
The highly compressed information content of numerous different "DNA fragments".



First Publication and "Strategic Invention" :
"Molecular Computation of Solutions to Combinatorial Problems". L. M. Adleman, Science 266: 1021-1024 (1994).



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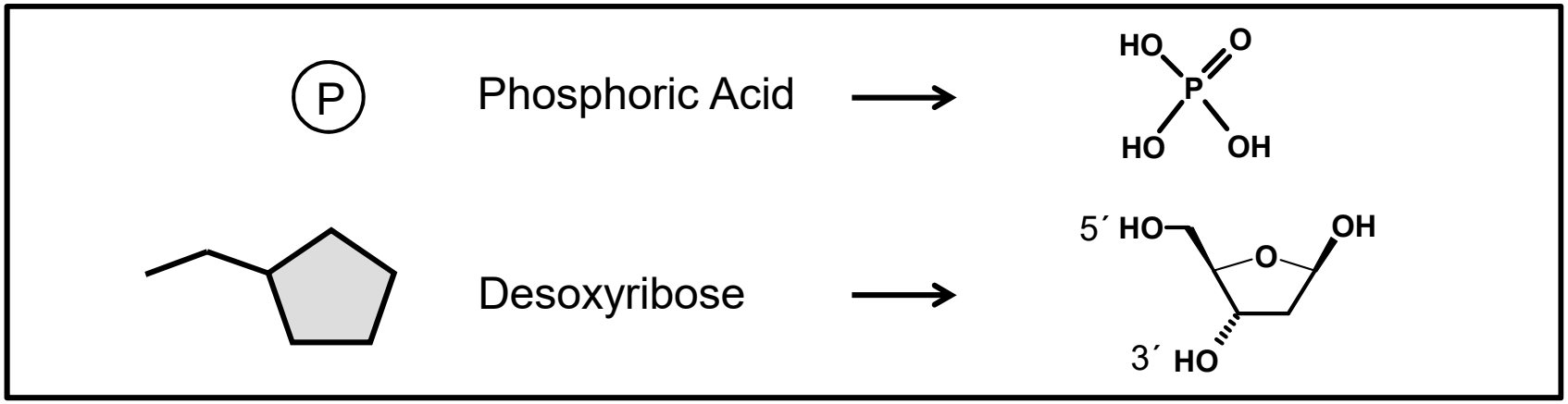
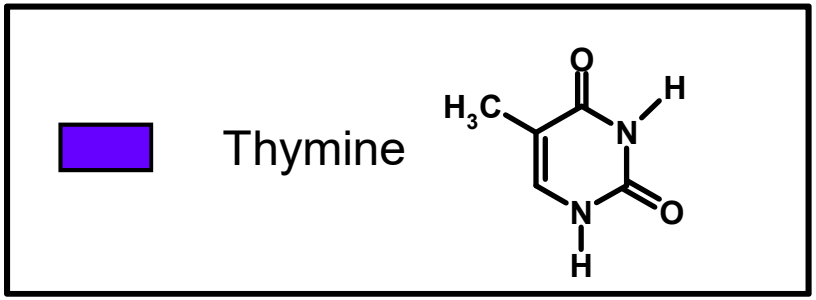
DNA Computer for Massive Parallel Data Processing

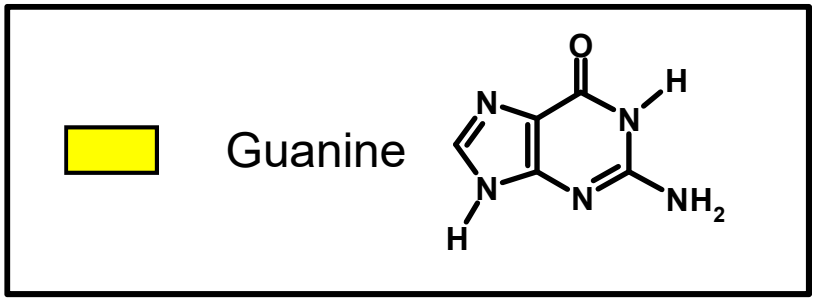
J.F. Miescher	Discovery of DNA as an acidic component of the cell nucleus.
E. Chargaff	(1:1) Ratios of each base pairs A-T and C-G in DNA.
R. Franklin	Analysis of X-ray diffraction patterns of DNA.
M. Wilkins	X-Ray diffraction experiments: Structural pattern of crystalline DNA.
J. Watson	Double helix model of DNA.
F. Crick	Double helix model of DNA.
A. Maxam	DNA sequencing using base-specific cleavages.
W. Gilbert	DNA sequencing using base-specific cleavages.
F. Sanger	DNA sequencing using chain termination syntheses.
C. Cantor	Pulsed gel electrophoresis for polynucleotide separation.
L. Hood	Automated DNA sequencing.
R. Letsinger	Synthesis of oligonucleotides using phosphoramidites.
R. B. Merrifield	Solid phase synthesis of biopolymers.
K. Mullis	PCR, polymerase chain reaction for DNA multiplication.
L. Adleman	Verification of the functional principle of a DNA Computer.

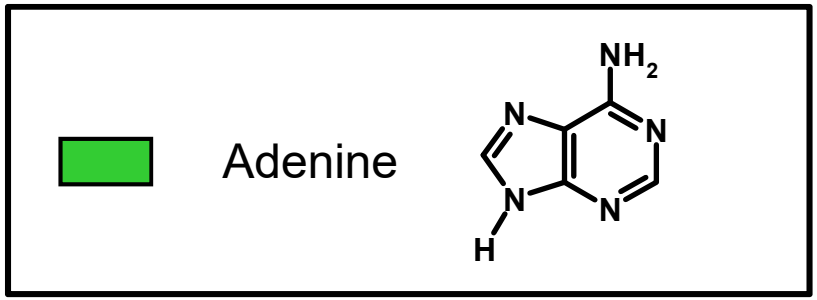
DNA Computer for Massive Parallel Data Processing

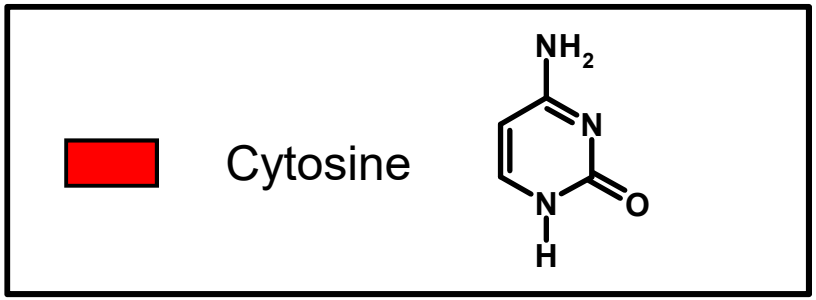
The Structure of DNA, Individual Building Blocks:











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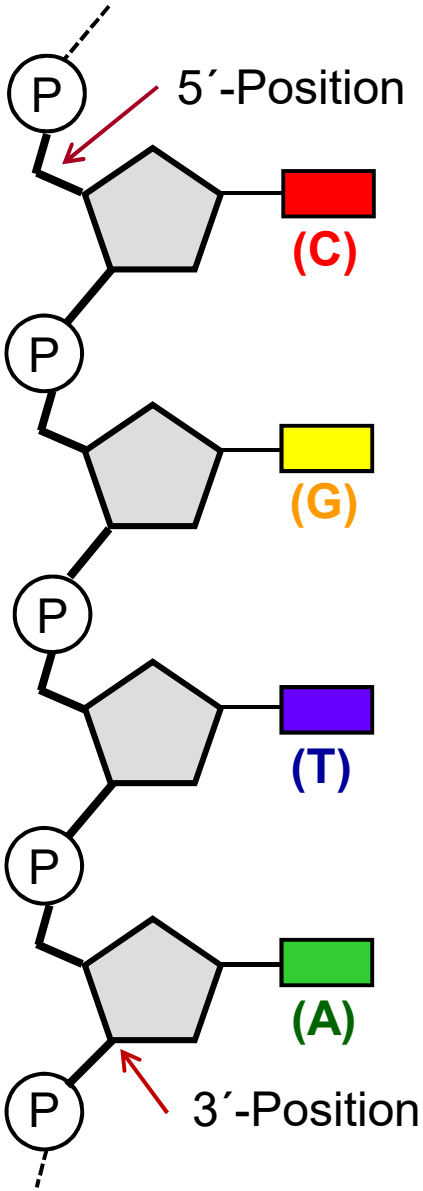
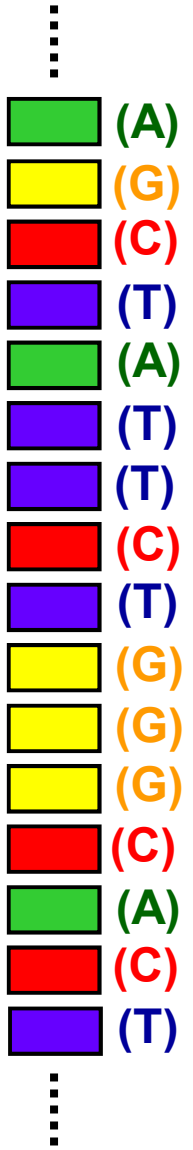
Oligonucleotide Section from a Single Strand of DNA:



Due to its characteristic **sequence of the bases** adenine (A), cytosine (C), thymine (T) and guanine (G), the oligonucleotide single strand serves as an **information store**.

This sequence is the basis for a universal programming language (Genetic code, including the code for protein syntheses).
The "back-bone" of the single strand, consisting of phosphate and sugar residues, ensures the stability of the information through its covalent chemical bonds.



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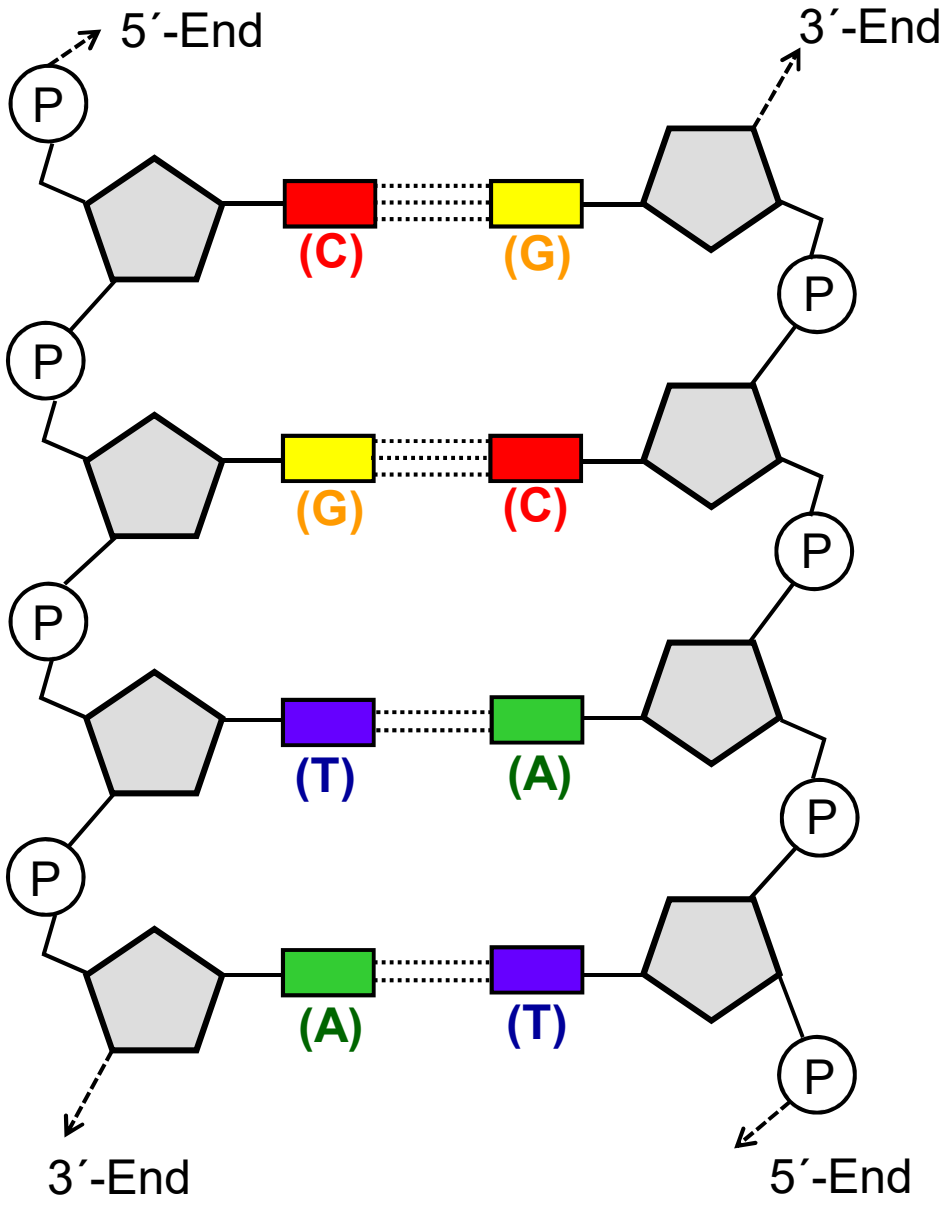
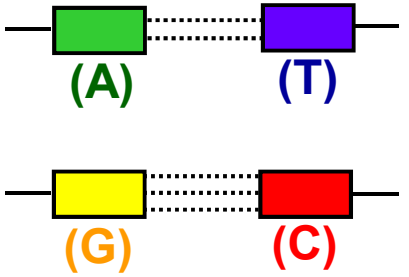
Double-Stranded Oligonucleotide, DNA Section (Scheme):





Complementary base pairs, the pairwise arrangements of which stabilize via 2 or 3 intermolecular hydrogen bonds ····· .

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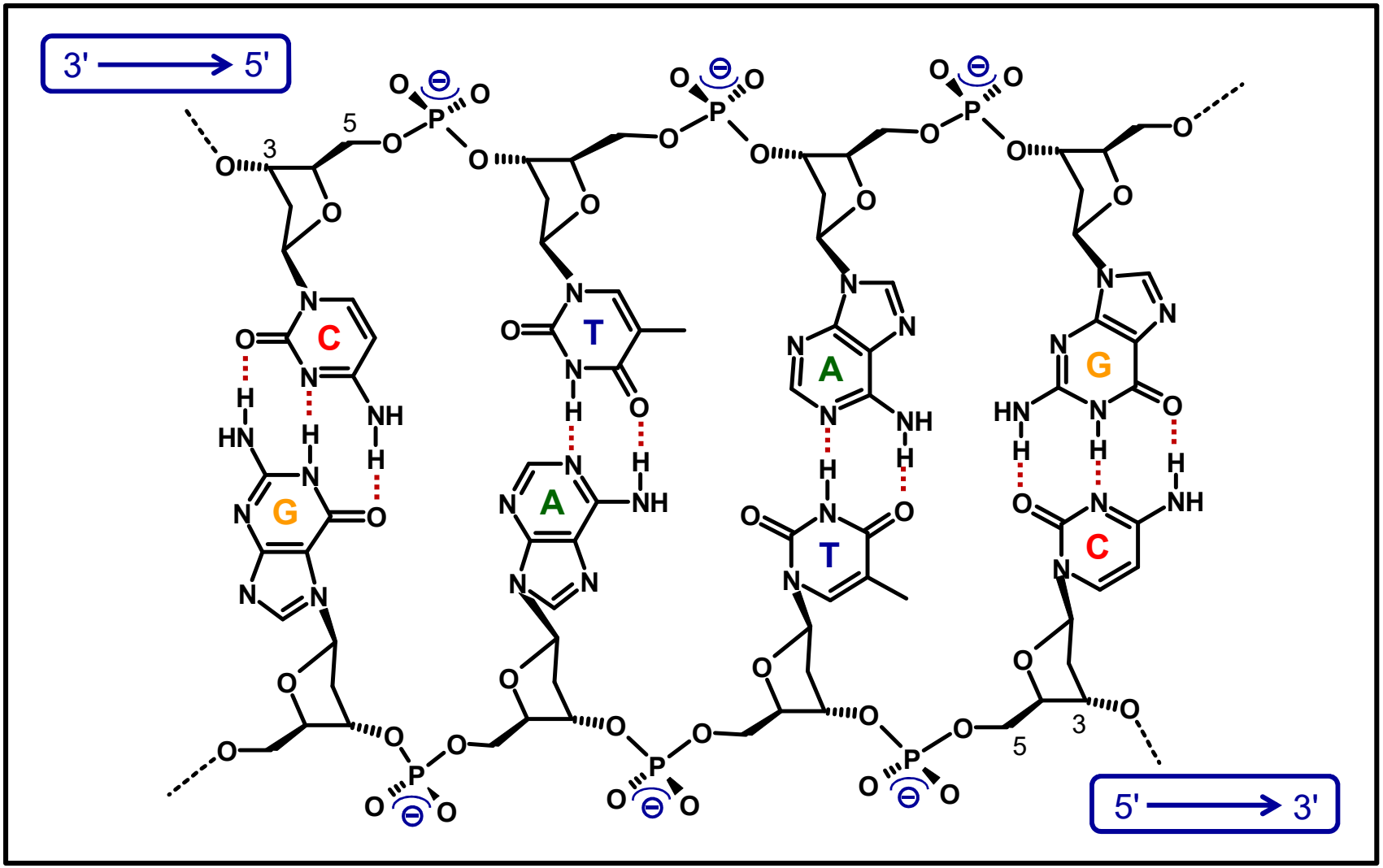
DNA-Molecule (Detail), Simplified Representation:



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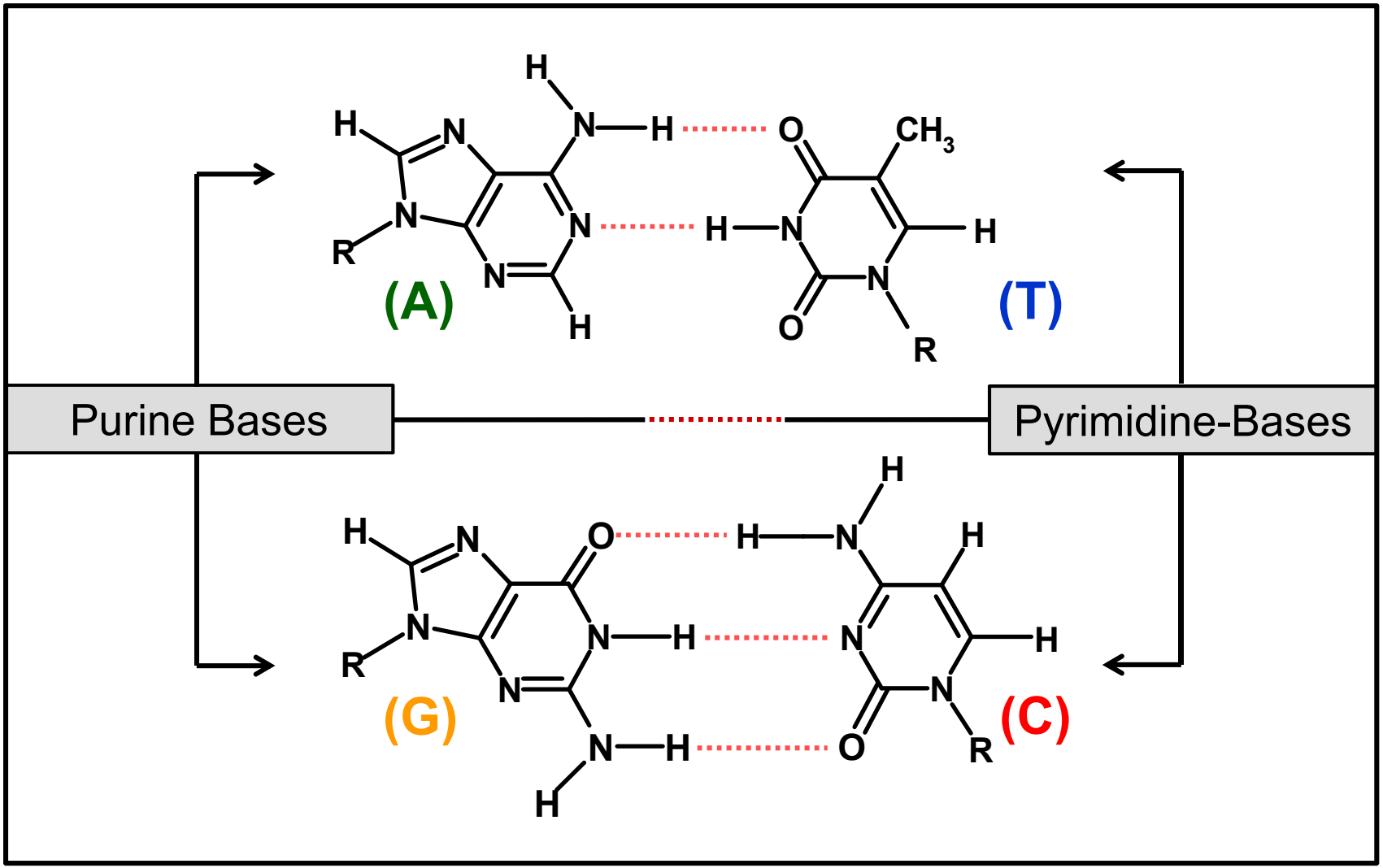
H^+-Bridges Between the Complementary DNA Bases:



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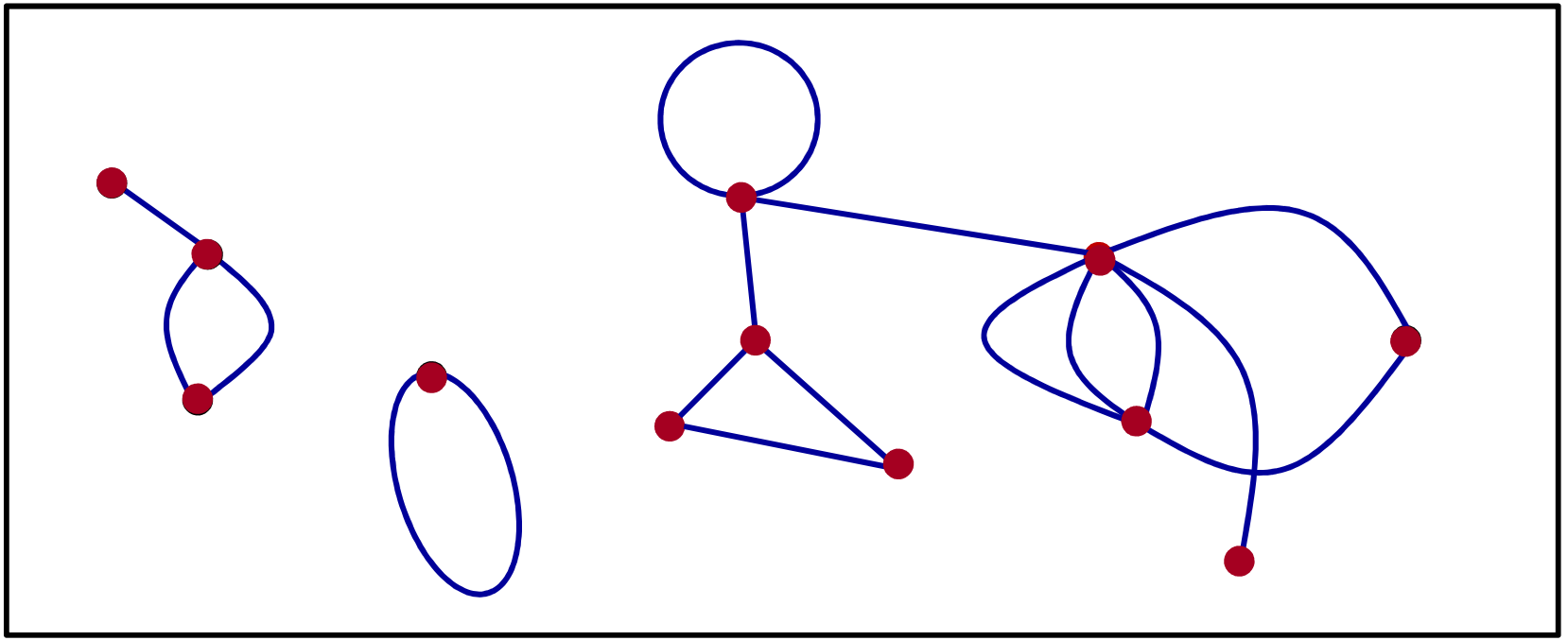
Graph ⟶ Mathematical **Definition**:
Non-empty set of points and a set of lines, each connecting two points or one point to itself. The points are called **vertices** (nodes) and the lines are called **edges**.



Example: Graph with **12 Vertices** and **16 Edges**.

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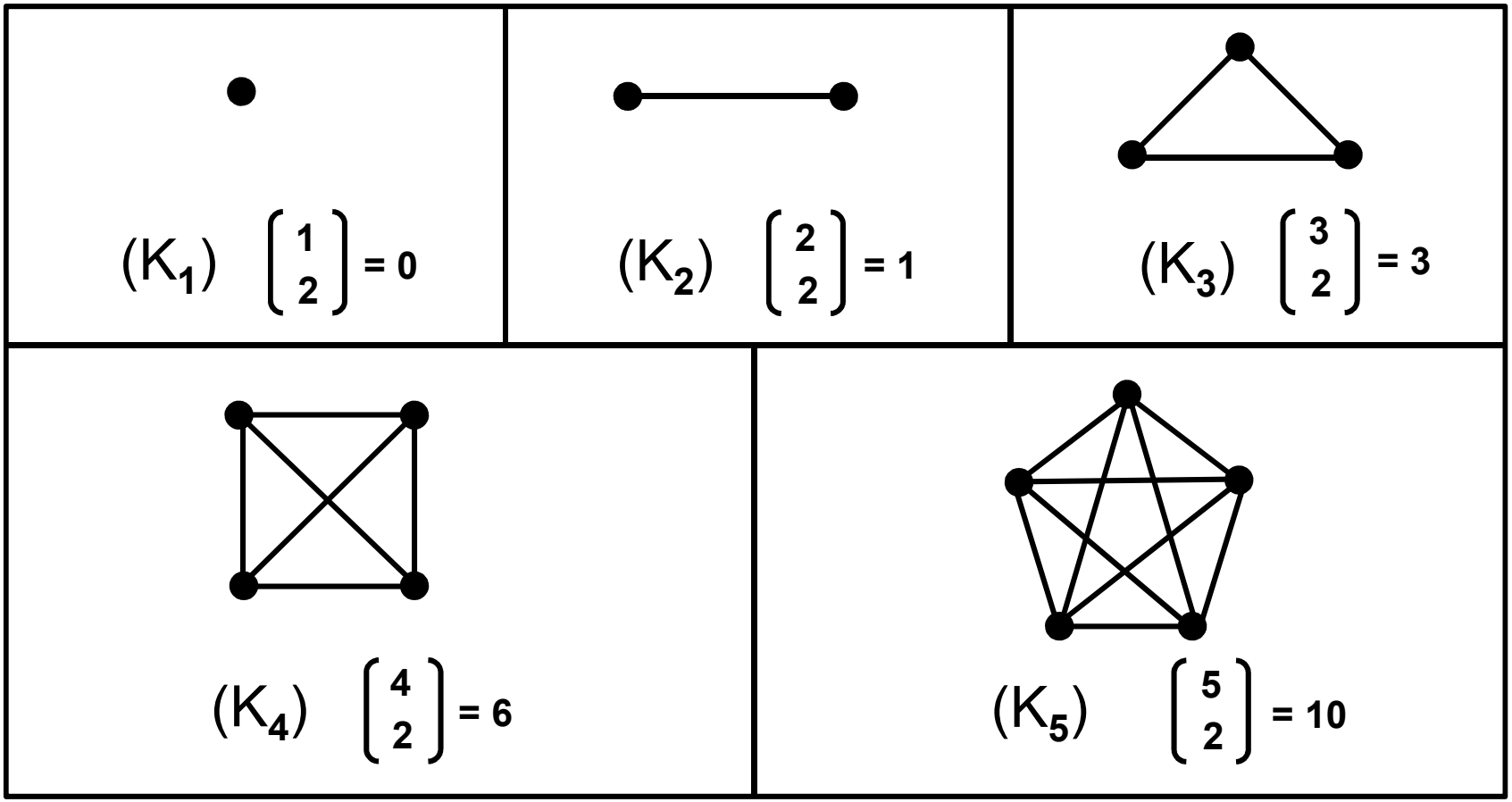
Graph Theory, **Complete Graph ("Simplex", (K_n):**



$$n \text{ Vertices} \longrightarrow \frac{n\,(n-1)}{2} \text{ Edges} \longrightarrow (K_n)$$

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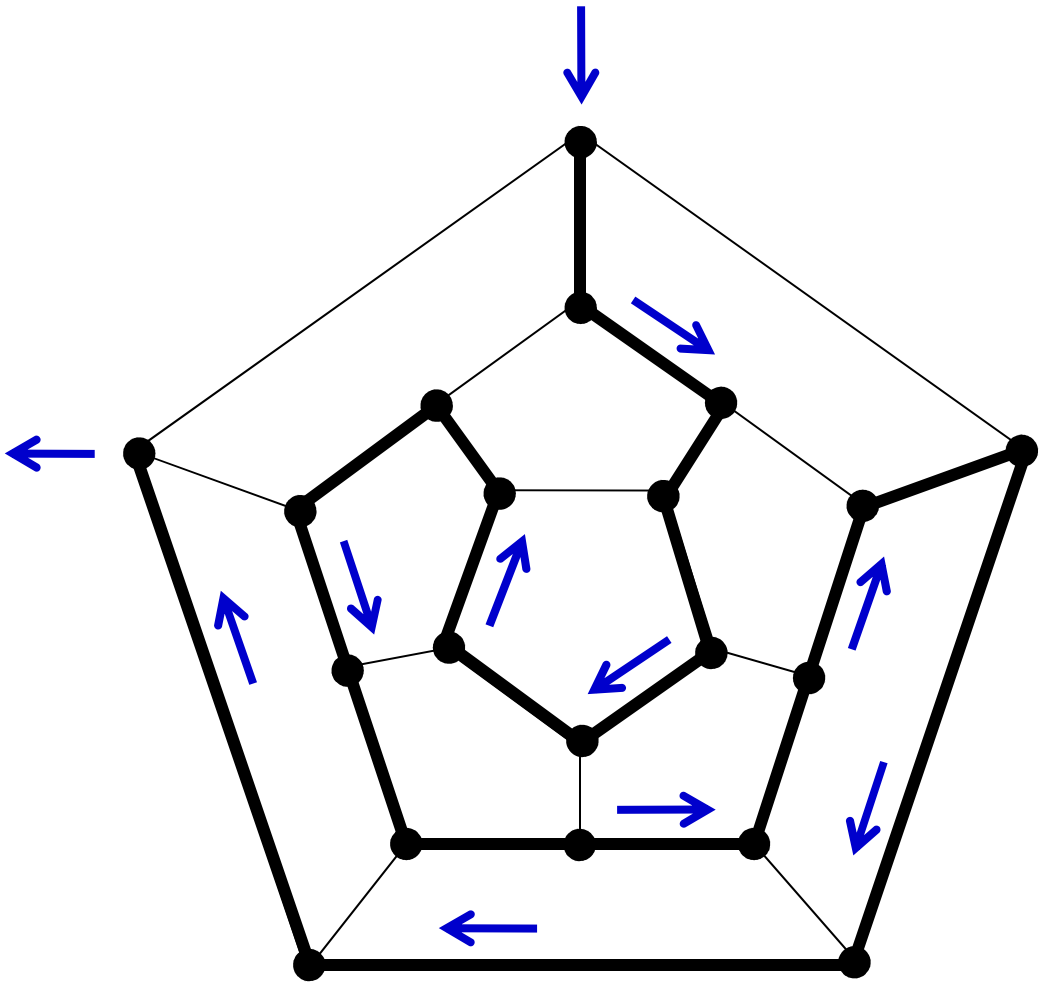
Connected Graph: Two vertices are always connected by at least one edge (line).



Example for a connected graph:
(Dodecahedron-Net)
20 Vertices, 25 Edges.

→**"Hamiltonian Path"**:
All **vertices** of a network are passed through exactly once.

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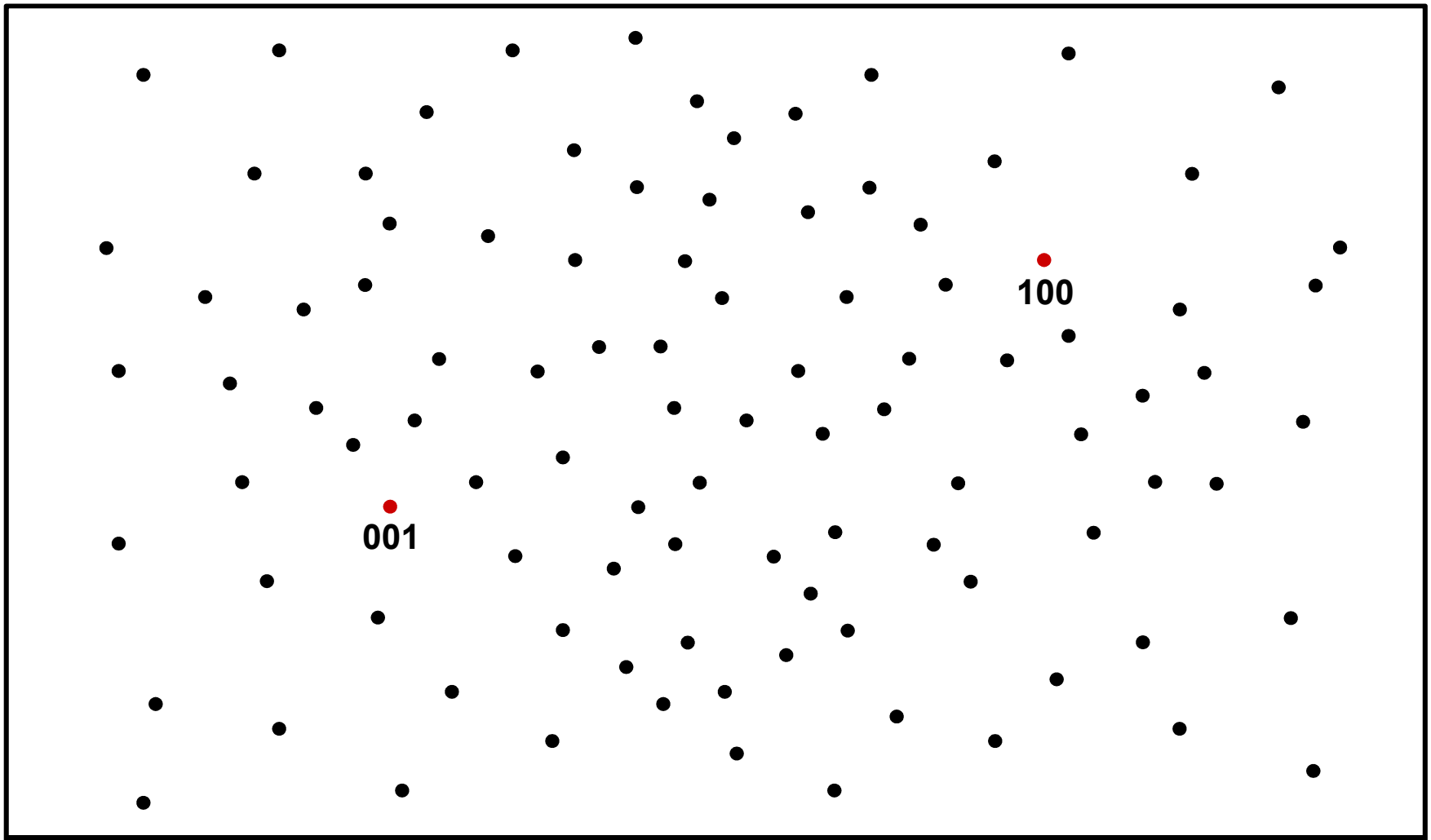
Application: Hamiltonian Paths in Complex Networks.



Graph with 100 Vertices. The edges are initially left out!

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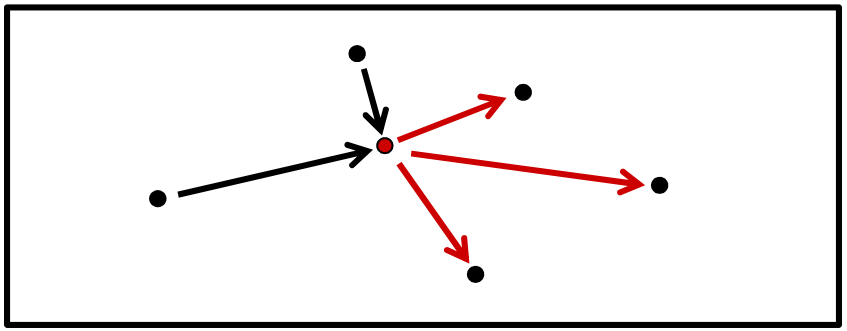
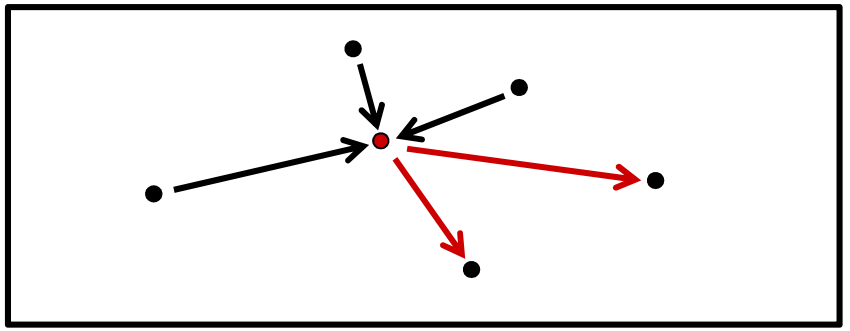
Application: Hamiltonian Paths in Complex Networks.

The following graph exists as a coherent network with defined paths: **100 vertices, 240 edges, 257 paths** (path: edge between two vertices with a defined direction of passage).

At least one path (vector) leads to each individual vertex directly along the corresponding edge.

Starting from each individual vertex, at least one other vertex from the total set of all vertices along the corresponding edge can be reached directly via path (vector).





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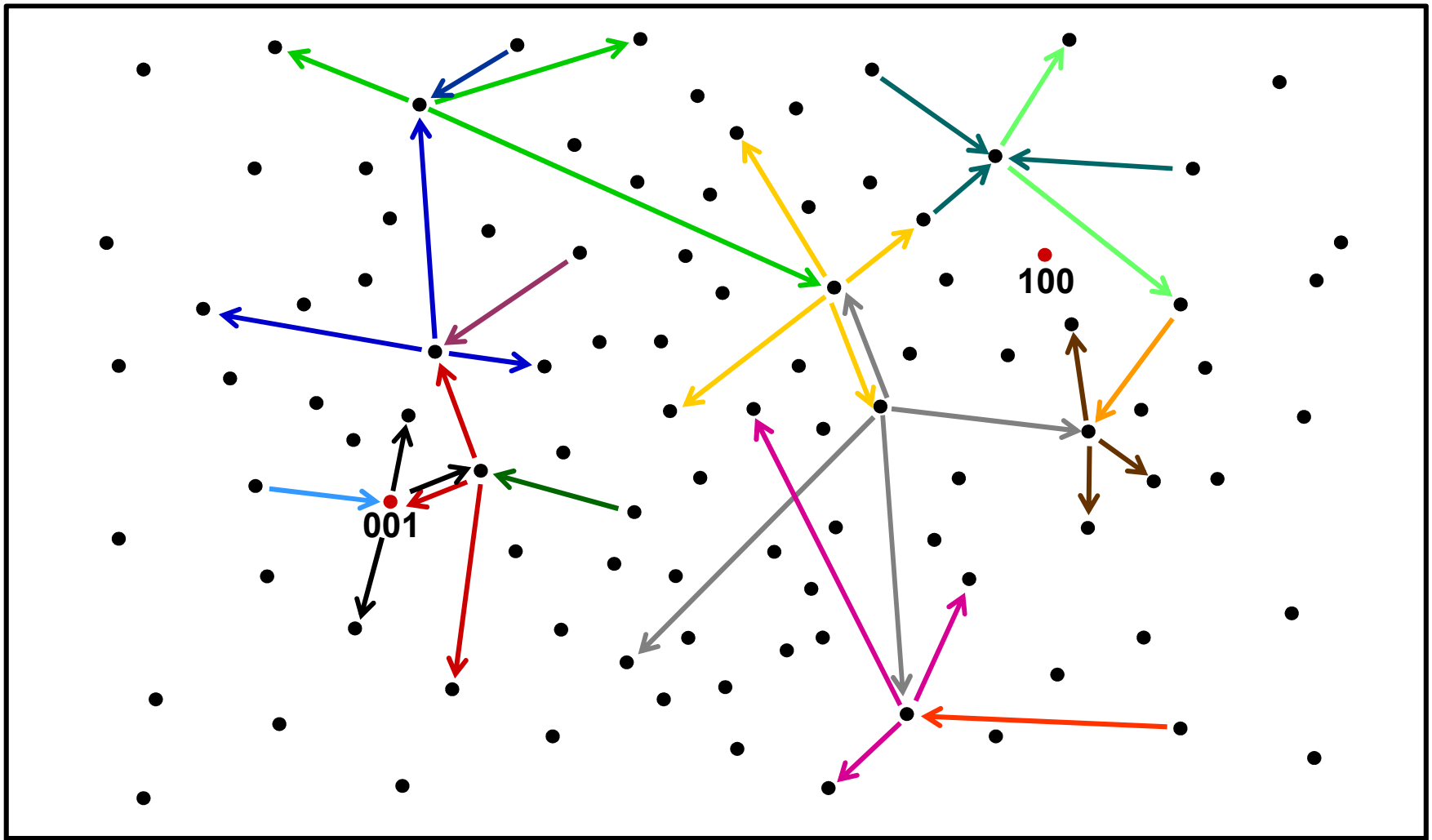
Application: Hamiltonian Paths in Complex Networks.



Definition and drawing of individual aligned **edges**.

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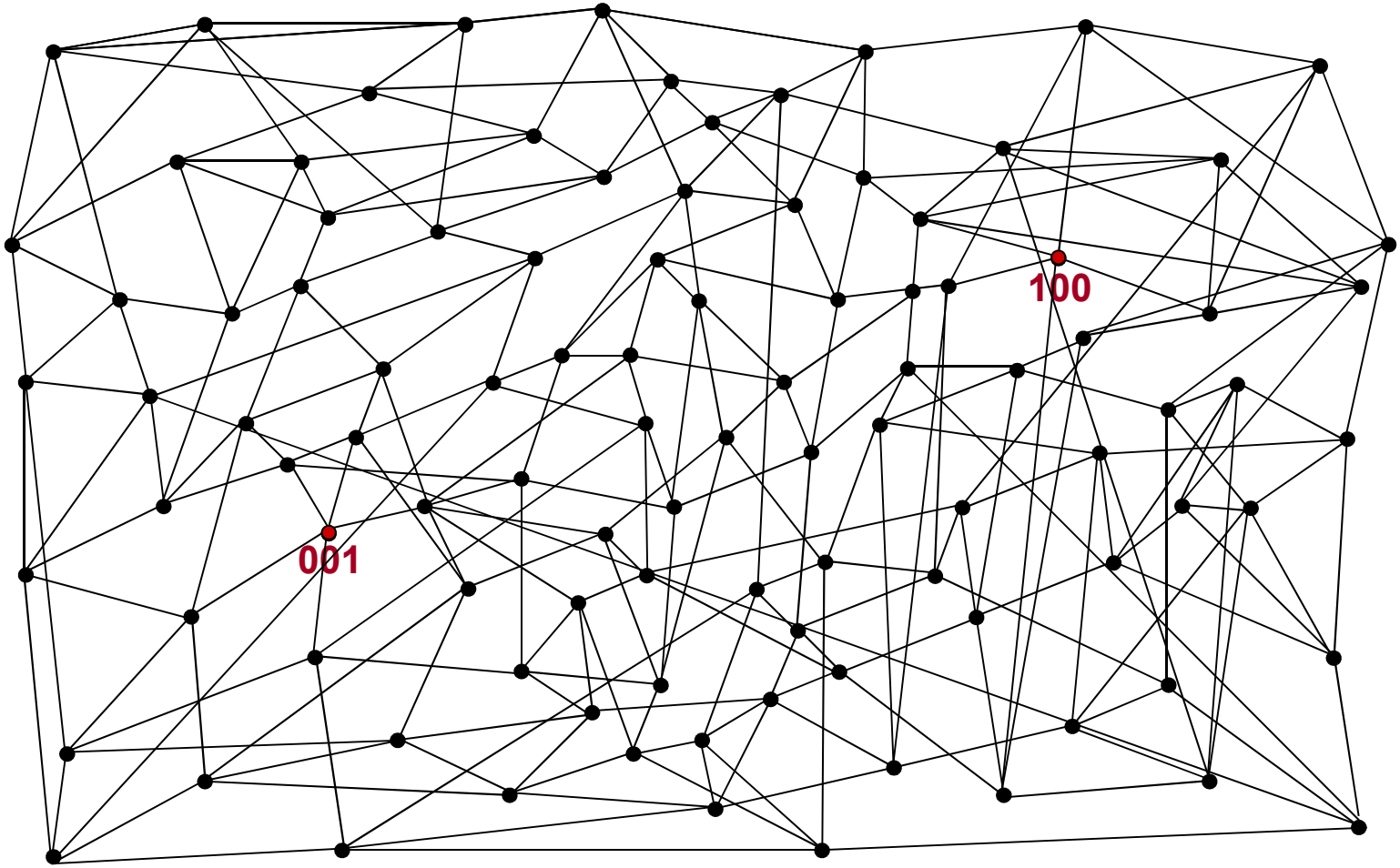
Application: Hamiltonian Paths in Complex Networks.



Graph with 100 vertices and 240 (directed) edges (here without arrows!).

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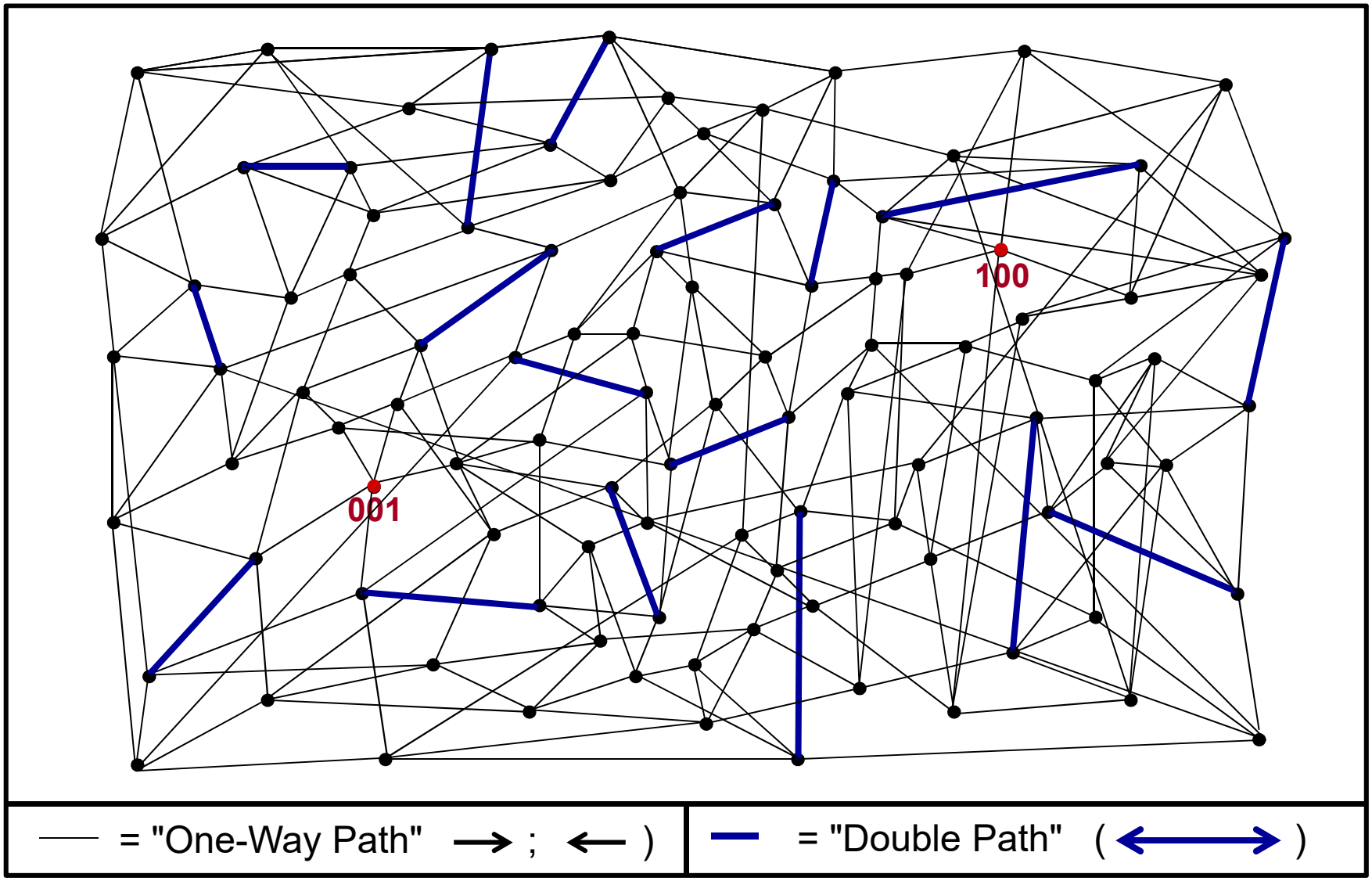
Sought: A/The Hamilton Path(s) from 001 to 100!



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Rough Approximation of all possible path combinations if an average of 2.5 further vertices can be reached from each individual vertex.

Approximation for all path combinations $\longrightarrow$ $2\left[(2,5)^{95}\right] \approx \mathbf{1,3 \times 10^{38}}$

Assumption:
The performance of a linear computer corresponds to 1 trillion (10^{12}) path sums per second.

Sequential calculation time: ≈ 1.3 x 10^{26} seconds ≈
4.0 x 10^{18} years! Age of the universe: approx. 1.6 x 10^{10} years!

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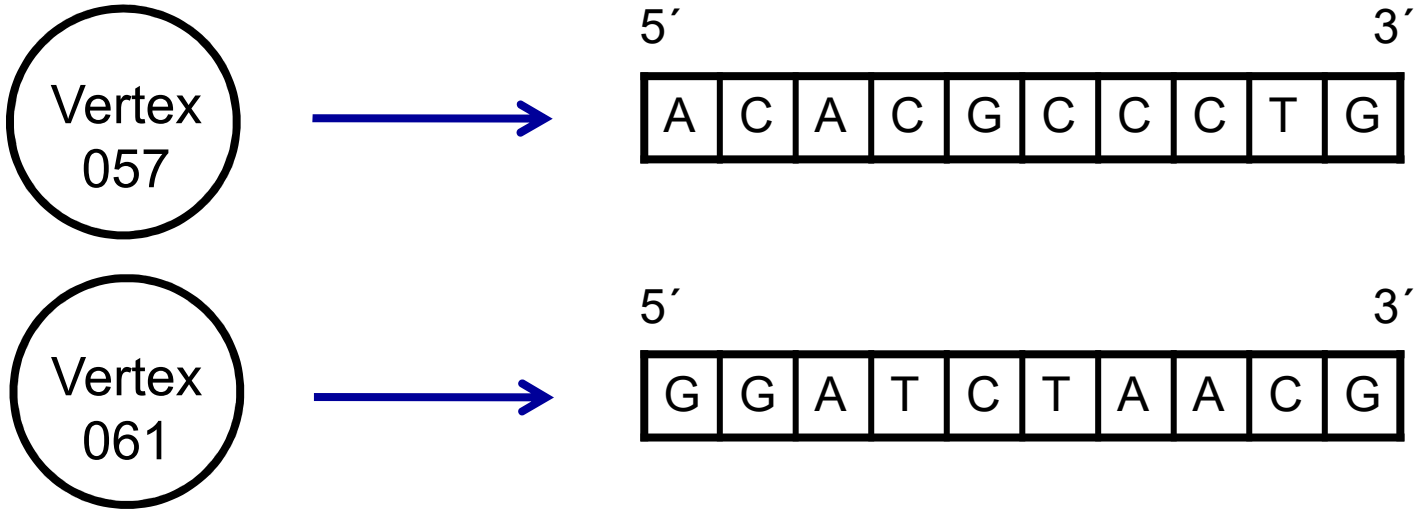
The "Hardware" Consists of Test Tubes, Defined Nucleotides, Separation and Analysis Devices.

Defined nucleotides ⟶

Exactly **one decanucleotide sequence** is assigned to each individual **vertex** 001, 002, 003 ..., 098, 099, 100.

Examples of defined "vertex decanucleotides":



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Defined Nucleotides:

Each of the 257 **paths** in the network is assigned a defined decanucleotide sequence, the base sequence of which is determined by the fact that the first five bases are complementary to the last five bases of the vertex from which this path leads away and the last five bases are complementary to the vertex to which this path leads.

Examples →

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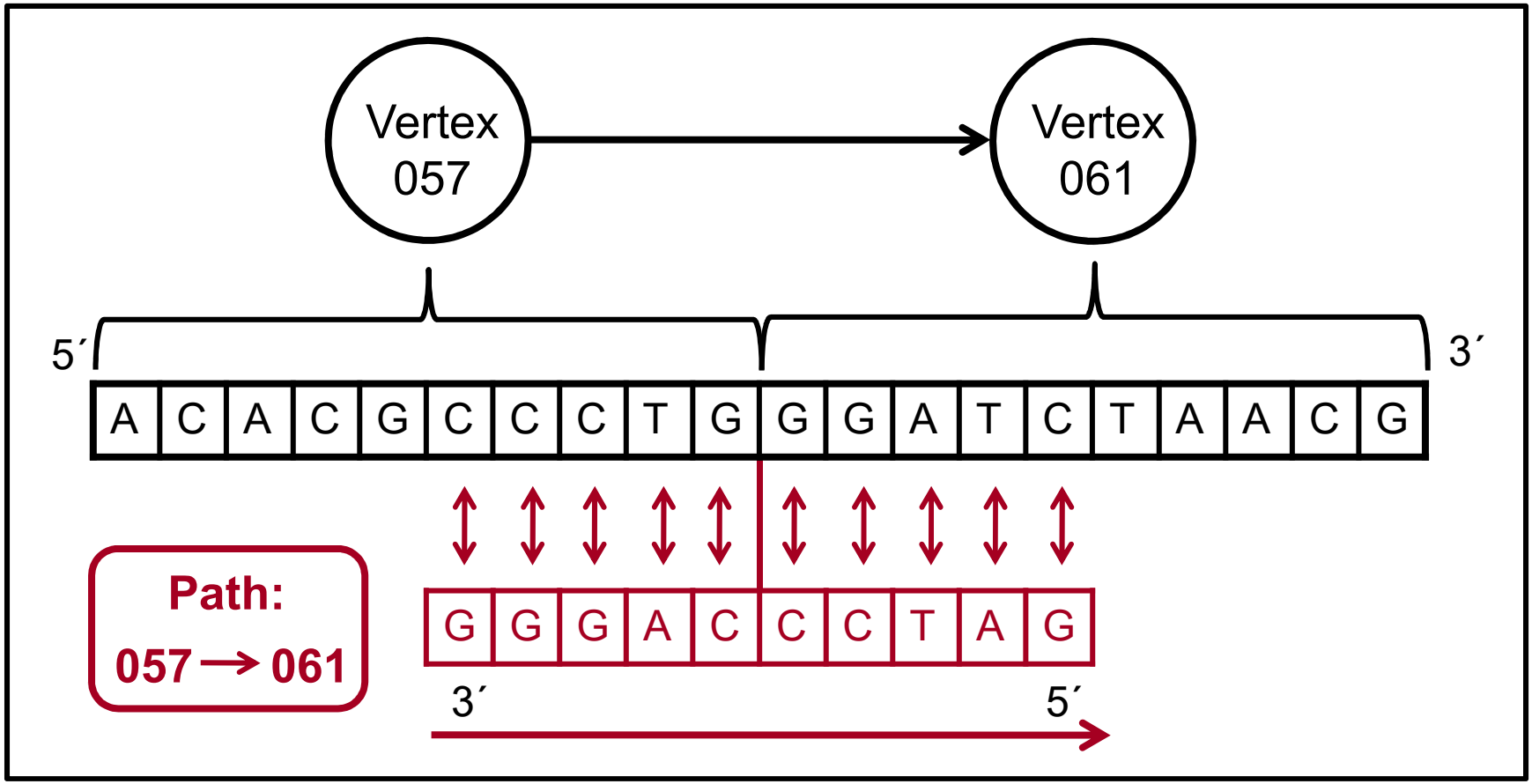
Example of a defined "path decanucleotide":



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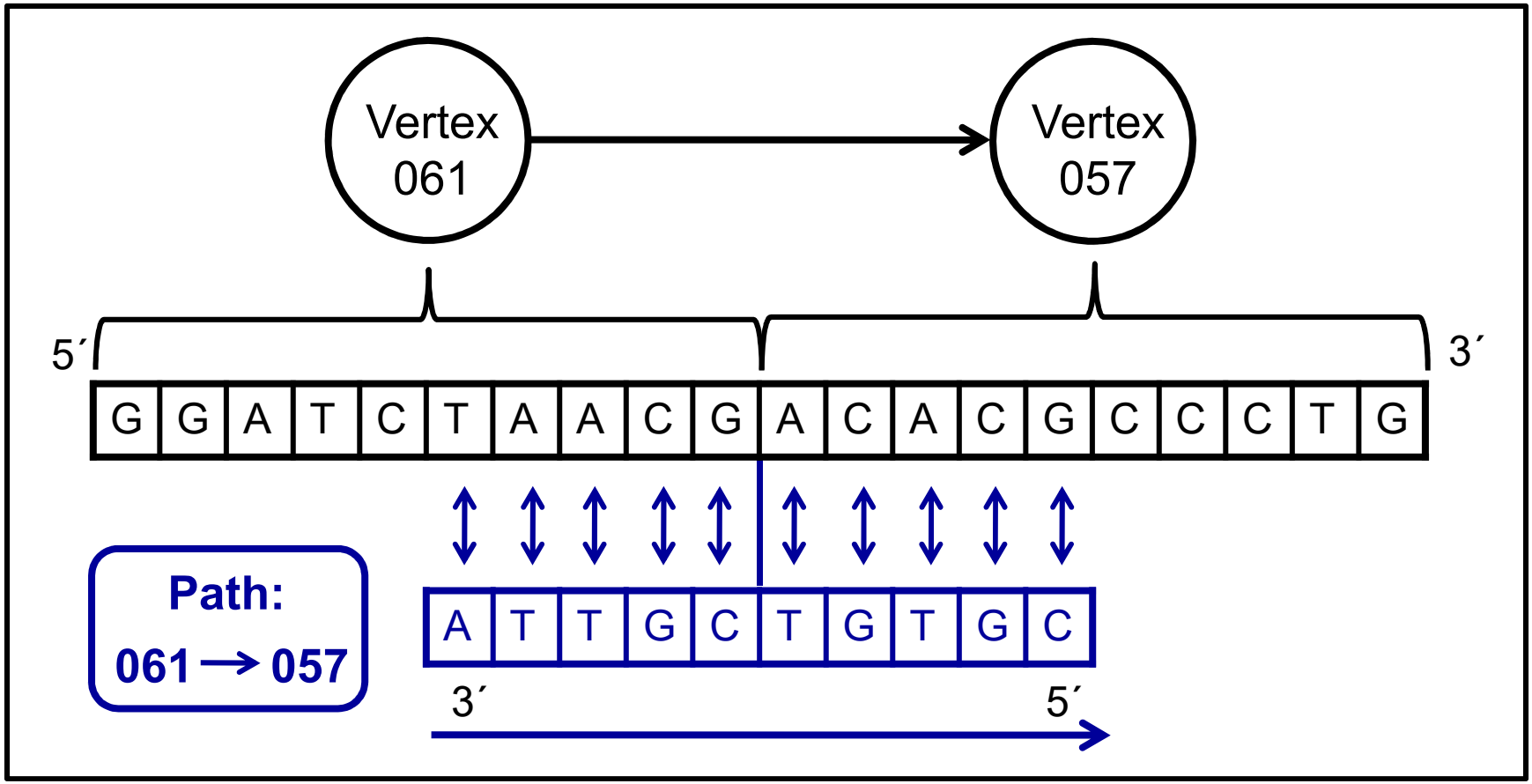
Example of a defined "path decanucleotide":



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The "Hardware" Consists of Test Tubes, Defined Nucleotides, Separation and Analysis Devices.

Defined Nucleotides:

Synthesis of the 100 different decanucleotides coding for the vertices and synthesis of the 257 path decanucleotides coding for the given paths, each determined by their complementarity, by means of an automated solid phase method, for example the cyclic carried out phosphite triester reaction.

Note: The number of *all* possible decanucleotides with *freely* chosen bases A, C, T and G for each of the 10 positions is: 4^n (with n = 10): 1.048.576.

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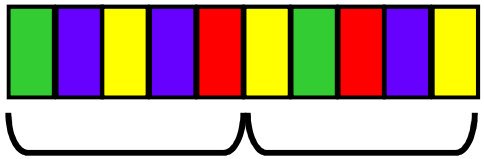
The "Hardware" Consists of Test Tubes, Defined Nucleotides, Separation and Analysis Devices.



2 Base Quintets

4^5 = 1024 Base quintets, from these result

$4^5/2$ = 512 non complementary base quintets

100 Decanucleotides formally correspond to 200 pairs of pentanucleotides, each consisting of two linked base quintets.
In order to avoid that individual vertices connect spontaneously and path decanucleotides are not unique, the formally assigned pentanucleotides have to meet the following conditions →

- They all must be different
  (Total selection: 4^5 = 1024)
- They must show no complementarity among each other
  (Total selection: $4^5/2$ = 512)

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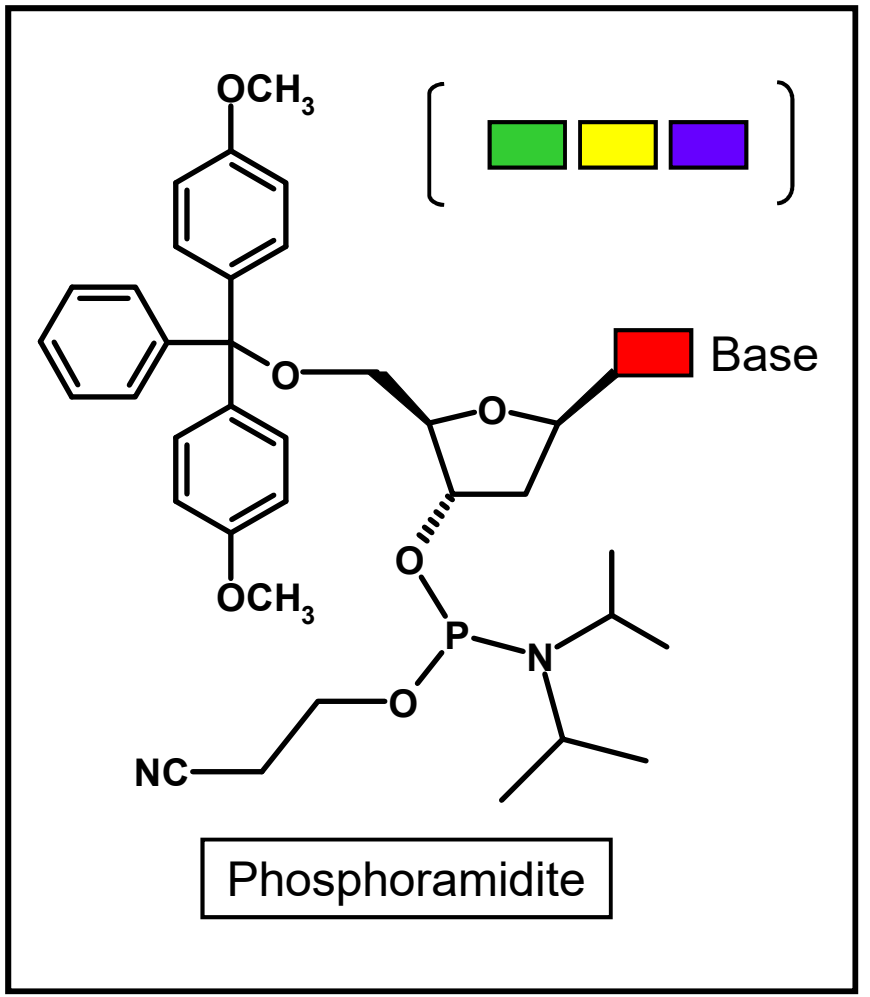
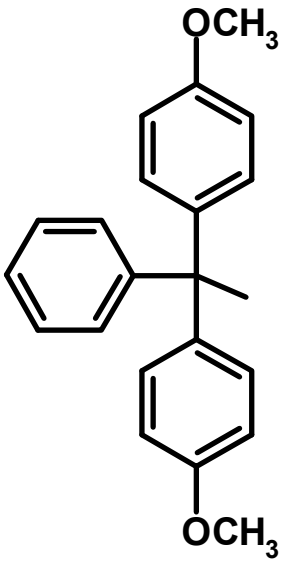
Polynucleotide Syntheses using the Automated Phosphite Triester Method (Solid-Phase Coupling, Merrifield Principle).



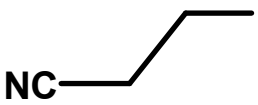
Phosphoramidite



Protective Groups

= **DMT**

Di-p-methoxytrityl



= β-CE

2-Cyanethyl

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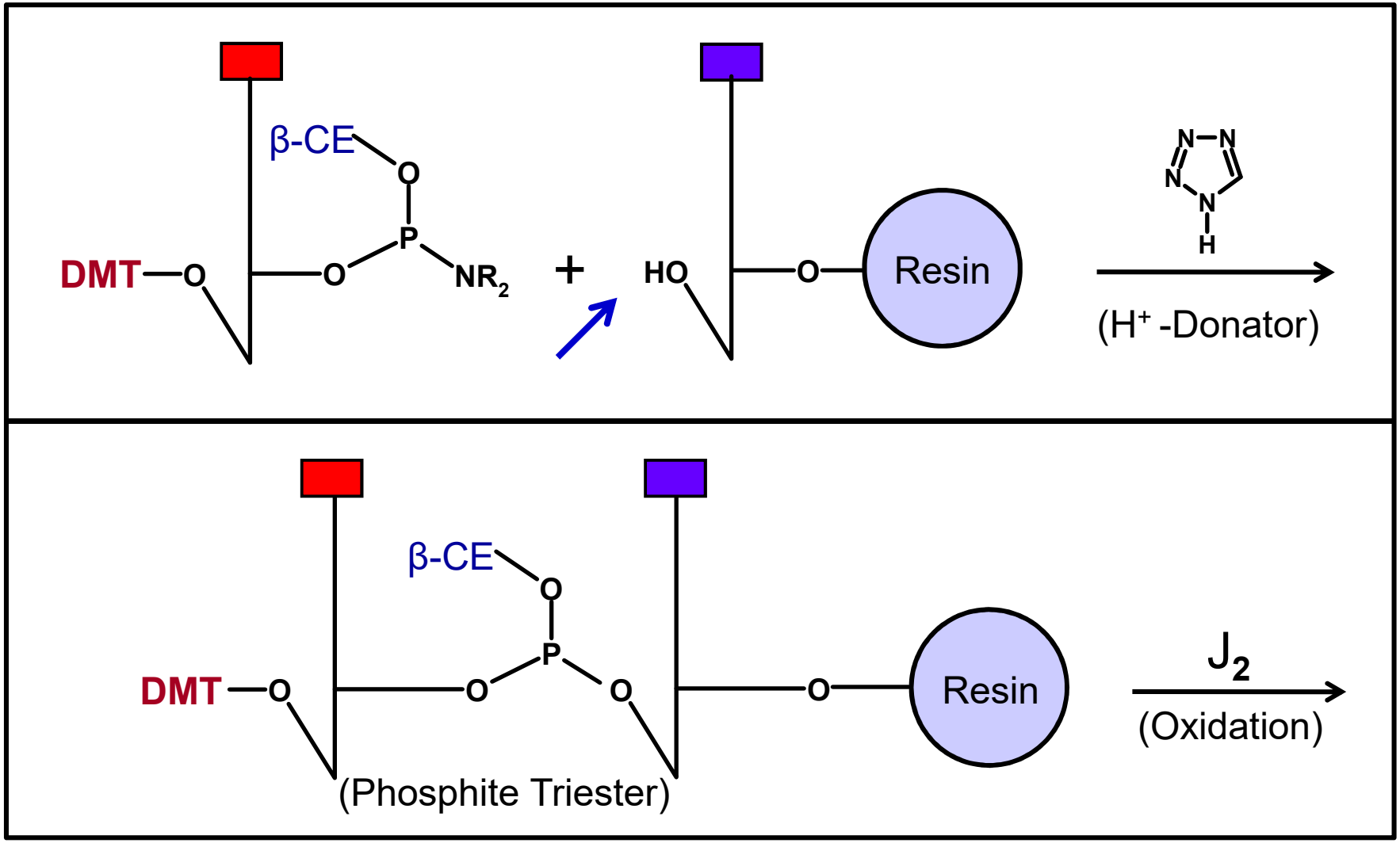

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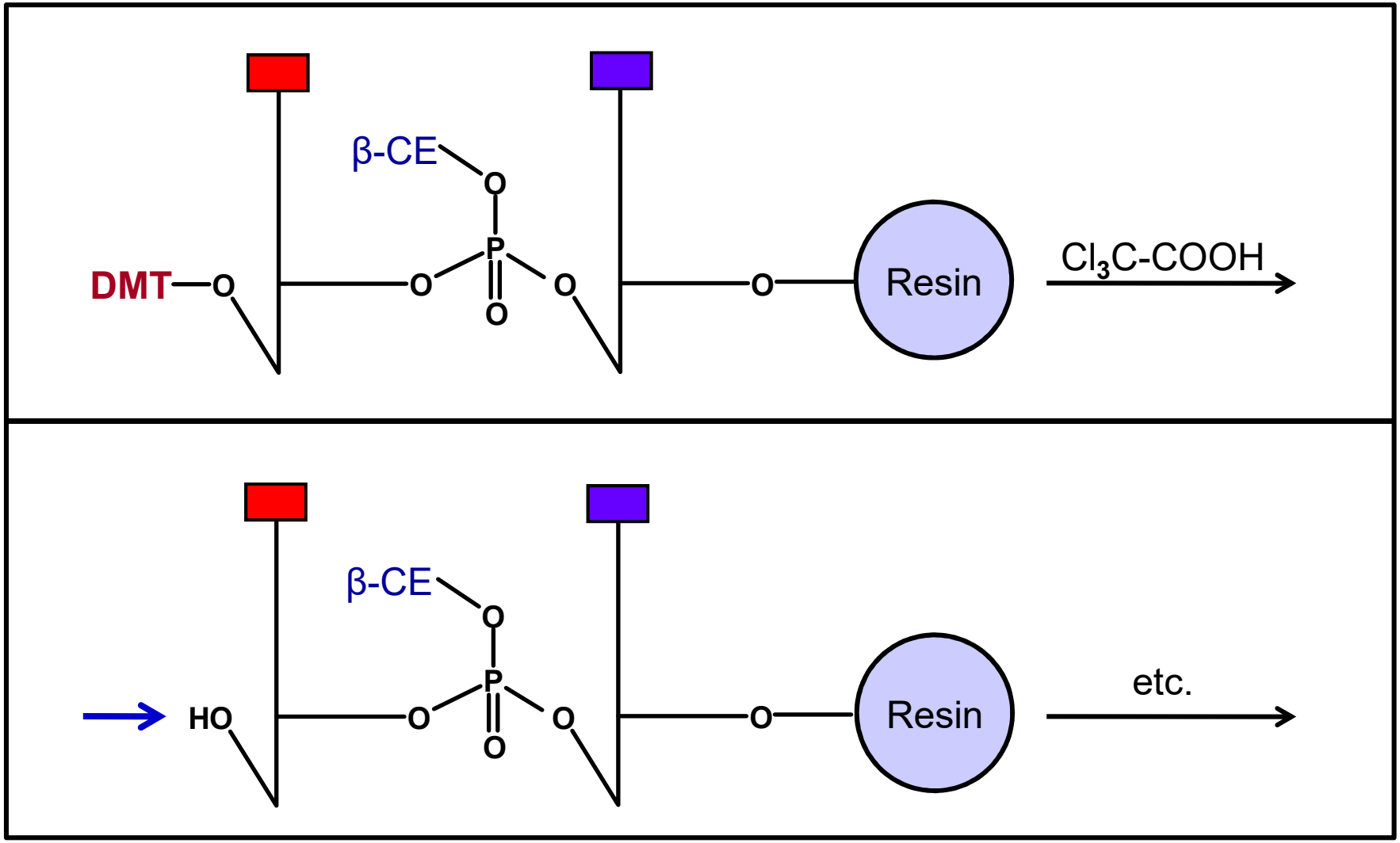

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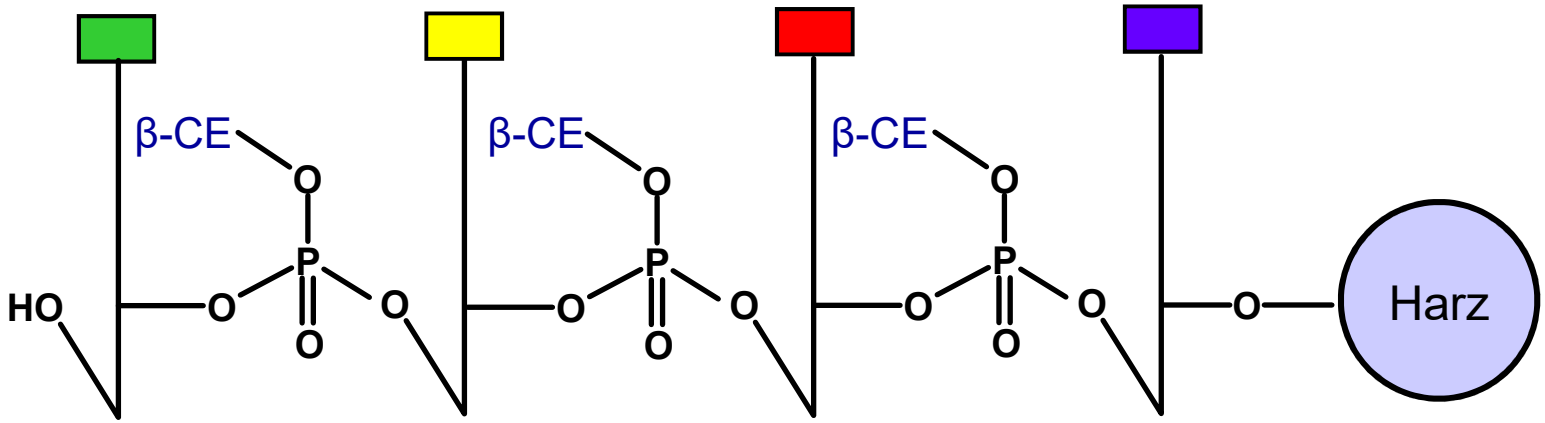

At the end of the reaction sequence, NH_3 is added (removal of all β– CE groups and cleavage of the polynucleotide from the resin).

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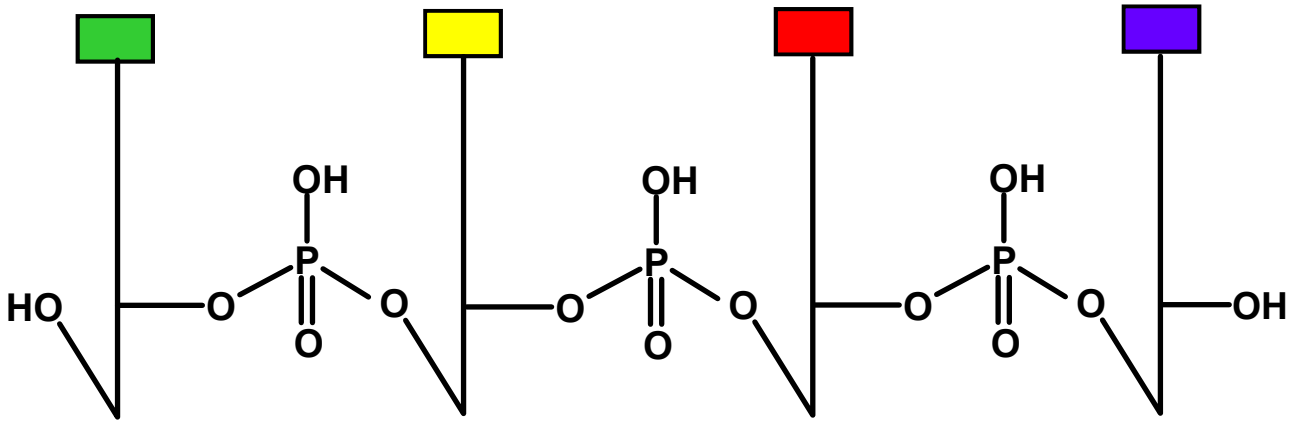
Polynucleotide Syntheses using the Automated Phosphite Triester Method (Solid-Phase Coupling, Merrifield Principle).



The polynucleotide is purified by HPLC or by electrophoresis on polyacrylamide gels.

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DNA – Computer: Adleman Algorithm for Solving Hamiltonian Path Problems, Five Steps (1. – 5.):

1.	Create "stable" random paths between the vertices 001, 002, 003,…, 097, 098, 099, 100.
2.	Discard all path combinations that do not start with vertex 001 and end with vertex 100.
3.	Discard all path combinationsare on which are not visited exactly 100 vertices.
4.	Discard all path combinations that do not visit each of the 100 vertices.
5.	If one or more path combinations remain, this/these is/are the solution(s). If not, there is no solution.

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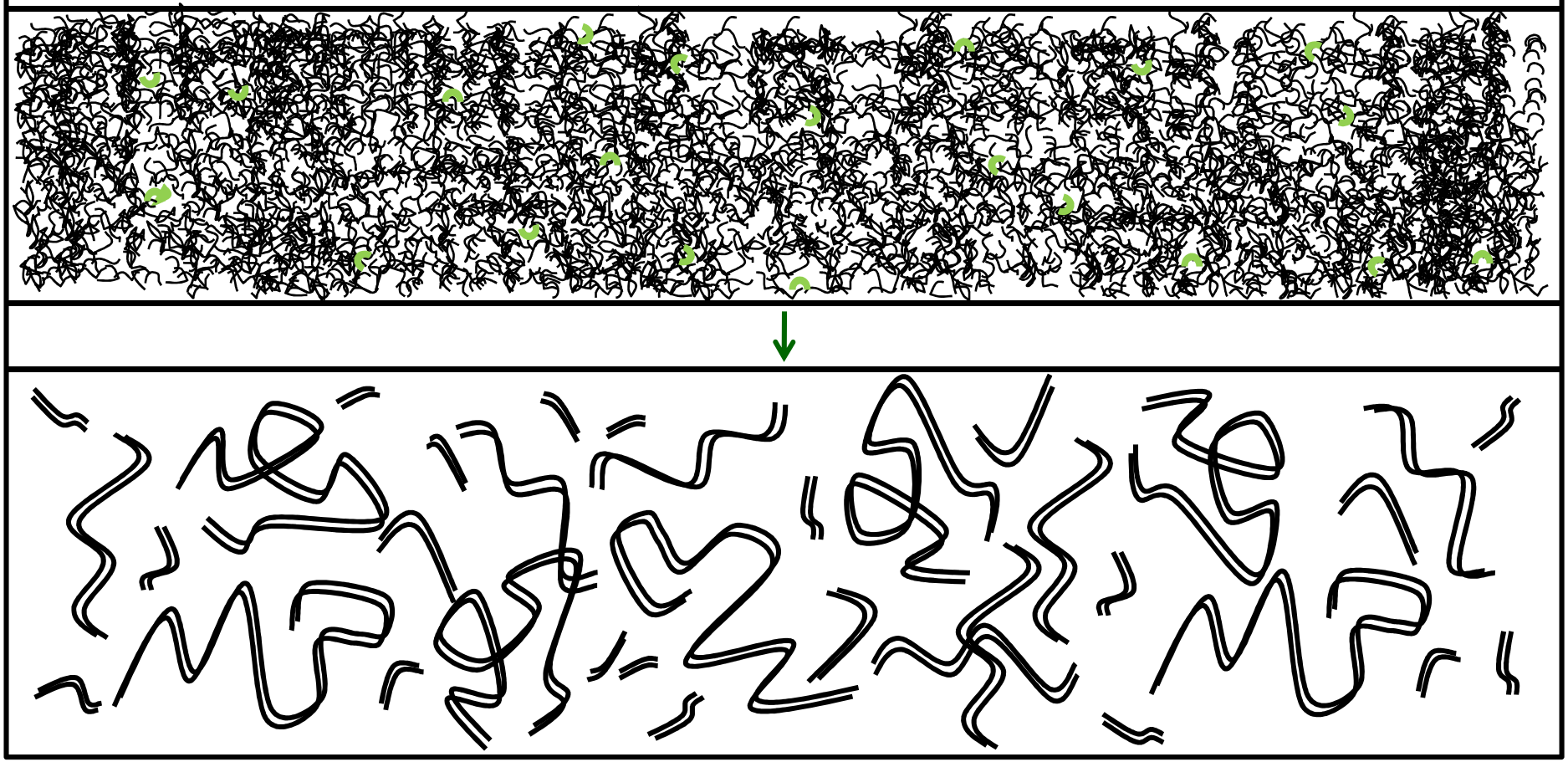
Step 1 of the Adleman Algorithm: Generate random paths.

Here: ligase-catalyzed DNA synthesis through simultaneous ligation and hybridization of hundreds of trillion decanucleotide molecules. Accordingly, through massive, parallel processing of information.



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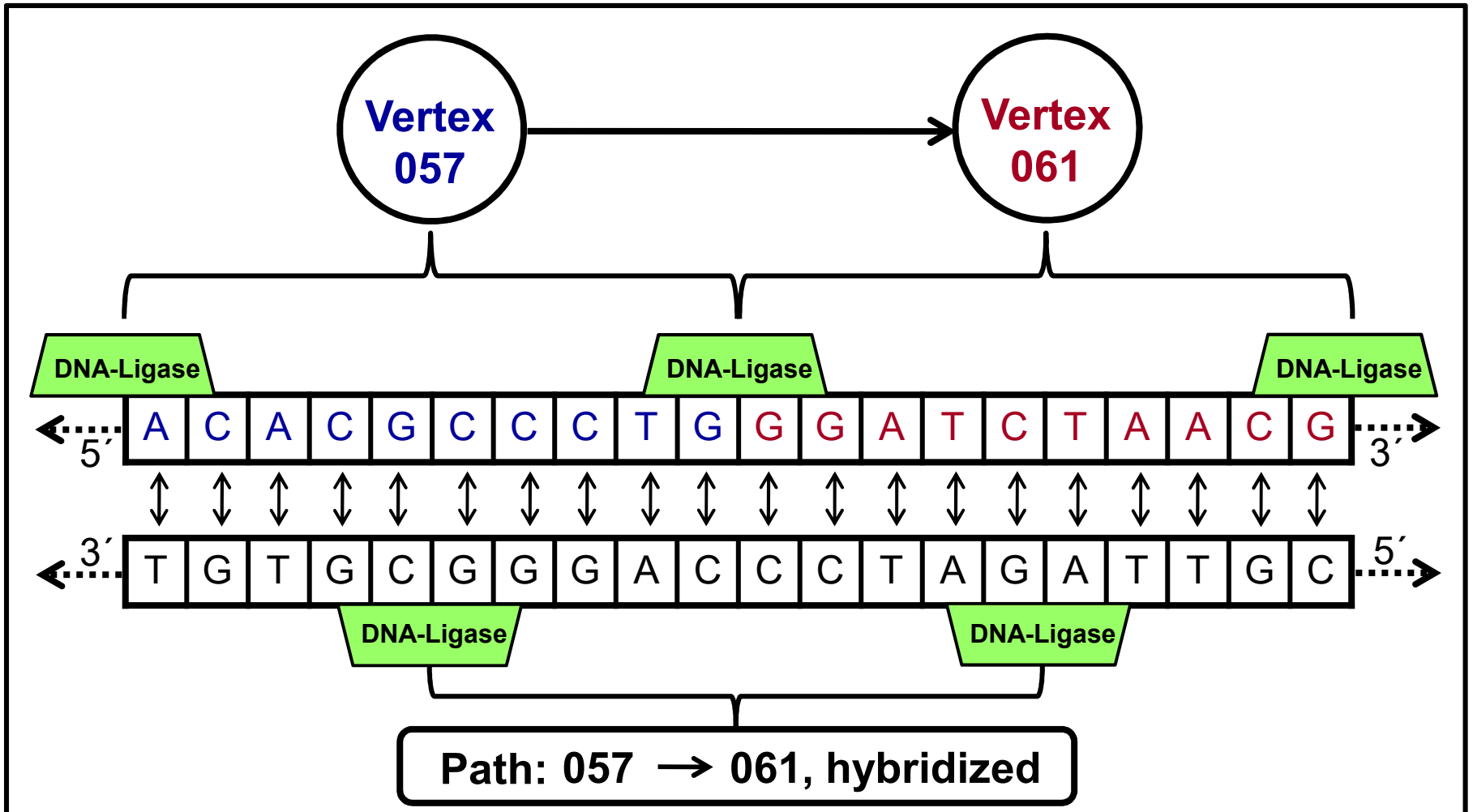
Step 1 of the Adleman Algorithm: Generation of random paths. Ligation and hybridization of the vertex- and path-DNAs (Detail).



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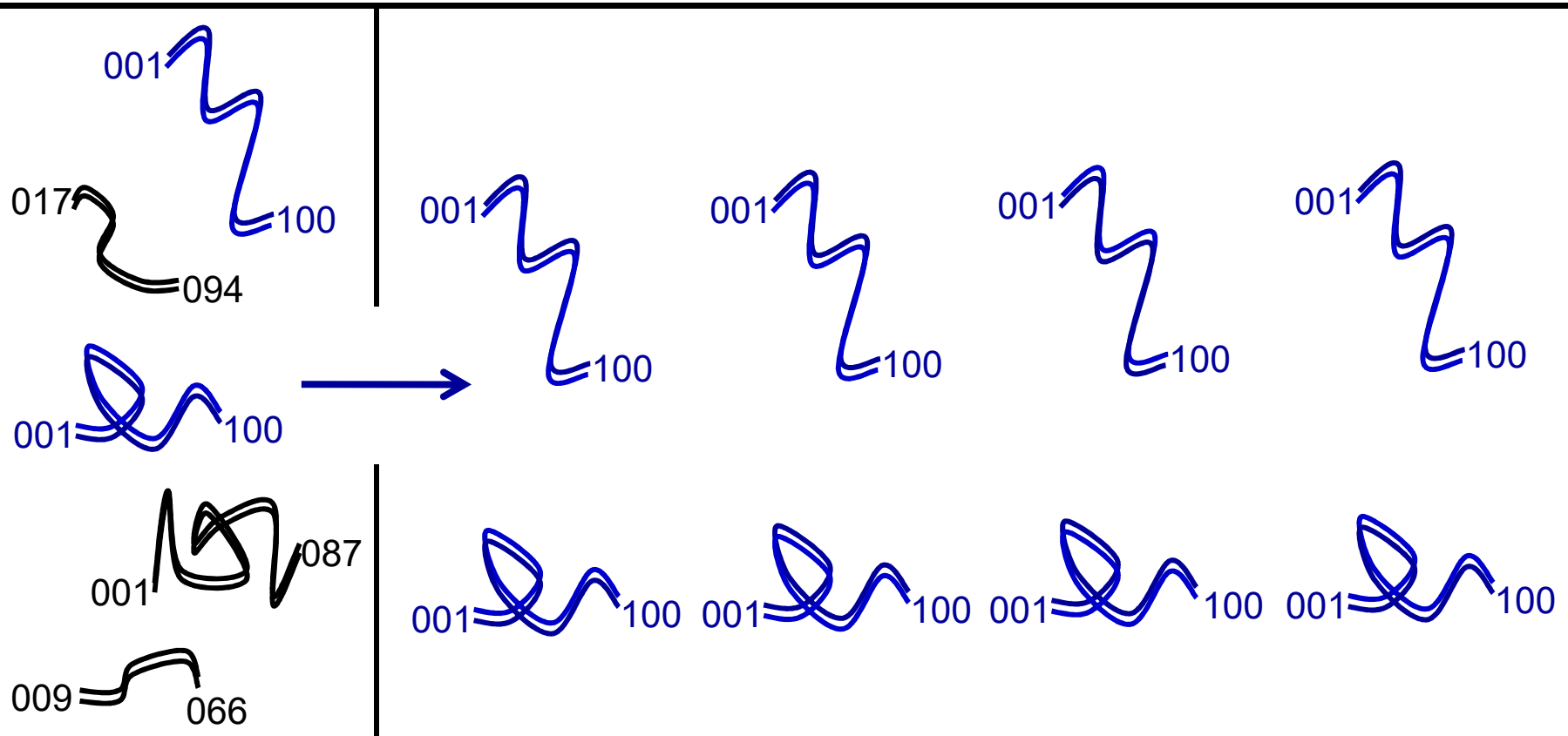
Step 2 of the Adleman Algorithm: Discard all path combinations that do not start with vertex 001 and end with vertex 100.

Here: Exponential multiplication of all DNA strands that start with vertex 001 and end with vertex 100 using the PCR technique:



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Step 2 of the Adleman Algorithm: PCR technique, polymerase chain reaction for the amplification of DNA.

The **P**olymerase **C**hain **R**eaction after K. Mullis takes place in three defined steps:

1) Strand separation of the concerning DNA by heating, namely at 95°C for 15 seconds.
2) Rapid cooling to 54°C and hybridization with the primers in solution.
3) Synthesis of new DNA at 72°C using Taq-DNA-polymerase as a heat-stable enzyme from *thermus aquaticus.*

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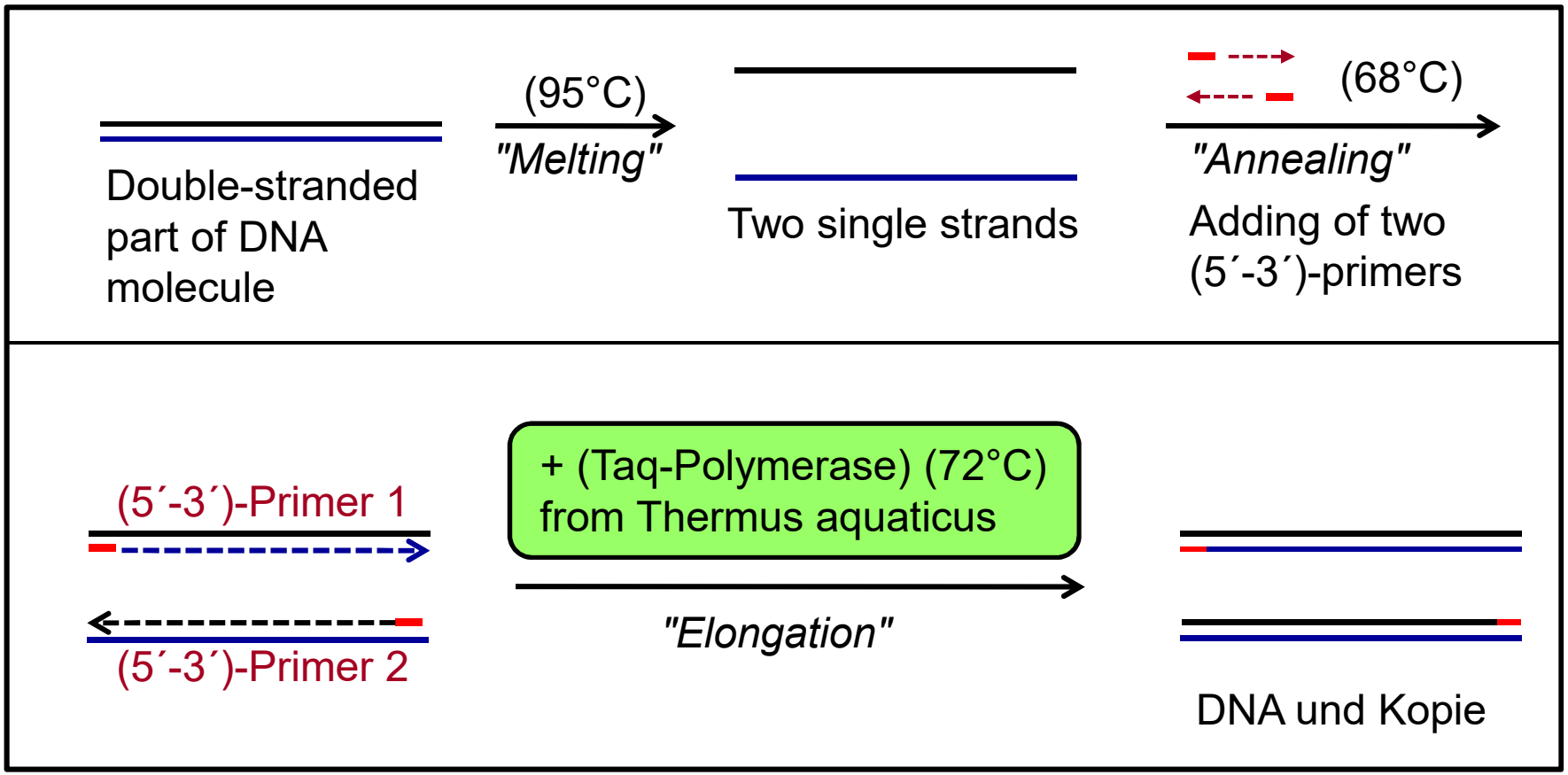
Step 2 of the Adleman Algorithm: PCR technique, polymerase chain reaction for the amplification of DNA.



Repeating of this cycle leads to an exponential accumulation of the desired DNA molecules.

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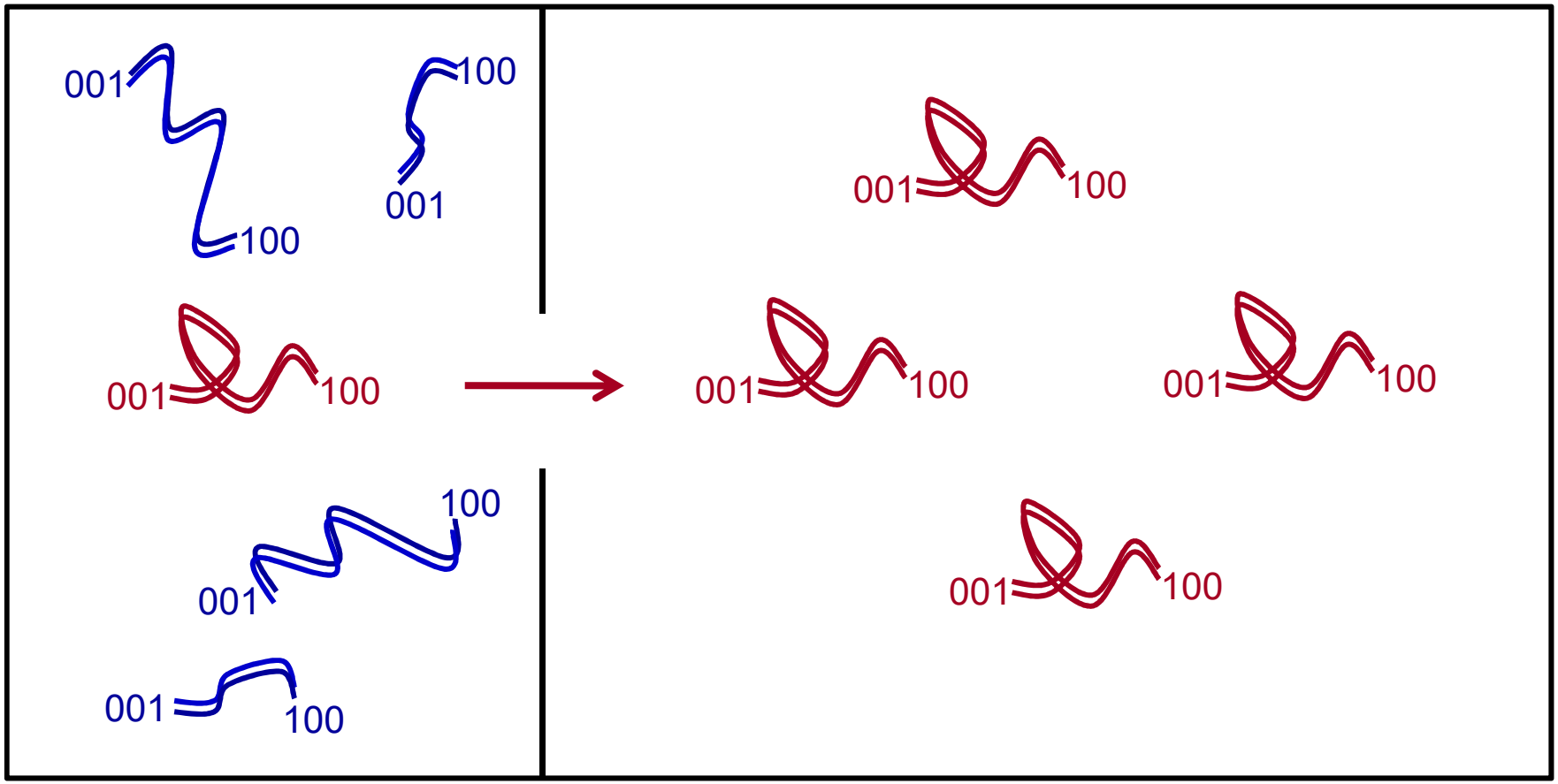
Step 3 of the Adleman Algorithm: Discard all path combinations on which are not visited exactly 100 vertices.

Here: Separation of those DNA molecules containing 1000 base pairs (100 x 10) by means of (pulsed) gel electrophoresis.



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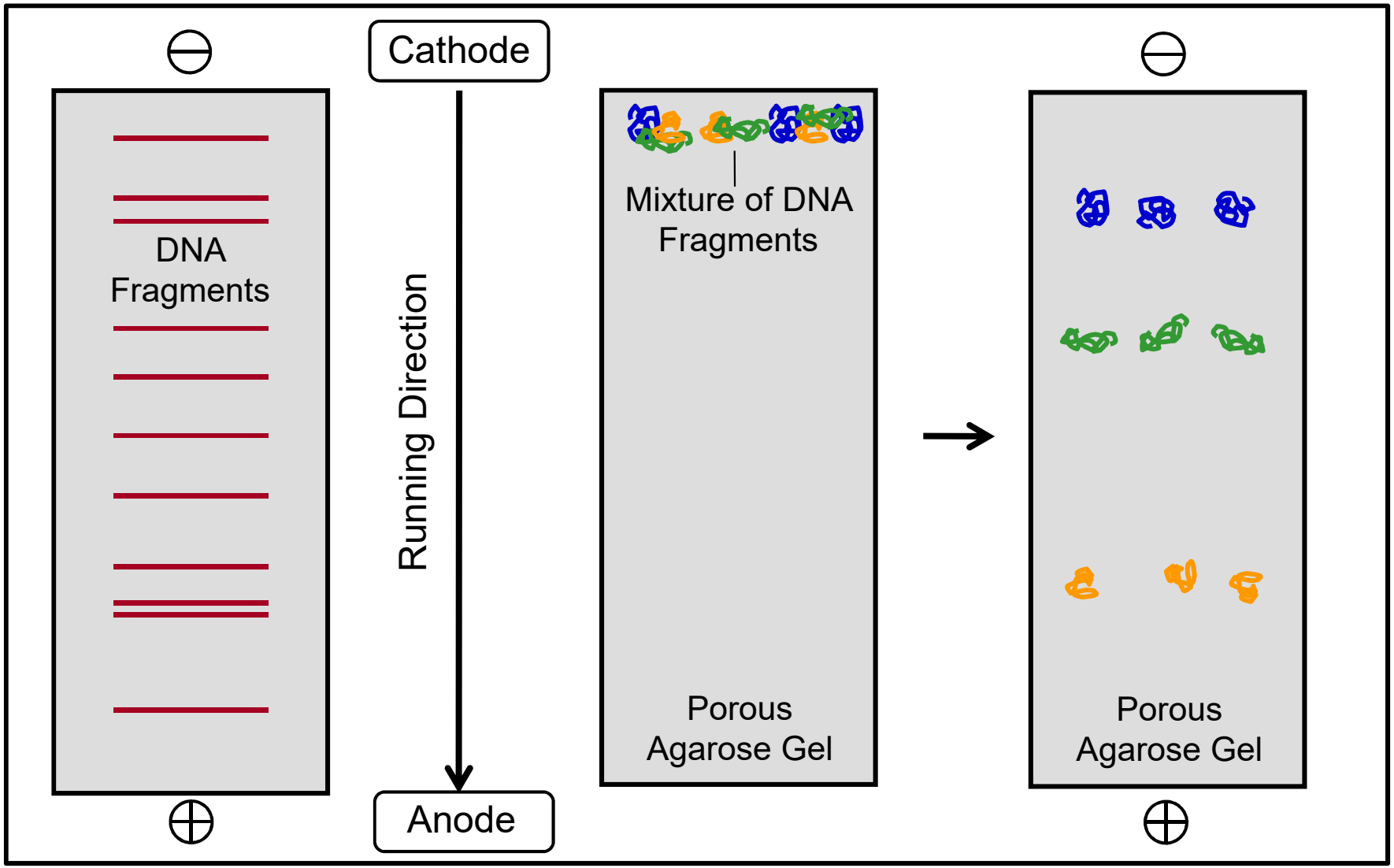
Step 3 of the Adleman algorithm: Conventional gel electrophoresis for the separation of DNA molecular fragments in homogeneous field.



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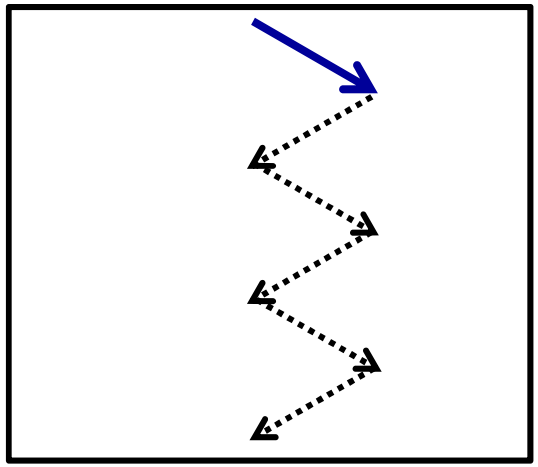
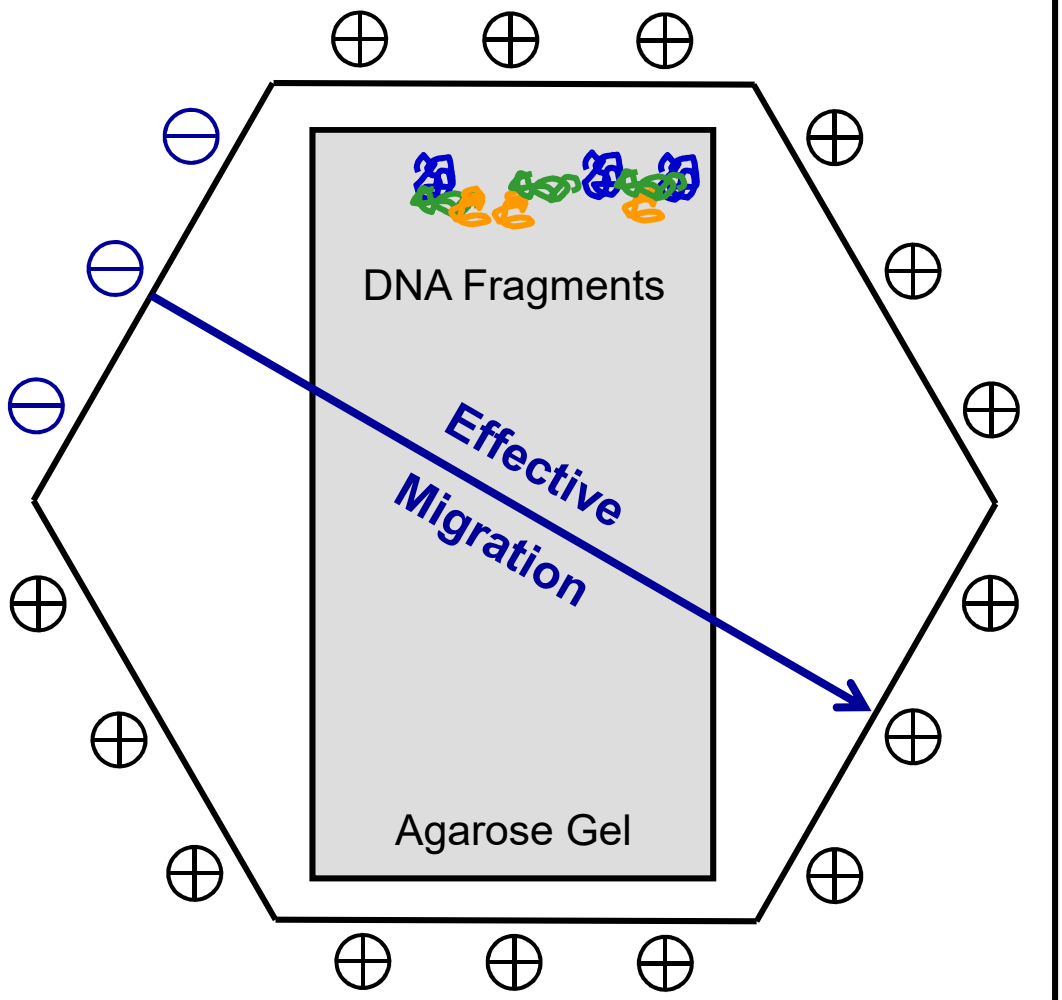
Step 3 of the Adleman algorithm: Pulsed Field Gel Electrophoresis for the separation of DNA molecule fragments in alternating fields.

Direction of the effective migration in the electric field: **+ 60°**. **C**ontour-Clamped **H**omogeneous **E**lectric **F**ield Method ("CHEF-Method").

DNA Migation:





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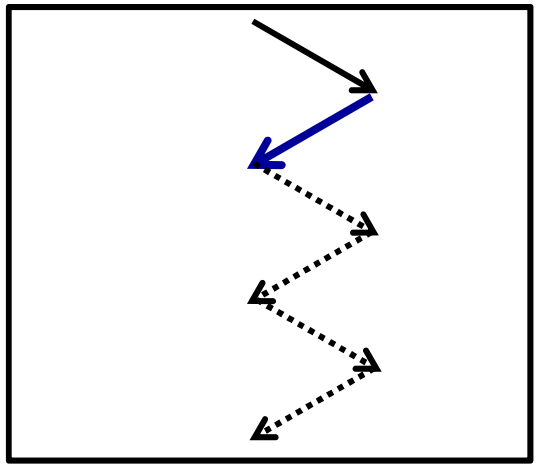
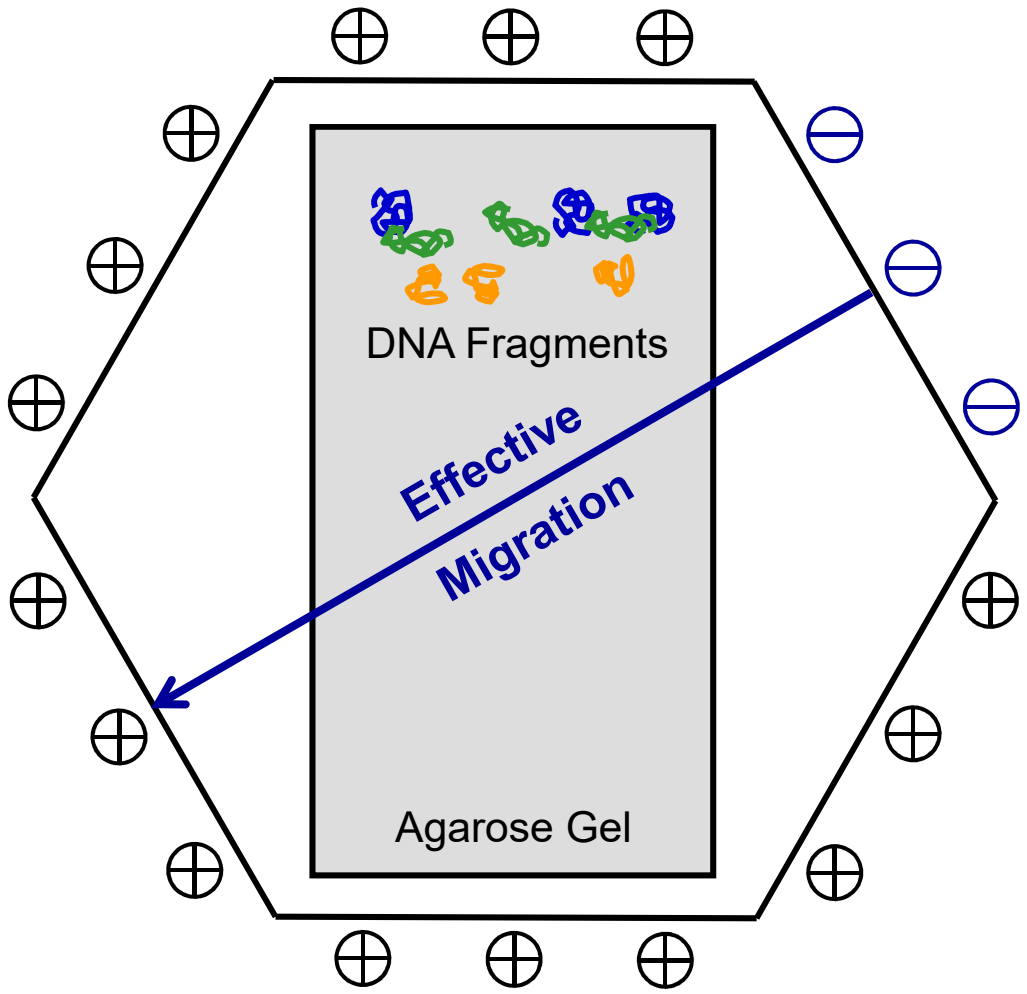
Direction of the effective migration in the electric field: **– 60°**. **C**ontour-Clamped **H**omogeneous **E**lectric **F**ield Method ("CHEF-Method").

DNA Migation:





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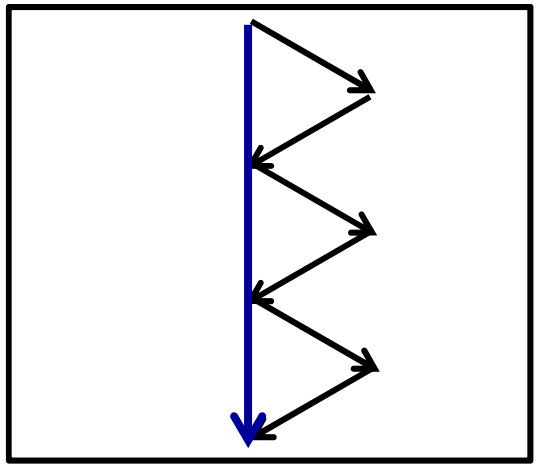
DNA Computer for Massive Parallel Data Processing

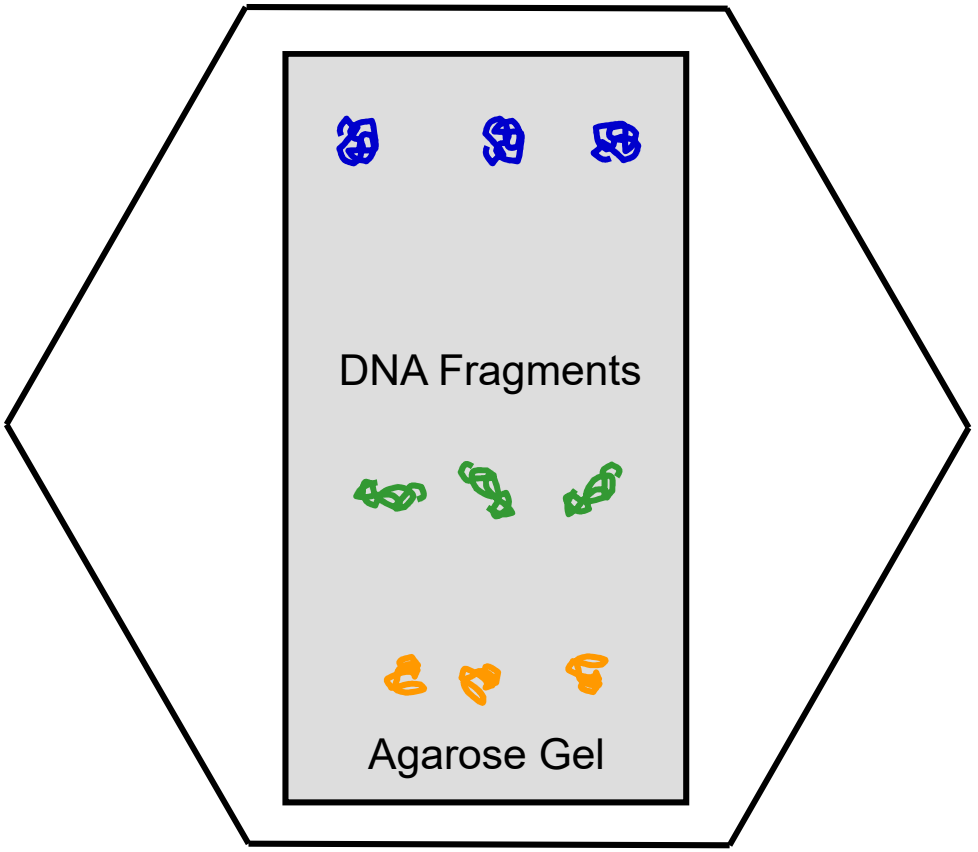
Step 3 of the Adleman algorithm: Pulsed Field Gel Electrophoresis for the separation of DNA molecule fragments in alternating fields.

Overall direction of the effective migration in the alternating electric field:
n x (− 60° / + 60°).
(„CHEF-Method“)

DNA Migation:



Final Result



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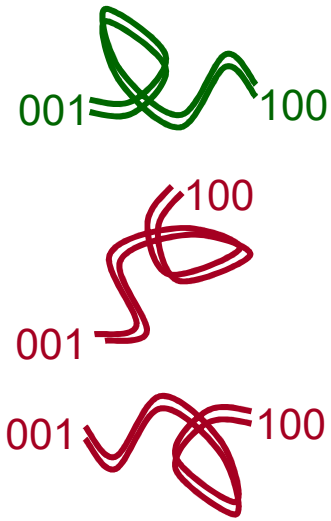
Step 4 of the Adleman algorithm: discard all path combinations that do not visit each of the 100 vertices.

Affinity separation using 100 different 1-μm magnetic balls, each of which has the complementary base sequence of a vertex of the network fixed on its surface. This process is carried out one after the other with all 100 differently coated magnetic balls.



These DNA molecules code for the Hamiltonian path(s).

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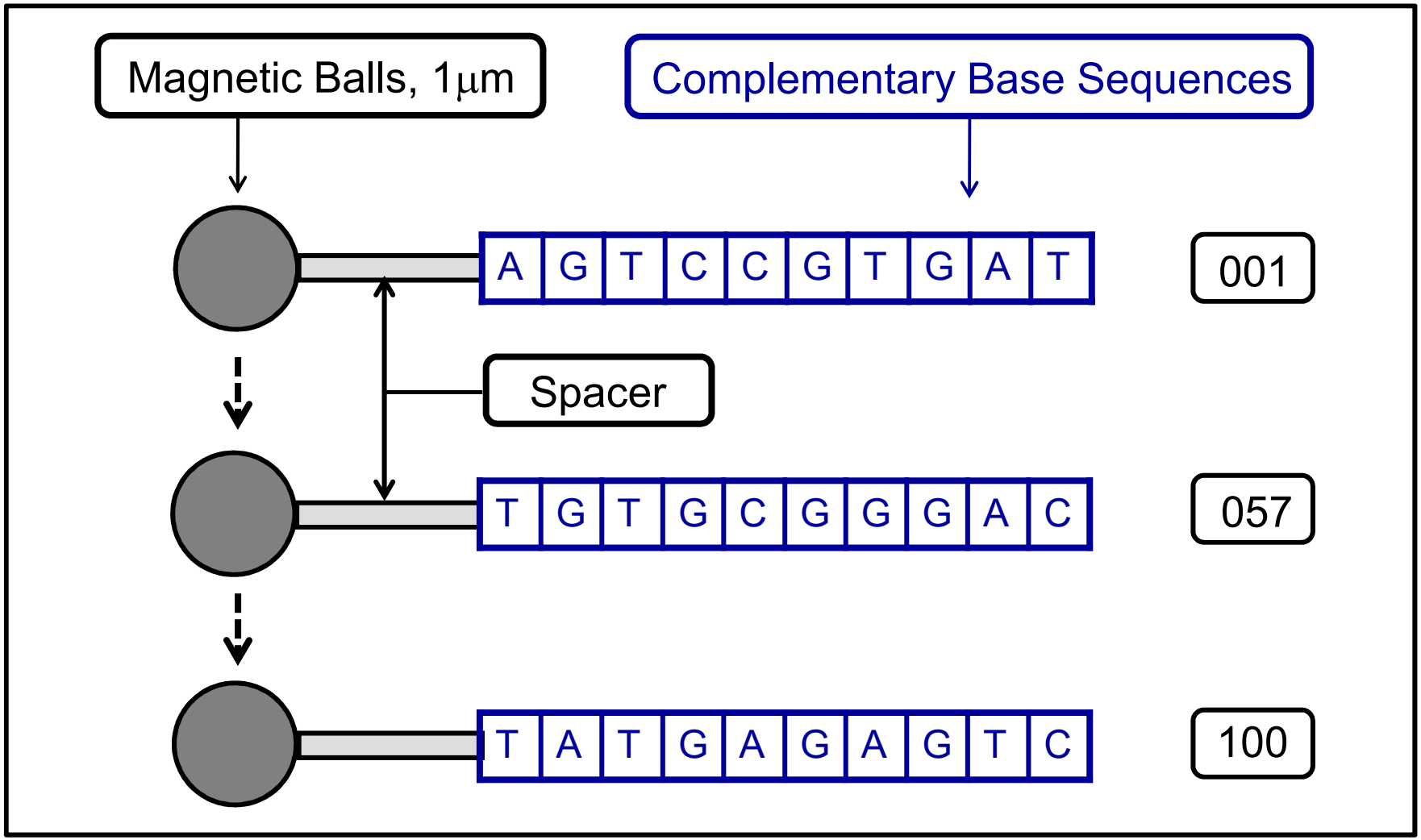
Step 4 of the Adleman algorithm: Affinity selection.
Evidence of the existing base sequence for each individual vertex.



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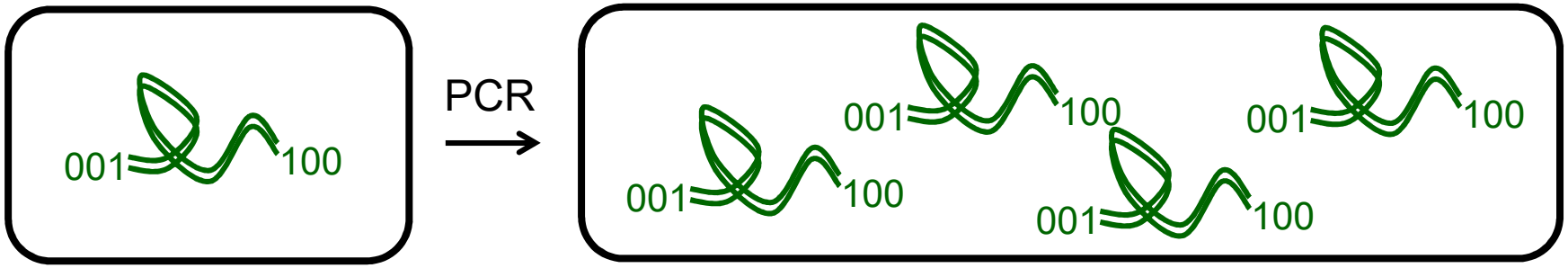
Step 5 of the Adleman algorithm:
If one or more path combinations remain, this is (are) the solutions.

Follow up steps:

Exponential enrichment of the remaining DNA molecules using the PCR technique.

Sequencing, i.e. determining the base sequence and thus the sequence of corners in the network, which represent the Hamilton path(s).



DNA Computer for Massive Parallel Data Processing

Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger; "Terminator Method":

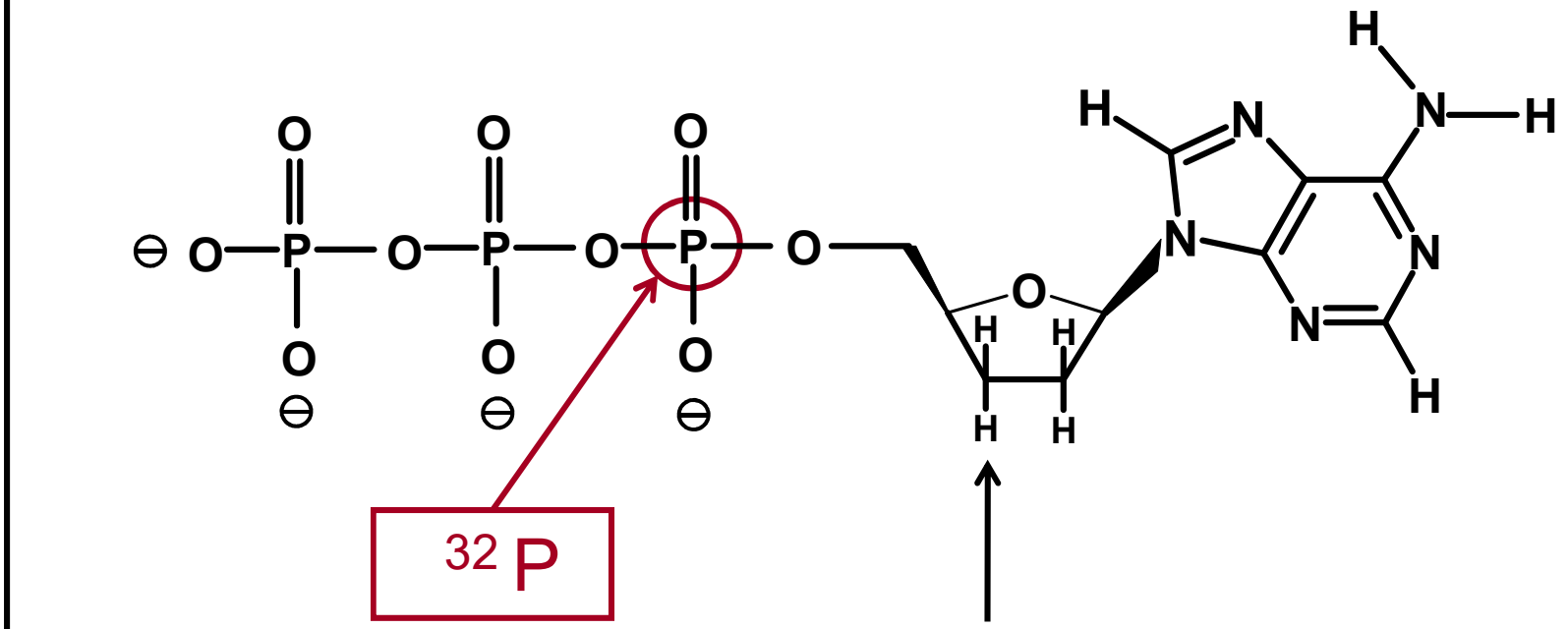
A mixture of uniform single strands with an unknown DNA sequence, a suitable primer, dATP, dCTP, dGTP and dTTP, as well as small amounts of **radioactively labeled** analog **di**deoxynucleoside triphosphates is reacted in the presence of Taq-DNA polymerase.

The resulting mixture of the chain termination fragments is separated with the accuracy of individual nucleotides by gel electrophoresis. The base sequence obtained is complementary to those of the unknown single strands:

DNA Computer for Massive Parallel Data Processing

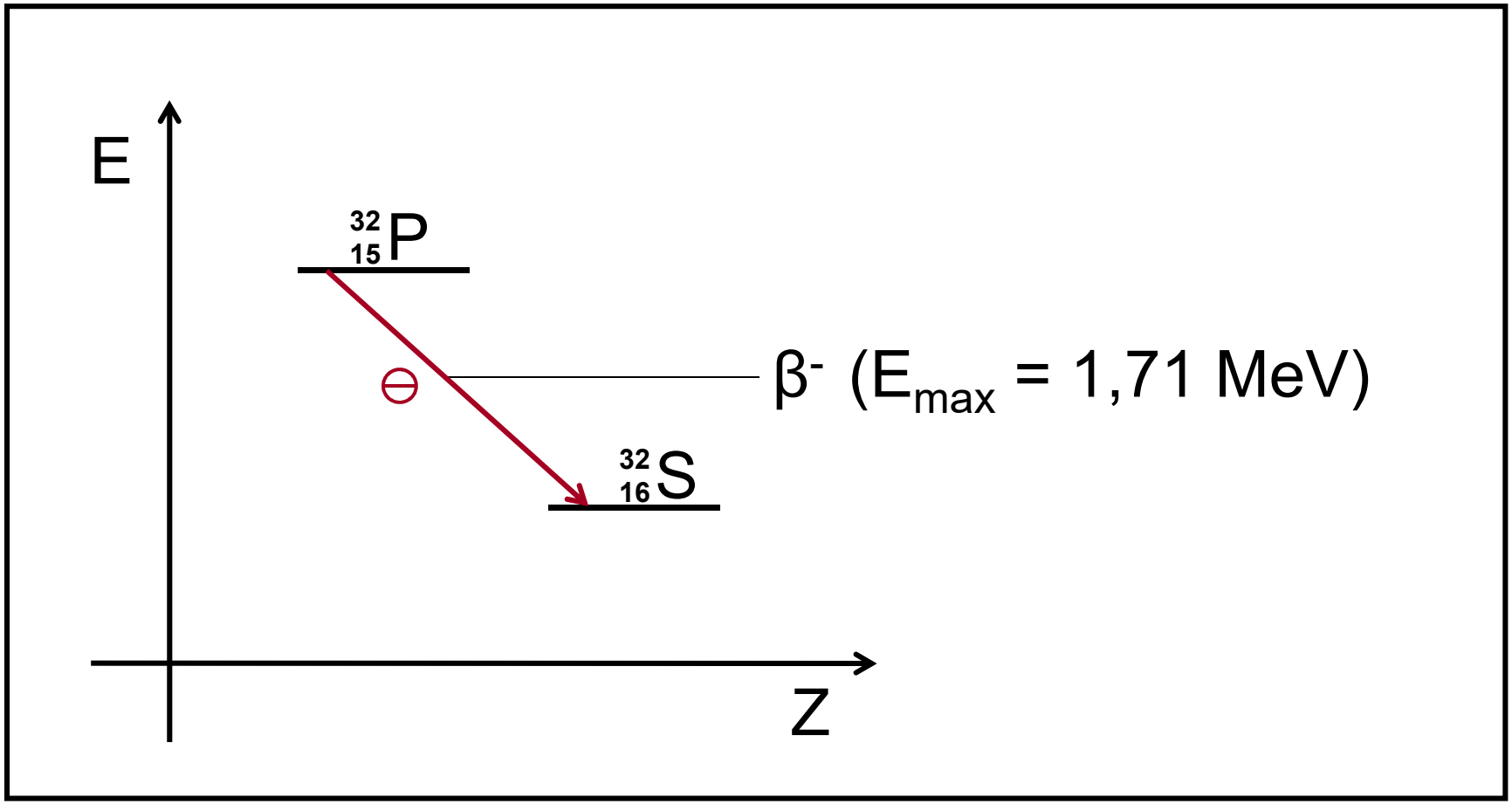
Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger ("Terminator Method");
Labeling of the respective dideoxy NTP with ^{32}P:

Example: ^{32}P-Didesoxy-Adenosin Triphosphate



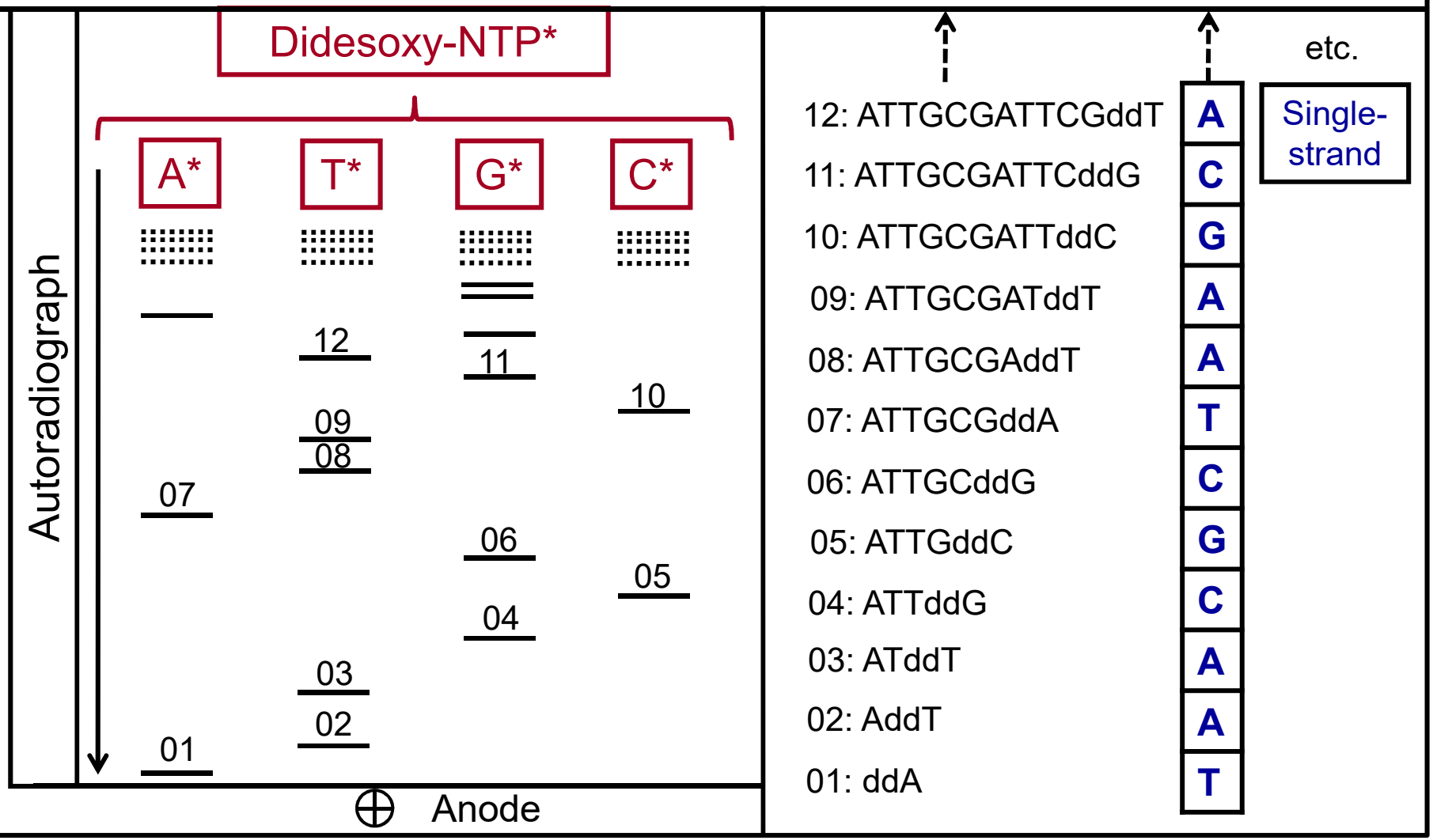
DNA Computer for Massive Parallel Data Processing

Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger ("Terminator Method");
Decay scheme of radioactive ^{32}P:



DNA Computer for Massive Parallel Data Processing

Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger ("Terminator Method");
Execution of gel electrophoresis with ^{32}P-labeled fragments:



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DNA Computer for Massive Parallel Data Processing

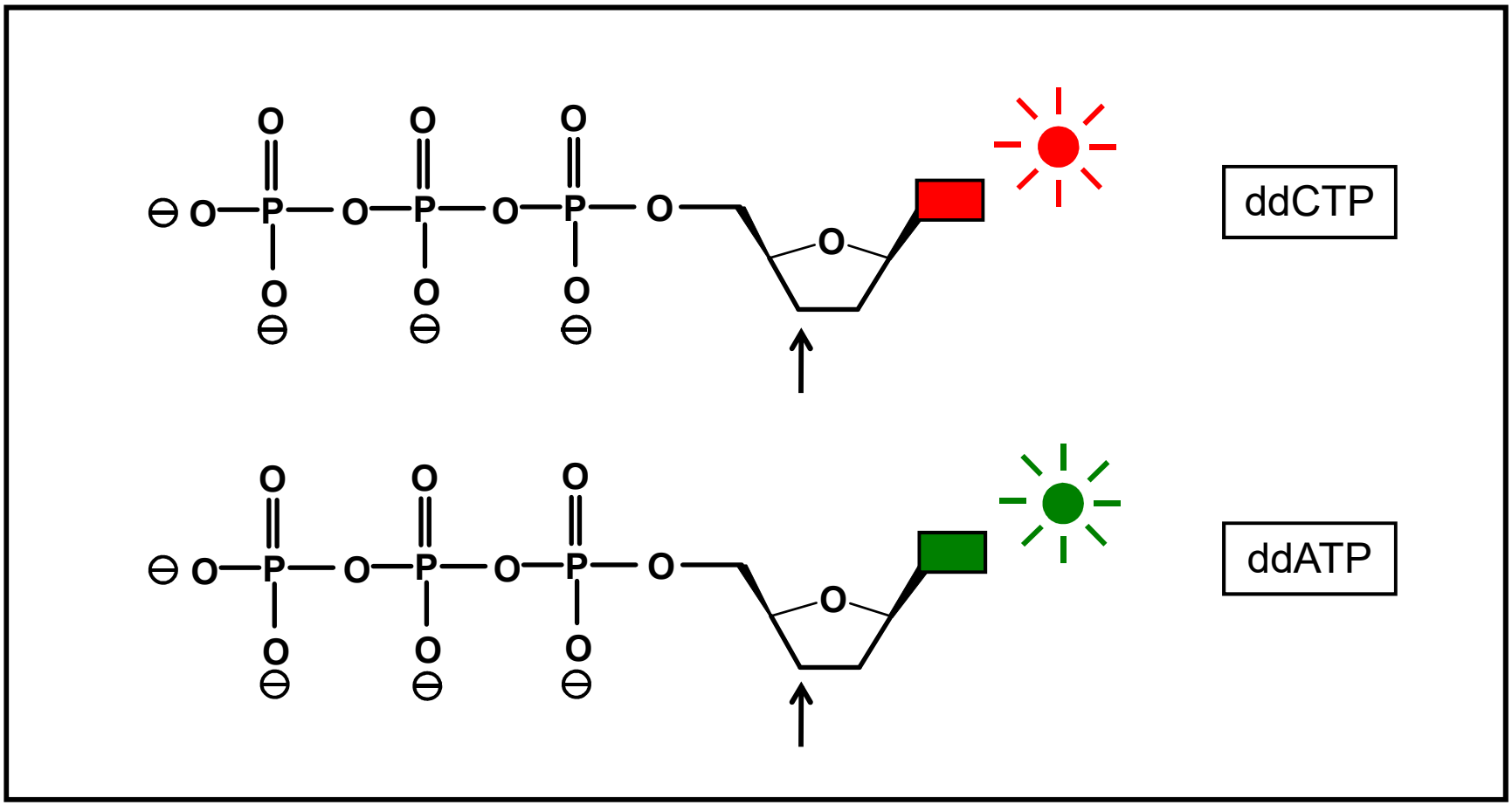
Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger ("Terminator Method"); Principle of operation for fluorescence sequencing:

A mixture of uniform single strands with an unknown DNA sequence, a suitable primer, dATP, dCTP, dGTP and dTTP, as well as small amounts of **fluorescence-labeled** analog **di**desoxynucleoside triphosphates is reacted in the presence of Taq-DNA polymerase.

The resulting mixture of the chain termination fragments is separated with the accuracy of individual nucleotides by gel electrophoresis. The base sequence obtained is complementary to those of the unknown single strands:

DNA Computer for Massive Parallel Data Processing

Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger, Fluorescence Sequencing; Dideoxy nucleoside triphosphates with fluorescent markers:



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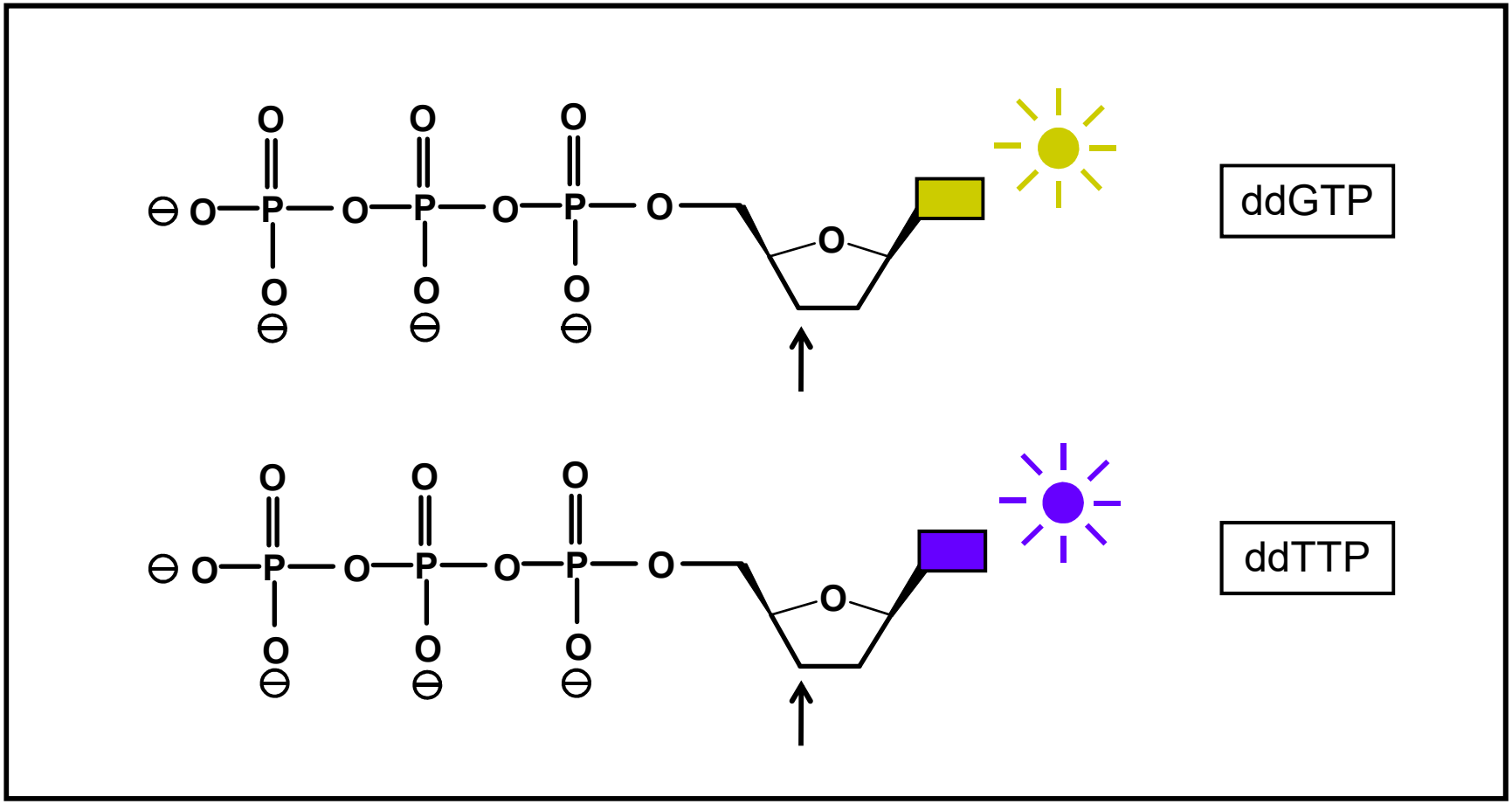
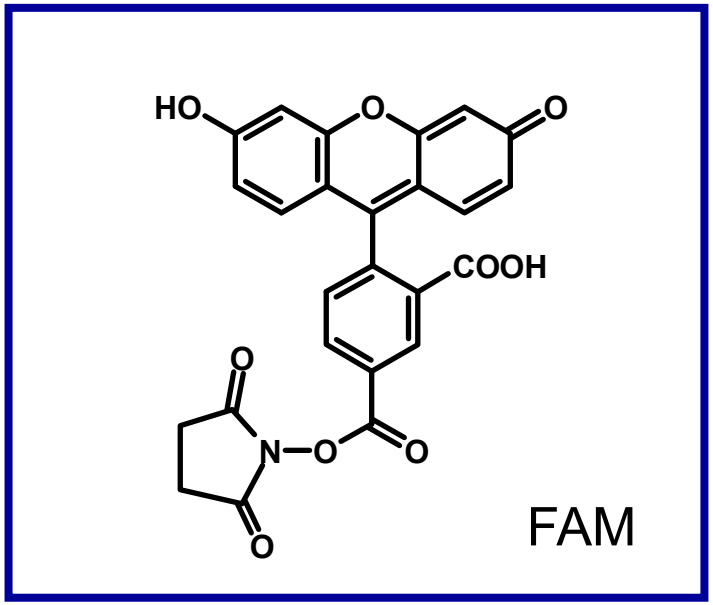
Enzymatic DNA sequencing using controlled chain termination according to Frederick Sanger, Fluorescence Sequencing; Dideoxy nucleoside triphosphates with fluorescent markers:

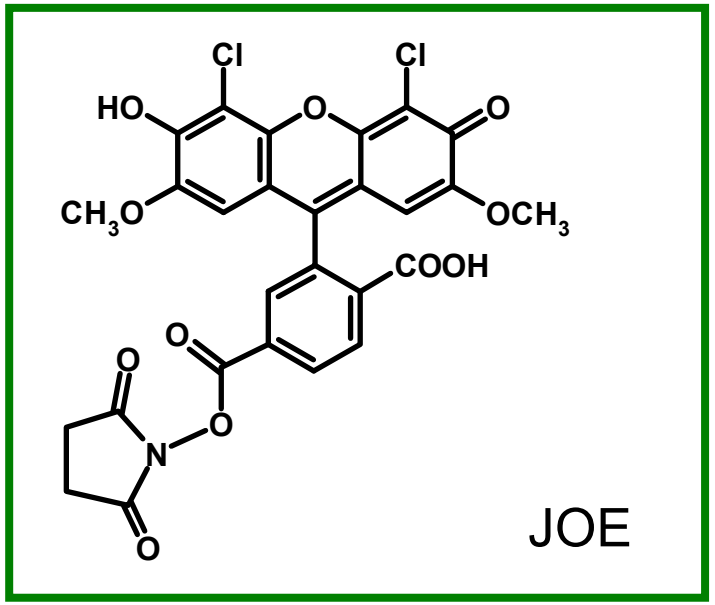


DNA Computer for Massive Parallel Data Processing

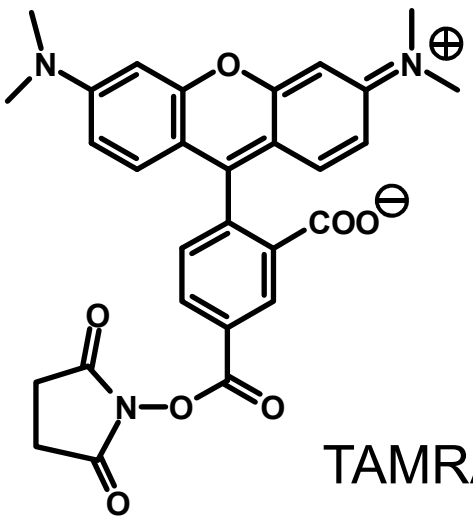
Fluorescent dyes (fluorophores) for the 4-color detection; Active Esters.



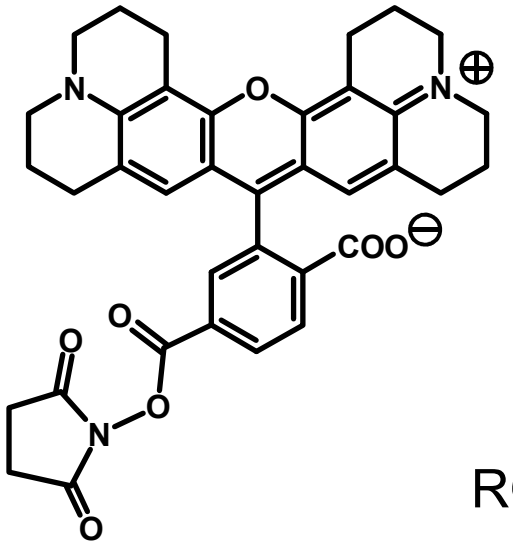
FAM



JOE



TAMRA



ROX

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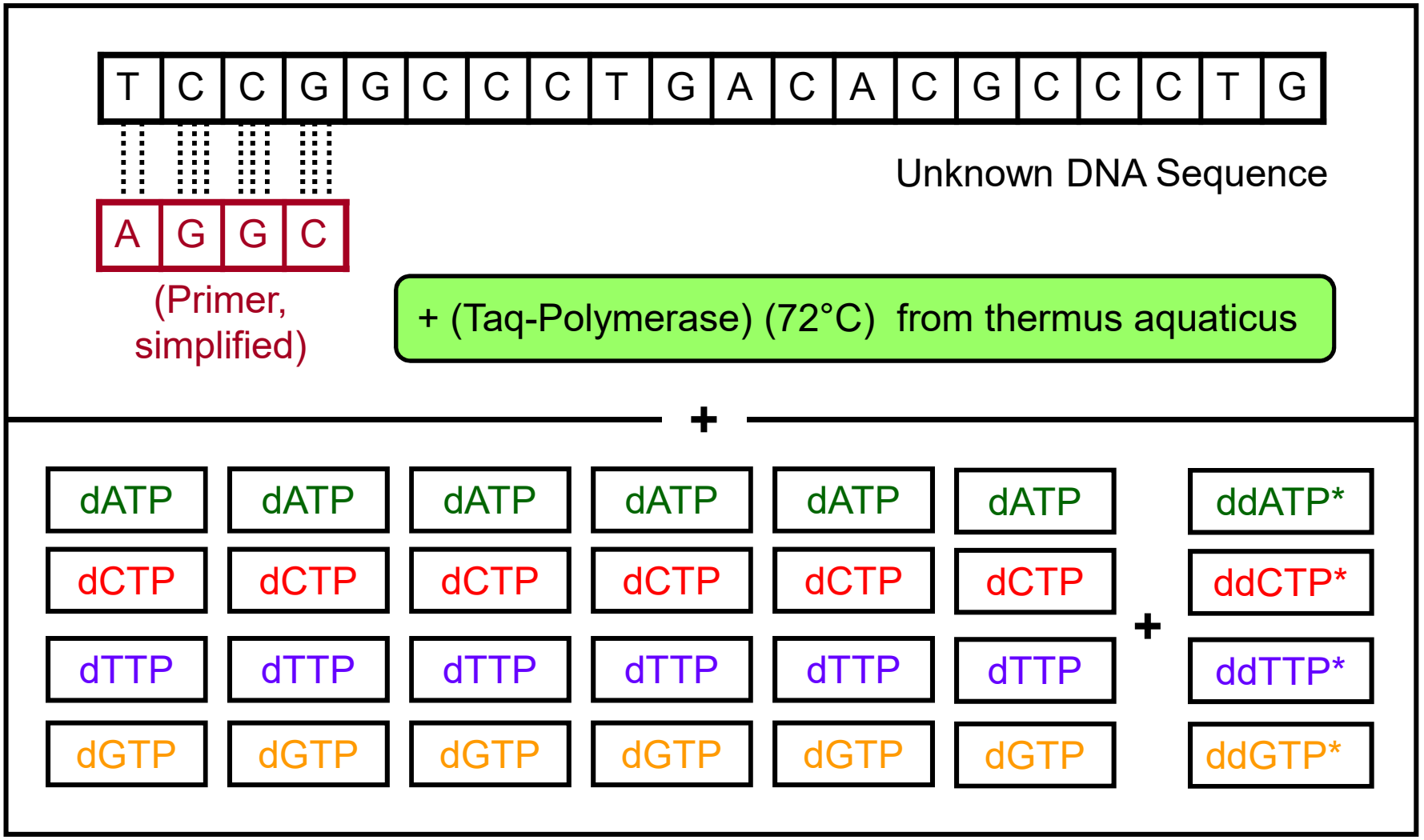
DNA Computer for Massive Parallel Data Processing

DNA Sequencing using controlled chain termination according to Frederick Sanger; Sequencing via fluorescence labeling:



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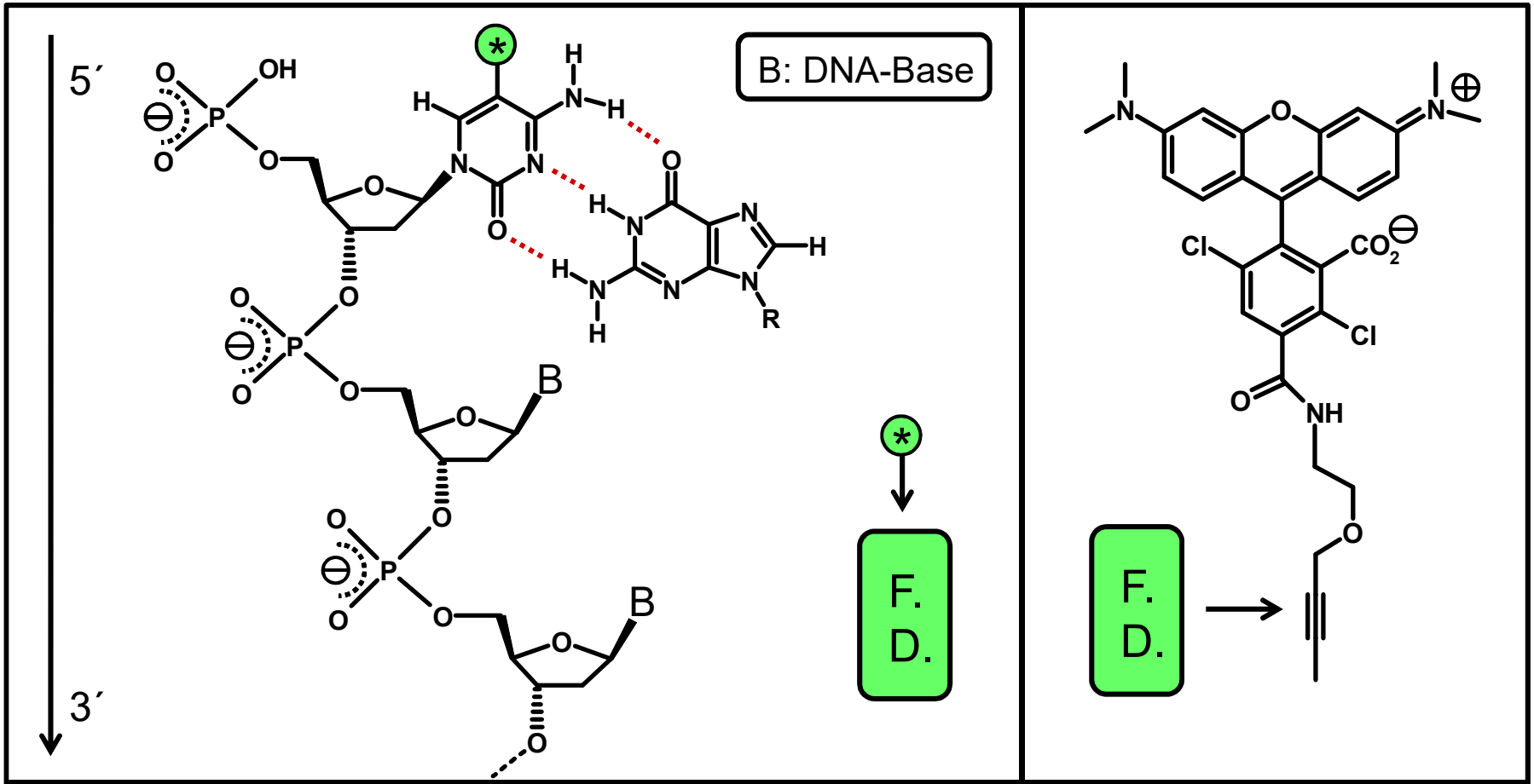
DNA Computer for Massive Parallel Data Processing

Frederick Sanger´s DNA sequencing; Chain start with a fluorescence-labeled PCR-5´-DNA-primer, (Dye Primer Method).



Deoxy-cytidine-monophosphate-building block*, dCMP*, covalently bound to a fluorescent dye.

F.D.: Fluorescence Dye, Fluorescent Dye.

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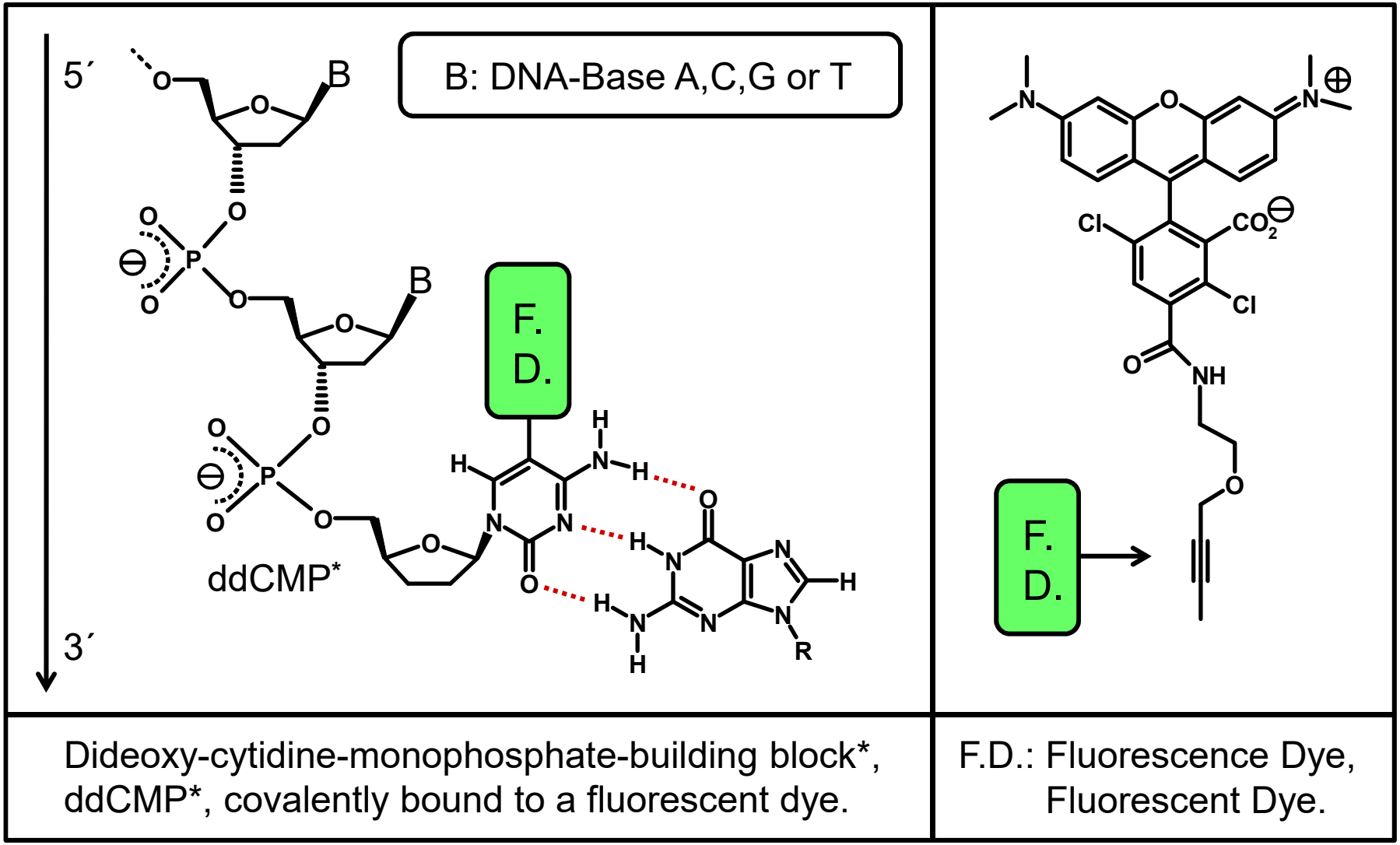
DNA Computer for Massive Parallel Data Processing

Frederick Sanger´s DNA sequencing; Chain termination with a fluorescence-labeled PCR-3´-dd-nucleotide, (Dye-Terminator Method).



Dideoxy-cytidine-monophosphate-building block*, ddCMP*, covalently bound to a fluorescent dye.

F.D.: Fluorescence Dye, Fluorescent Dye.

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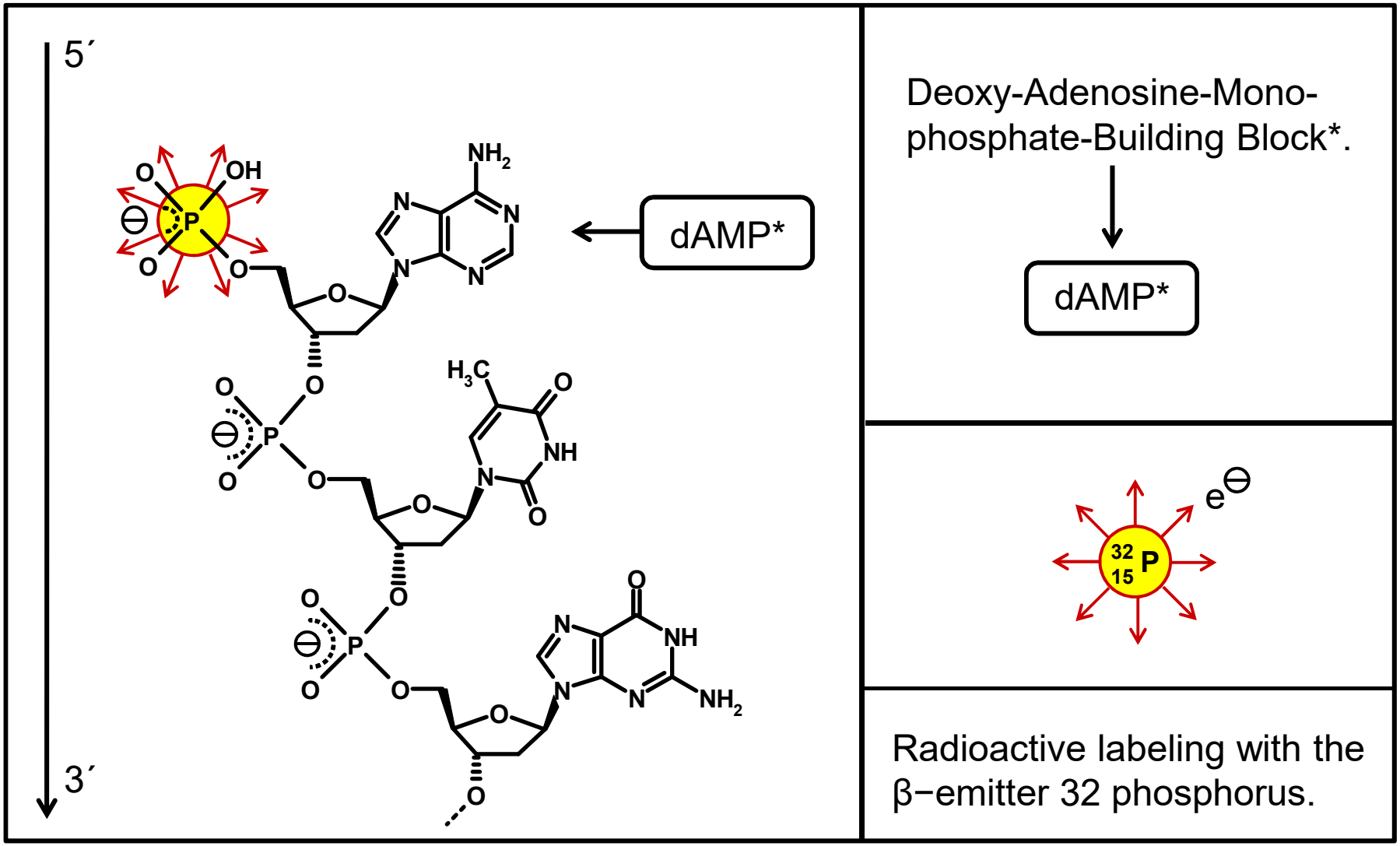
Frederick Sanger´s DNA sequencing; Chain start with a radioactively labeled (^{32}P) PCR-5´-primer, (Dye-Primer Method):



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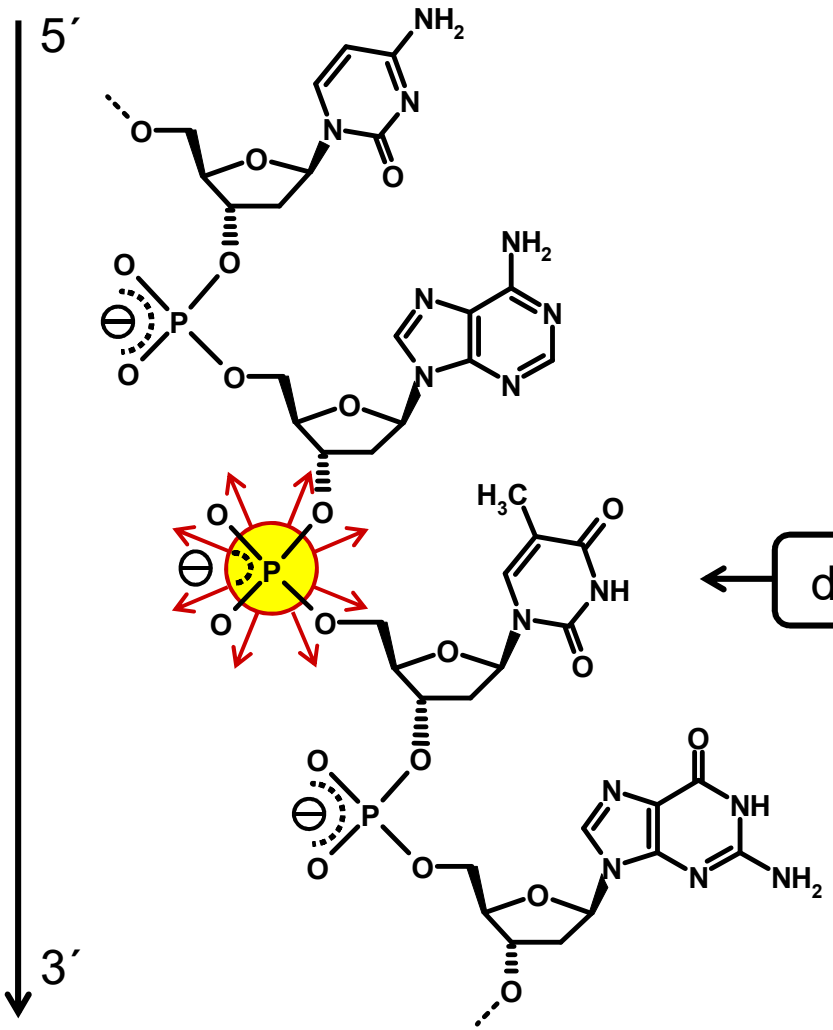
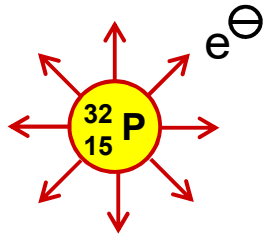
Frederick Sanger´s DNA sequencing; Chain growth with a radioactively labeled (^{32}P) PCR-nucleotide building block:



Deoxy-Thymidine-Mono-phosphate-Building Block*.

dTMP*



Radioactive labeling with the β−emitter 32 phosphorus.

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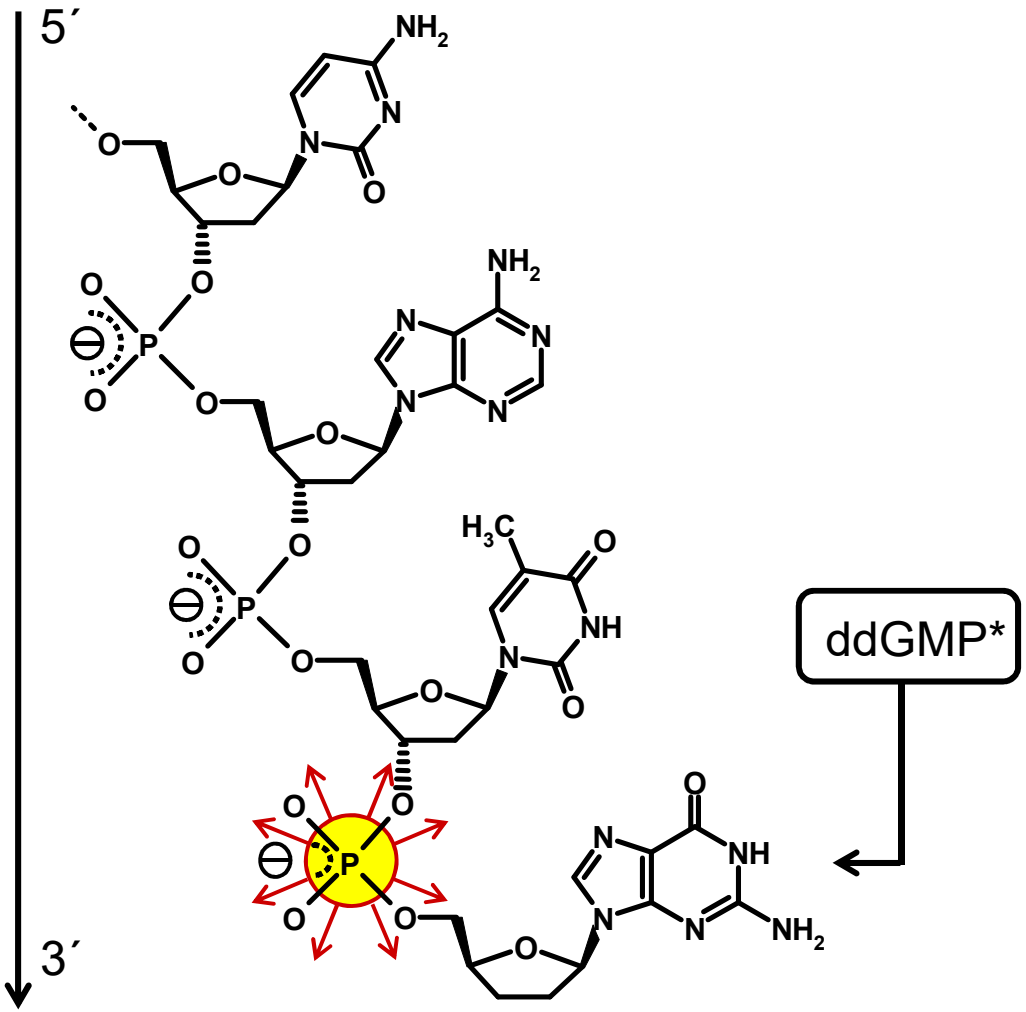
DNA Computer for Massive Parallel Data Processing

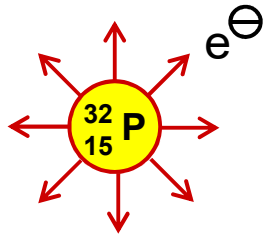
Frederick Sanger´s DNA sequencing; Chain termination with a radioactively labeled (^{32}P) PCR-3´-DNA-terminator:



Dideoxy-Guanosine-Mono-phosphate-Building Block*.

↓

ddGMP*



Radioactive labeling with the β−emitter 32 phosphorus.

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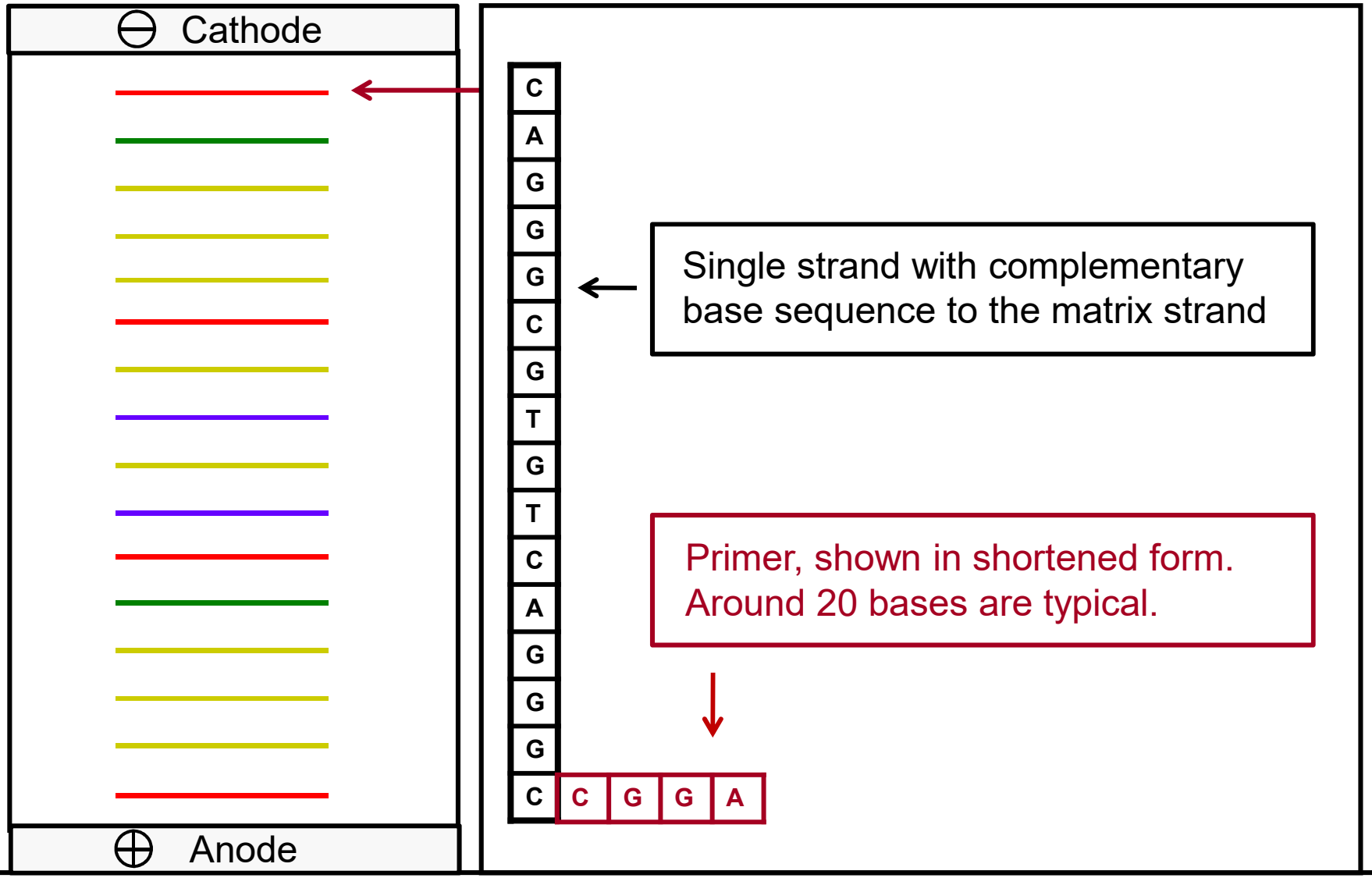
DNA Sequencing using controlled chain termination according to Frederick Sanger; Gel Electrophoresis on Polyacrylamide Gel:



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DNA Computer for Massive Parallel Data Processing

Frederick Sanger's DNA Sequencing;
Chain termination with fluorescent dye-labeled dideoxy nucleoside triphosphates (terminator method):

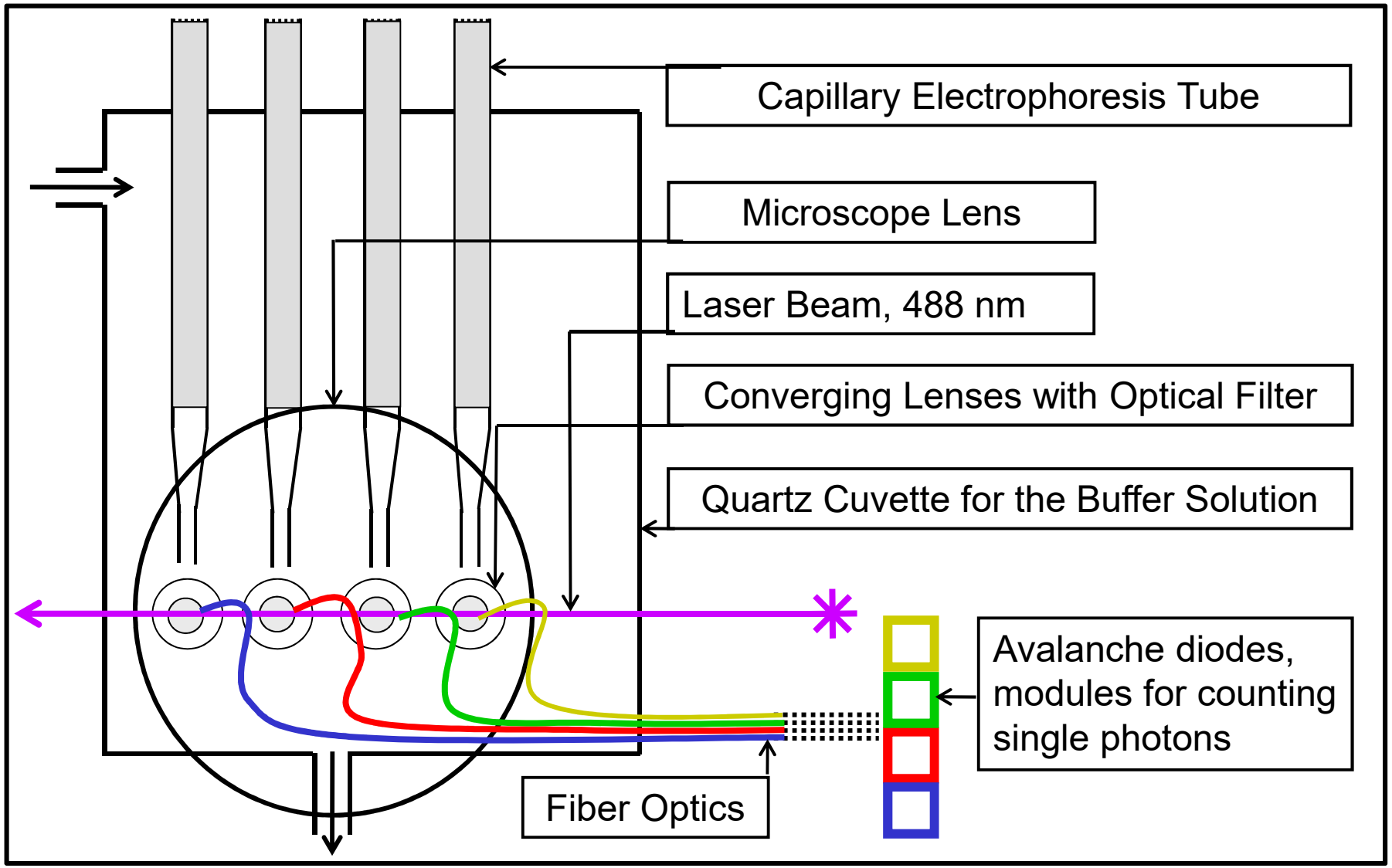
- For the start of the process: Addition of an oligonucleotide as a sequencing primer. This primer can be labeled with a fluorescent substance. (Primer marking).
- Chain growth is catalyzed enzymatically by a heat-stable *Taq* polymerase.
- Cyclic execution of the reaction, resulting in high fragment yields.
- 4 Dye - 1 Lane method in electrophoresis.
- High level of automation using capillary separation and laser fluorescence spectroscopy.

DNA Computer for Massive Parallel Data Processing

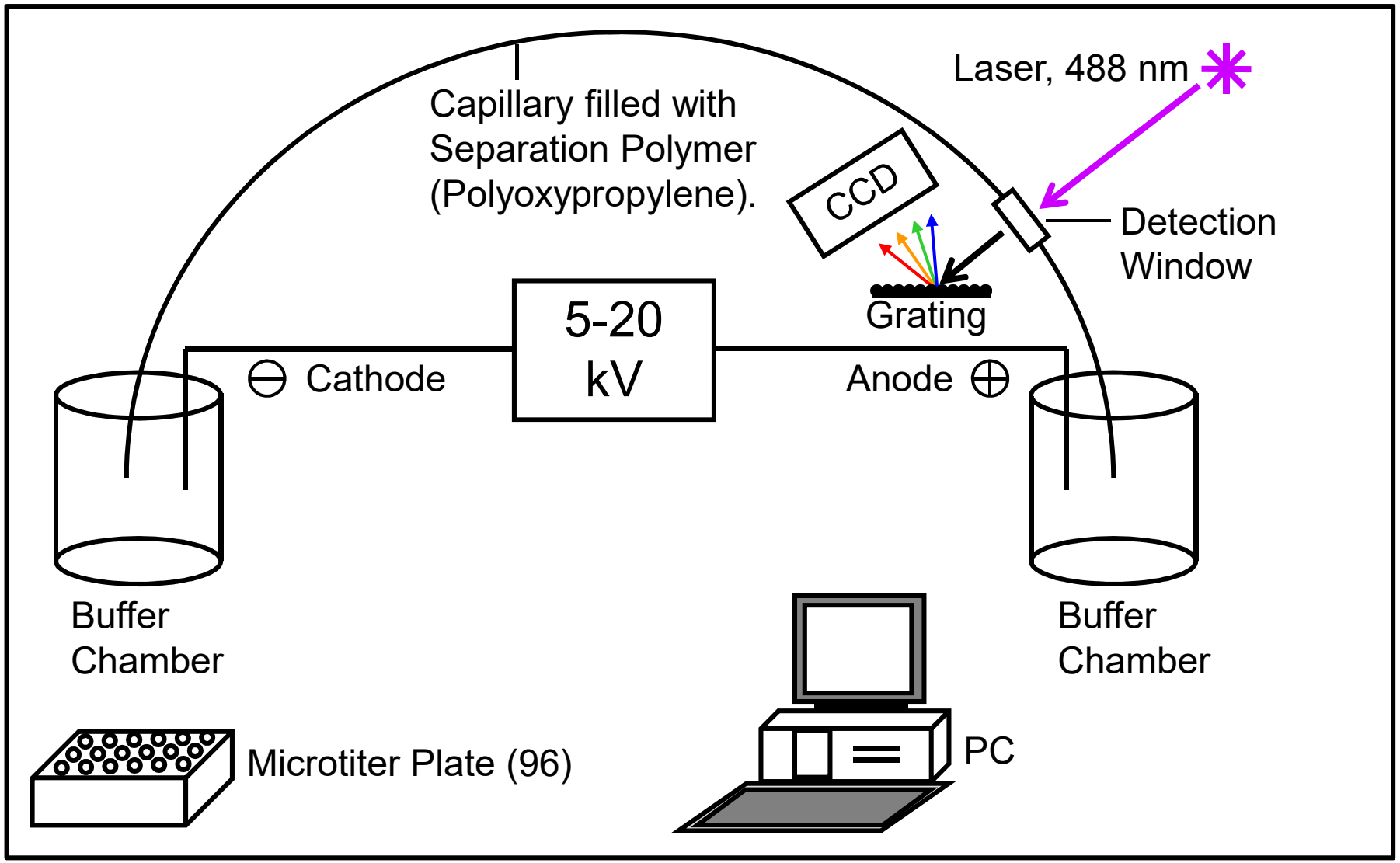
Frederick Sanger's DNA Sequencing;
Chain termination with fluorescent dye-labeled dideoxy nucleoside triphosphates (terminator method):

- Fluorescein derivatives with different substituent patterns can be used to label the chain termination fragments (ddNTPs) (ddNTP labeling).
- The dye molecules significantly enlarge the DNA building blocks linked to them and thus influence the running behavior of the DNA fragments on the gel or in the capillary.
- The labeled ddNTPs are, however, very poorly accepted by the Tac polymerase. Proportion of the incorporation ratio dNTP: ddNTP = 1000 : 1.

DNA sequencing using controlled chain termination according to Frederick Sanger; Sheath Flow Electrophoresis, detection with laser-induced fluorescence spectroscopy:



DNA sequencing using controlled chain termination according to Frederick Sanger; Capillary Electrophoresis, detection with laser-induced fluorescence spectroscopy:



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Application for a Strategic Invention:

"Process for massively parallel information processing using defined physical-chemical interactions"
(Fictitious example for demonstration).

Patent Autority

Patent Claims (Excerpts, purely fictitious information)

1. Molecules, molecular, ion or atomic arrangements, the individual components of which are the same or different, to which one can clearly assign information through characteristic links and / or defined spatial arrangements, which are suitable for coding, information storage, information transfer as well as for calculations with massive parallel data processing.

2. Methods for the synthesis, arrangement, fixation or production of molecules, molecular arrangements, ion arrangements or atomic arrangements according to claim 1.

→ **Abstractness**

→ **Openness**

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Application for a Strategic Invention:

"Process for massively parallel information processing using defined physical-chemical interactions"
(Fictitious example for demonstration).

Patent Autority

Patent Claims (Excerpts, purely fictitious information)

3. Methods for the calculation and optimization of networks, characterized in that information-containing coding molecules, molecule, ion or atom arrangements according to claim 1 react or interact simultaneously, and the resulting products or associates are analyzed for their information content..

4. Procedure for the calculation of Hamilton routes for the rapid solution of complex (transport) route and route tasks in air traffic, rail transport, freight transport, in logistics, material flow and production systems, as well as storage systems, distribution systems, laboratory machines and courier services, characterized in that one Molecules, molecule or atomic arrangements according to claim 1 are used as information carriers.

→ **Openness**

→ **Variety/Scope**

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Application for a Selection Invention:

"DNA computer for massive parallel data processing to optimize air traffic routes"
(Fictitious example for demonstration of the difference)

Patent Autority

Patent Claims (Excerpts, purely fictitious information)

1. DNA fragments in the form of single-stranded oligonucleotides with base sequences, each consisting of five to thirty independent, non-complementary nucleotides, which code for nodes and edges in a connected graph and which, in the presence of the enzyme ligase, randomly and simultaneously into DNA strands polymerize with different lengths and information content ..., etc.

2. Methods for the synthesis of DNA fragments according to claim 1, characterized in that after the solid phase synthesis according to Merrifield protected phosphoramidite building blocks ..., etc.

3. IT system and IT method for calculating the shortest flight routes based on complementary DNA fragments as information carriers, characterized in that defined oligo-nucleotides are assigned to each individual airport and each planned flight route in such a way that ..., etc.

→ **Focusing** → **Concretization**

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Task for a Case Study on R&D Project Management

!

Plan a suitable project for your research subject "DNA computers for the massive parallel data processing"!

- General framework: The research project to be planned is pioneering for your start-up company or for your research institute!
- Define what you consider to be a plausible target system for this research project: chemical-technical, potentially economical and time-related goals, taking into account possible, reasonable fields of application. Use additional data and facts from the Internet / WWW to assess the application potential, the state of science and the social environment!
- Roughly estimate the personnel and material expenses necessary for the complete achievement of the target system!
- Decide on an appropriate project organization!
- Determine the target-relevant tasks and classify them according to the number of specialist functions involved in their solution!
- Based on this, carry out a rough project structure planning (sketch)!
- Sketch a simple project phase plan by using bars on time axes according to the technique of Henry Gantt!
- Make a plausible SWOT analysis for the research project!

Further literature (specialist books, specialist articles) on the subject: "DNA computers for the massive parallel data processing".

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- T. Buchholz, M. Kutrib, Molekulare Computer. Rechnen im Reagenzglas., Spiegel der Forschung , das Wissenschaftsmagazin der JLU Giessen , 15, 1, 27–36, 1998.
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- L. M. Adleman, Rechnen mit DNA., Spektrum der Wissenschaft, 2000, 50–57, Heidelberg.
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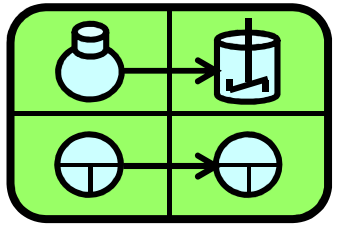
- D. Voet, J.G. Voet, Biochemistry, John Wiley & Sons, Hoboken, 2016.
- By Jeremy M. Berg, John L. Tymoczko, Gregory J. Gatto jr., Lubert Stryer, Biochemie, Springer Spektrum, Berlin, 2018.
- F. Wang, H.Lv, Q. LI, J. LI, X. Zhang; J. Shi, L. Wang, C, Fan, Implementing digital computing with DNA-based switching circuits, Nature Communications, 11, 121, 2020.
- D. Wöhrle, H. Wöhrle, Materialien in Rechnern und digitalen Computern, Chemie in unserer Zeit, 54, 220-233, 2020, and the literature cited therein.

R&D Project Management
in the Chemical Industry



Supplementary Module 02 for (Bio) Chemists (m/f/d)

Information Material *for the subject matter:*
"Suitable" points in time for market launch.

"Juvenile Hormone Mimics to Control Stinging and Sucking Insects".

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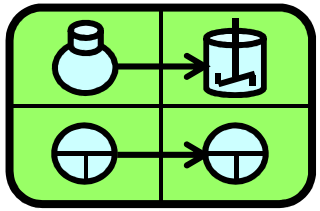
R&D Project Management in the Chemical Industry



Subject Matter	***Innovation; "Suitable Points in Time for Market Launch".***

Chemical-Biological Basics: "Juvenile Hormone Mimics to Control Stinging and Sucking Insects".

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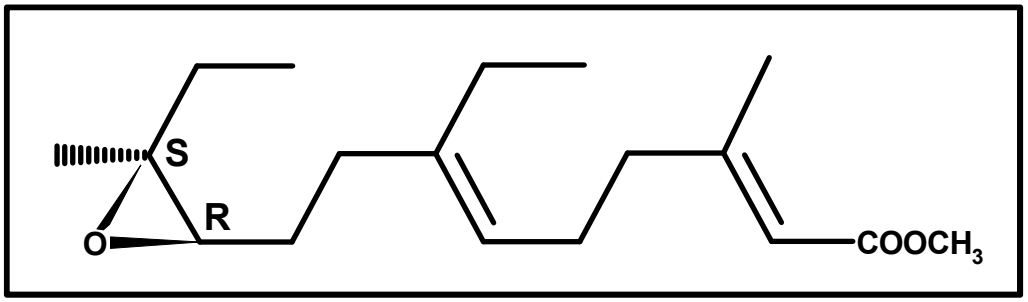
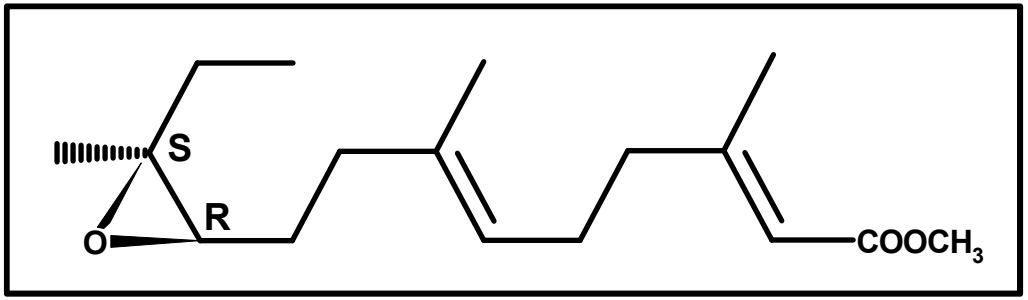
Innovations, Suitable Points in Time for Market Launch

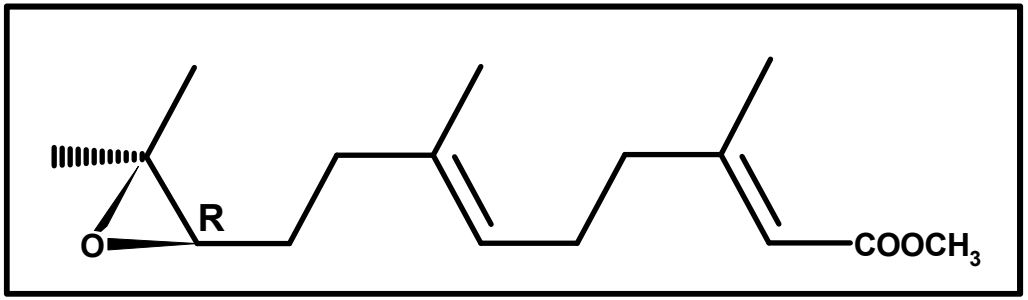
Insect Juvenile Hormones from the Corpora Allata:



JH I, Product from the hyalophora cecropia (Silkworm).



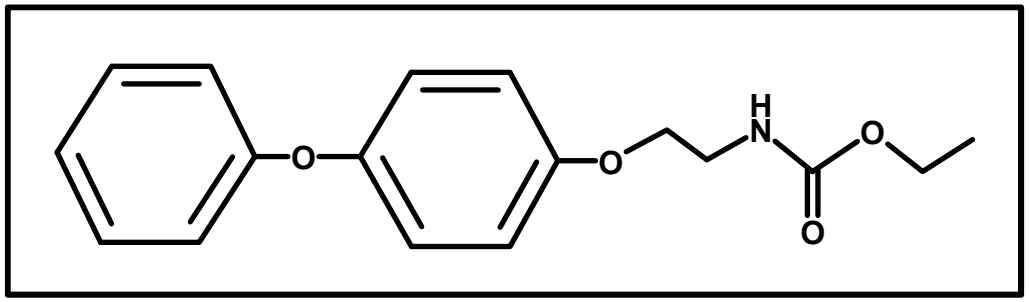
JH II, exists only in Lepidoptera (Butter-flies/Moths).



JH III, is formed in the organism of all insect species.

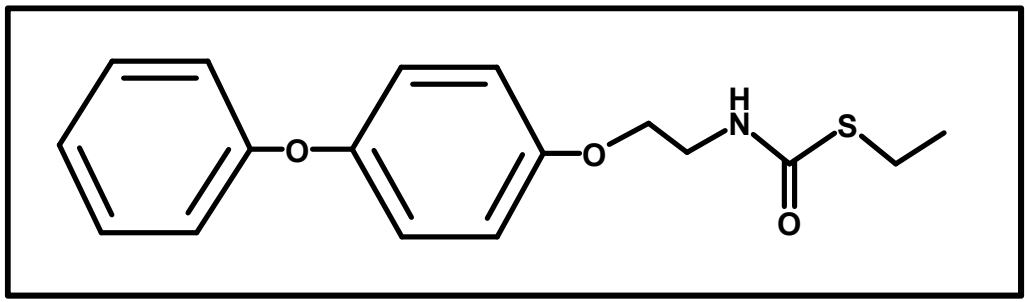
Innovations: Characteristic "Economic Success"

Suitable Points in Time for Market Launch: **JH-Mimicries**.



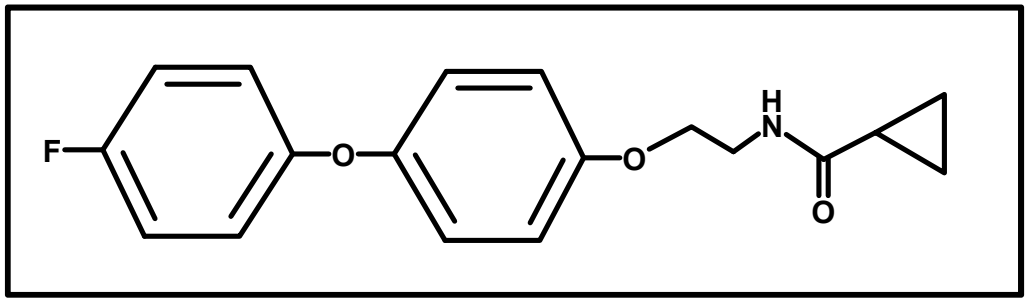
Fenoxycarb, Insegar®; Maag, 1985. Today still a trade product in Syngenta Group.

Examples



RO 137.744, 1985.
Former trial product from Hoffmann La Roche.

Examples



EP 372.330, 1987.
Former laboratory and test product from BASF.

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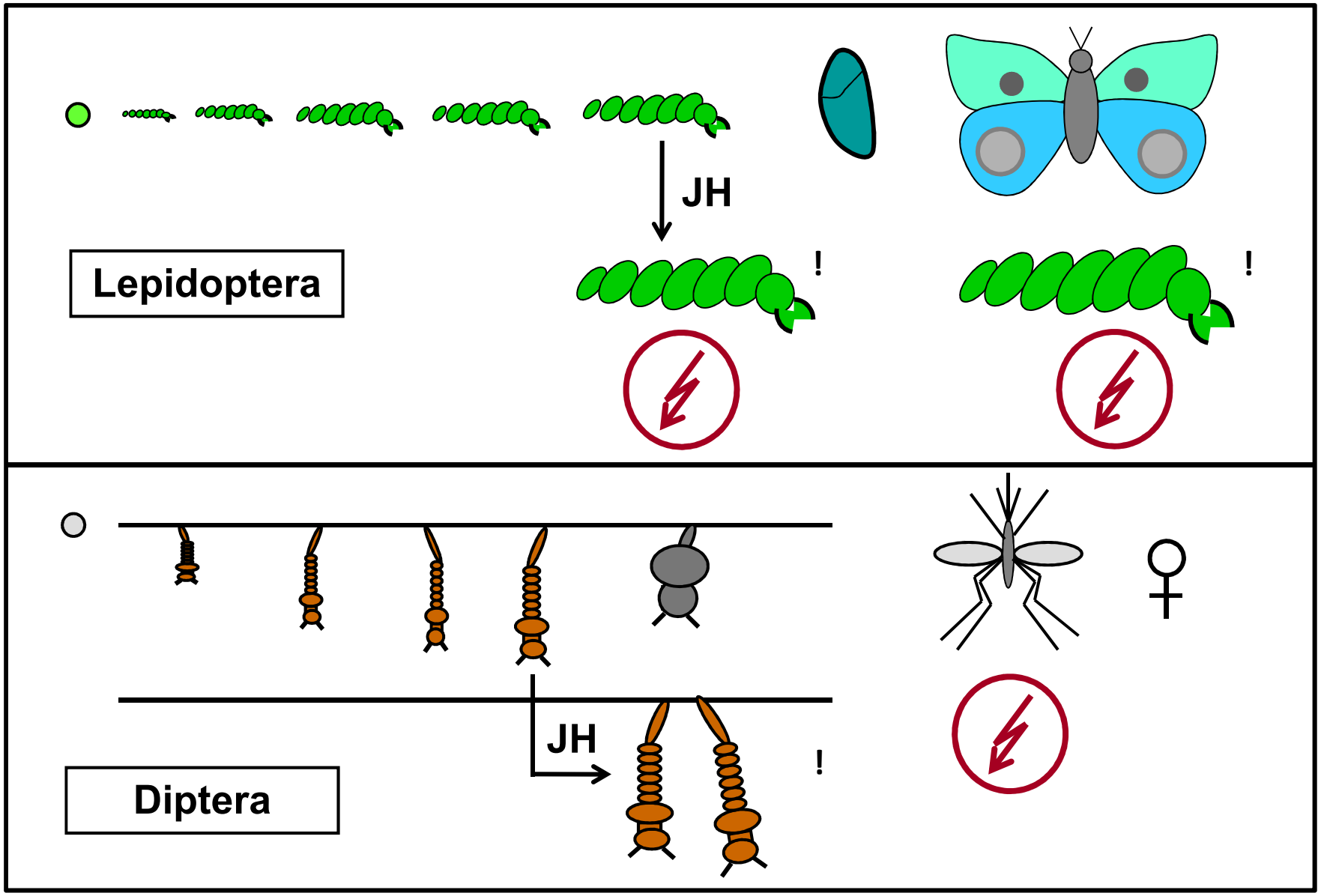
Juvenile Hormone Mimics: Holometabolic Insects.



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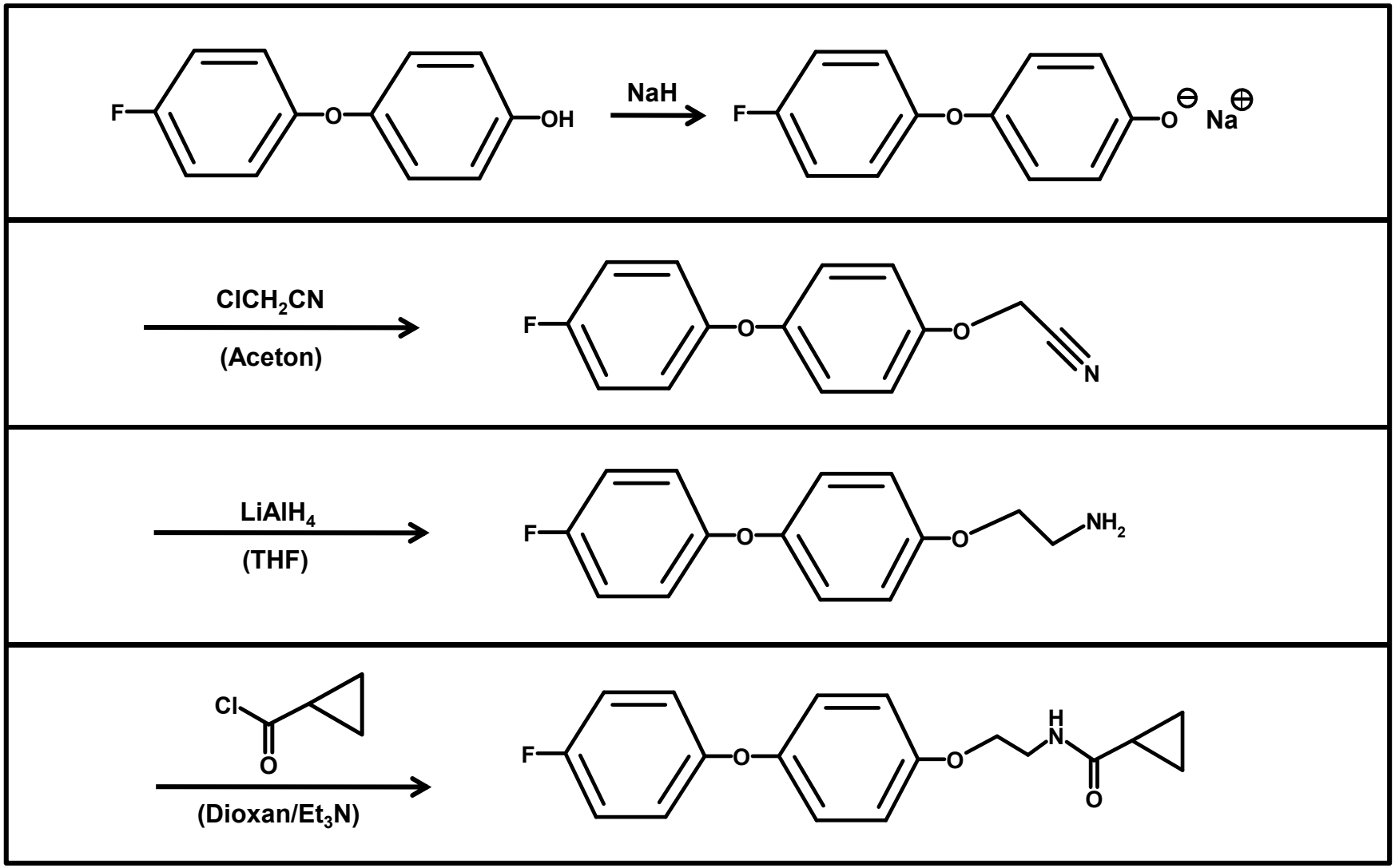
Innovations, Suitable Points in Time for Market Launch

Juvenile Hormone Mimic, Laboratory Synthesis:



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Juvenile Hormone Mimics; Market Decision: BT!

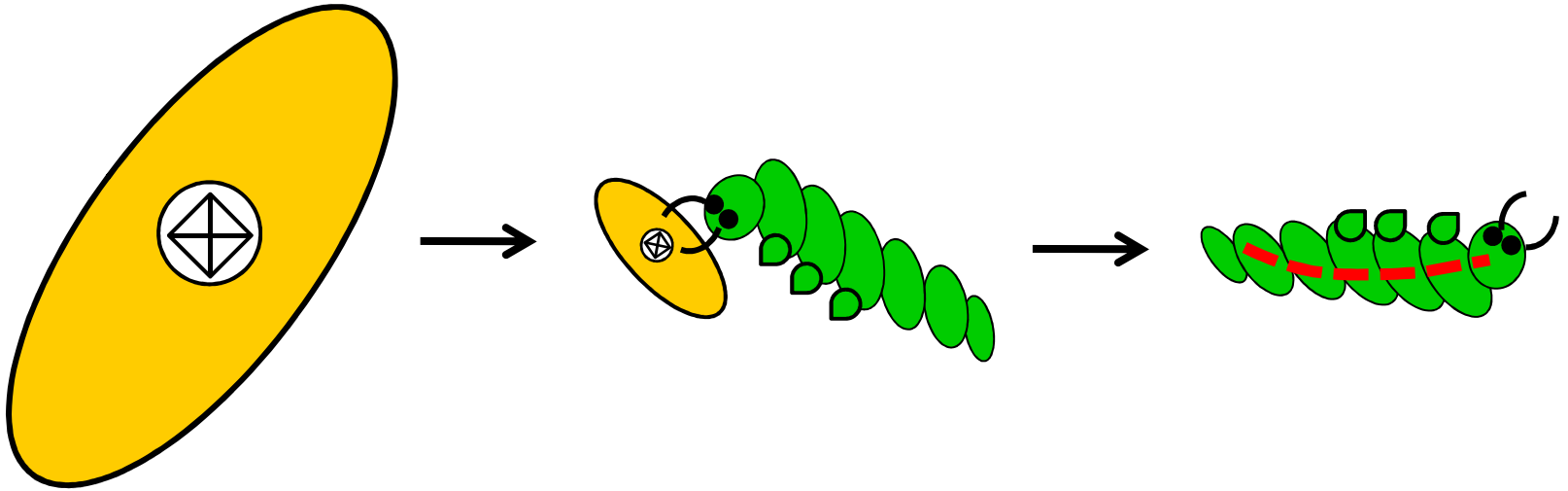
Simultaneous introduction of BT toxin against diptera!

Reduced market opportunities for JH mimics! ⊖

- BT, Bacillus thuringiensis, gram-positive soil bacterium (δ-endotoxin).
- Crystalline protein toxin from Bacillus thuringiensis spores.
- Destroys the intestinal epithelial cells of insects (perforation).
- Effective against Diptera, Lepidoptera and Coleoptera.
- Commercial products: Biotrol BTB, Thuricide HP.
- Low long-term effect in field trials.
- Therefore, as a new problem-solving approach: incorporation of toxin-coding genes into crops; → Transgenic plants.

Juvenile Hormone Mimics →

Market Decision: Bacillus Thuringiensis, BT!



Bacillus spore with crystalline inclusion containing the toxin.

Is eaten by the insect larva: The "cry protein" is released.

Insect larva dies from the destruction of its intestinal tract.

(⊛ Cry-Protein = Crystalline Protein)

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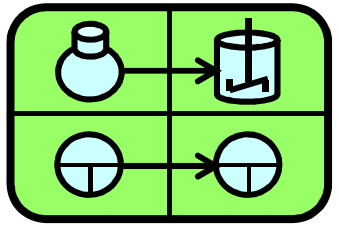
Further literature (specialist books, specialist articles) on the subject: "Juvenile Hormone Mimics to Control Stinging and Sucking Insects".

- A. Nakayama, H. Iwamura, T. Fujita, Quantitative structure-activity-relationship of insect juvenile hormone mimetic compoundes, J. Med. Chem. 27, 1493, 1984.
- A. Nakayama, H. Iwamura, A. Niwa, Y. Nakagawa, T. Fujita, Development of juvenile hormone active oxime-O-ethers and carbamates, J. Agric. Food Chem. 33, 1034, 1985.
- L.M. Riddiford, "Cellular and molecular actions of juvenile hormone I. General considerations and premetamorphic actions". Advances in Insect Physiology.,24: 213–274, 1994.
- W. Draber, T.Fujita, Rational Approaches to Structure, Activity and Ecotoxicology of Agrochemicals, CRC Press, Ann Arbor, 1992.
- H.F. Nijhout, Insect Hormones, Princeton University Press, 1994.
- T.S. Dhadialla, G.R. Carlson, D.P. Le, Annual Review of Entomology 43(1), 545-569, 1998.
- J.J. Sullivan, Chemistry and Environmental Fate of Fenoxycarb. Reviews of Environmental Contamination and Toxicology, Vol 202., Springer, New York, 2010.
- L.A. Defelipe, E. Dolghih, A.E. Roitberg, M. Nouzova, J.G. Mayoral, F.G. Noriega, A.G. Turjanski, "Juvenile hormone synthesis: "esterify then epoxidize" or "epoxidize then esterify"? Insights from the structural characterization of juvenile hormone acid methyltransferase", Insect Biochemistry and Molecular Biology. 41 (4): 228–235, 2011.
- W. Goodman, M. Cusson, The Juvenile Hormones, in: L.I. Gilbert, Insect Endocrinology, Academic Press, Cambridge/U.S.A., 2012.
- K.P.C. Vollhardt, N.E. Schore, Organic Chemistry: Structure and Function, W.H.Freeman and Company, New York, 2018.
- J. Clayden, N. Greeves, S. Warren, Organische Chemie, Springer Spektrum, Heidelberg, 2017.

R&D Project Management
in the Chemical Industry



Supplementary Module 02 for (Bio) Chemists (m/f/d)

Information Material *for the subject matter:*
Task for a case study, chemical-biological bases.

Synthetic Mimics of Antimicrobial Proteins ("SMAMPs").

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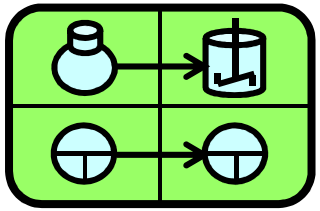
R&D Project Management in the Chemical Industry



Subject Matter	**Task for a Case Study, Chemical-Biological Bases.**

Synthetic Mimics of Antimicrobial Proteins ("SMAMPs").

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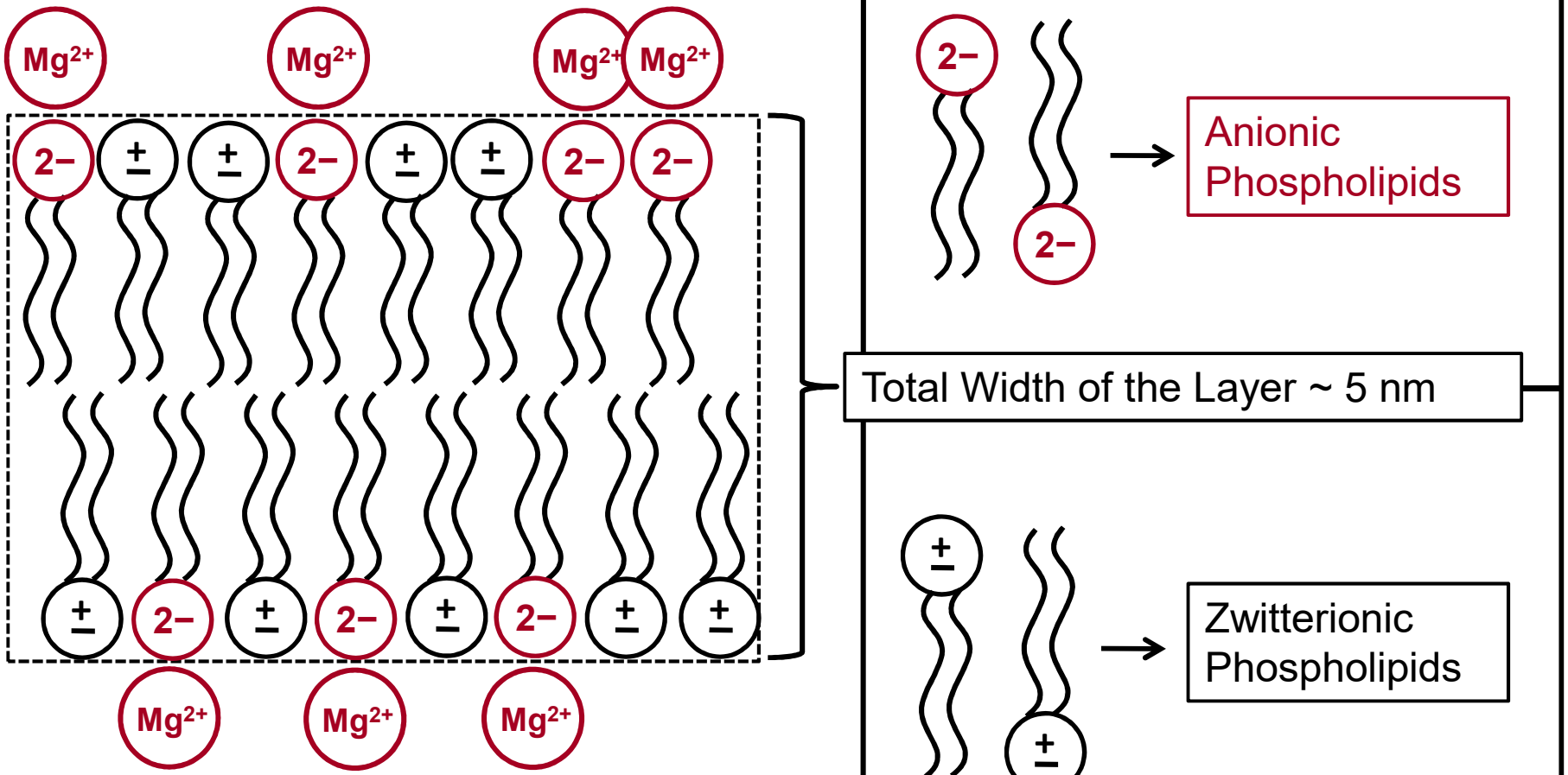
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities.
Bacterial Cell Membrane (1): Lipid Bilayer, Structure.



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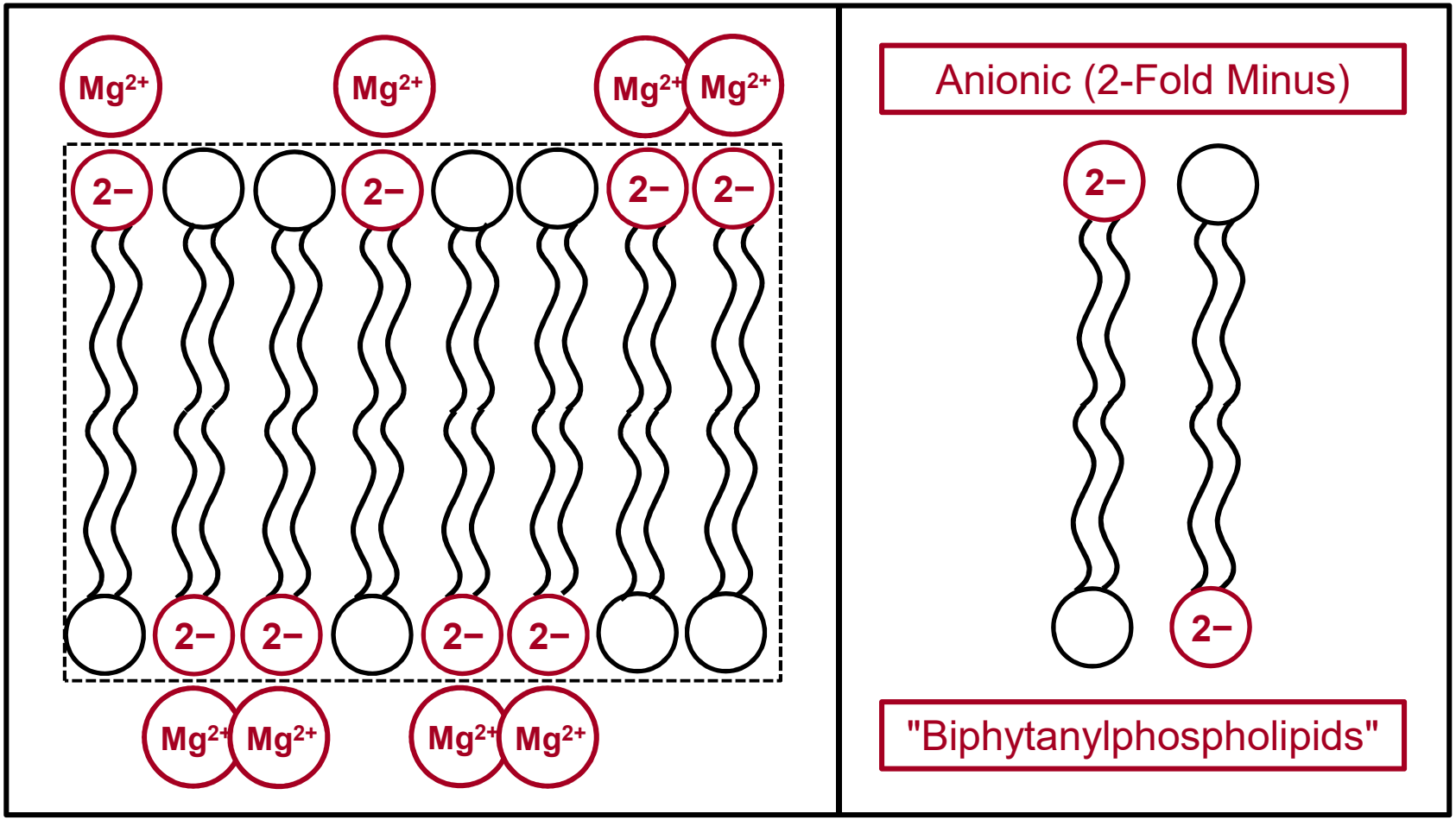
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities.
Bacterial Cell Membrane (2): Lipid Single Layer, Structure.



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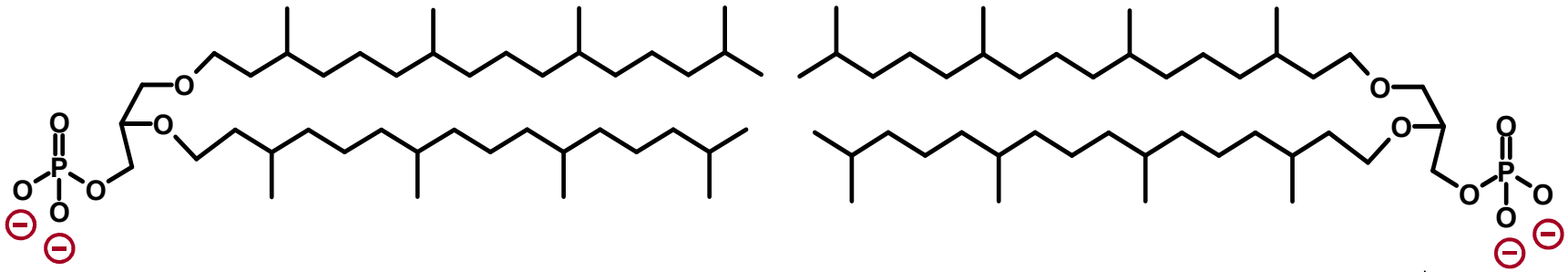
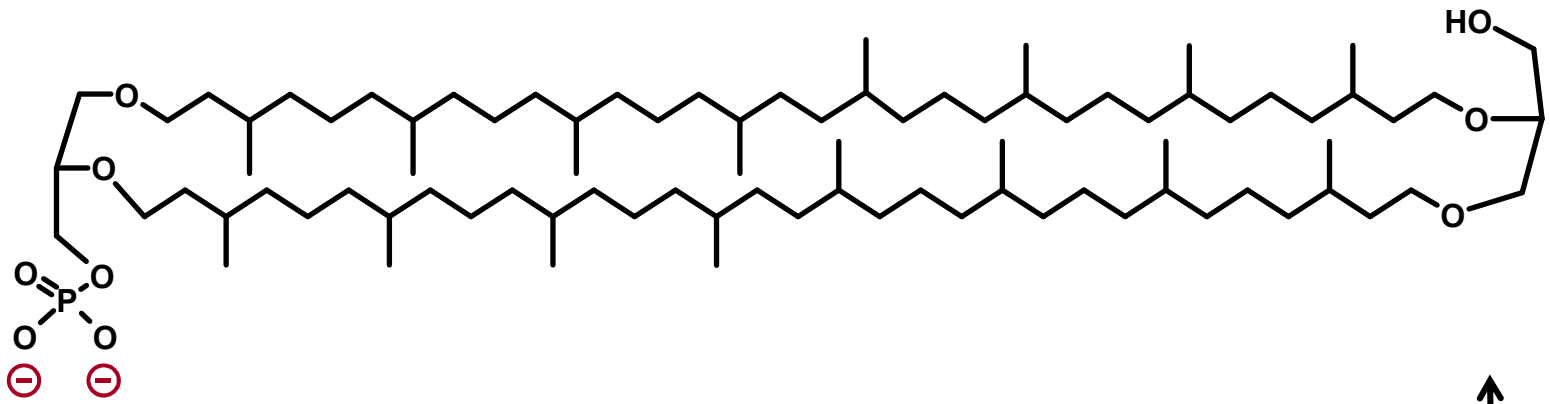
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Bacterial Cell Membrane, Basic Chemical Building Blocks: Glycerol Diether/Diglycerol Tetraether.



Double layer from two glycerol phytanyl diethers



Single layer from diglycerol biphytanyl tetraethers

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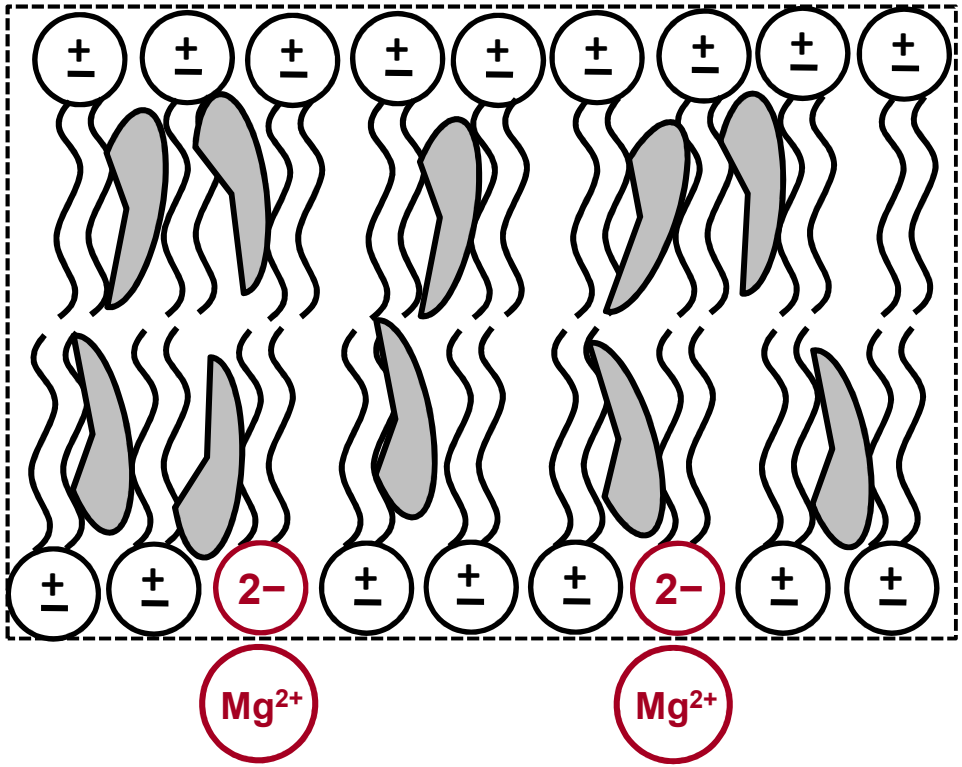
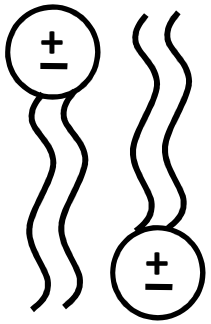
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities. Eukaryotic Cell Membrane: Lipid Bilayer, Structure.

Cholesterol serves as a "freeze protection agent" to block the phase transition from liquid crystal to gel when the cell membrane cools down!





→ Zwitterionic Phospholipids

→ Cholesterol

→ Anionic Phospholipids

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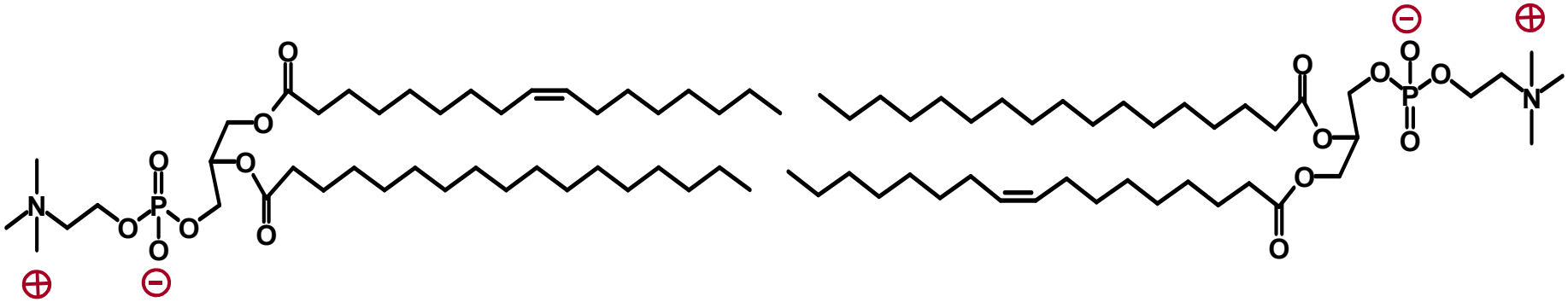
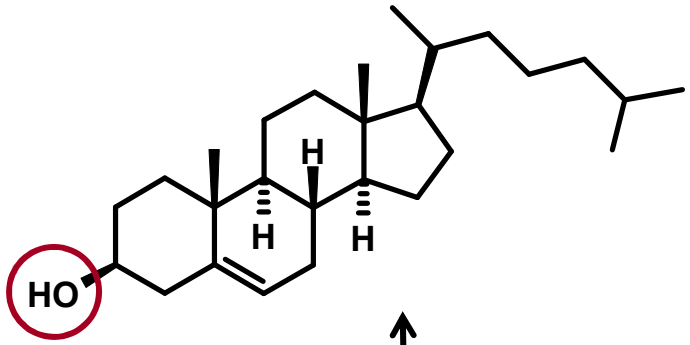
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities.
Eukaryotic Cell Membrane: Phospholipid Bilayer.



Zwitterionic glycerol triester

○ → Polar part of the molecule



Cholesterol (5-Cholesten-3β-ol)

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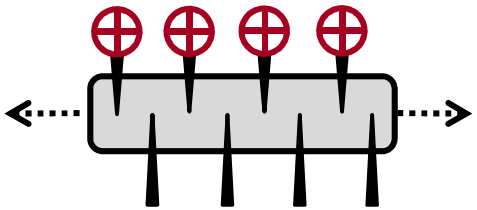
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Starting Point: Natural, Antilinflammatory Proteins.

- The body's own proteins with 33-47 amino acids, "defensins".
- These show broad microbicidal effects, e.g. by destroying (lysing) the cell membrane of the pathogen, and they are robust against the formation of resistance.
- With inflammation, their concentration in blood increases.
- They carry cationic (⊕) and hydrophobic (▲) amino acid residues on the primary structure in a local toggle mode.

- The defensins therefore have protein structures with local limited, amphiphilic arrangements.

Structural Scheme



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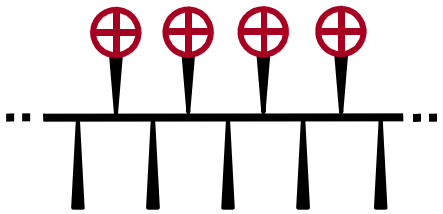
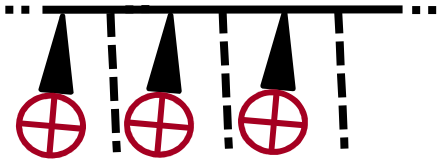
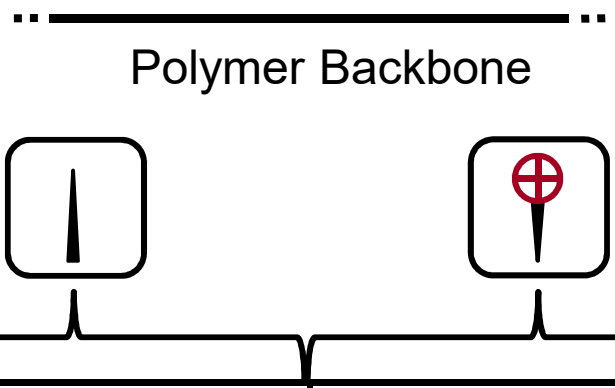
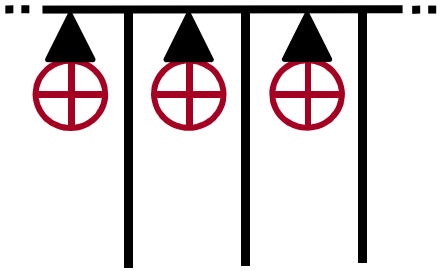
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Amphiphilia of SMAMP Polymers, Structural Schemes.
(SMAMP: Synthetic Mimic of Antimicrobial Proteins).

Top View	Side View as f(φ)
	
	
Hydrophobic Group / Hydrophilic Group	φ: ⟶ Viewing Angle

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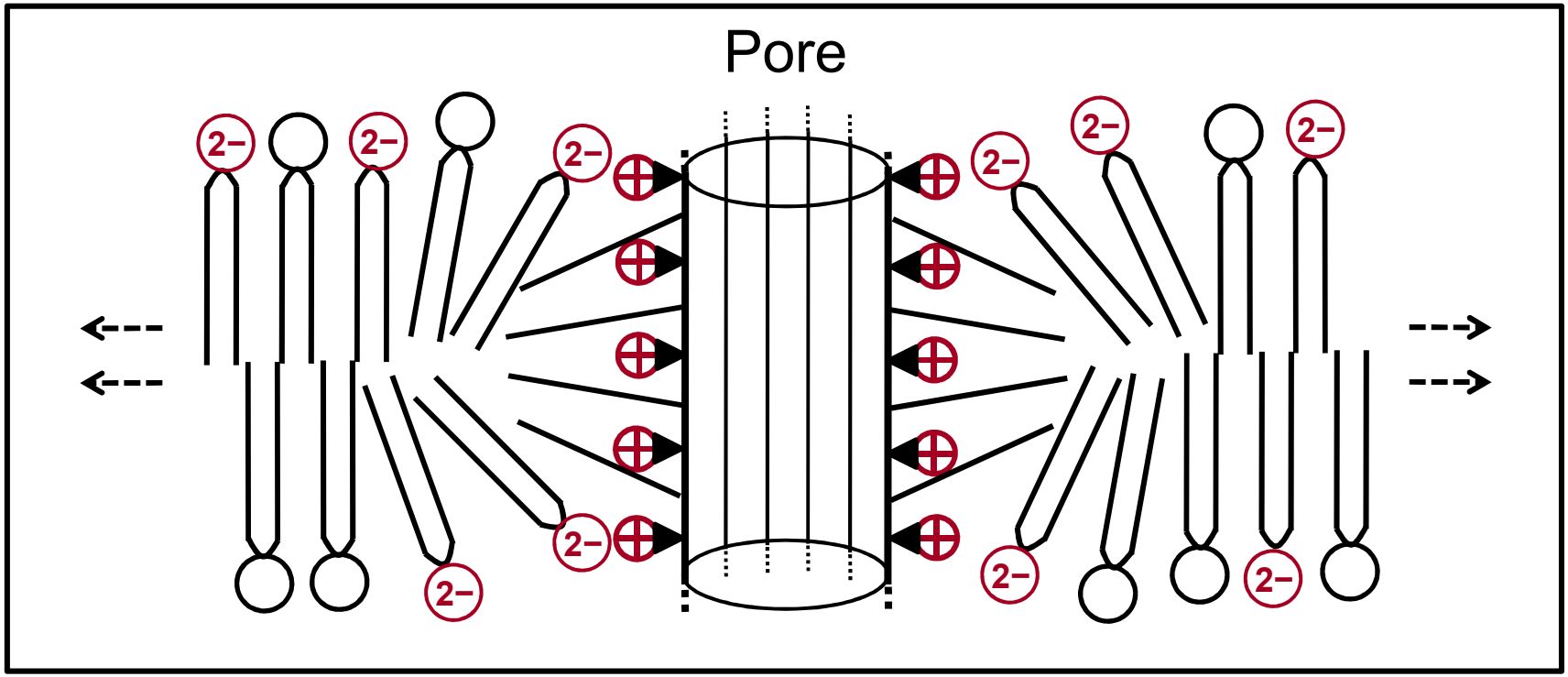
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities:
Possible Mechanism of Cell Lysis: Pore → Formation.



"Barrel-Stave-Model" →

Formation of pores in the membrane

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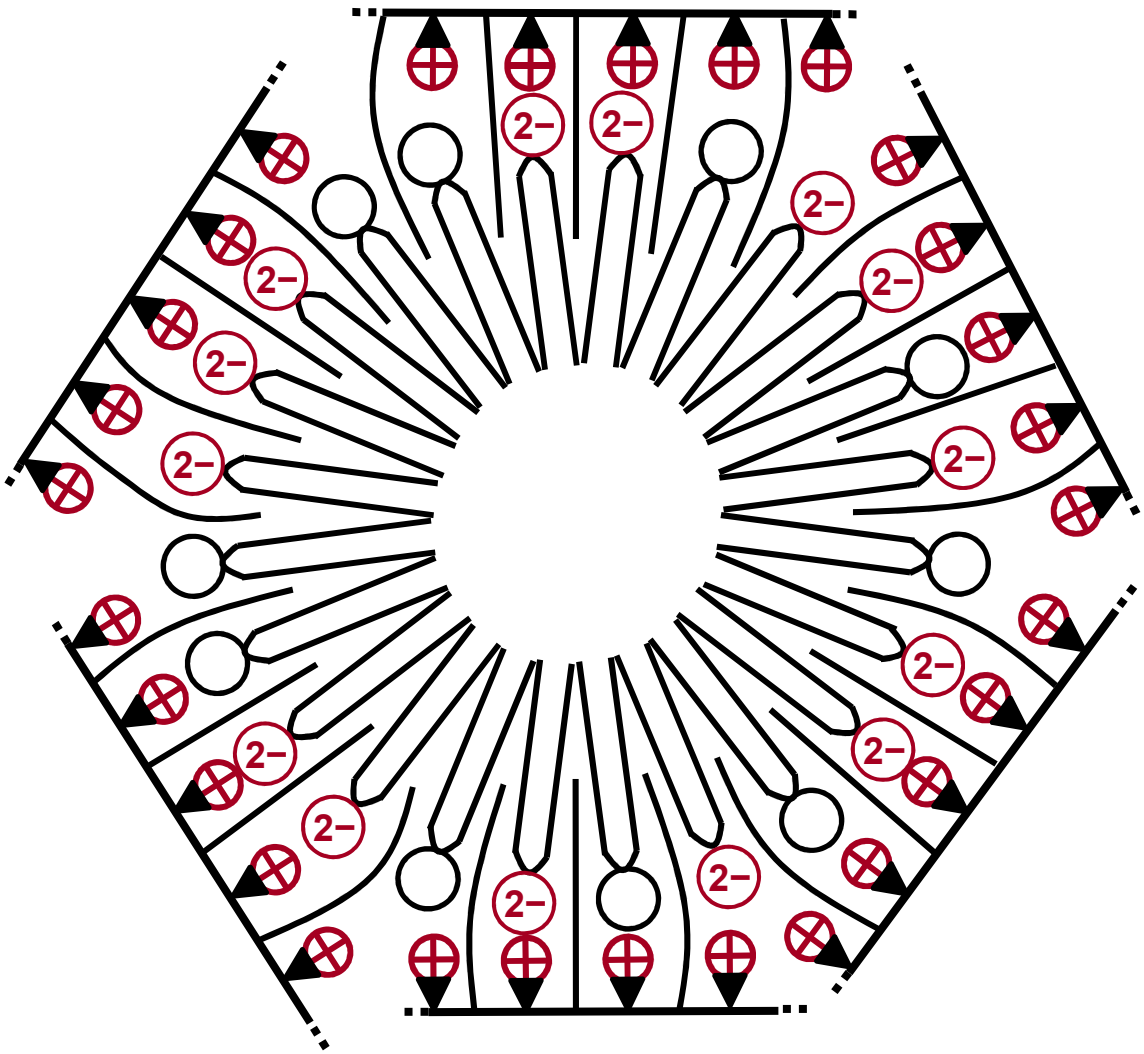
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities:
Possible Mechanism of Cell Lysis: Micelle → Formation.



"Carpet-Model"

→ Formation of micelles

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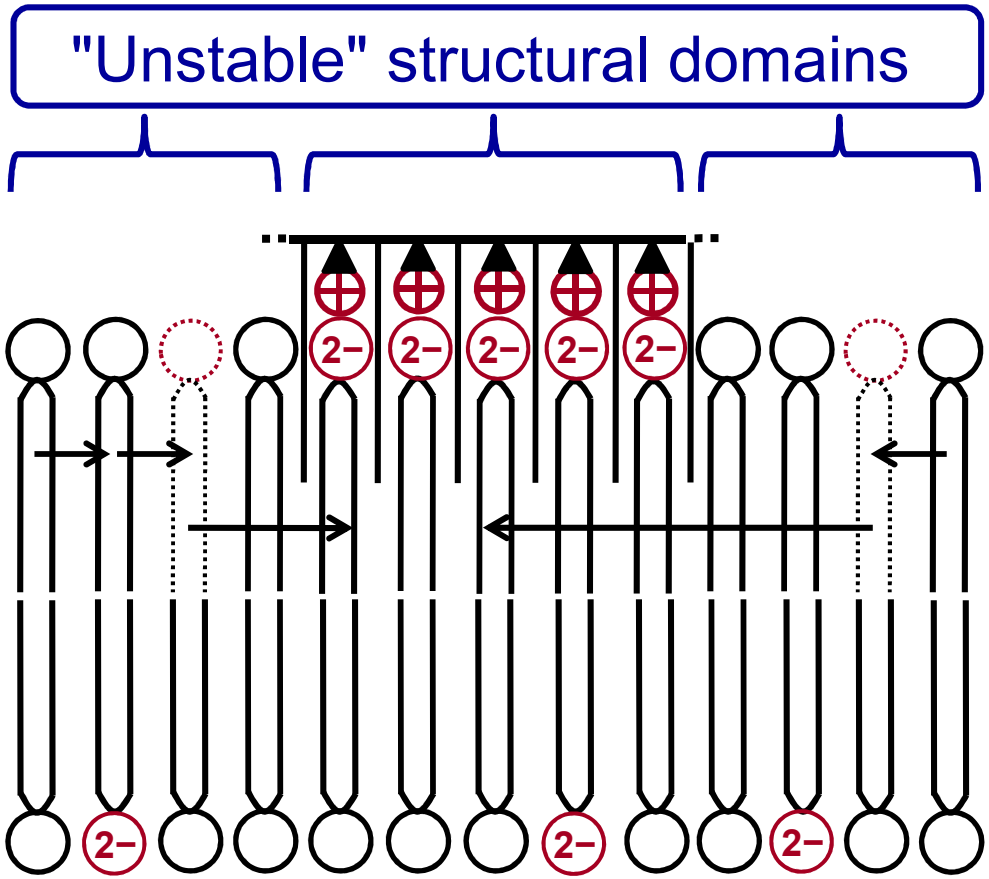
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities:
Possible Mechanism of Cell Lysis: →
Aggregation of Double Negatively Charged Anions.



"Aggregation-Model"

→ Disruption of the neutral lipid molecules´ near-order.

→ Membrane defects

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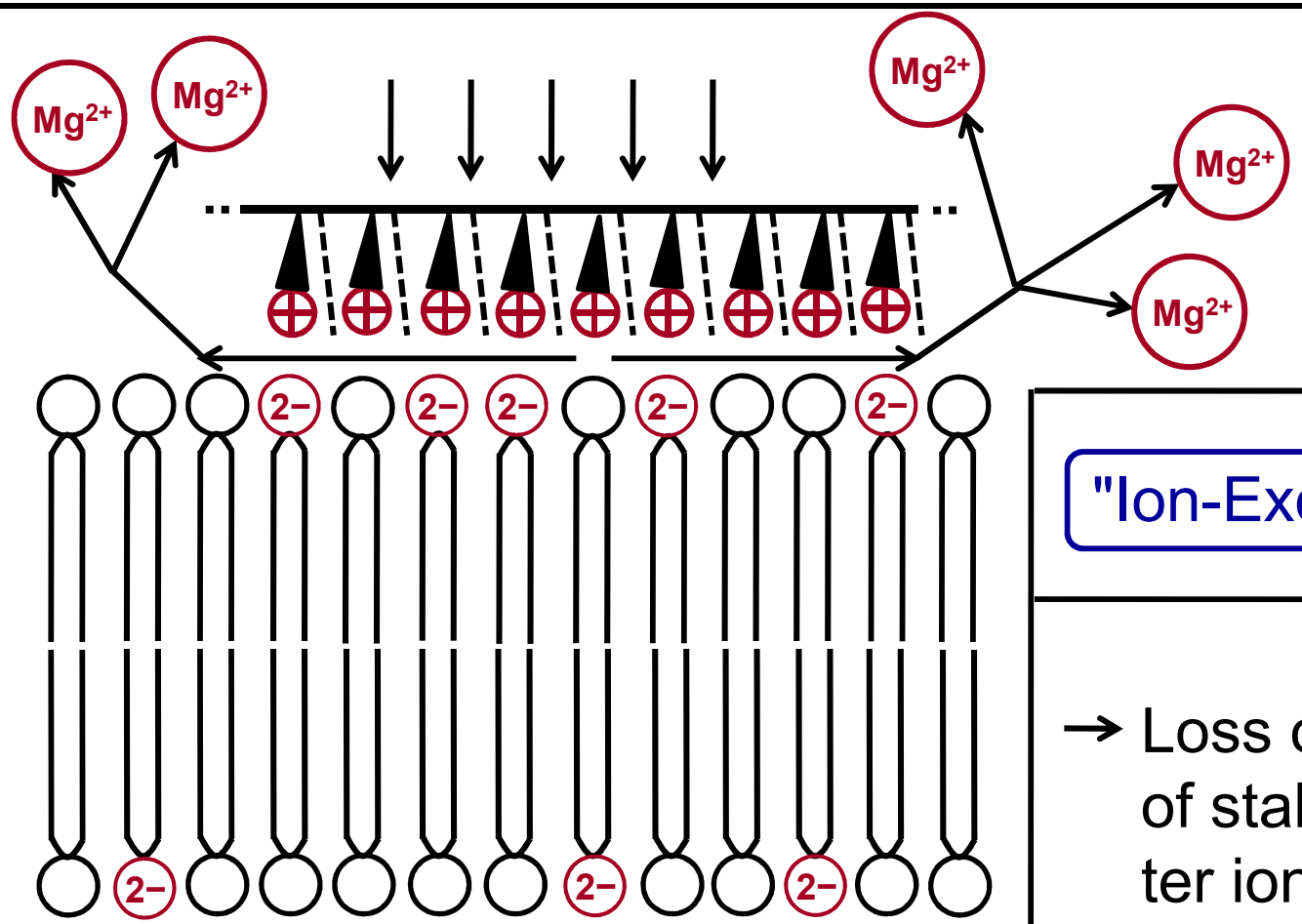
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities:
Possible Mechanism of Cell Lysis: → Ion Exchange.

Removal of the Mg^{2+}-ions detached from the cell surface.



"Ion-Exchange-Model"

→ Loss of the structure of stabilizing counter ions (Mg^{2+}).

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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: MIC_{90} ⟶ Definition.

The minimum inhibitory concentration **MIC_{90}** is the concentration of SMAMP polymer in µg/ml at which 90% of the growth of a bacterial culture is inhibited.

The focus is on tests with the following multi-resistant germs:

- Escherichia coli (Large Intestine)
- Bacillus subtilis (Soil, Manure)
- Enterococcus faecium (Intestine)
- Staphylococcus aureus (Nasal Cavity, Lungs)
- Klebsiella pneumoniae (Pneumonia)
- Serratia marescens (Starchy Media)
- Salmonella typhimurium (Typhoid Fever, Diarrhea)
- Shigella dysenteriae (Bacteria Dysentery)

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: MIC_{90} ⟶ Definition.

The minimum inhibitory concentration **MIC_{90}** is the concentration of SMAMP polymer in µg/ml at which 90% of the growth of a bacterial culture is inhibited.

Typical measured values for SMAMPs: 10 µg/mL (E.coli)
05 µg/mL (S.aureus)

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: MIC_{90} ⟶ Definition.

Determination of the minimum inhibitory concentration in the laboratory, practical procedure/experiment:

The microbe species to be examined is cultivated overnight in a Müller-Hinton nutrient solution at 37°C and brought to an optical density of 0.001 at λ = 600 nm with fresh nutrient solution (corresponds to approximately 10^5 cells per ml).
The SMAMP polymer is dissolved in dimethyl sulfoxide at a concentration of 40 mg/ml. This "stock solution" is added to the previously prepared nutrient solutions in various quantities. After 6 hours at 37°C the respective optical density is measured in the spectrophotometer (at λ = 600nm). The optical density of the SMAMP-free bacterial culture is used as a reference sample under the same conditions.

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: HC_{50} ⟶ Definition.

The hemolytic concentration, **HC_{50}** , is the concentration of SMAMP polymer in µg/ml at which 50% of a sample's red blood cells are destroyed.

Freshly drawn, red blood cells from humans are used which have been separated from the serum.

Typical measured values for SMAMPs: ⟶ 50 µg/ml

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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

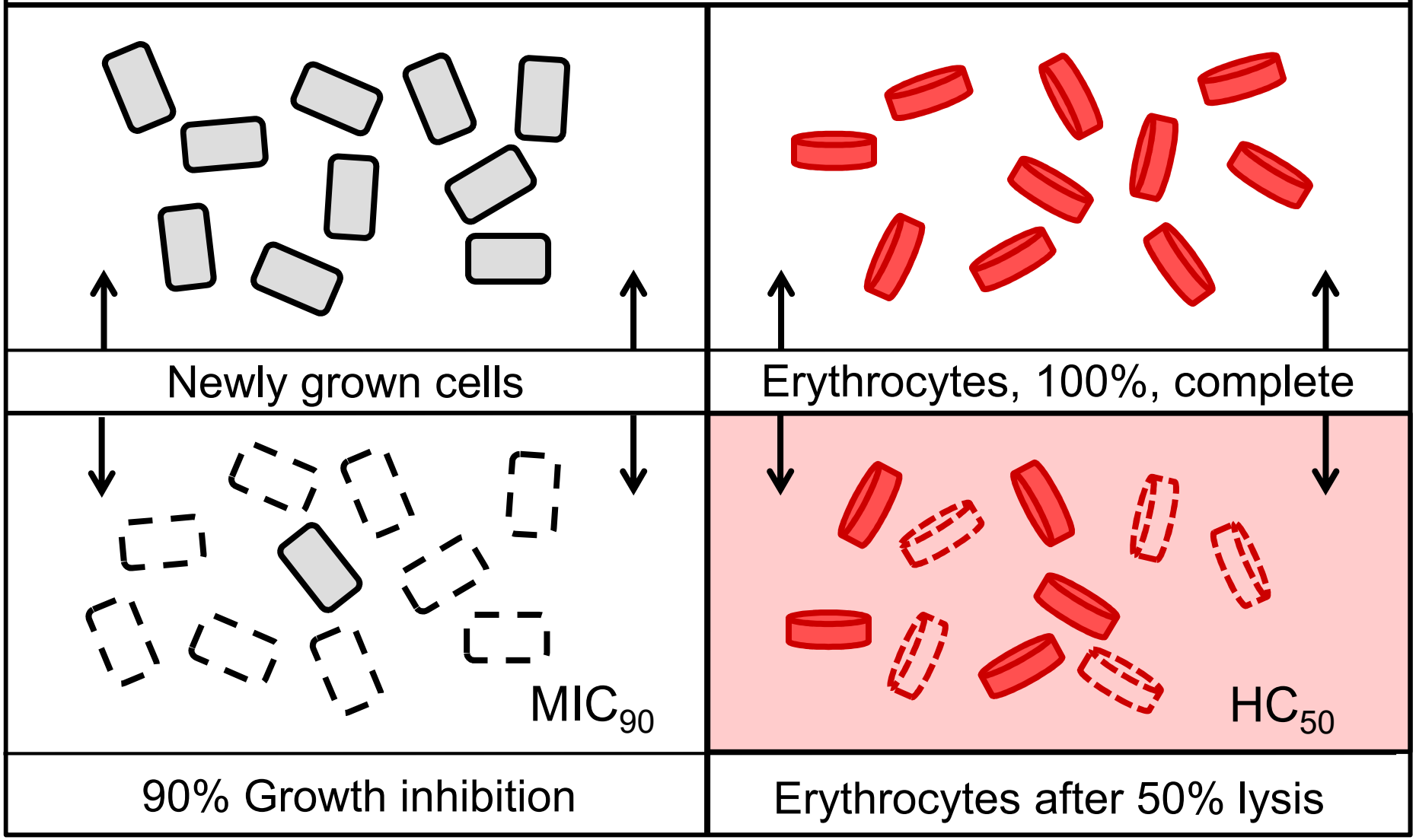
Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: HC_{50} ⟶ Definition.

Determination of hemolytic activity in the laboratory, practical procedure/experiment:

30 µg red blood cells are suspended in 10 µl tris-buffered, physiological NaCl solution, filtered on a 22 µm polyethersulfone membrane, resuspended and centrifuged and suspended three times each. The solution of the SMAMP polymer in DMSO is added to 100 µl of suspension, and the mixture is kept at 37°C for 30 minutes with stirring. After centrifugation, the absorption of the supernatant is measured at 414 nm (hemoglobin). Reference is a sample which was completely (100%) hemolyzed with Triton-X-100.

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: MIC_{90} and HC_{50} ,Visualization.



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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities: Measurement of Biological Effects: Definition of Selectivity.

The selectivity erythrocyte toxicity/bacterial cell toxicity is defined as follows:

Selectivity of a SMAMP polymer → $\frac{HC_{50}}{MIC_{90}}$

Maganin (frog defensin) has a selectivity of 10, human defensins show selectivities of around 100.

The aim for practical usability as a disinfectant is therefore a selectivity value that is as high as possible.

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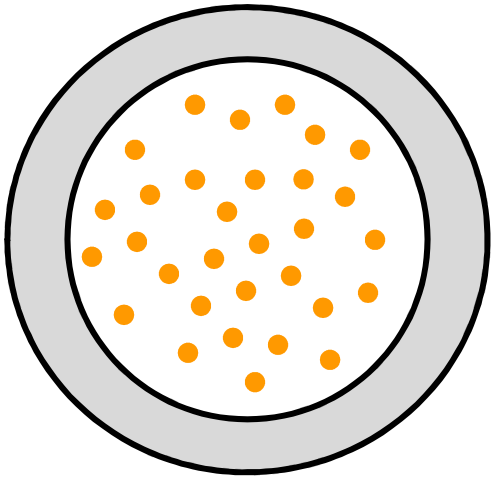
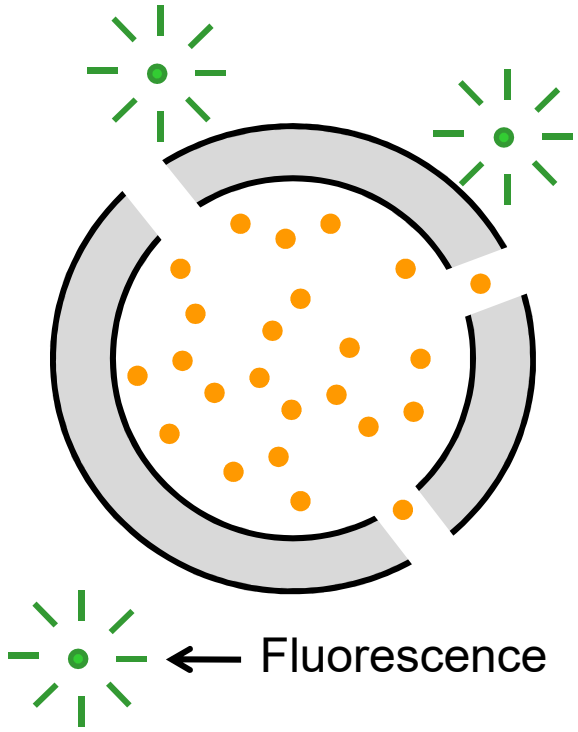
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

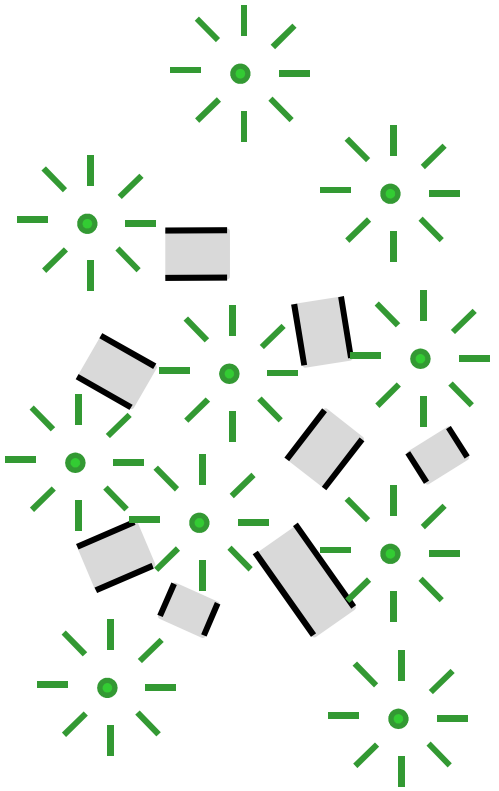
Surface-Active Polymers with Microbicidal Activities;
Stability of Vesicle Membranes: "Dye Leakage Test".



Phospholipid vesicles with a self-quenching fluorescent dye: ●



By adding a SMAMP: Defects in the phospho-lipid membrane.



Triton-X addition: complete lysis of the phospholipid vesicle.

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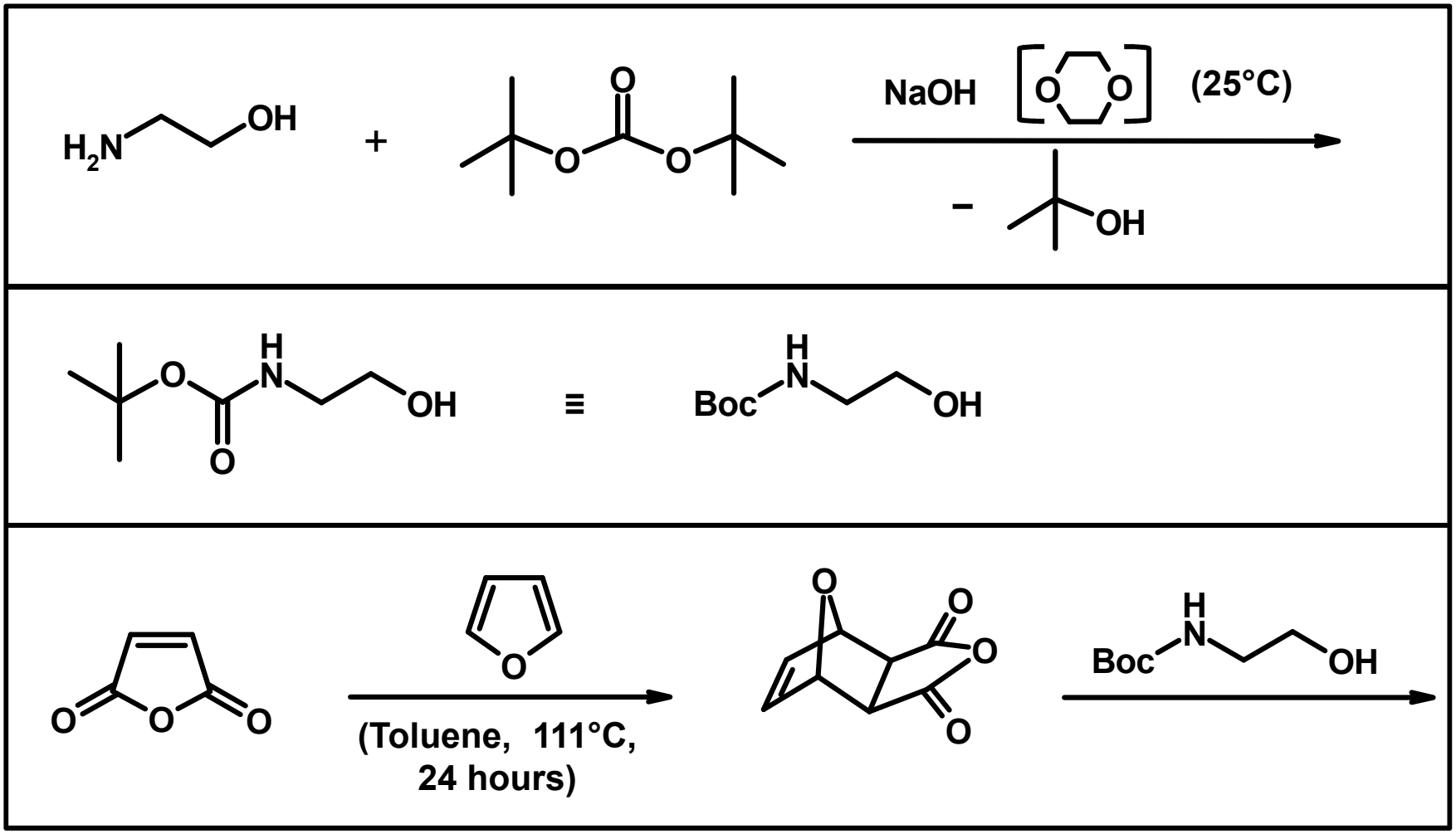
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of Poly(Oxanorbornenes): Monomer Buildup (1).



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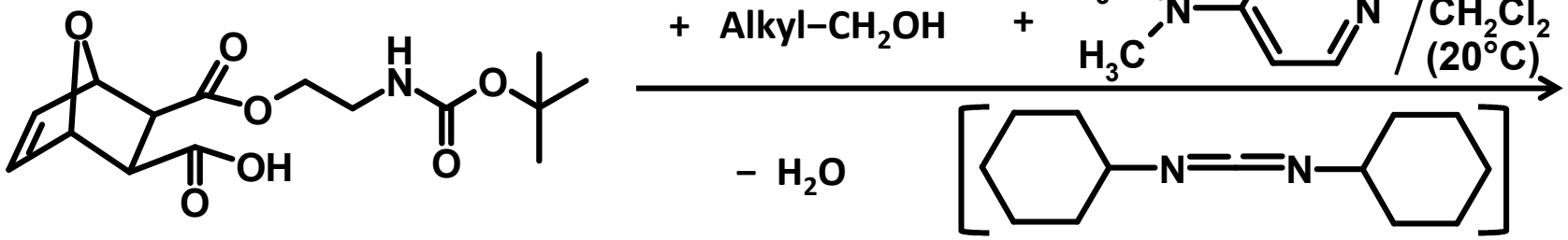
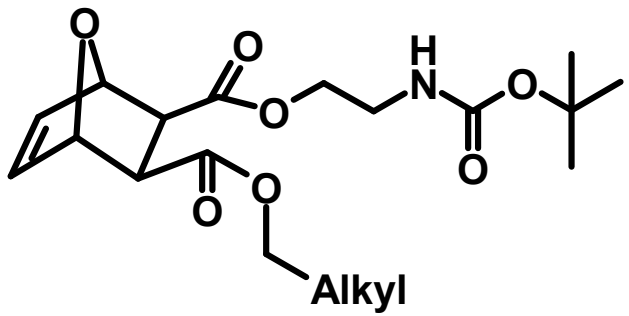
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of Poly(Oxanorbornenes): Monomer Buildup (2).

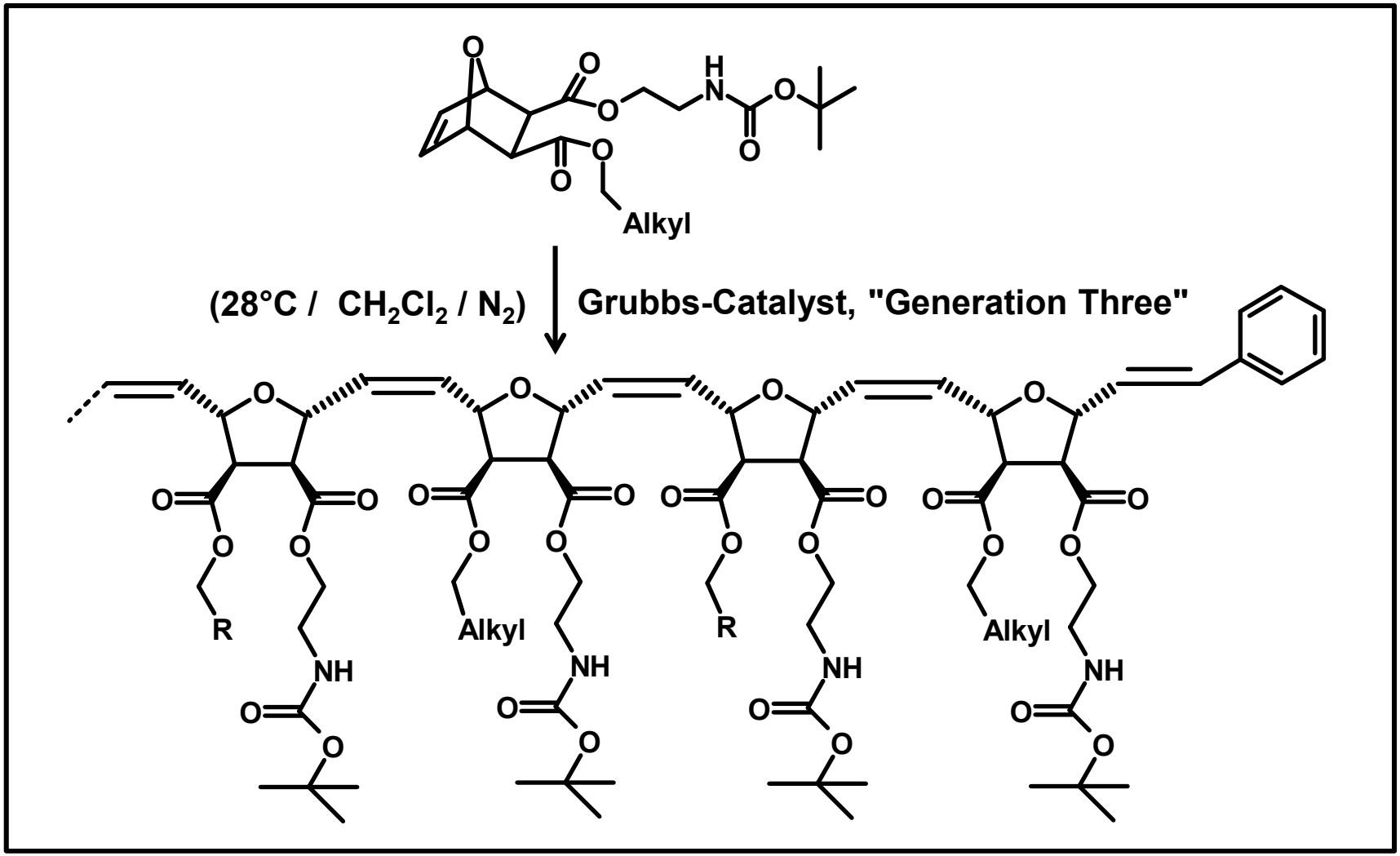




"Steglich Esterification" under very mild conditions in the presence of 4-dimethylaminopyridine.

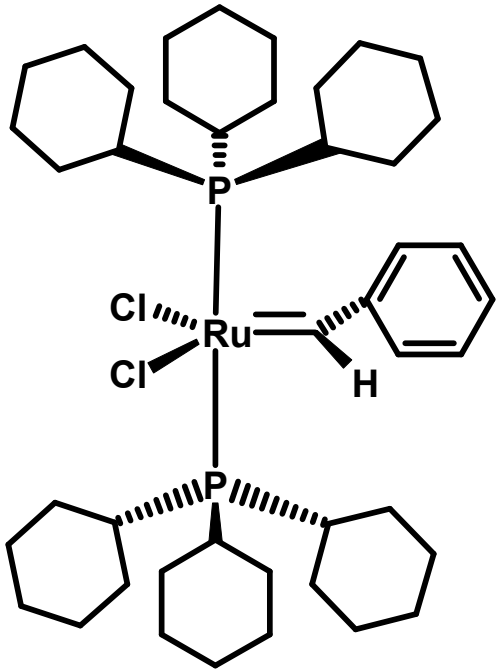
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of Poly(Oxanorbornenes): ROMP of the Monomer.

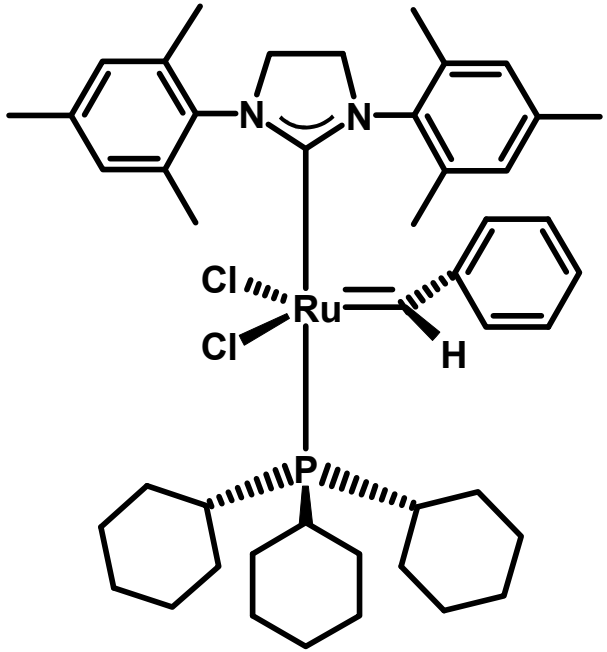


Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

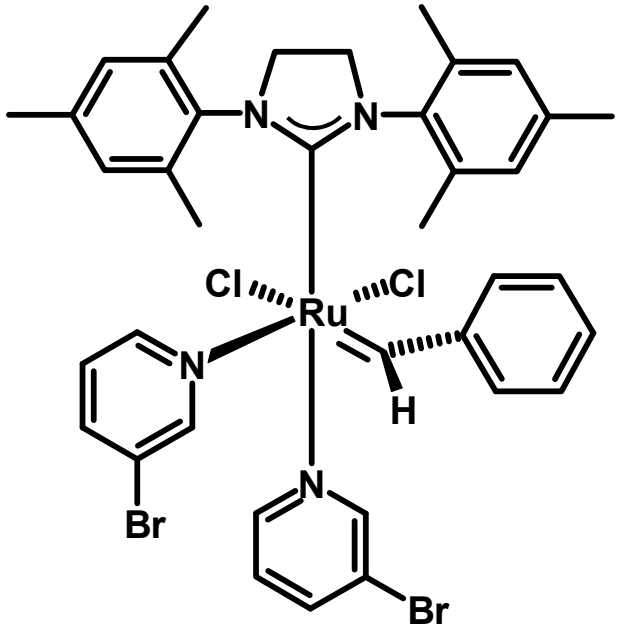
Surface-Active Polymers with Microbicidal Activities;
Synthesis of Poly(Oxanorbornenes): Grubbs-Catalysts.



"Generation One"



"Generation Two"



"Generation Three"

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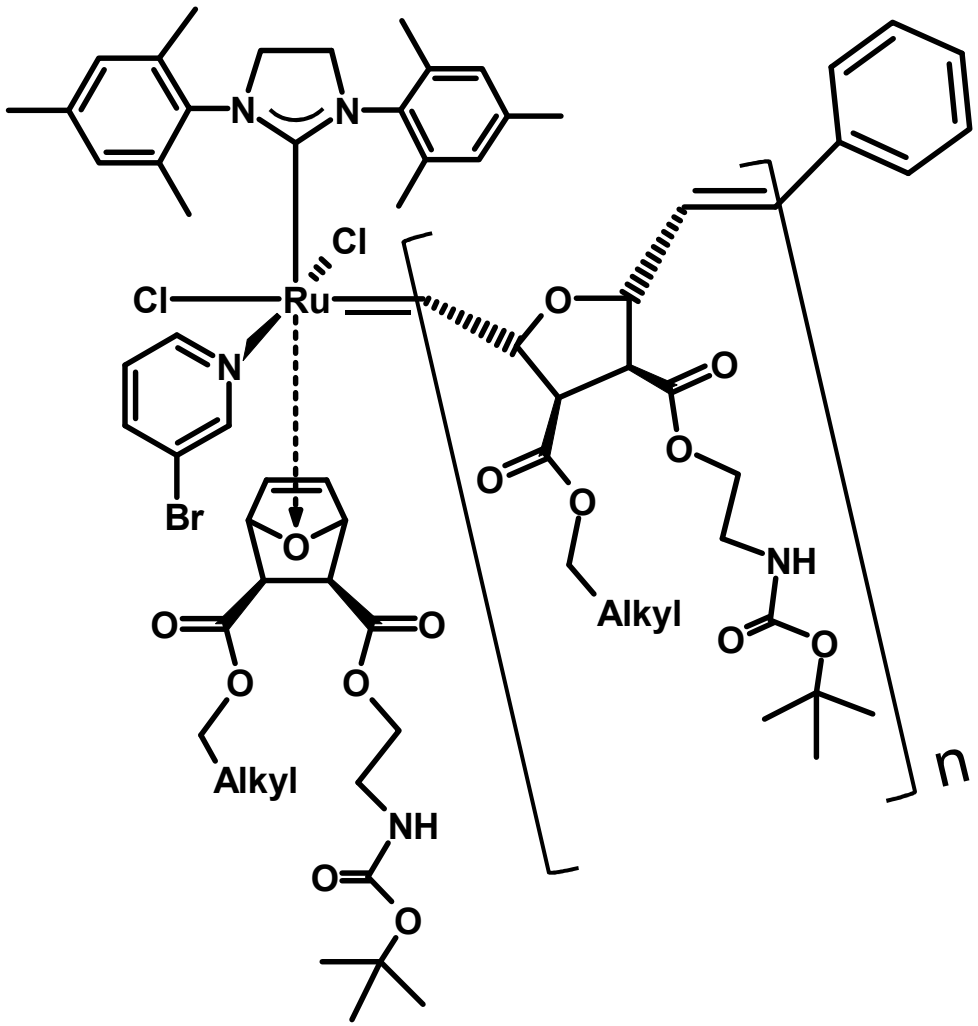
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Grubbs-Catalysts, Mechanism of the ROMP.



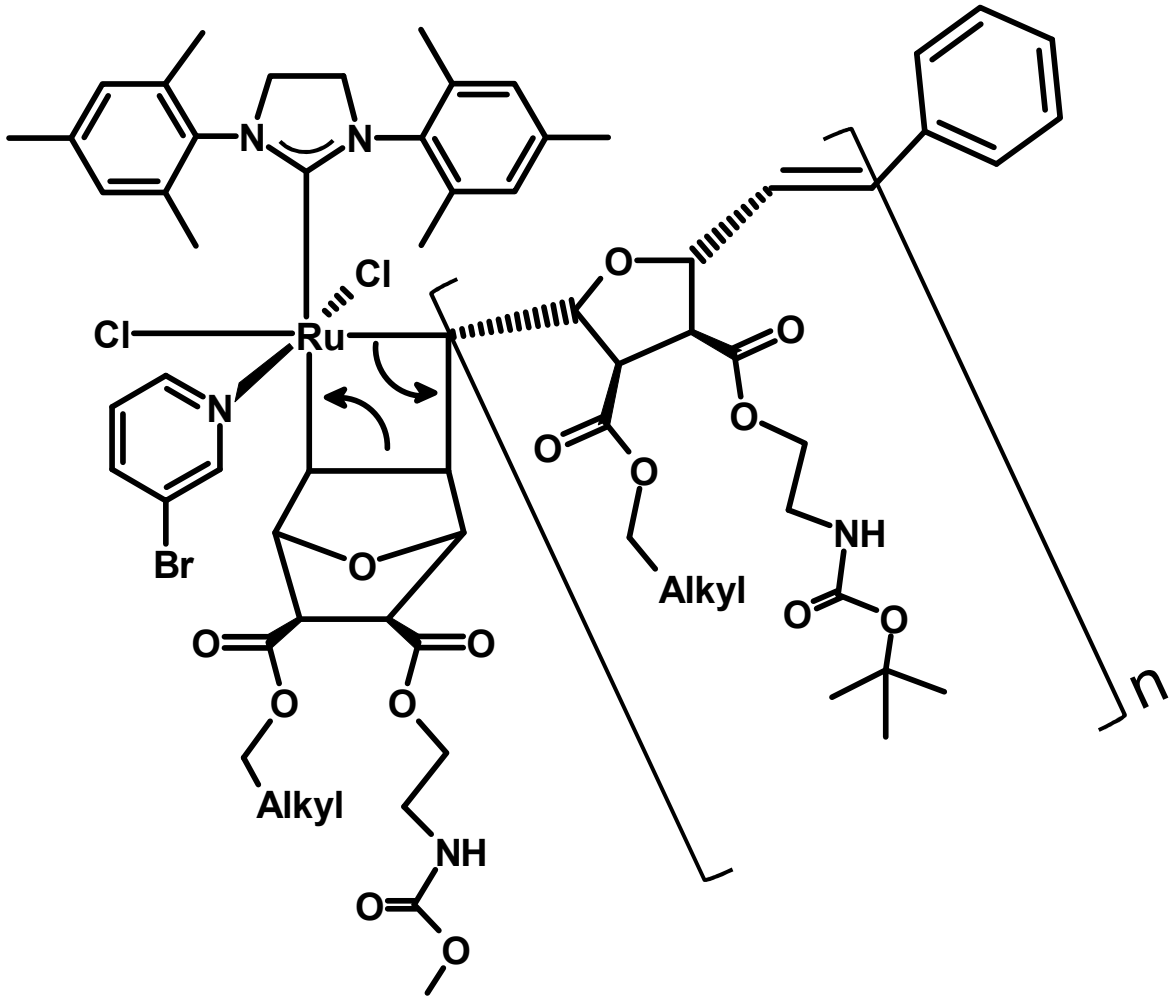
Olefin-Addition

↓

Formation of a π-complex with the metal carbene

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Grubbs-Catalysts, Mechanism of the ROMP.



(1)

[2+2]–Cycloaddition: Formation of a metalacyclobutane.

(2)

[2+2]–Cycloreversion: Formation of a (n + 1)-metalcarbene.

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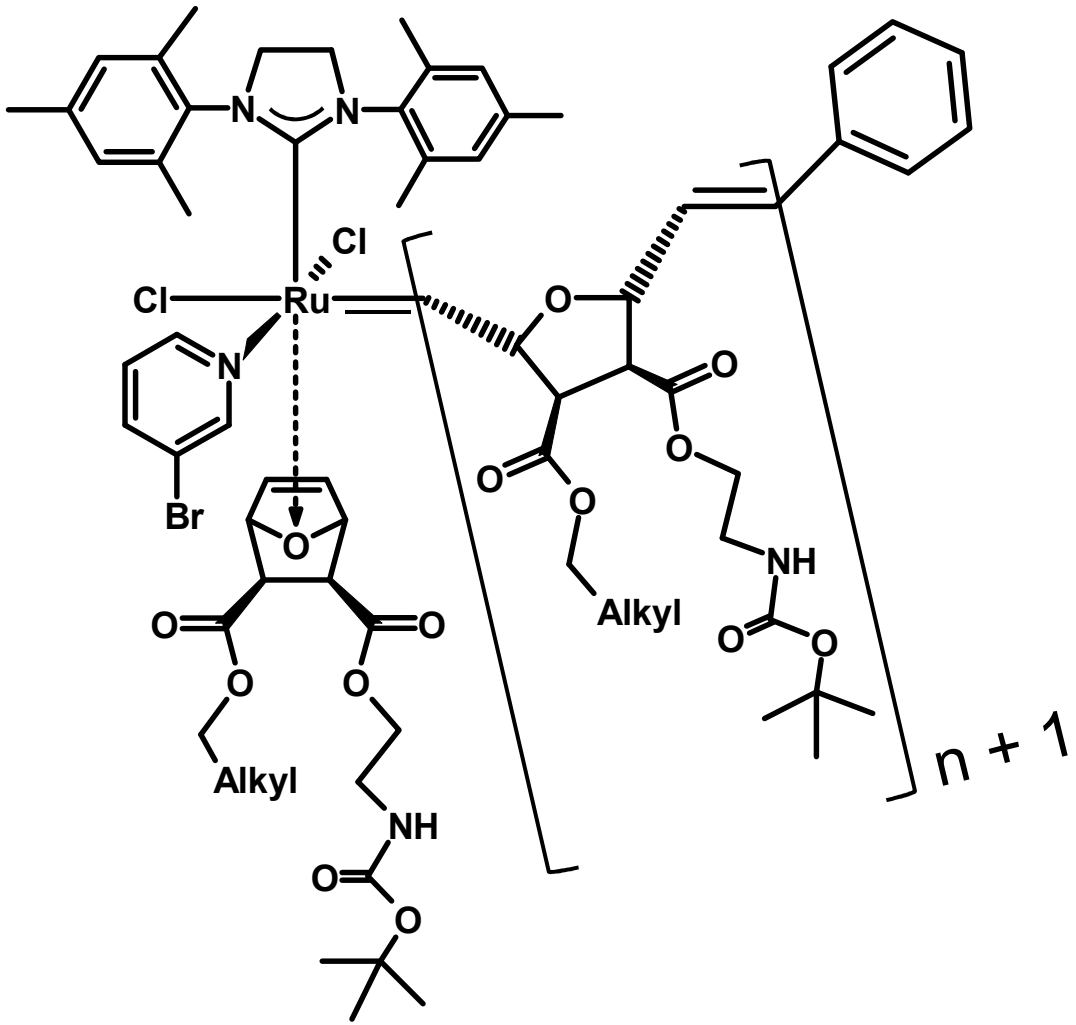
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Grubbs-Catalysts, Mechanism of the ROMP.



Olefin-Addition

↓

De-novo formation of a π complex on the n + 1 metal carbene.

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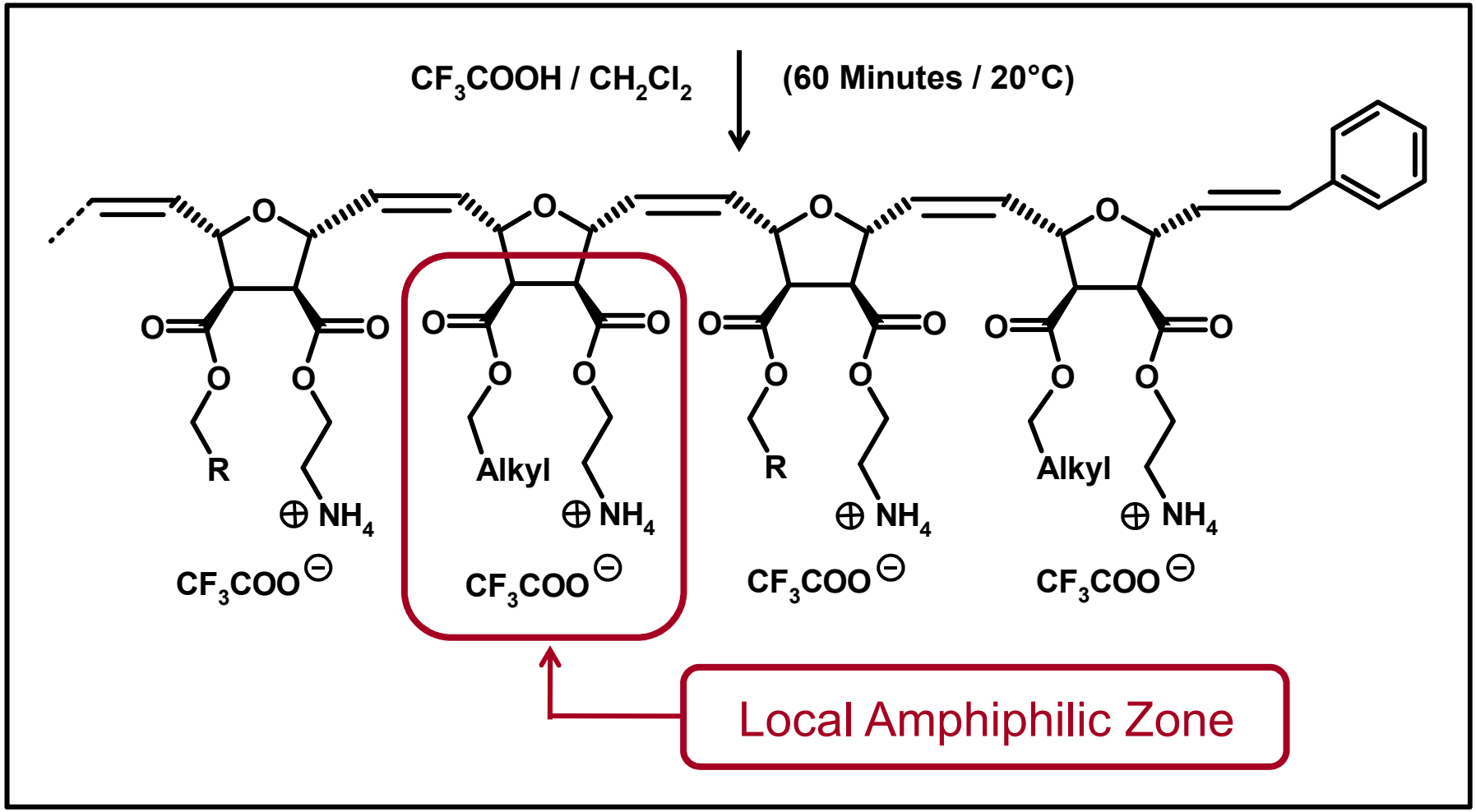
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of Poly(Oxanorbornenes): Cleavage of Boc-Group.



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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; New Poly(Oxanorbornenes) through ROMP-Reactions: Biological and Technical Profile of Requirements. →

Effectivity against multi-resistant hospital bacteria, "Superbugs"

MIC_{90}-Values ⟶

S. aureus:	≤ 30 µg/mL
E. coli:	≤ 10 µg/mL
E. faecium	≤ 10 µg/mL
B. Subtilis	≤ 05 µg/mL

HC_{50}: ≥ 1.000 µg/mL

Technical profile of the coating materials:

- Stability above 150°C.
- Applicability in the form of a film-forming dispersion.
- Adherence to glass or metal surfaces like a coating.

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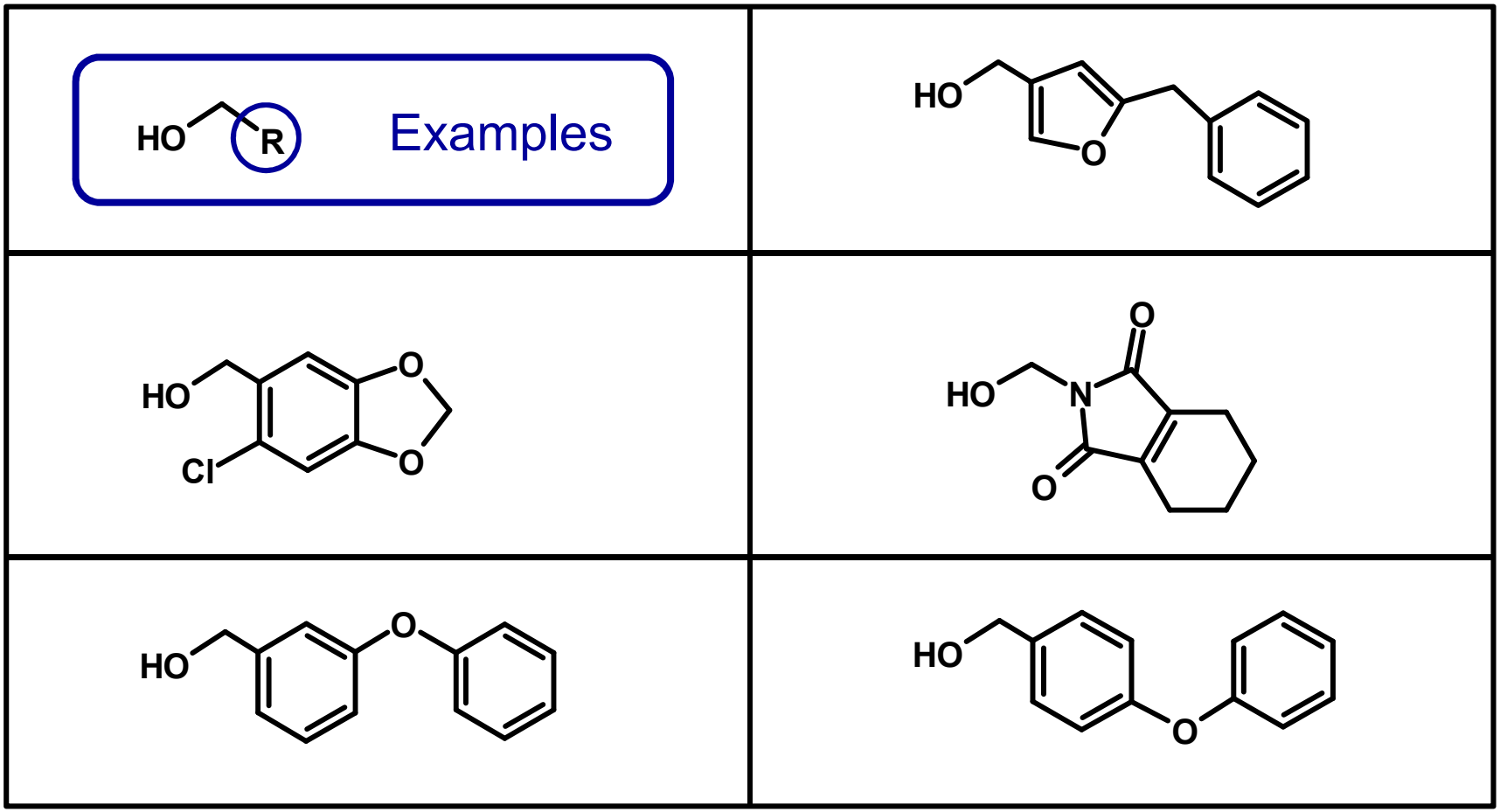
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; New Poly(Oxanorbornenes): Incorporation of Alcohols of the Type RCH_2OH with R = (Hetero)Aryl, (Hetero)Cycloalk(en)yl.



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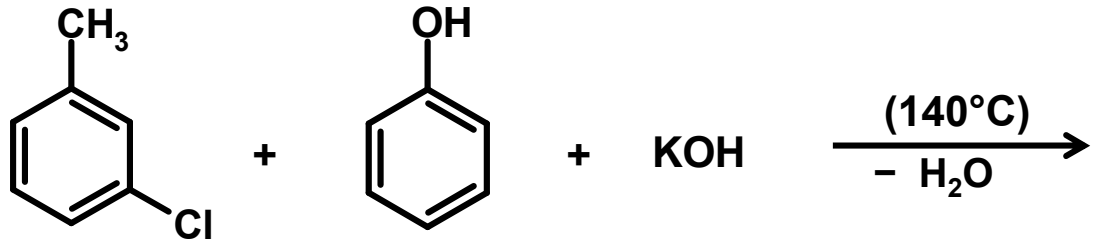
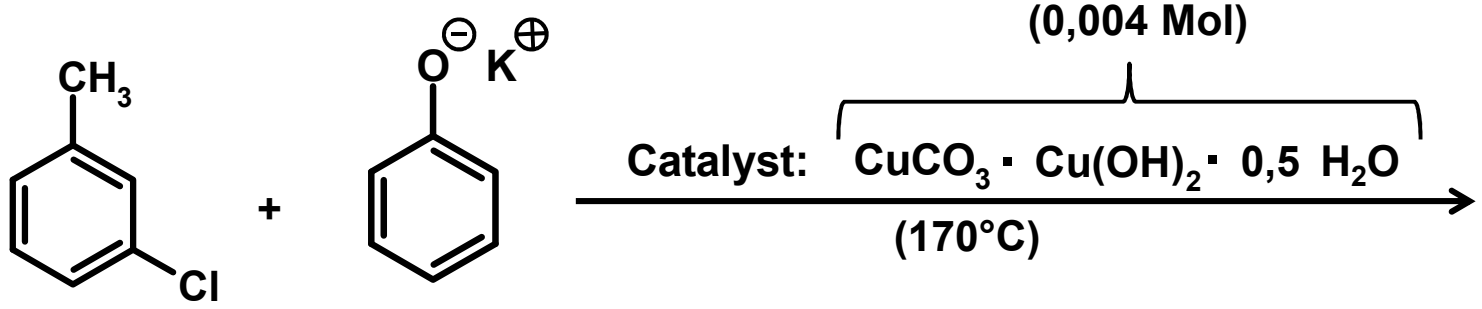
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of 3-Phenoxy Benzyl Alcohol (1).

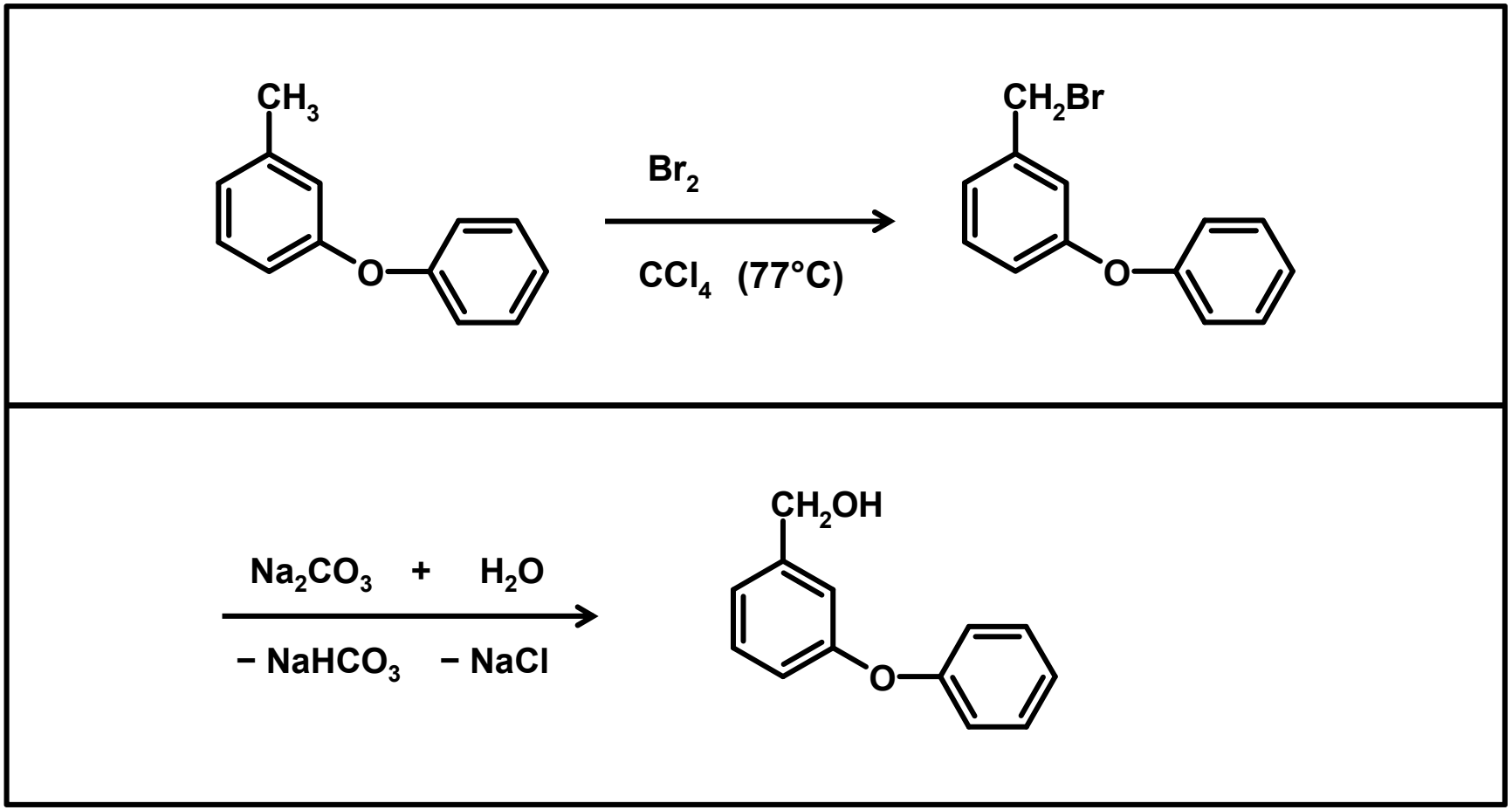




(EP 0051 235A1 from 12.05.1982)

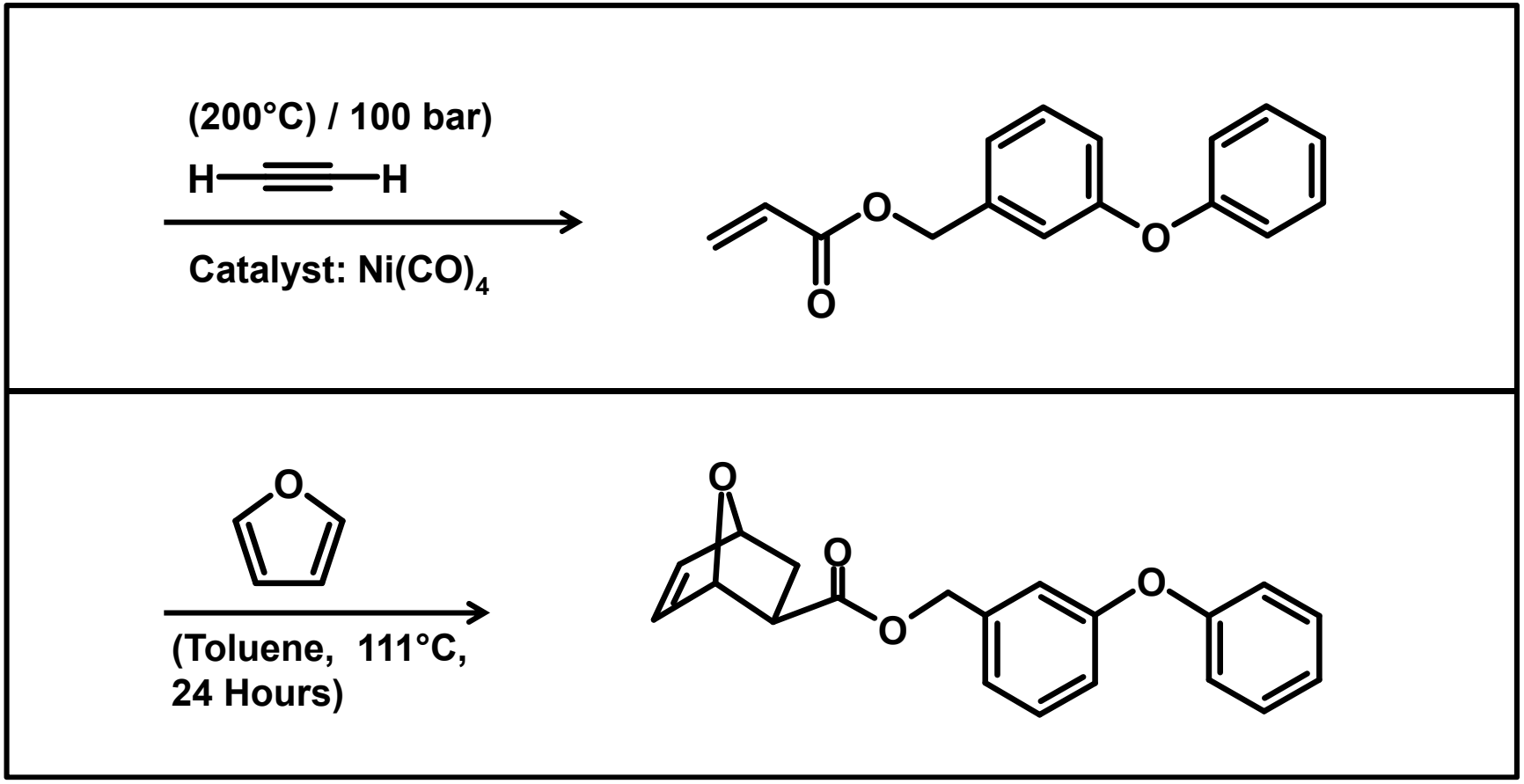
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of 3-Phenoxy Benzyl Alcohol (2).



Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Synthesis of the 3-Phenoxy Benzyl Ester of Oxanorbornene Carboxylic Acid.



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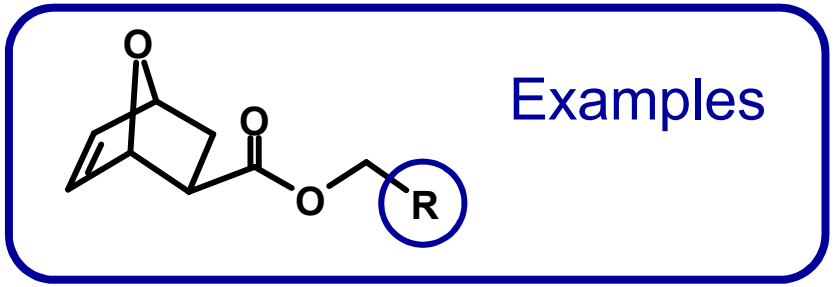
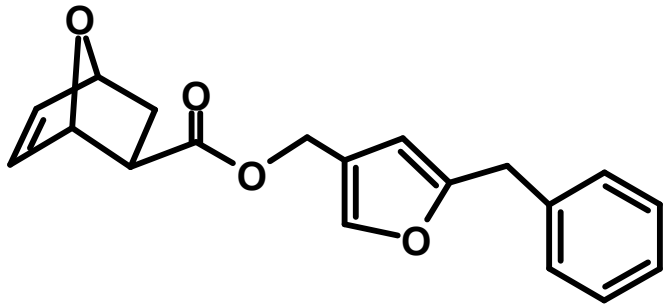
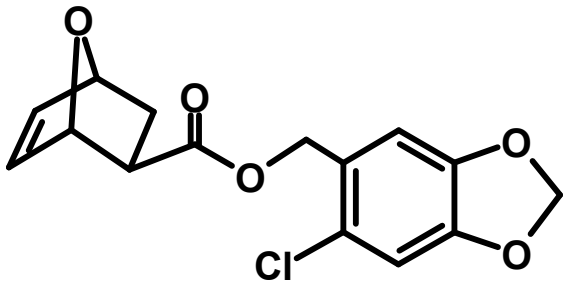
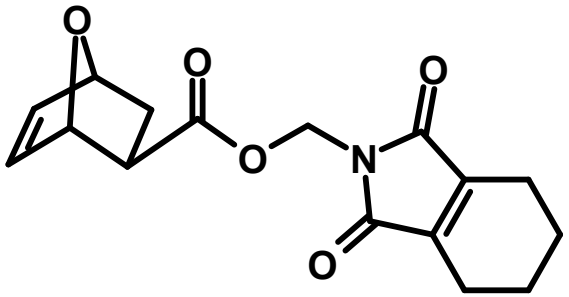
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

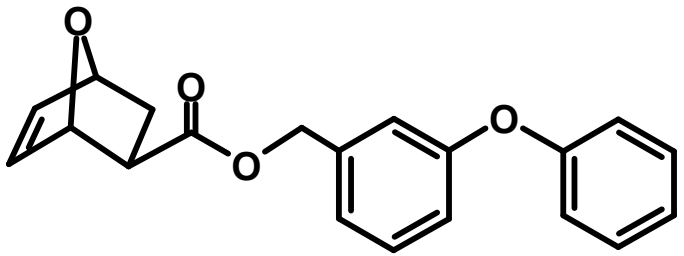
Surface-Active Polymers with Microbicidal Activities;
New Poly(Oxanorbornenes): "Membrane Active" Monoesters.

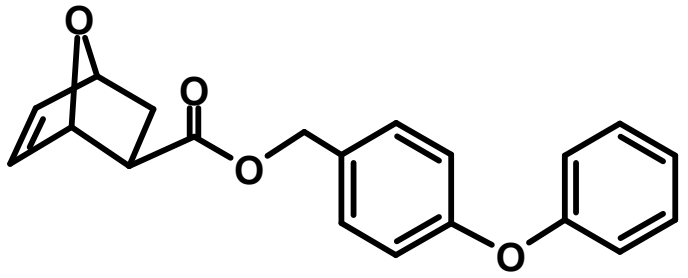












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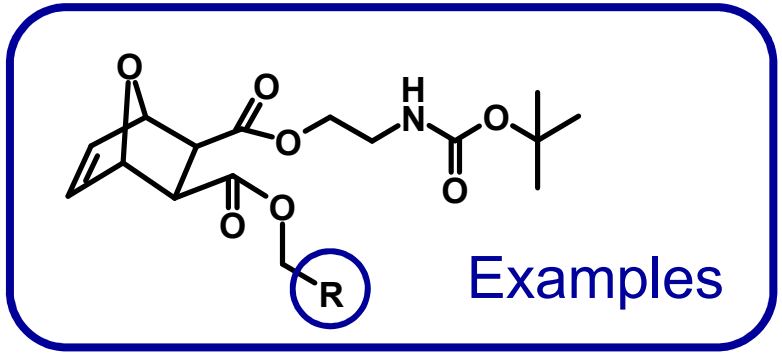
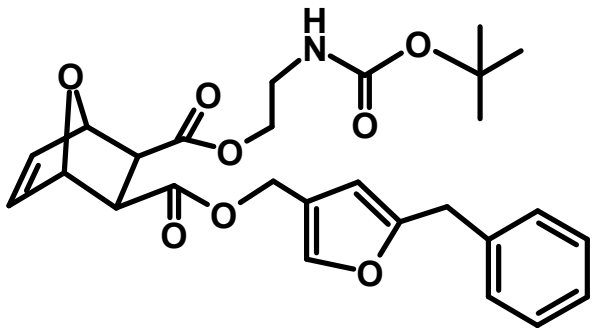
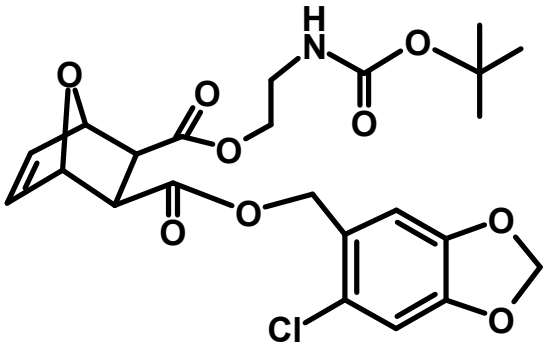
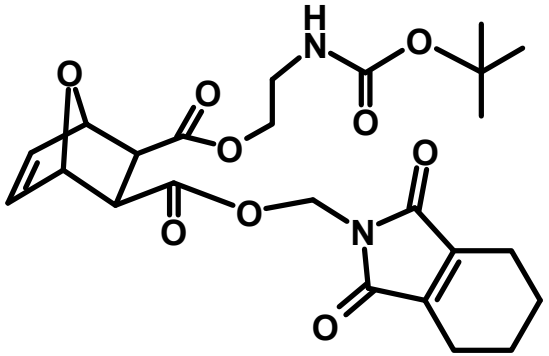
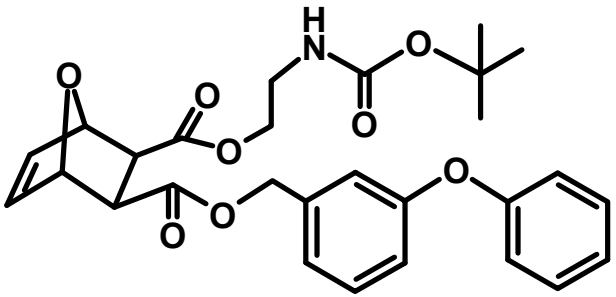
Surface-Active Polymers with Microbicidal Activities; New Poly(Oxanorbornenes): "Membrane Active" Diesters.

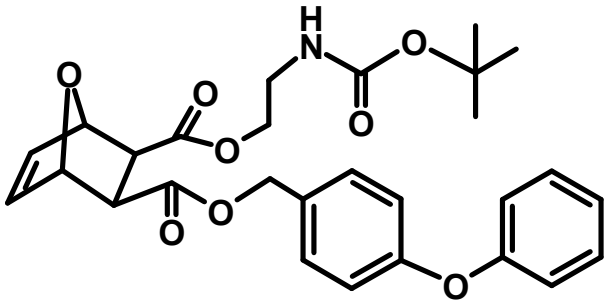












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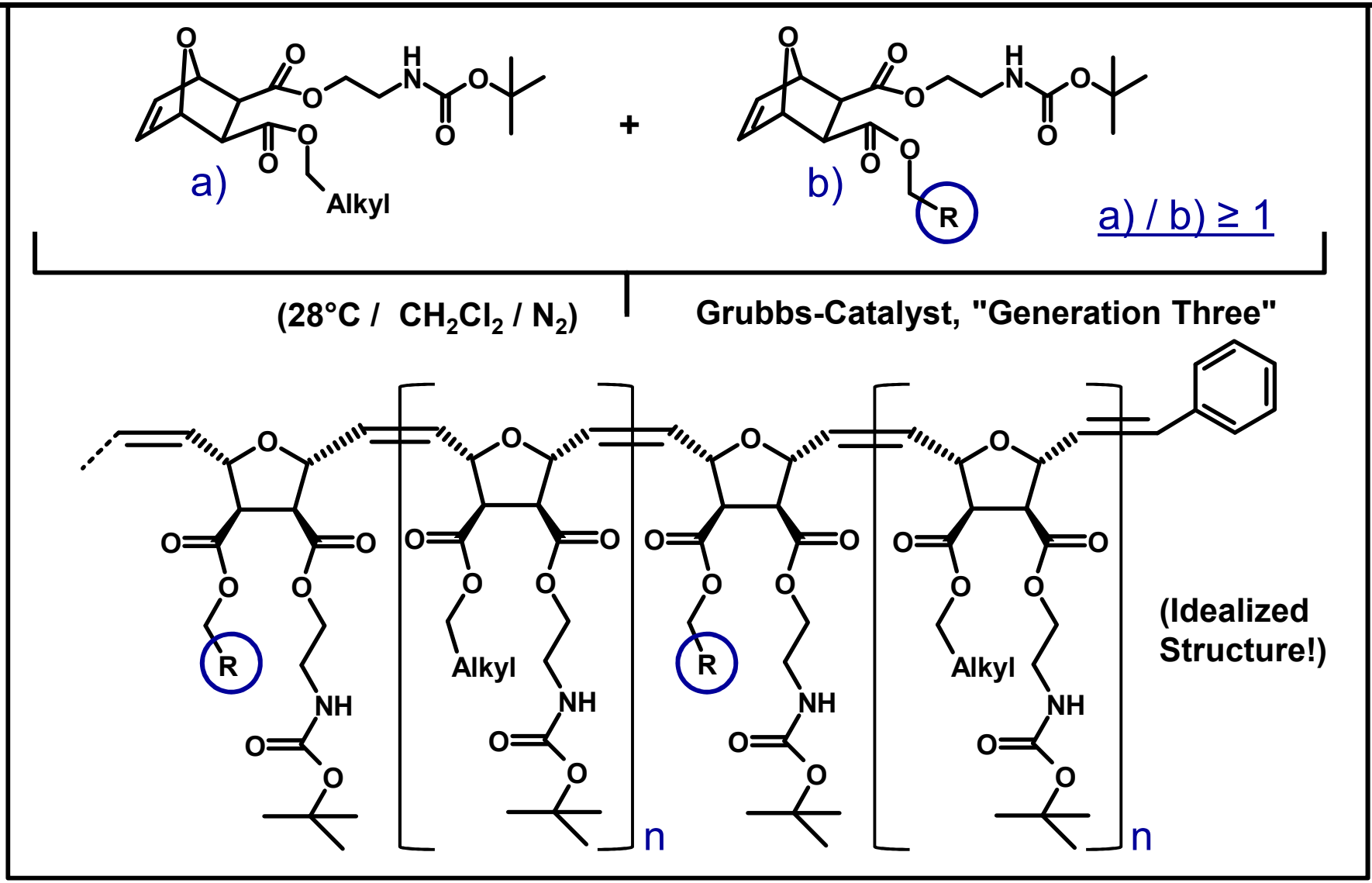
Surface-Active Polymers with Microbicidal Activities; Synthesis of Poly(Oxanorbornene)s: ROMP, Stoichiometry.



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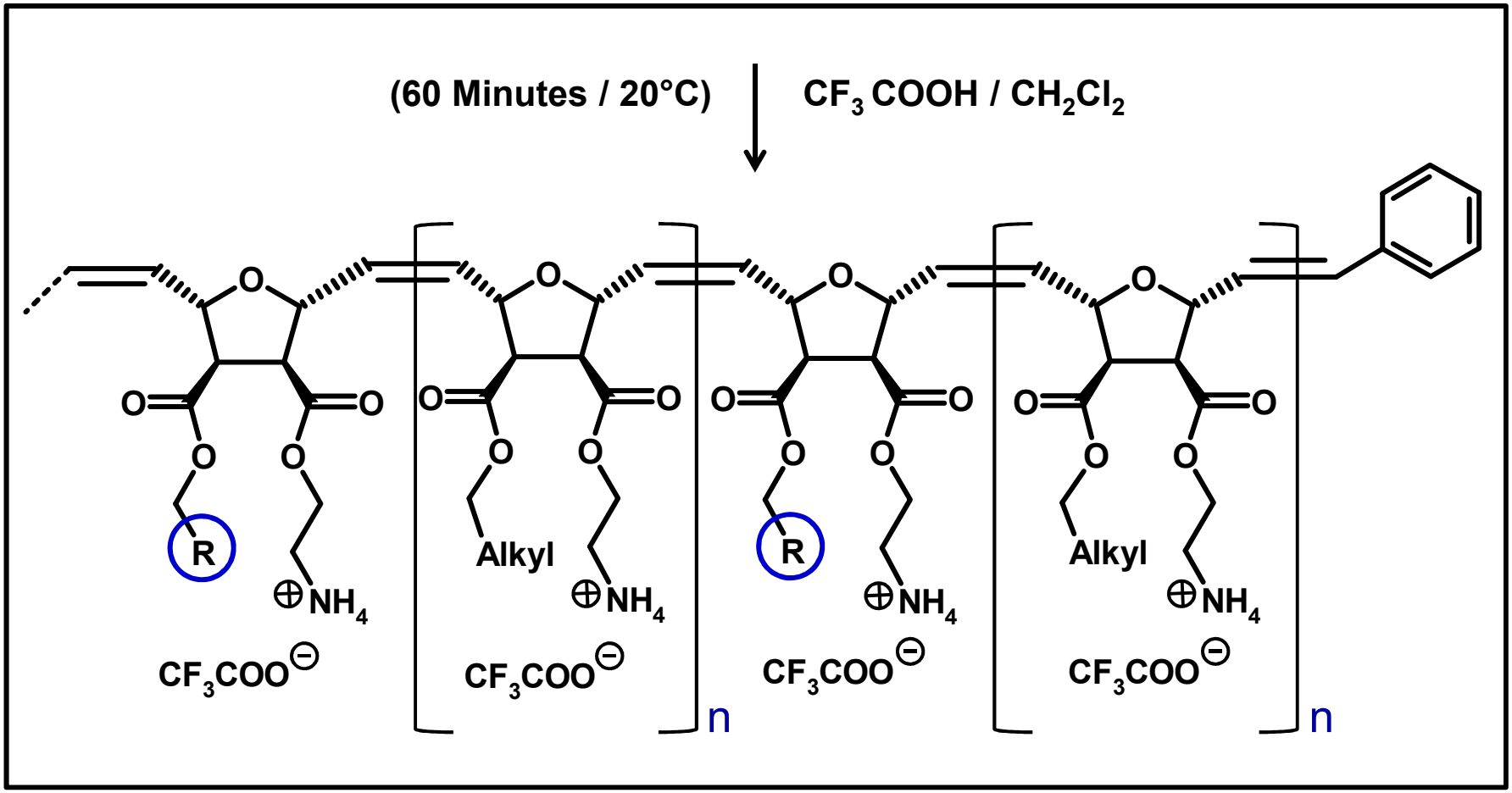
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

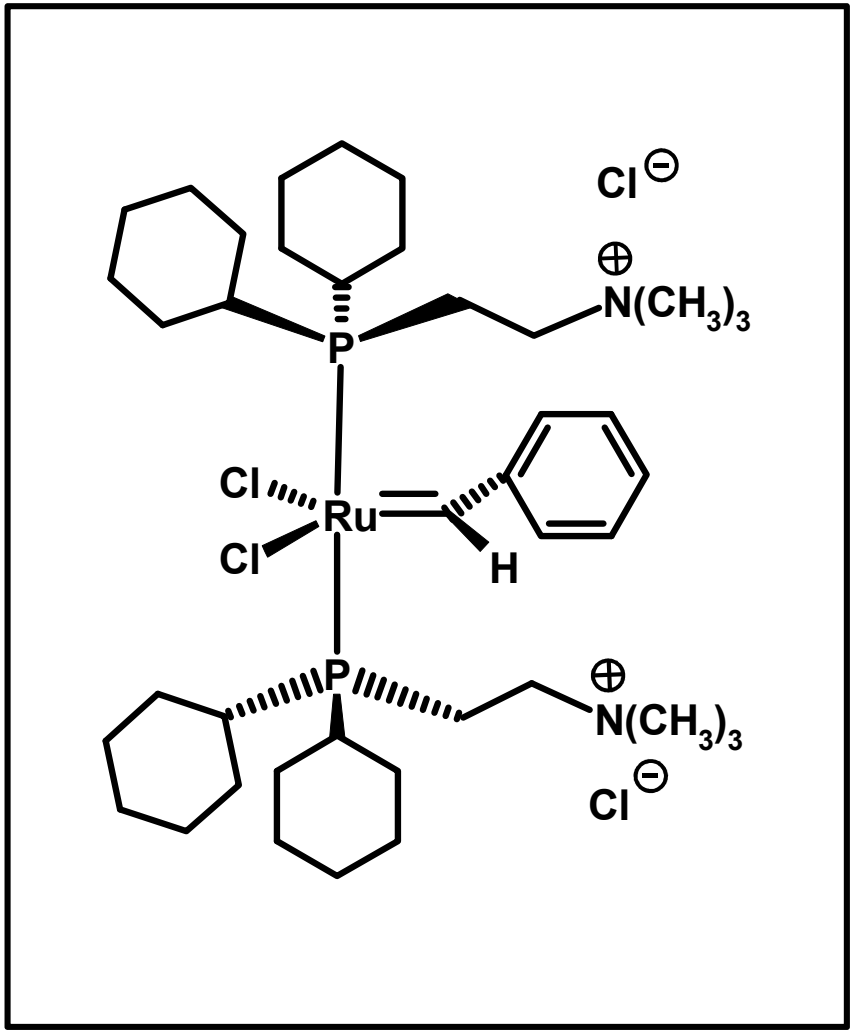
Surface-Active Polymers with Microbicidal Activities;
Synthesis of Poly(Oxanorbornene)s: Elimination of Boc-Group.

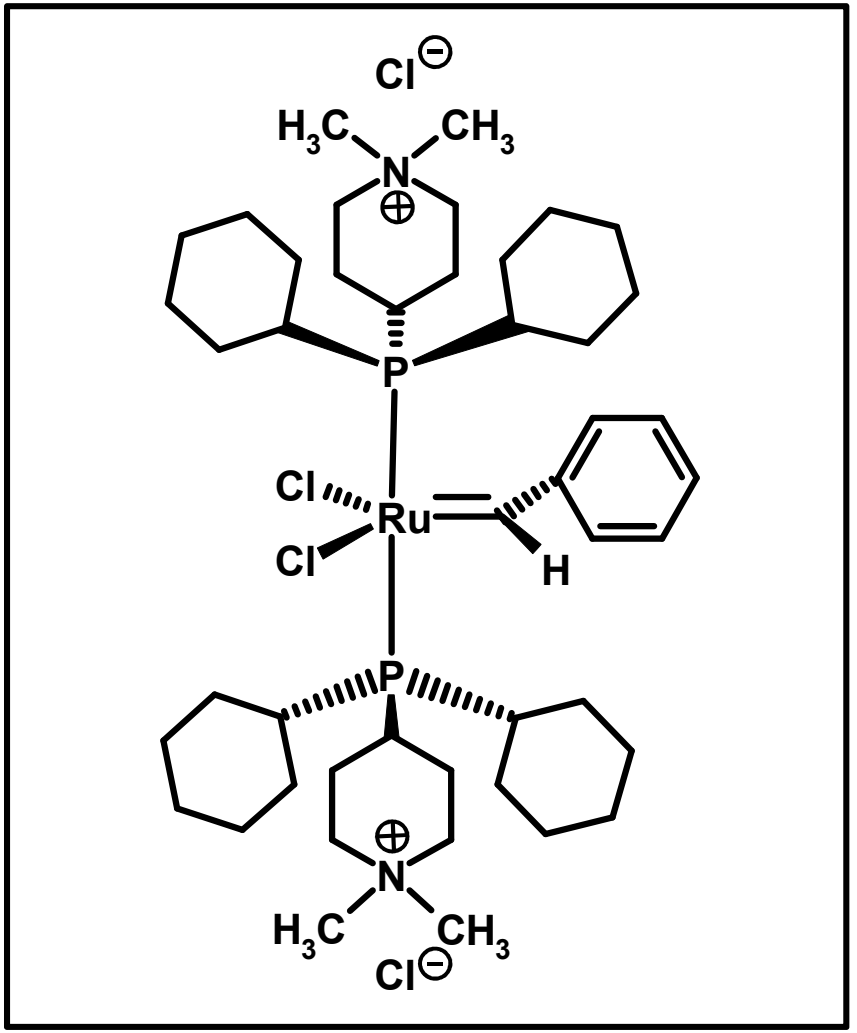


(n = 1, 2, 5, 10, 20,…)

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Water-Dilutable Ruthenium Catalysts, Examples.





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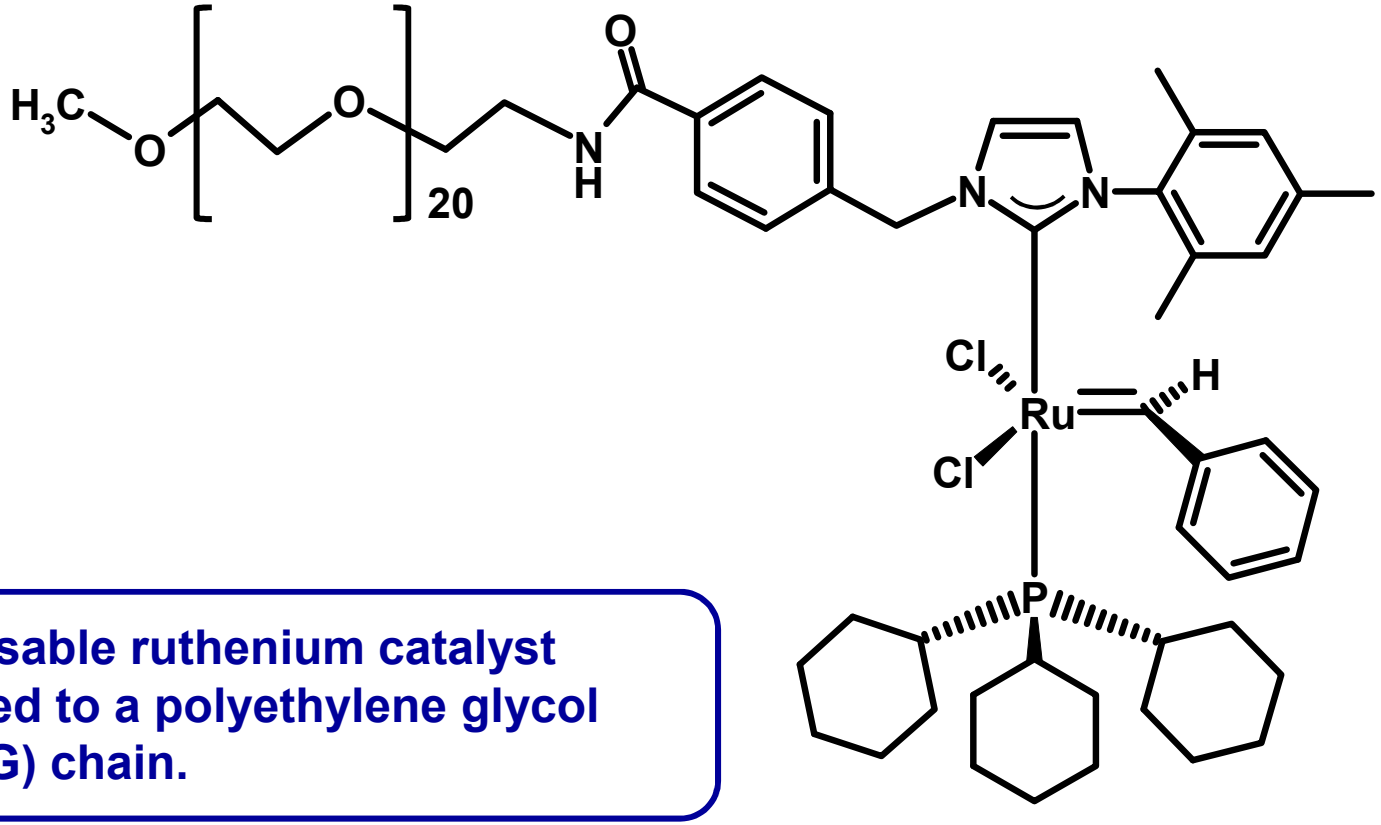
Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

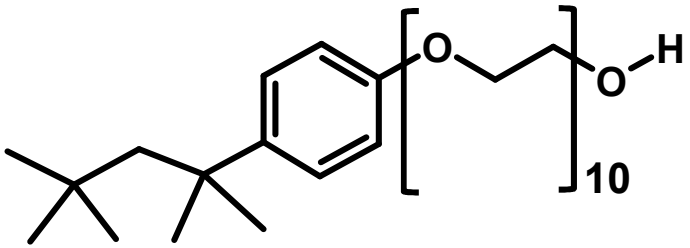
Surface-Active Polymers with Microbicidal Activities; Water-Dilutable Ruthenium Catalysts, Examples.



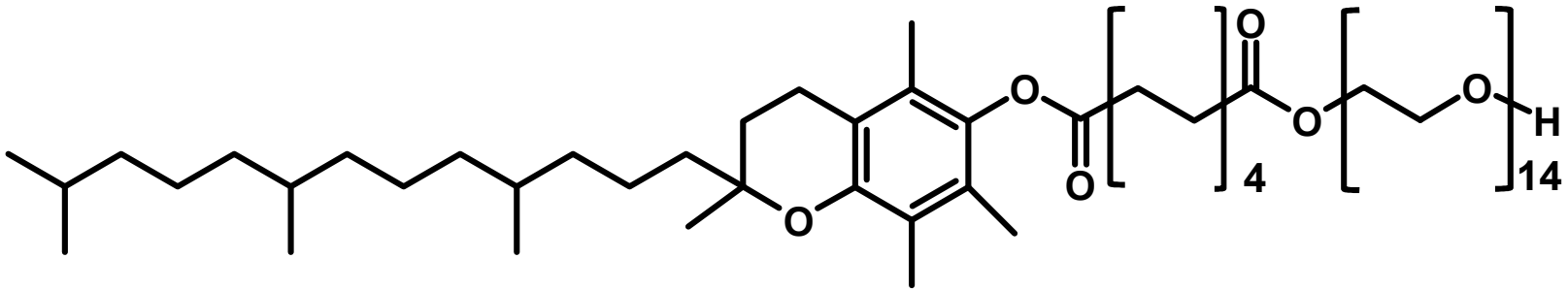
Reusable ruthenium catalyst linked to a polyethylene glycol (PEG) chain.

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; ROMP in Aqueous Medium: Suitable Surfactants, Examples.



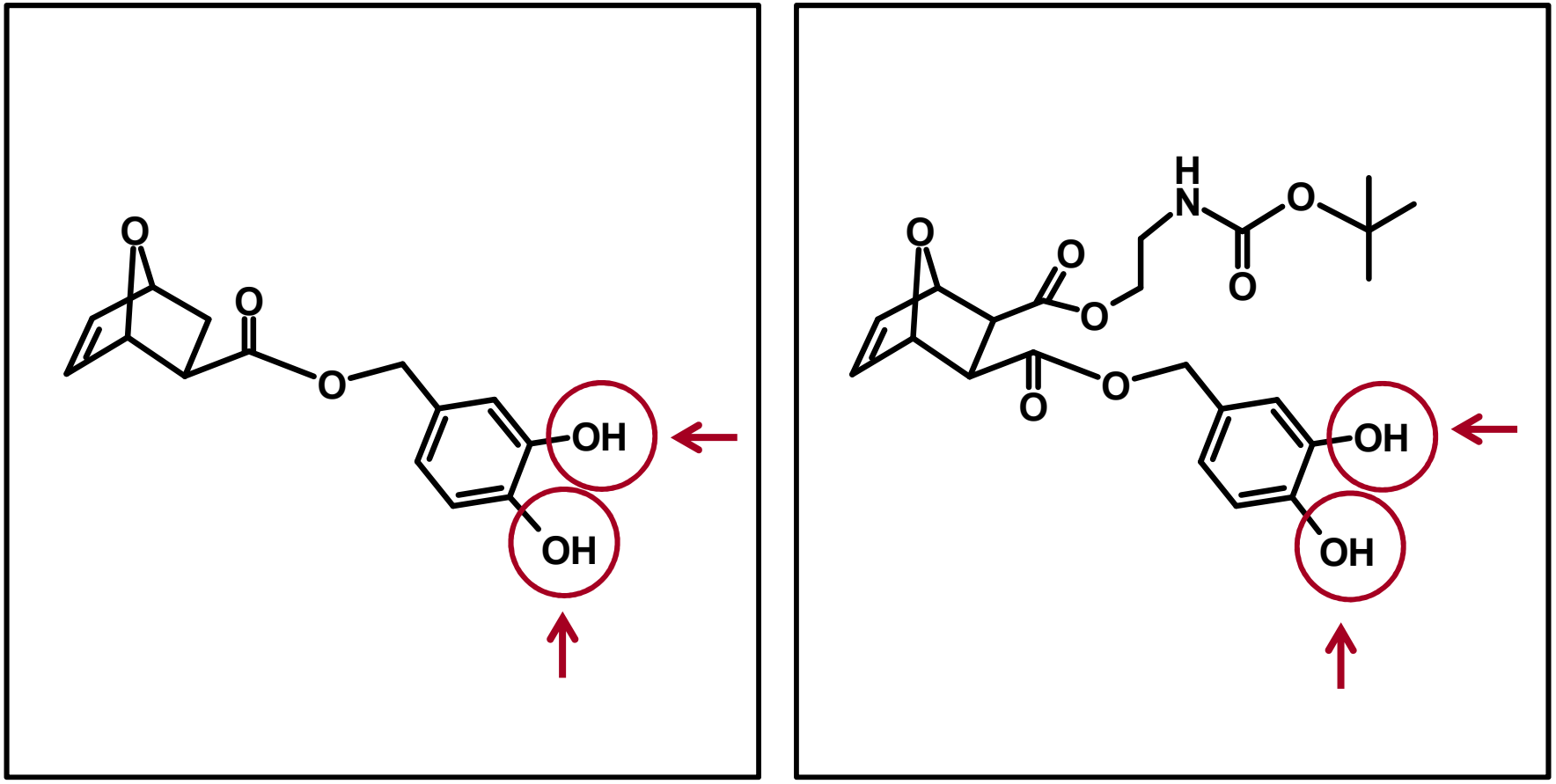
Triton X-100



PTS: Polyethoxy-α-tocopheryl-sebacat

Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; New Poly (oxanorbornene)s: Incorporation of Small Amounts of Protocatechyl Esters as "Adhesion Promoters".



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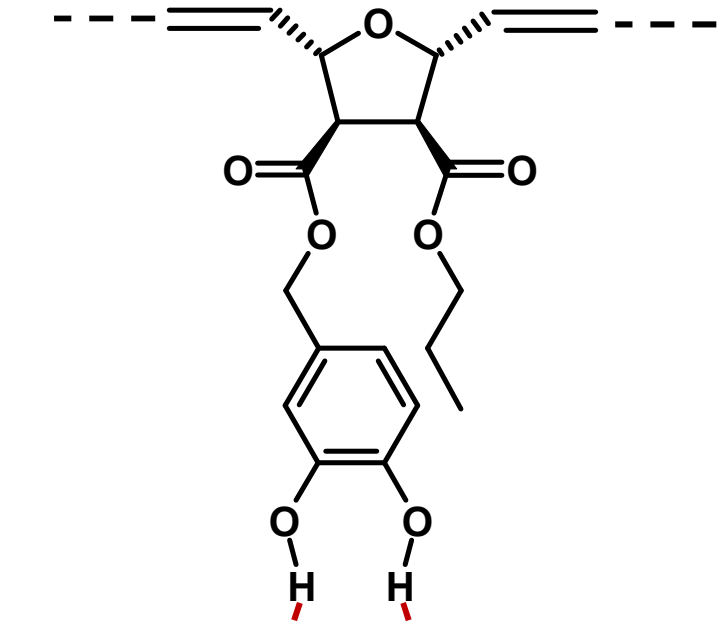
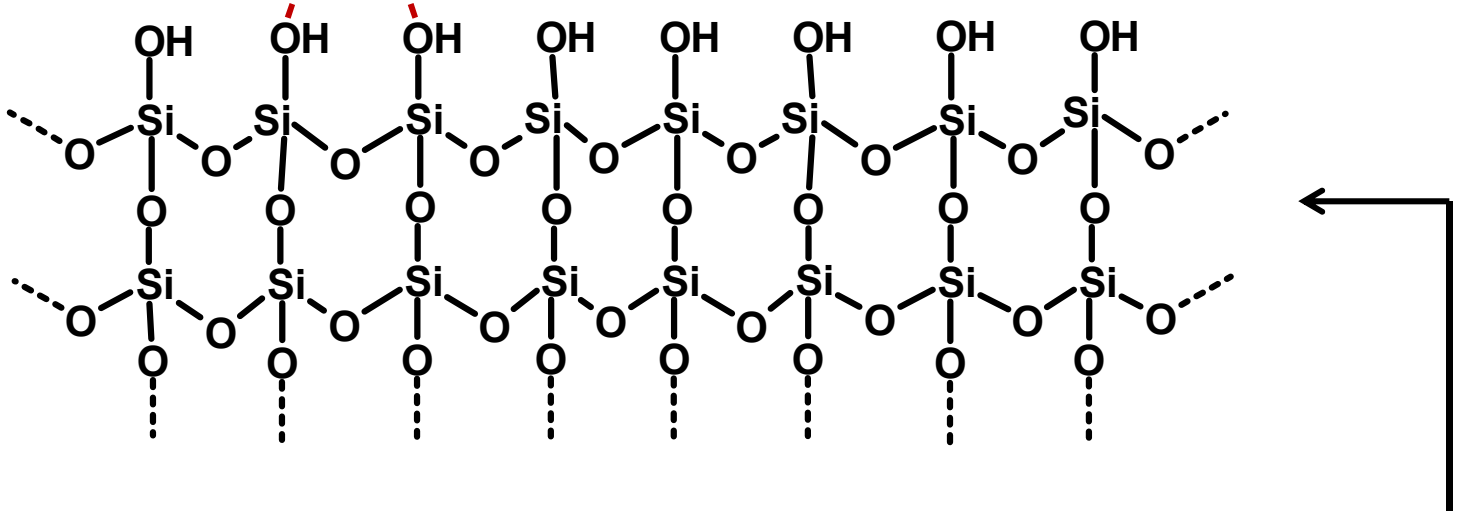


Protocatechylester as adhesion promoter. Example: Adhesion on glass surfaces.



(Glass or SiO_2-Surface: Idealized Structure!)

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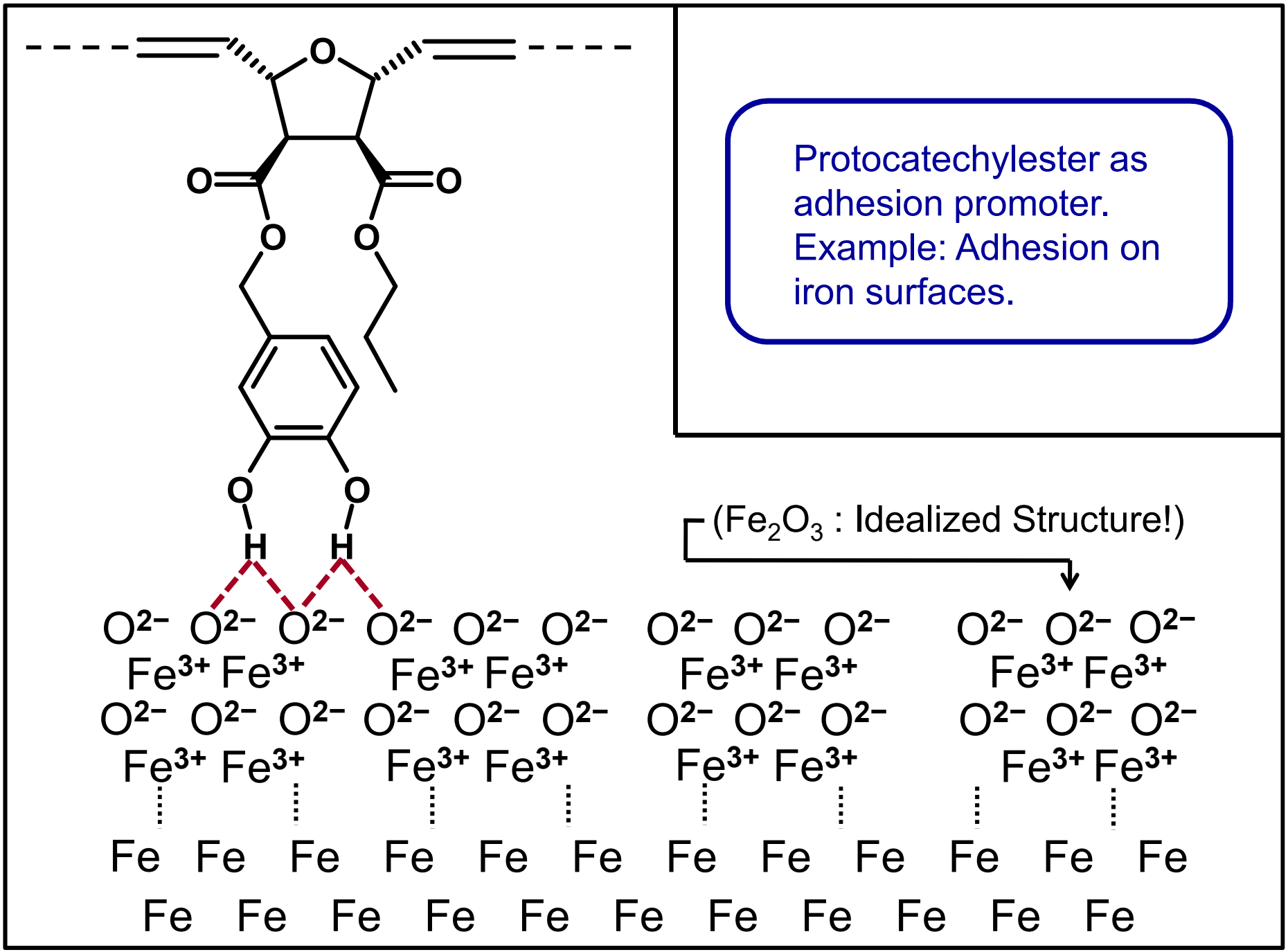

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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Potentials for Application, Some Examples.

- Water filtration for the quick and easy extraction of low-germ drinking water in the (sub) tropics.
- Food additive for long-term preservation.
- Packaging industry: Alternative to pasteurization.
- Commercial kitchens, restaurants: prevention of the contamination with coli or salmonella pathogens.
- Hospital, operating room: germ-free devices / containers.
- Pharmacies / Medical Care: Germ-free drugs and aids.
- Intensive agricultural production, slaughterhouses: ensuring compliance with prescribed hygiene.

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Synthetic Mimics of Antimicrobial Proteins (SMAMPs)

Surface-Active Polymers with Microbicidal Activities; Commercial Application/Market Growth for Antibiotics.

Forecast for the antibiotics market:

- Worldwide growth from sales of € 48,000,000,000 in 2020 to sales of around € 57,900,000,000 in 2028 (average growth rate: approximately + 4,5% per year).

Facts and market importance:

- Largest market: The U.S., with a four-fold increase in the market for prescription microbicide preparations in the past 10 years (approximately 15% growth per year).
  State protection programs are running, e.g. against the recurrence of tuberculosis.
- In 2020, approximately 1,700,000 Americans got infected with pathogens in hospitals (!).
- Annual sales of antibiotics in Germany (2020): € 820,000,000.

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Task for a Case Study on R&D Project Management

!

Plan a suitable project for your research subject "Synthetic Mimics of Antimicrobial Proteins (SMAMPs)"!

- General framework: The research project to be planned is pioneering for your (start-up) company or for your research institute!
- Define what you consider to be a plausible target system for this research project: chemical-technical, potentially economical and time-related goals, taking into account possible, reasonable fields of application. Use additional data and facts from the Internet / WWW to assess the application potential, the state of science and the social environment!
- Roughly estimate the personnel and material expenses necessary for the complete achievement of the target system!
- Decide on an appropriate project organization!
- Determine the target-relevant tasks and classify them according to the number of specialist functions involved in their solution!
- Based on this, carry out a rough project structure planning (sketch)!
- Sketch a simple project phase plan by using bars on time axes according to the technique of Henry Gantt!
- Make a plausible SWOT analysis for the research project!

Further literature (specialist books, specialist articles) on the subject: "Synthetic Mimics of Anti-Microbial Proteins (SMAMPs)".

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- K.V. Reddy, R.D. Yedery, C. Aranha, "Antimicrobial peptides: premises and promises". International Journal of Antimicrobial Agents. 24 (6): 536–47, 2004.
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Further literature (specialist books, specialist articles) on the subject: "Synthetic Mimics of Anti-Microbial Proteins (SMAMPs)".

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- J.M. Sanderson, Peptide–lipid interactions: insights and perspectives, Organic & Biomolecular Chemistry, 2005, 201-212.
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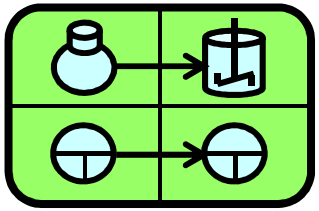

End of Supplementary Module 02

Rainer Buerstinghaus