

PART 1



How Do Molecules "See"?



Recall

A key observation featured in "***Cell Biology – A Not So Typical Introduction***" was the remarkable resemblance between the structure of neurons and dark energy/matter distribution in the universe.

Dark Matter/Energy Simulation

https://www.youtube.com/watch?v=Ssxd_dvnuYo

(this video is amazing)
Illustris project

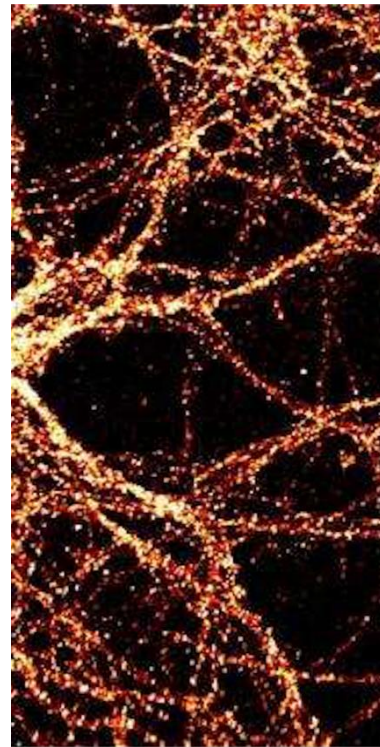
Yellow: normal matter
Purple: dark matter
Black: Dark Energy



Hippocampal Neurons

© Yu, H et al (2015)
Nat Neurosci 18:836-43

©
<https://medicalxpress.com/news/2015-04-neurons-constantly-rewrite-dna.html>



From this resemblance we took that “**fundamental patterning in nature is independent of scale**” = you will find recurrent organizing principles in things that may seem completely unrelated ...let say: quantum mechanics, biology, sociology, or urban planning.

Recall

Likening the structure of the Universe to that of biological structures based on phenomenological similarity creates an interesting puzzle. **Why?**



Answer: analogy calls for equating visible matter (5%) **and** invisible dark energy/matter (95%) with macromolecules in living systems ...

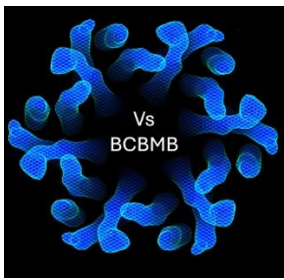
....dark matter is called "dark" because we cannot directly see it = **the analogy implies that in a living system, any given molecule sees mostly "nothing/empty space"**.

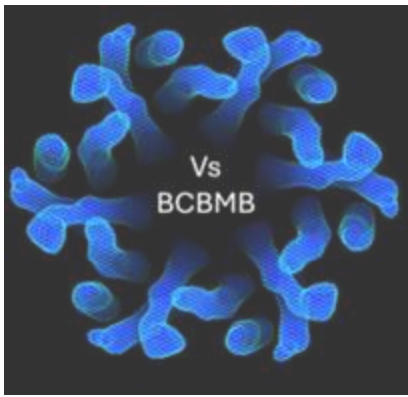
➔ this not only is true, but life is even more extreme in that most molecules "see" only a tiny fraction of 1% of all other molecules (in most cases don't even see identical copies of themselves).

➔ **How then can biology work if any one molecule "sees" mostly nothing/"empty" space?**

Answer: works because what may look like "empty" space to any one molecule **is not really** empty = we don't see dark energy/matter directly....but....it's still there, and it sure impacts us! ➔ Same holds in biology: any one molecule doesn't see most of what is around it ...but...that "something" is still there and impacts all the things that can't see it (and that it cannot see either).

➔ **In other words:** components of a complex system neither need nor want to "see" everything (in fact, they must not "see everything") to know what to do because **operating instructions are issued AND moderated by the entire ensemble.**





Starting Point

While any given molecule does not "see" most of what is around it, it also is NEVER unaffected. In fact, we realized that within a biological system everything seems to be sensing everything else at once!



This **coherence/"boundedness"** and ability to sense/being impacted by everything at once **is an emergent property that stems from each molecule's ability to "see" a select subset of other molecules around it.** This selective "vision" snowballs into something that is akin to "six degrees of separation" for the entire ensemble.

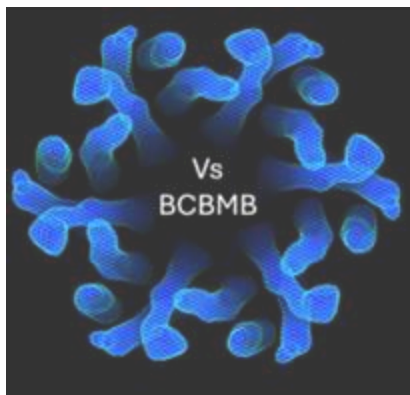
By the end of the THIS lecture you should be able to explain

- How molecules "see" (= recognize) each other,

And By the end of the Part 2 you should also be able to explain

- How molecules select other molecules to engage with
- Whether engagements will be shortlived or are more committed, and
- What implication molecular recognition mechanisms have for molecular evolution.





How Do Molecules “See” = Recognize Each Other?



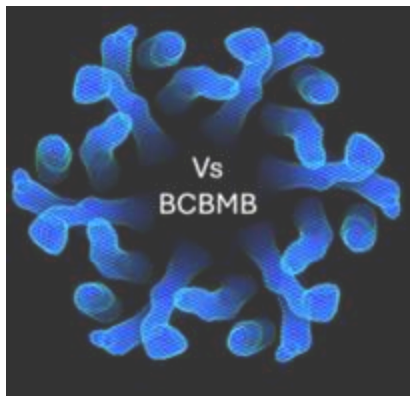
Thought Experiment: Close your eyes and imagine that a friend gives you an envelope with an object inside. Now imagine taking the object out of the envelope. Without opening your eyes or asking your friend – what exactly would you do to determine what the object is?

Doing this experiment with students in my class this is what this looked like (yes, they had their eyes closed, and yes, they knew I took a picture while they had fun with this)



Having done this experiment for several years, none of the students ever figured out what they had in their hands (a page from a book that taught blind children how to count...the objects on the cards were embossed, and each card had braille marking for the children to read).

BUT –the point of the exercise was not to exactly find out what this object was. Rather – what DID matter was that the students (and hopefully you if you did the exercise when prompted) observed themselves, paying attention to **what they/you did and how**.



How Do Molecules “See” = Recognize Each Other?



Lets compile **what** they/you did and **how**.



They/You touched the objects

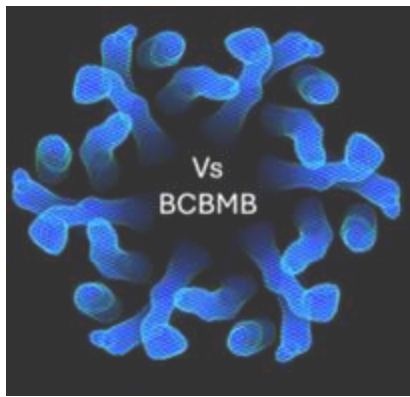
- what exactly does that mean?
- likely used tip of finger
- **why fingertip?** why not elbow, foot, or nose?
- fingertip it is...**just one**?
- what exactly did you do with your fingertips? scanned? tapped? triangulated?
- did you use **more than one hand** to explore?
- **why just one active hand?**

- **scale/resolution/sensitivity**
- **likely: “no!” more than one**

- **likely: no (other used to just hold on)**
- **object is small and “flat”**

.... more things could be added here.

Also important to note: your fingertips do NOT float in vaccum, they are attached to a bigger structure!



A World Without Sight – Sound – Smell.....



.....relies on **Touch**

Having gone through the “human scale” exercise, we can translate your observations to the molecular scale, answering the first big question:

How does “touching” work at the molecular level?

Answer: not much different from human physiology if we find the proper equivalencies

→ Through the exercise you (hopefully) realized there are a **scaffold, a probe, and a process**

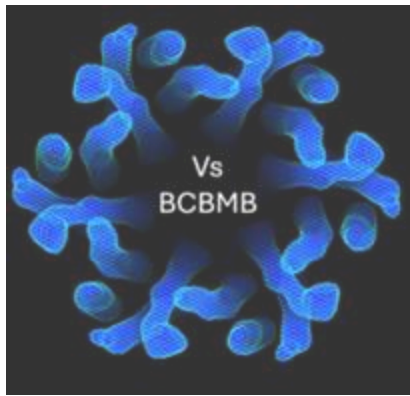
What is the scaffold? *exercise: body/arms/hand*

molecular scale: all parts of molecule that are not used for sensing

→ the “scaffold” aligns and position the molecular scale “probes”

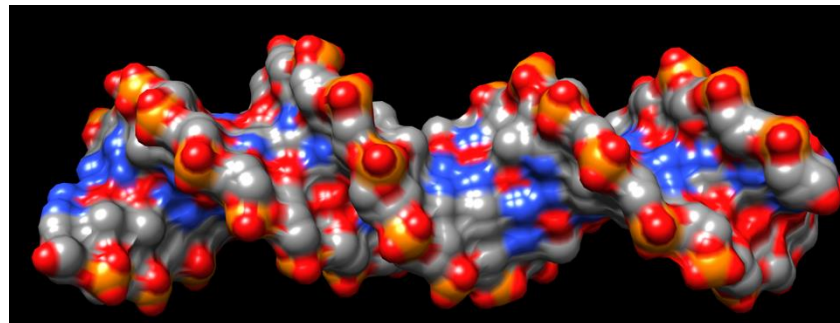
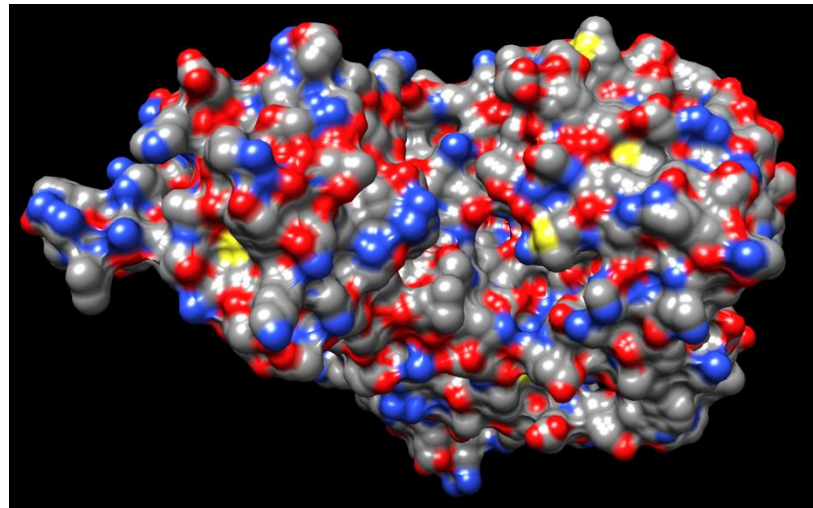
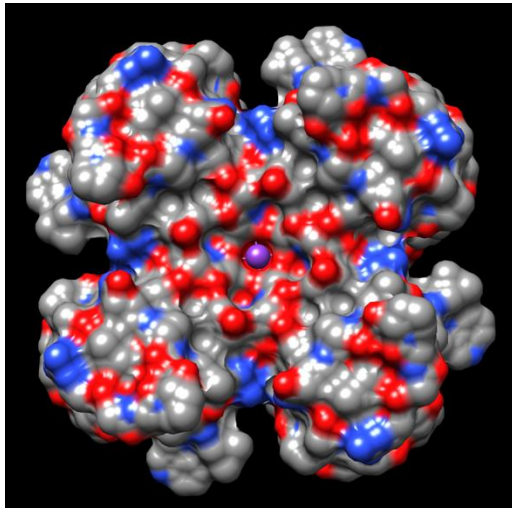
→ in real space (2D or 3D) this creates a **pattern on a surface!**

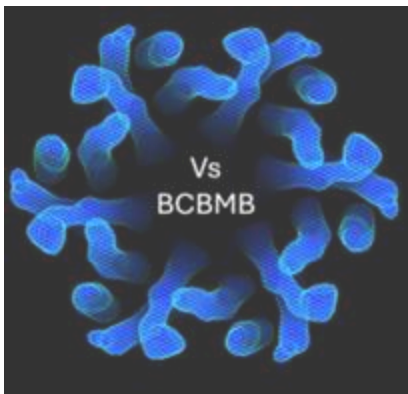
Examples for Surface Patterns



Images show three biological macromolecules that can be found inside each cell. The surface is colored by atom type.

Can you see differences?





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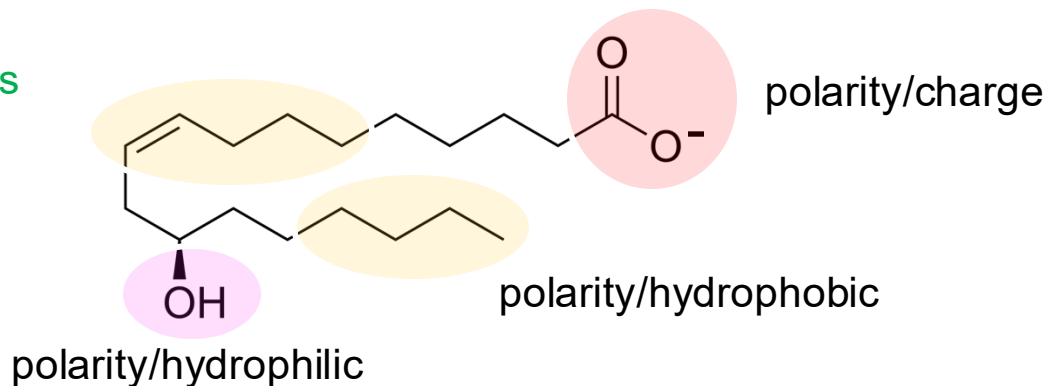
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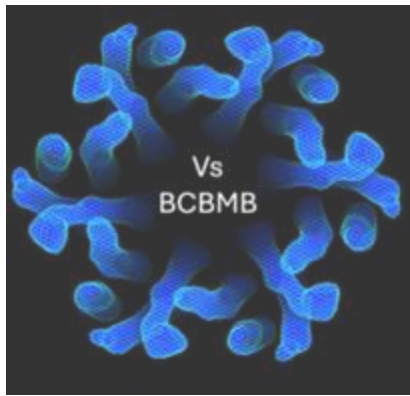
→ in real space (2D or 3D) this creates a **pattern on a surface!**

What is the probe?

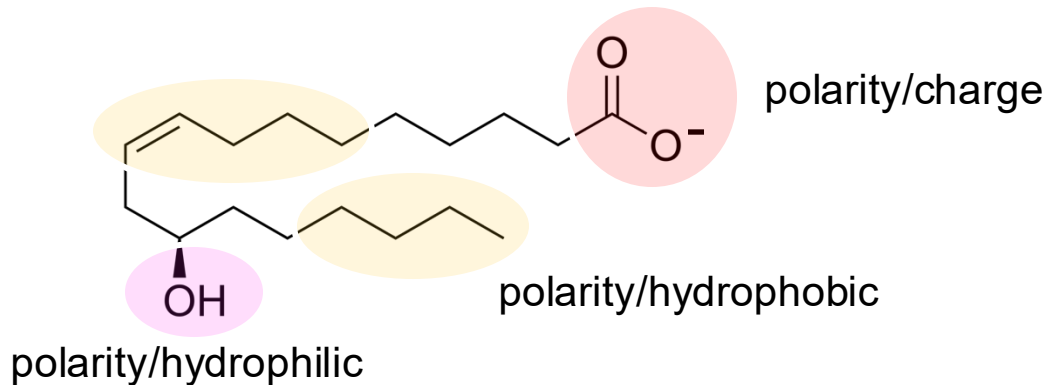
exercise: finger tips

molecular: chemical properties
and/or functional groups. **Why?**



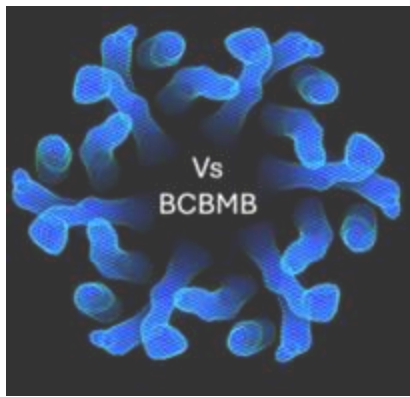


Weak Interactions are at the Core of Life

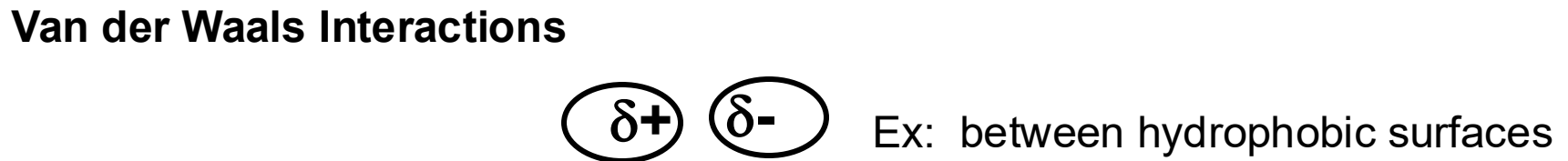
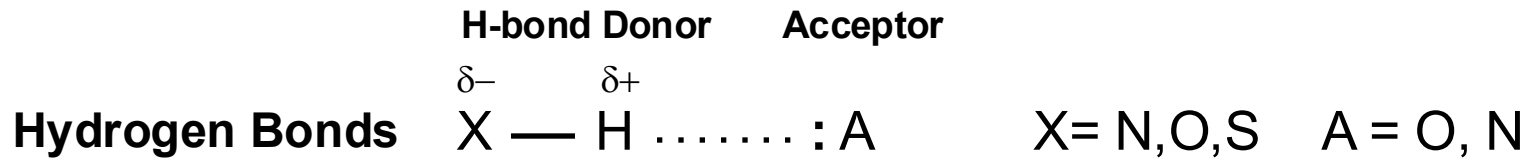
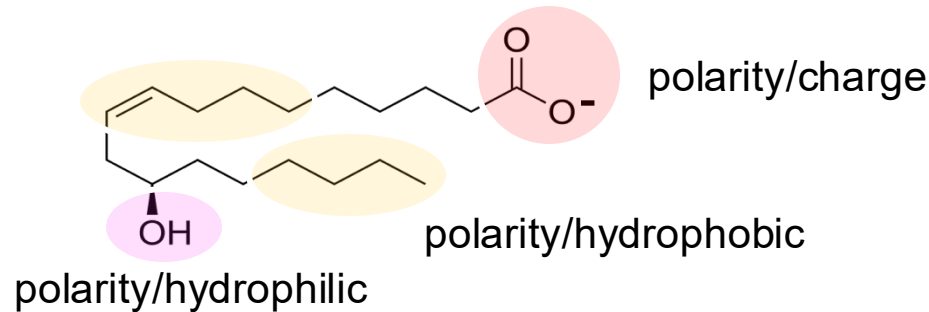


Charge, hydrophilicity, and hydrophobicity give rise to three types of **transient, non-covalent, weak interatomic attractions and repulsions**, commonly referred to as **weak interactions**

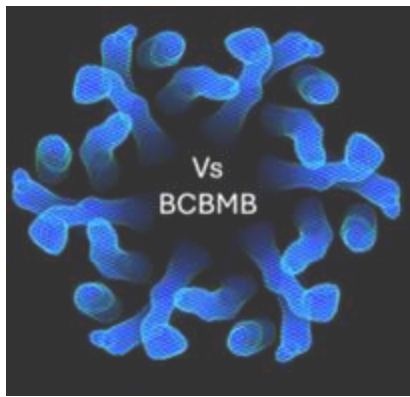
Hydrogen Bonds, Ionic Interactions, Van der Waals Interactions



Weak Interactions are at the Core of Life



→ At the molecular level, the probes (= equivalent to “fingers”) are functional groups that are mounted on a molecular scaffold (=“hands/arms”)



Weak Interactions Allow Molecules to “See” - Why?

Weak interactions are transient and differ in **energy**

Hydrogen Bonds (typically 2-4kcal/mol, ps-lifetime) \geq Ionic Bonds (~ 1.4 kcal/mol in water at 3Å distance, single charge each ion) $>$ Van der Waals Interactions (~ 0.5 kcal/mol $\rightarrow \sim$ “kT” [energy scale factor in physics])

Comment: ionic interactions are ruled by Coulombs Law $F \sim (q_1q_2)/(\epsilon r^2)$ [q: charge, r: radius, ϵ : dielectric constant] \rightarrow **very** context dependent = tunable

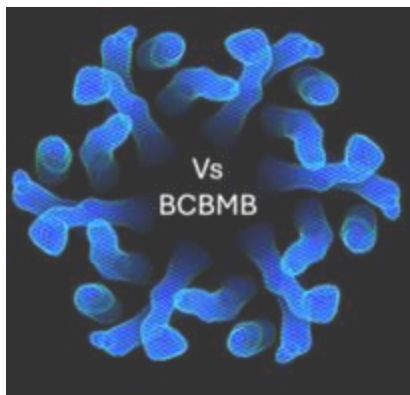
Comment: typical bond energy for covalent bond (e.g. carbon-hydrogen) is 100kcal/mol (this is why weak interactions are called “weak”)

Weak interactions also differ in **geometry**

Hydrogen Bonds: linear (2-3Å donor-H to acceptor biological macromolecules; very narrow angular tolerance of only 2°) \rightarrow spatially very restricted!

Ionic Bond: spherical (reach.... up to $\sim 4\text{\AA}$) \rightarrow spatially degenerate

Van der Waals: spherical (direct contact of atomic surfaces) \rightarrow spatially degenerate

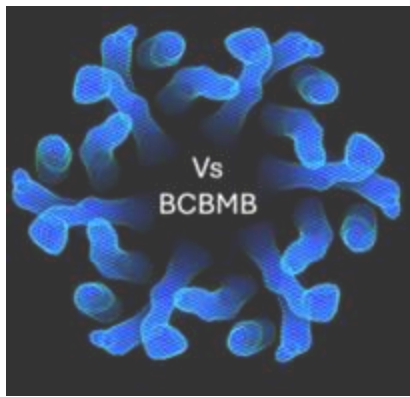


Weak Interactions Allow Molecules to “See” - Why?

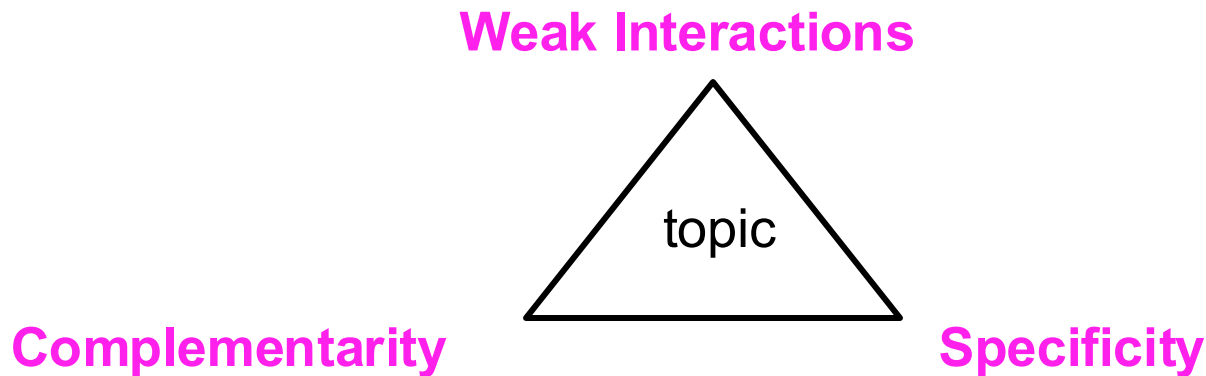
Summary Conclusion: The **combination of energy** (=strength) and **geometry** (=spatial distribution) is perfect to give molecules “vision” because it **allows to substitute sight with scanning (=process)** of the **physical and chemical surface properties** that result from the strategic placement/display of functional groups by the scaffold.

➔ Molecular sight amounts to a **pattern recognition** process; the short lifetime of weak interactions allows this scanning to happen at the timescale of molecular collisions (covered in a different lecture that explains how and why enzymes function at all)

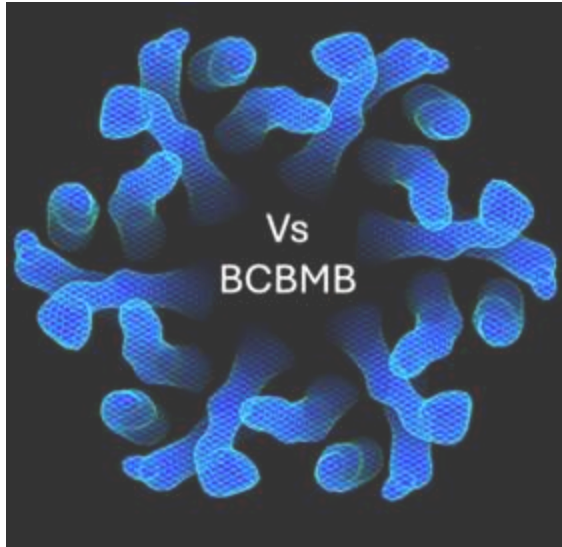
➔ molecular recognition and **specific** engagement occur when two surfaces are mutually matched through **complementary** physical and chemical properties



The following diagram arguably is the **singly most important correlation for understanding ALL of life at the molecular level.**



The significance of this diagram lies in its simple message: **if it doesn't fit, it doesn't interact.** (eg a pair of glasses and your knee).



Slides are freely available at
vsbcbmbstudy.com