A Novel Super Anti-Oxidant
with Excellent Intra-Dermal Penetration for Topical Formulations

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We introduce a novel super-anti-oxidant which is bio-compatible and has excellent penetration into skin. The super-anti-oxidant can accept, modulate, stabilize, and contain free-radicals and thus break the perpetual chain-reaction cascade of free-radicals which is a typical problem mediated by used [oxidized] anti-oxidants.

A Novel Super Anti-Oxidant

In this presentation, I will discuss:

- Introduction to oxidative stress and degrees of severity of free-radical damage.
- Strategies in designing synergistic groups of anti-oxidants.
- When oxidative stress and aging become synonyms: introduction to aging/anti-aging theories.
- Nanotechnology and anti-oxidants' intra-dermal delivery and positioning: from nano-cosmeceuticals to personalized formulations.
- A novel super anti-oxidant and derivatives.
- Future prospects.

What is Oxidative Stress?

The Relative Reactivity of Reactive Oxygen Species

SYMBOL	NAME	MOLECULAR SPECIES CATEGORY
$^{*}OH$	Hydroxyl radical	Extremely reactive
$^{1}O_2$	Singlet oxygen	Extremely reactive
$ONOO^{-}$	Peroxynitrite anion	Extremely reactive
$^{*}O_2^{-}$	Superoxide	Intermediately reactive
H_2O_2	Hydrogen peroxide	Moderately reactive
NO^{*}	Nitric oxide radical	Moderately reactive
C^{*}	Ascorbate free radical (oxidized Vitamin C)	Low reactivity
E^{*}	Tocopheroxyl free radical (oxidized Vitamin E)	Low reactivity

Low-Reactivity Oxidants Can Create High-Reactivity Oxidants

CHEMICAL PATHWAY	EXPLANATION
$*O_2^- + H_2O_2 \rightarrow O_2 + *OH + OH^-$ $*O_2 + NO* \rightarrow ONOO^-$	Intermediately and moderately reactive molecular species such as superoxides and hydrogen peroxide are not very dangerous to bio-systems. However, interactions between low reactivity molecular species can produce highly reactive and dangerous molecular species.
Transition Iron Ions $Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + *OH + OH-$ $Fe^{+++} + *O_2^{--} \rightarrow Fe^{++} + O_2$ $*O_2^- + Fe^{+++} \rightarrow O_2 + Fe^{++}$ **Transition Copper Ions** $Cu^+ + H_2O_2 \rightarrow Cu^{++} + *OH + OH^-$ $Cu^{++} + H_2O_2 \rightarrow Cu^+ + *O_2^- + 2H^+$	Transition metal ions mediate production of extremely strong oxidants from more moderate oxidants' species.

The Good and The Bad

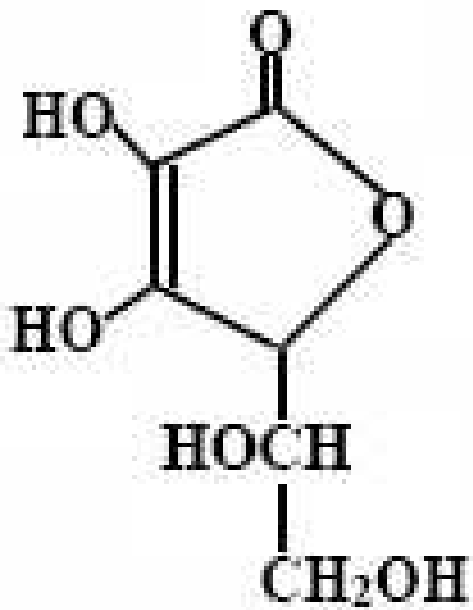
POSITIVE AND NEGATIVE ASPECTS OF FREE RADICALS AND PEROXIDES

POSITIVE	NEGATIVE
ROS are synthesized and used by the body's defense system to kill bacteria. ROS are used by the body for detoxification and also play a role in immune system activity. Nitric oxide, a common free radical, is now recognized to play an important role in control of vasodilation and in neurotransmission. H_2O_2 is used by the enzyme thyroperoxidase as a substrate in the production of tyroxin in the thyroid gland and is generated there. Thyroperoxidase catalyzes iodine attachment to thryoglobulin. H_2O_2 is generated in peroxisomes to aid in the degradation of fatty acids and other molecules, and H_2O_2 is used for detoxification reactions involving the liver cytochrome P-450 system.	Excessive production of ROS leads to oxidative stress and disease. Hydrogen peroxide, nitric oxide, and superoxide can be transformed into the dangerous hydoxyl radical. Peroxynitrite anion can cause damage to DNA, generate lipid peroxide, death of nerve cells and related degenerative diseases. Cumulative oxidative stress can result in cancer, heart disease, and accelerated aging.

Antioxidants to the Rescue

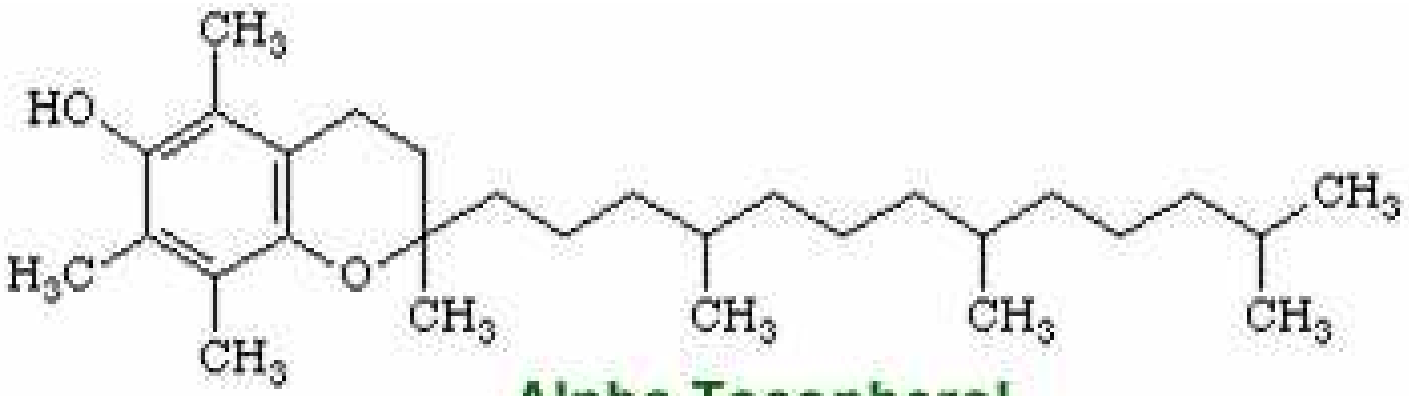
- **Anti-oxidants** have gained enormous popularity in recent decades, and are used as additives in almost all foods and skincare products.
- Since **oxidation** is one of the processes by which materials degrade, anti-oxidants were first widely used as preservatives:
  - sliced apples and potatoes turn brown because of oxidation;
  - dipping the slices in lemon juice, which contains the anti-oxidant Vitamin C, delays the oxidation process.

Common Antioxidants



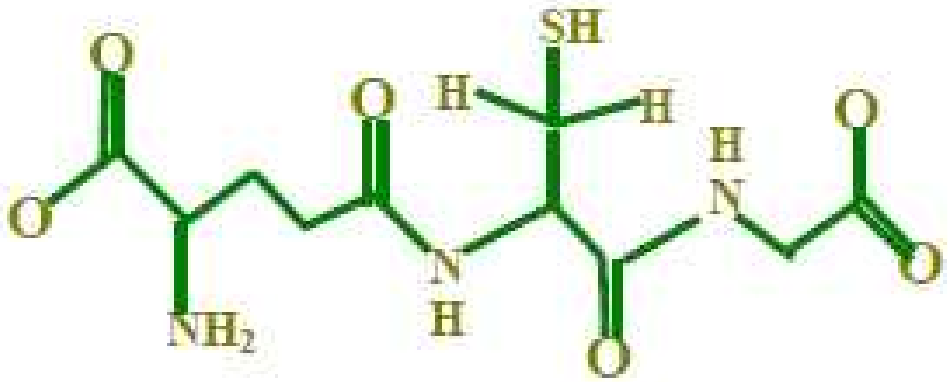
Ascorbic Acid
(Vitamin C)

Common Antioxidants



Alpha Tocopherol (Vitamin E)

Common Antioxidants



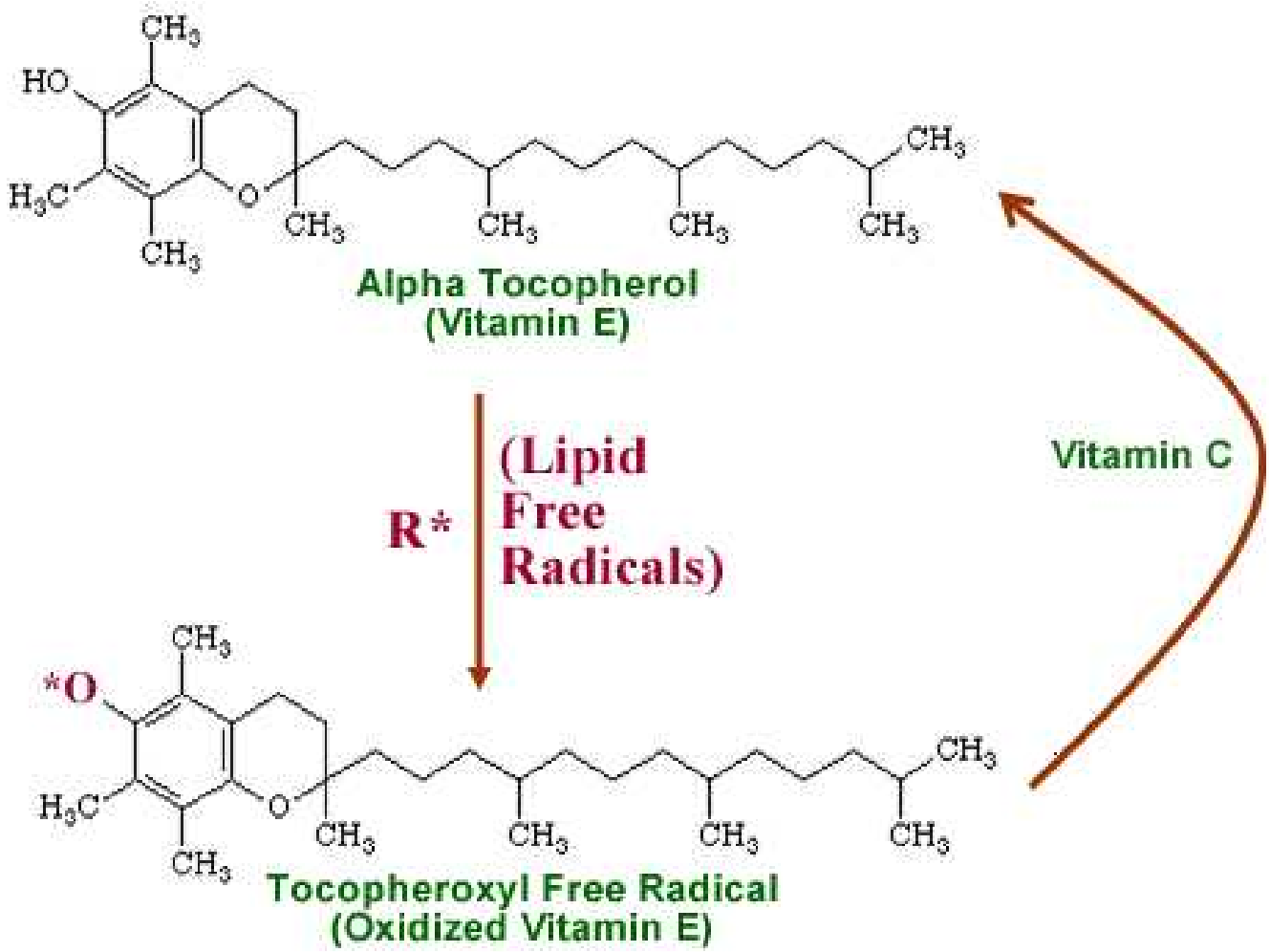
Glutathaione (GSH)

Strategies in Designing Synergistic Groups of Anti-Oxidants

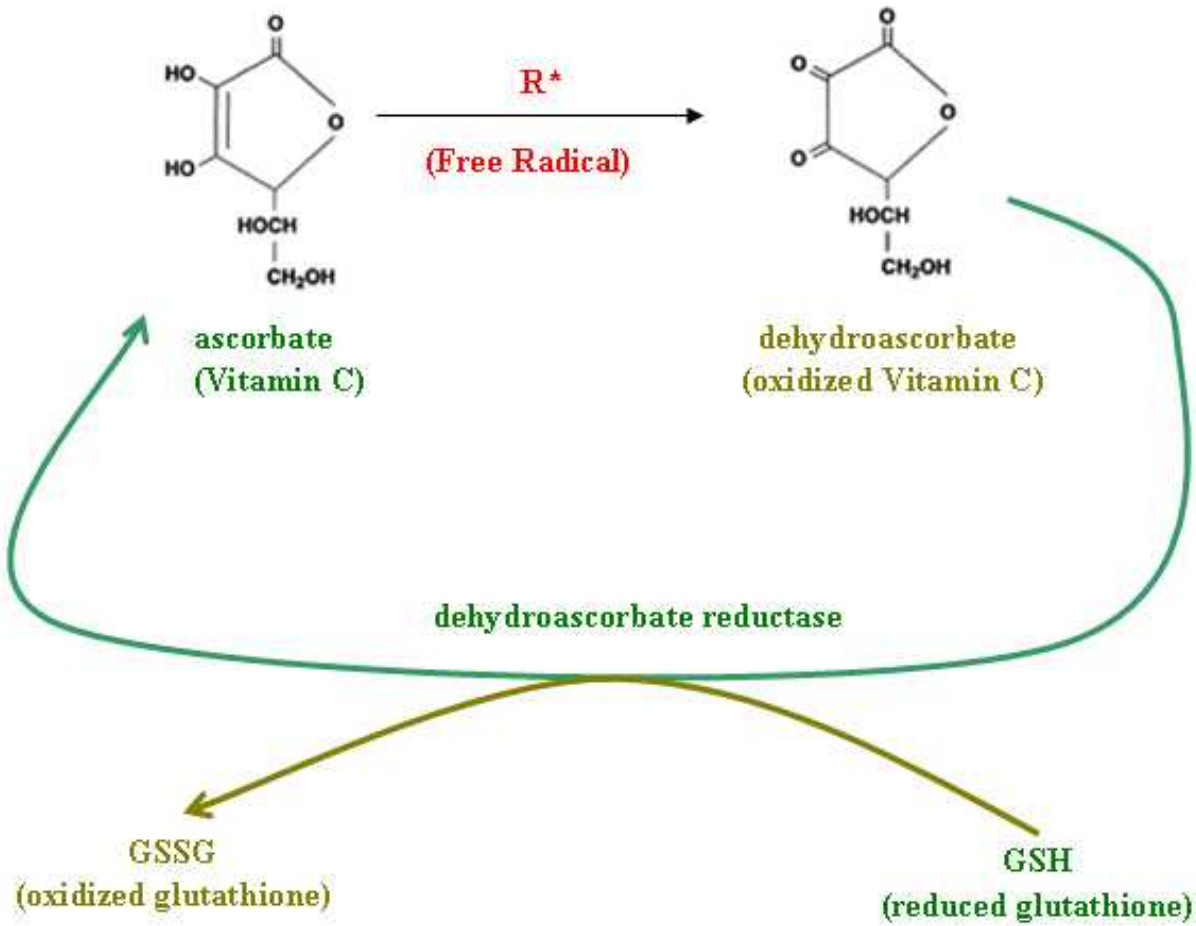
- The use of single anti-oxidants may fall short of satisfactory results.

- Anti-oxidants are best if added in synergistic combinations.

Recycling of Antioxidants



Recycling of Antioxidants



Antioxidants and Anti-Aging

- When **peroxidation** began to be emphasized as a critical factor in the aging and cancer processes, the term "**anti-oxidant**" become almost synonymous with the term "**anti-aging**".
- This connection to anti-aging studies raised the status of anti-oxidants so that, rather than being considered mere preservatives, anti-oxidant ingredients were assumed to have value in saving and prolonging life.

Aging Theories

The immune system decline theory

The neuroendocrine system decline theory

The somatic cell mutation theory

The genetic program theory

The error accumulation theory

The selected physiological states theory

The generation and scavenging of free radicals theory

The cross-linking of molecules theory

The increased entropy theory

The lipofuscin accumulation theory

The cell loss theory

Defining Aging

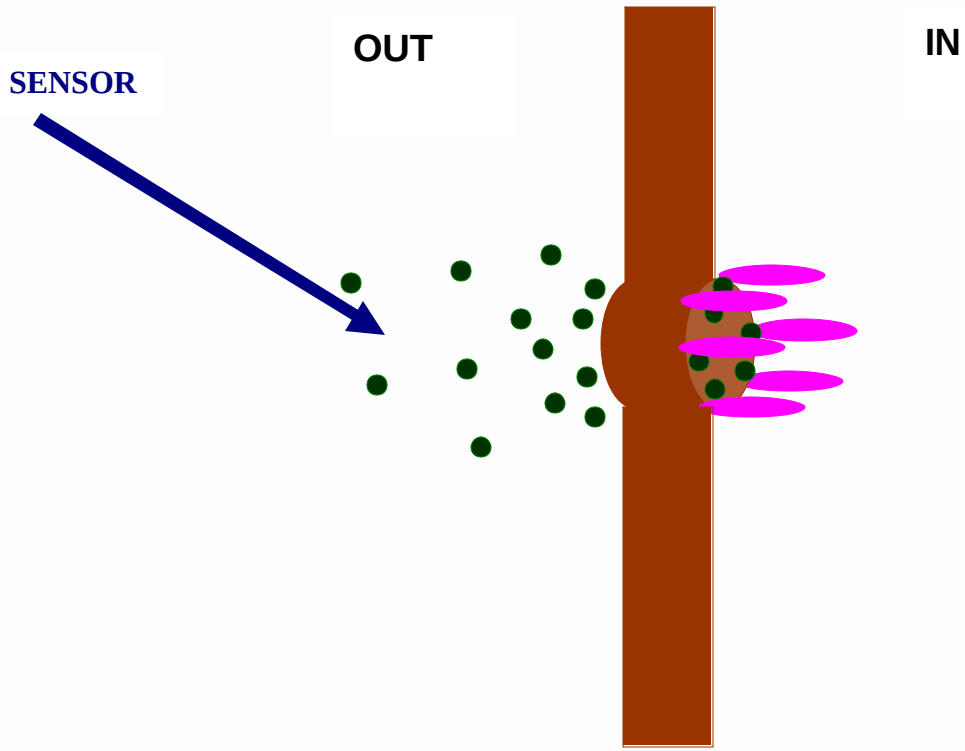
- It's easy for people to recognize age; people still try to make it hard.
- It's hard for scientists to measure age; scientists still try to make it easy.

The Theory of Nano-Structural Loss

- **What is the "Nano-Structural Loss" aging model?**
- **What is the nanotechnological basis of intervention in bio-structural aging?**

The Nano-Structural Loss Theory of Aging: Chemical vs Physical Signals

Bio-Systems Understand Chemistry but not Physics



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Chemical vs Physical Signals

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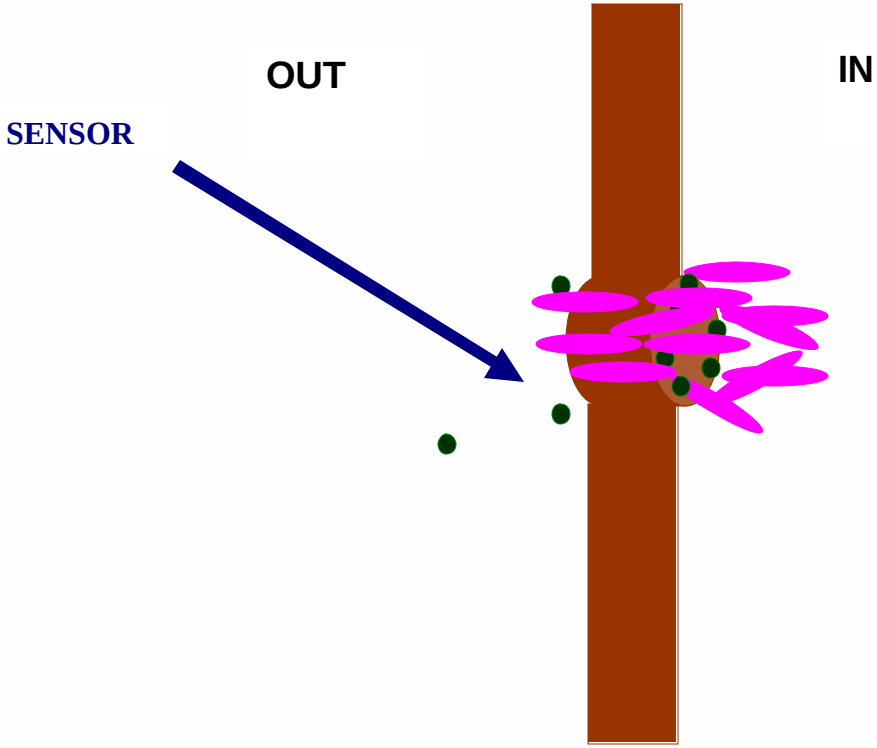
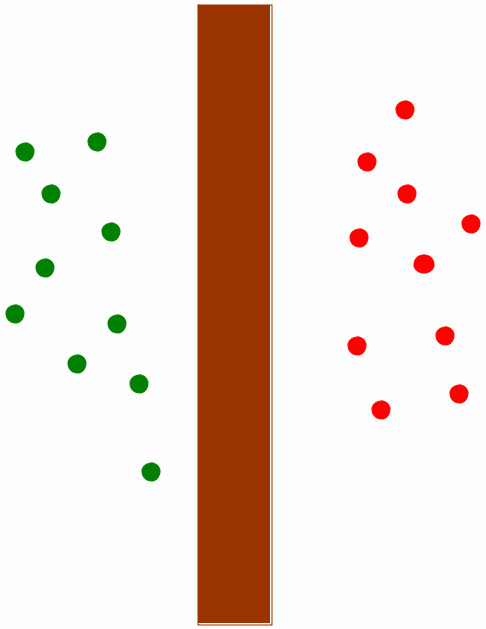


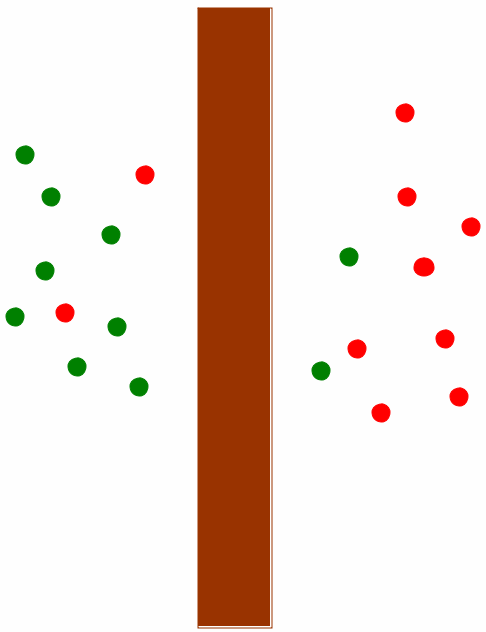
The Nano-Structural Loss Theory of Aging:
What is Compartmentalization?

Loss of Compartmentalization



The Nano-Structural Loss Theory of Aging:
What Is Semi-Permeability?

Loss of Selective Permeability (Semi-Permeability Loss)

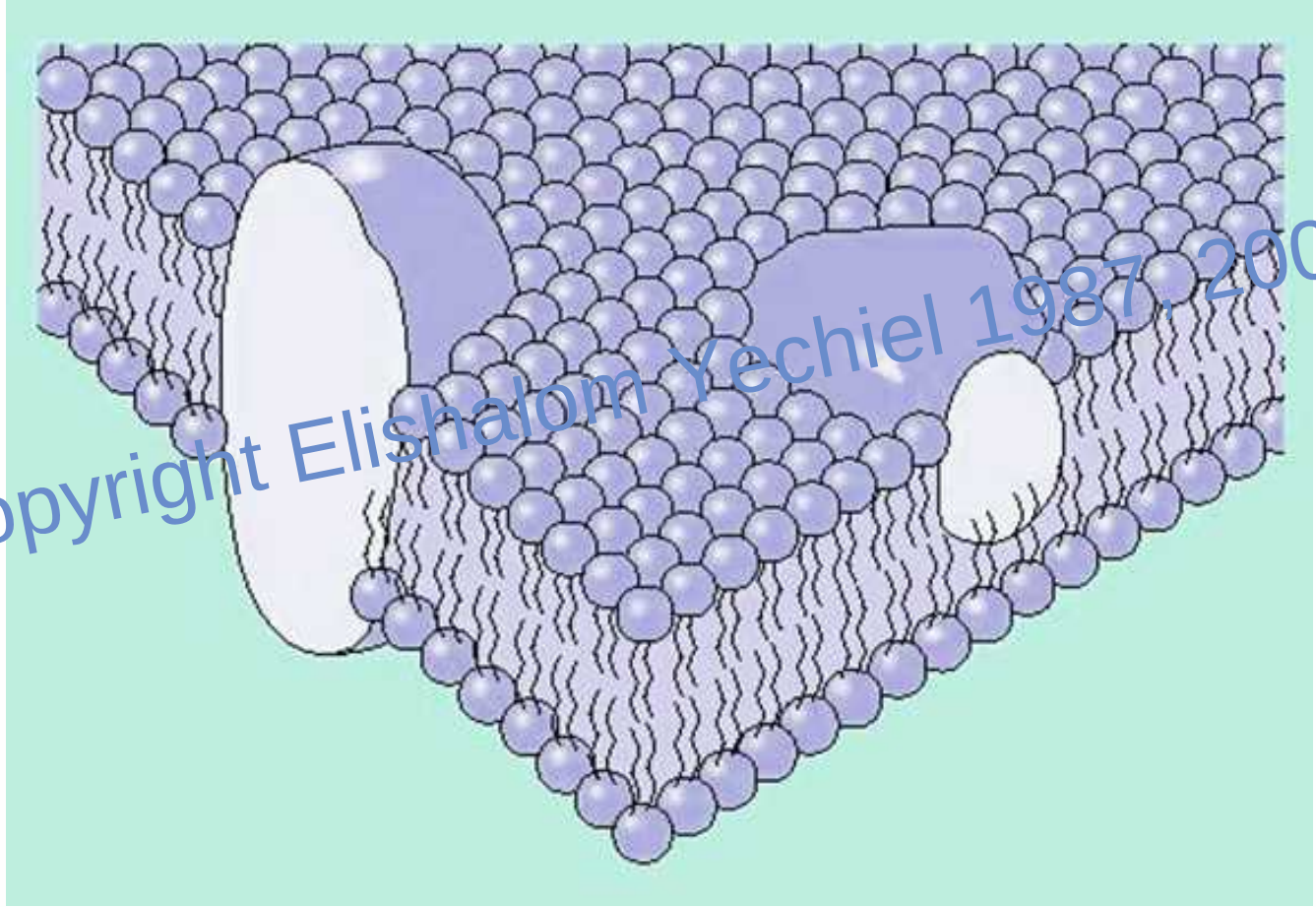


The Nano-Structural Loss Theory of Aging: Identifying Aging-Sensitive Nano-Structures in Cell Membranes

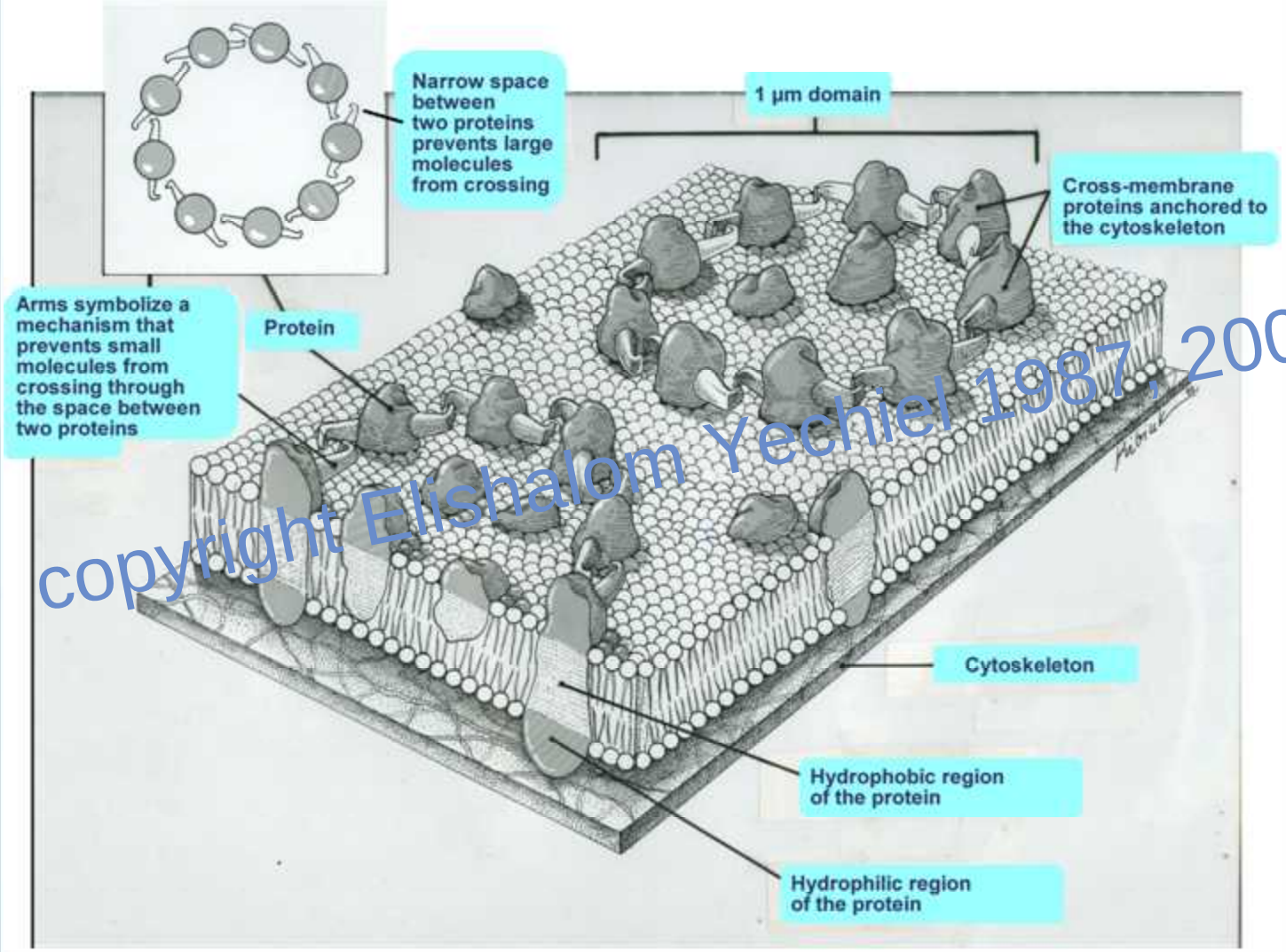
- **Nano-structures in bio-membranes and their aging-related loss of organization**
- **Relevancy to topical formulations and anti-oxidants**

The Fluid Mosaic Model (Singer & Nicholson):

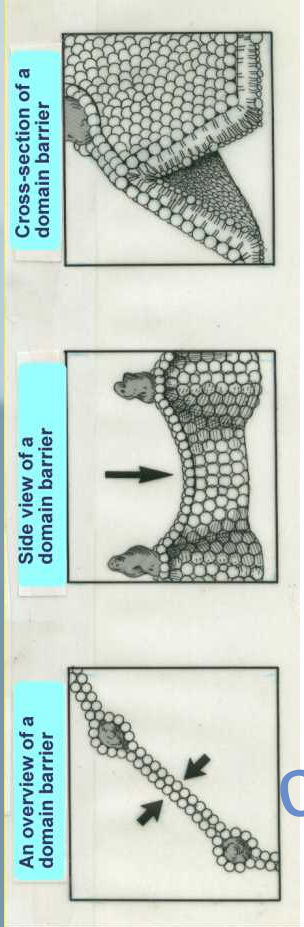
A Passive View of Cell Membrane Structure

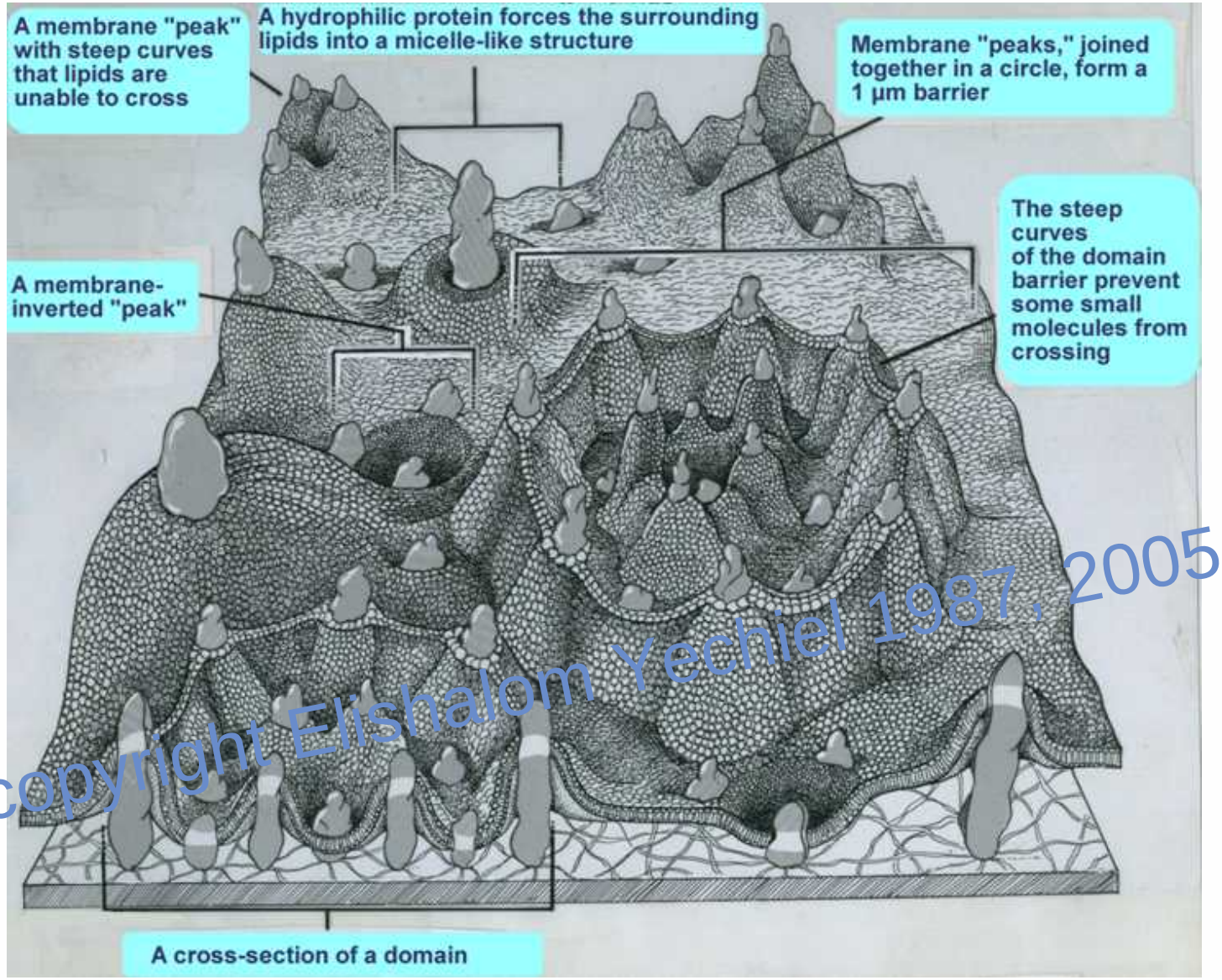


The Membrane Nano-Domain Model:
Lateral Domains in Cell Membranes



The 3D Membrane Nano-Domain Model





A Super Anti-Oxidant

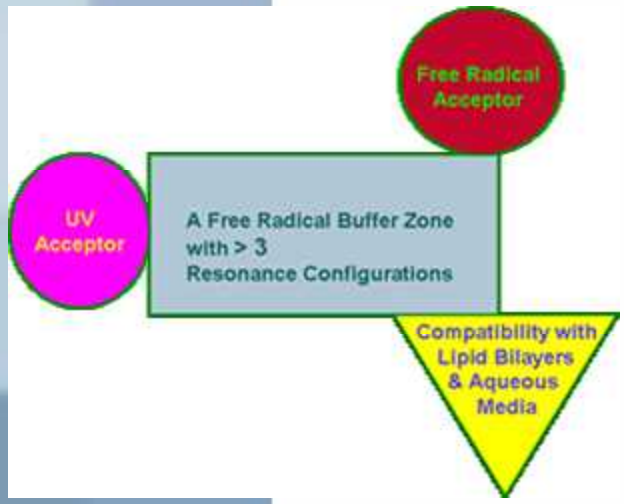
Free Radical Acceptor

UV Acceptor

A Free Radical Buffer Zone with > 3 Resonance Configurations

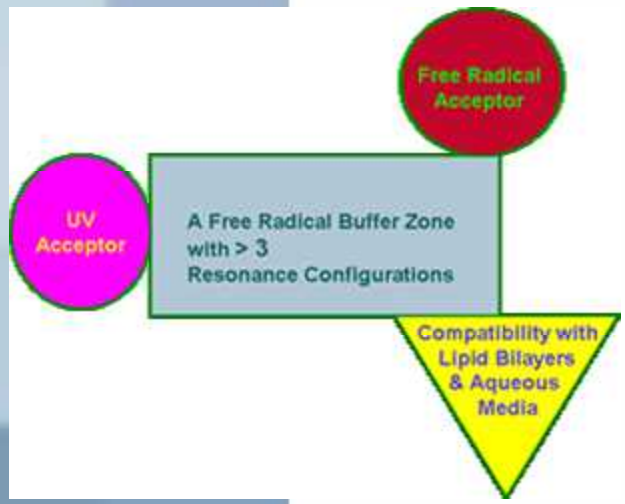
Compatibility with Lipid Bilayers & Aqueous Media

A Super Anti-Oxidant



- Engineered to be effectively transported into skin.
- While easily able to permeate the skin independently, it can be combined with some of our nano-vehicles for improved deep and targeted delivery.
- Protective of internal environment at site of penetration.

A Super Anti-Oxidant

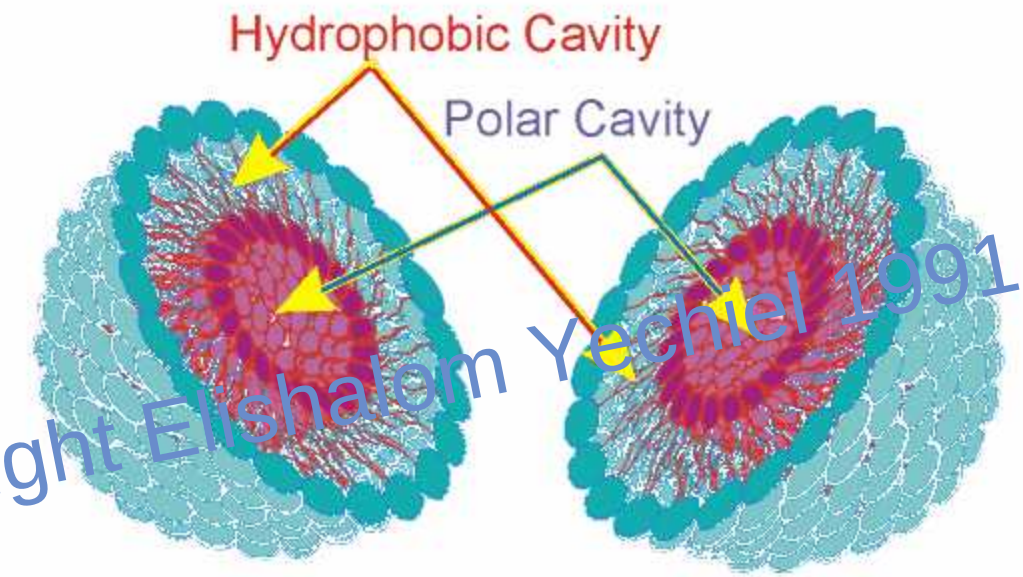


Can be inserted into skin by:

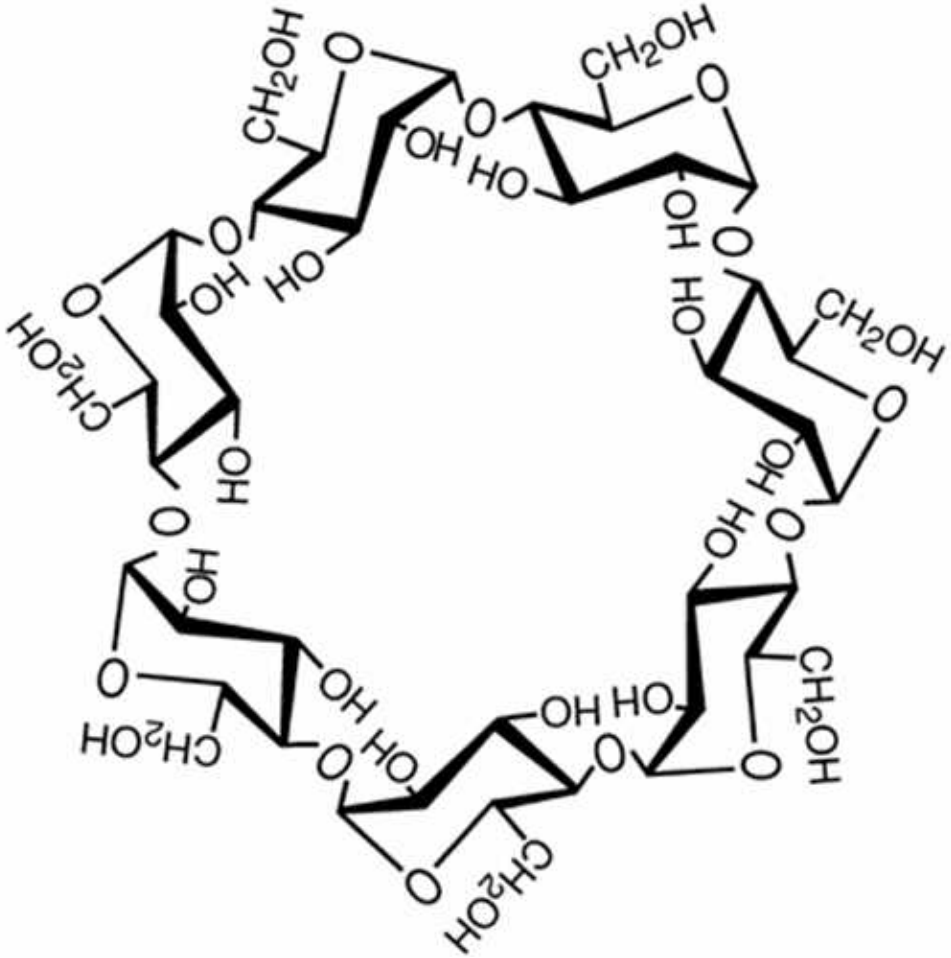
- liposomes
- nano-emulsion
- nano-encapsulation in cyclodextrin

What Understanding Aging Means: How Nanosomes Carry Actives

Liposomes can encapsulate and transport water-soluble ingredients in their polar cavity and oil-soluble ingredients in their hydrophobic cavity.



What Understanding Aging Means:
Nano-Encapsulation in Cyclodextrin



What Understanding Aging Means:
How Nano-Technology Enables Interference in Bio-Structural Aging

- Topical Intervention In Skin Aging
- Rapid Absorption of Actives
- Deep Absorption of Actives
- Modulation of Odor and Color of Actives
- Targeting Cellular and Sub-Cellular Action Sites
- Increasing Efficacy and Shelf Life of Actives
- Enabling Synergistic Cooperation of Actives

FOR MORE INFORMATION

- This model of bio-nano-structures and time-sensitive structural loss related to oxidative stress will be discussed in detail in the online *Journal of Topical Formulations* May 2006

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