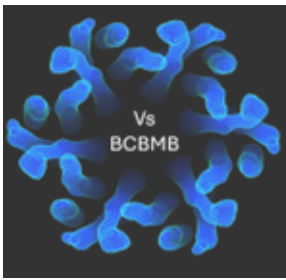


How Do Molecules See?



PART 1



This is a Tutorial/Silent Lecture



What is a Tutorial/Silent Lecture?

a sequence of "slides" formatted to guide you through the exploration/study of the topic

you are the main actor in this active learning experience

think of it as working with a tutor without having to pay for it

as the slide sequence unfolds, you will get opportunities to engage with the material

➤ **by thinking about/answering questions,**

(my answer is always provided on the next slide).

➤ **by completing a "short assignment"**

(it never will take more than a few minutes, if at all that long),

➤ **by watching a short video/clip**

(the embedded links will take you to my YouTube@VsBCBMB channel;

key moments are captured as still and are shown in the slide-deck, in case you don't want to watch the videos)

of course, you can skip the active learning aspect and look at the answers right away.

Why Give This a Go?

➤ **benefits: you set the pace** taking as much or as little time as you need.

➤ you **can turn tutorials/silent lectures into fully immersive experiences** (eg playing your favourite music while working through the content),

➤ **or invite friends to over the Q&A structured/guided materials together,** discussing the questions before looking at answers.

each of these features help you to hold on to the material.

Recall

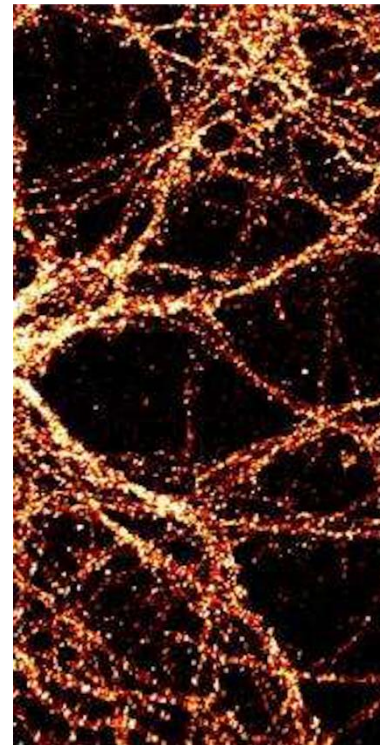
A key observation featured in
"From Cell Biology to Social Media, the Internet and More"
was the remarkable resemblance between the structure of neurons and dark
energy/matter distribution in the universe.

Dark Matter/Energy Simulation

[https://www.youtube.com/
watch?v=Ssxd_dvnuYo](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](https://medicalxpress.com/news/2015-04-neurons-constantly-rewrite-dna.html)

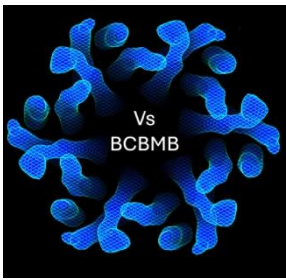
From this resemblance we took that
"fundamental patterning in nature is independent of scale"
= you will find recurrent organizing principles in things that may seem completely
unrelated ...let say: quantum mechanics, biology, sociology, or urban planning.

Recall

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



....try to remember



Recall



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

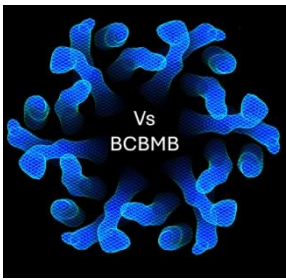
Answer: analogy calls for equating visible matter (5%) **and** invisible dark energy/matter (95%) with macromolecules in living systems ...

....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?**

...do you remember?....



Recall



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

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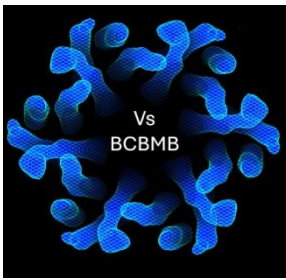
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→ **How then can biology work if any one molecule "sees" mostly nothing/"empty" space?**

Answer: works because what may look like "empty" space **is not empty** = we don't see dark energy/matter directly....but....it's still there, and it sure impacts us!

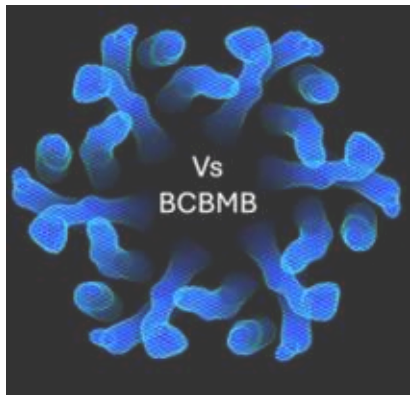
→ same holds in biology: any one molecule doesn't see most of what is around it ...but...that "something" is still there and impacts all the things that can't see it (and that it cannot see either).

→ **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.

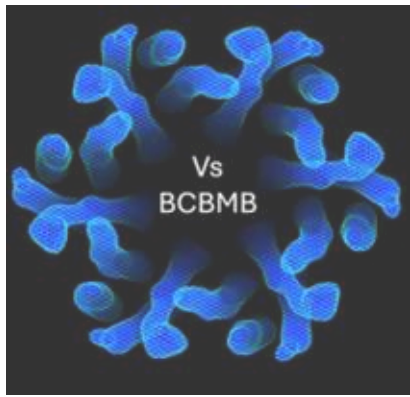
by the end of the THIS chapter you should be able to explain

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

And by the end of 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.

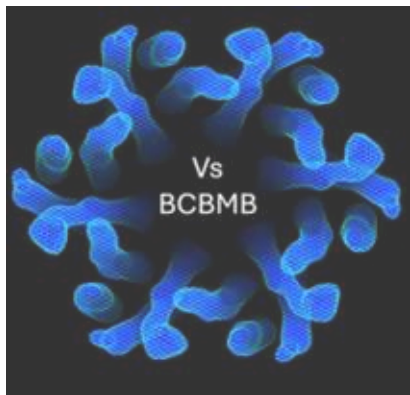




How Do Molecules “See” = Recognize Each Other?

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?





How Do Molecules “See” = Recognize Each Other?



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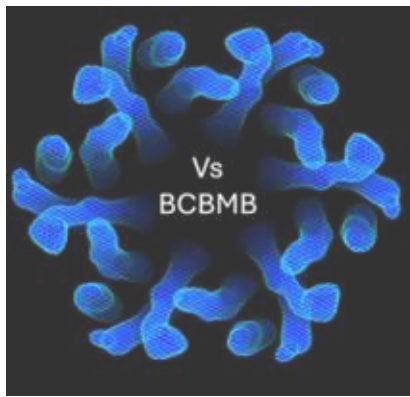
Doing this experiment with students in my class this is what this looked like
(yes, they had their eyes closed, and yes, they knew I took a picture while they had fun with this)



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 find out what exactly 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?



let's compile **what** they/you did and **how**.

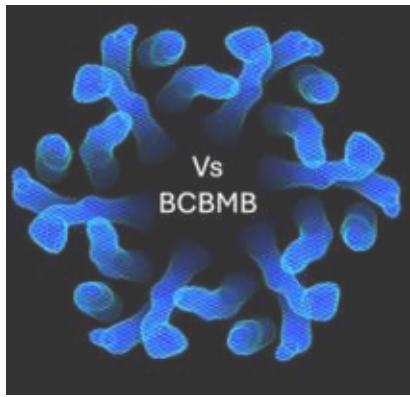


They/You touched the objects

- 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**
- **possibly all of those?**
- **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!



The Conclusion From this Experiment A World Without Sight – Sound – Smell.....

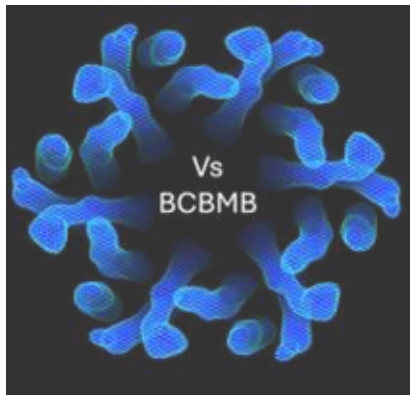


.....relies on **Touch**

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?**

...try to think of something!



The Conclusion From this Experiment A World Without Sight – Sound – Smell.....



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having gone through the “human scale”
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the molecular scale, answering the first big
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How does “touching” work at the molecular
level?

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

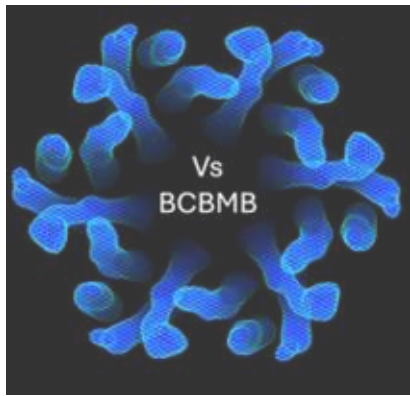
→ Through the exercise you (hopefully) realized there are a **scaffold, a probe, and a process**

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

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

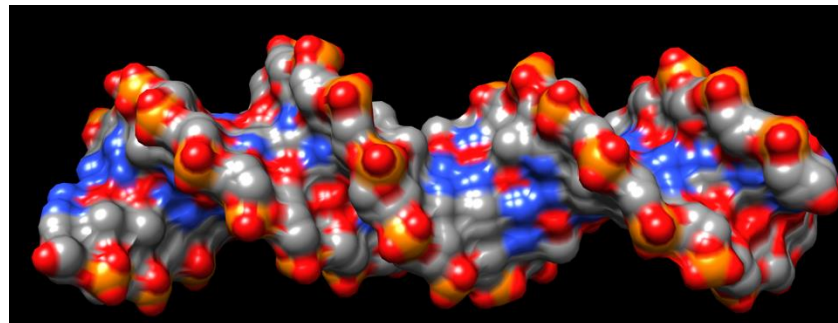
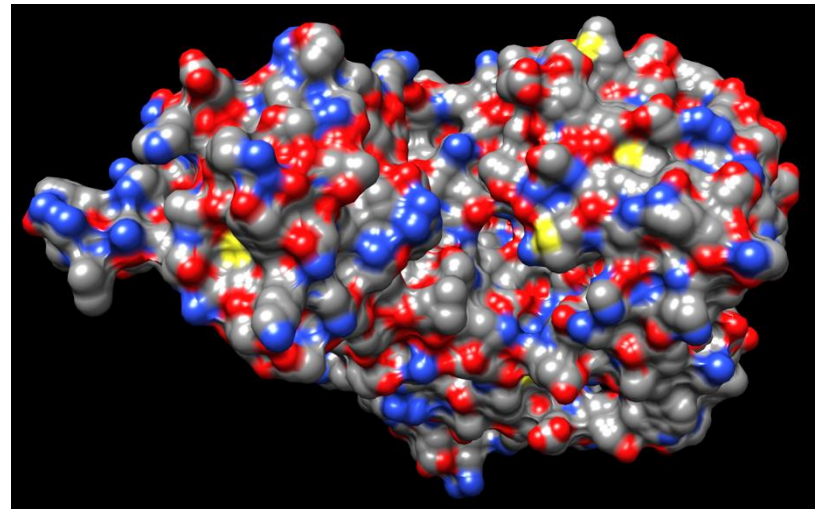
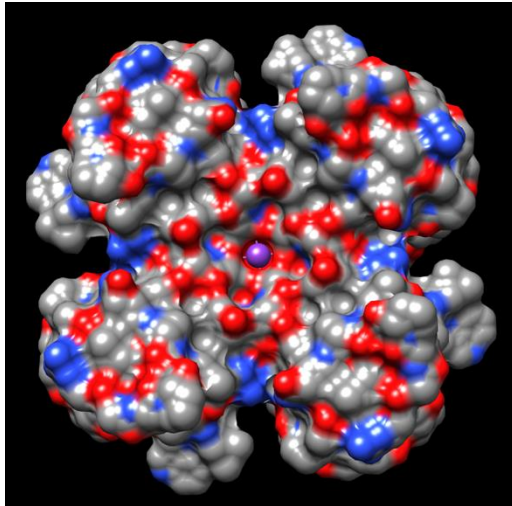
- the “scaffold” aligns and position the molecular scale “probes”
- in real space (2D or 3D) this creates a **pattern on a surface!**

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 the differences?



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?

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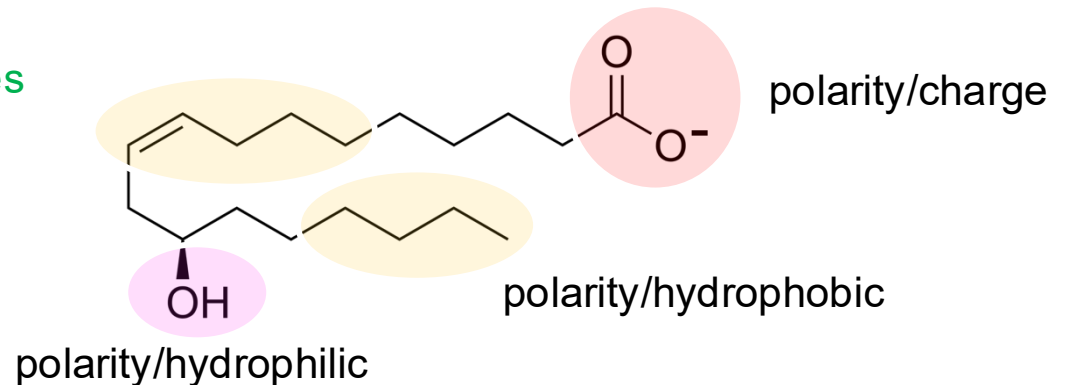
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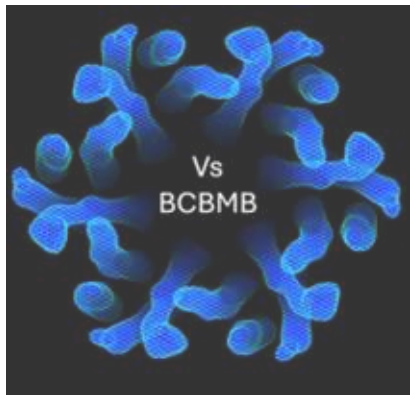
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What is the probe?

exercise: *finger tips*

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

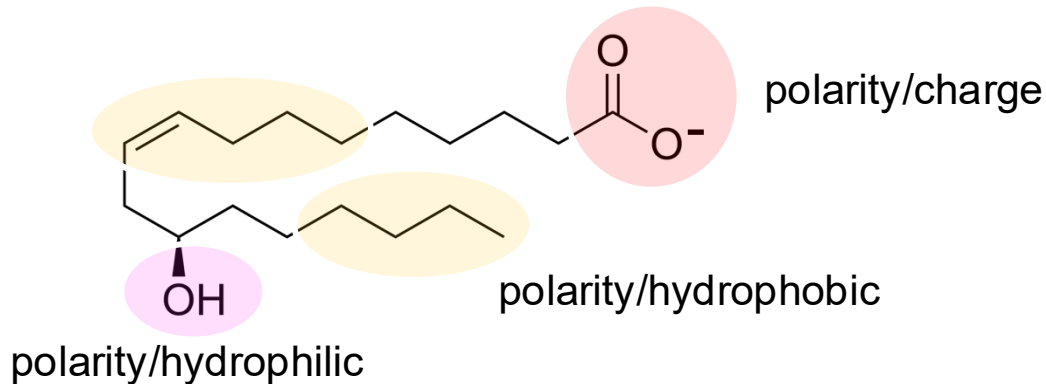




Weak Interactions are at the Core of Life



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

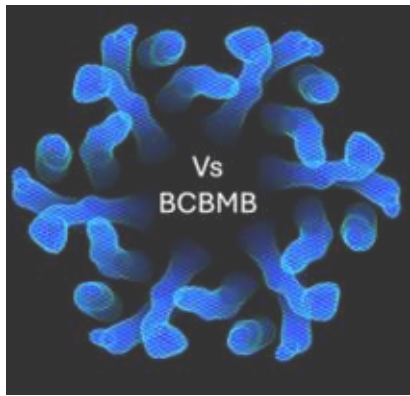


throughout chapters, words highlighted in **pink** are overarching themes = true concepts that help unifying and explaining why things happen in certain ways.

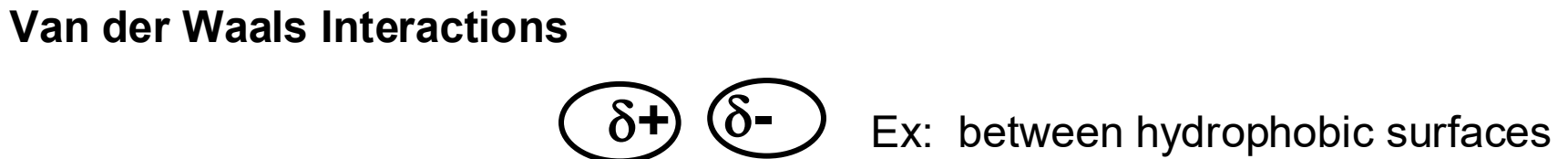
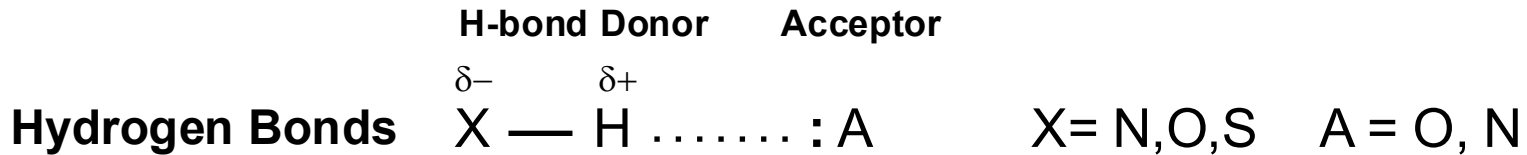
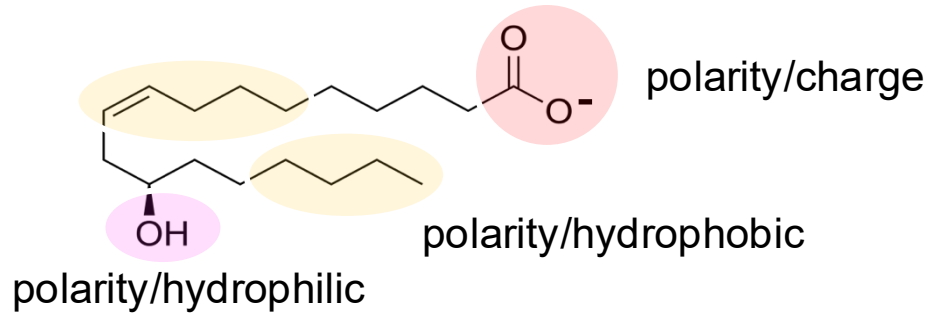
If you are interested in exploring how concepts help you to organize and to understand your knowledge, consider registering for my 50min workshop on "Conceptual Frameworks". You can find more detail and registration access here:

<https://vsbcbmbstudy.com/online-workshops-details>

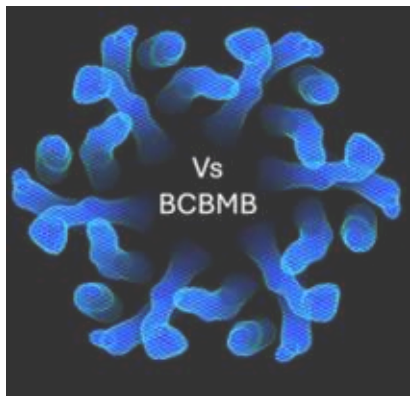
The **weak interactions** at the heart of Biology are
Hydrogen Bonds, Ionic Interactions, Van der Waals Interactions



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, picosecond-lifetime) **≥** **Ionic Bonds** (~1.4 kcal/mol in water at 3Å distance, single charge each ion) **>** **Van der Waals Interactions** (~0.5 kcal/mol → ~“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] → **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”)

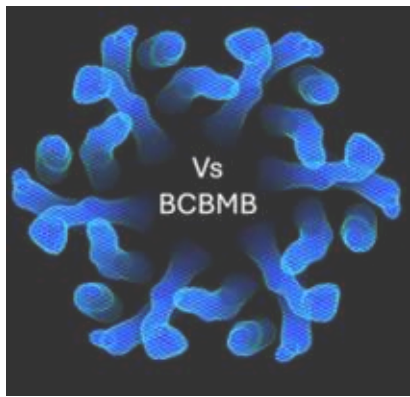
Weak interactions also differ in **geometry**

Hydrogen Bonds: linear (2-3Å donor-H to acceptor)

very narrow angular tolerance of only 2° → spatially very restricted!

Ionic Bond: spherical (reach.... up to ~4Å) → spatially degenerate

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

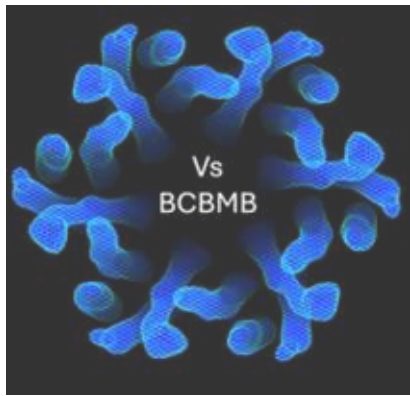


Weak Interactions Allow Molecules to “See” - Why?

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 the Advanced Biochemistry Chapter on Enzymes)

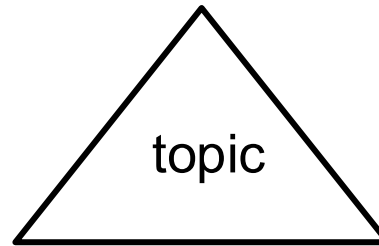
→ molecular recognition and **specific** engagement occur when two surfaces are mutually matched through **complementary** physical and chemical properties



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



Weak Interactions



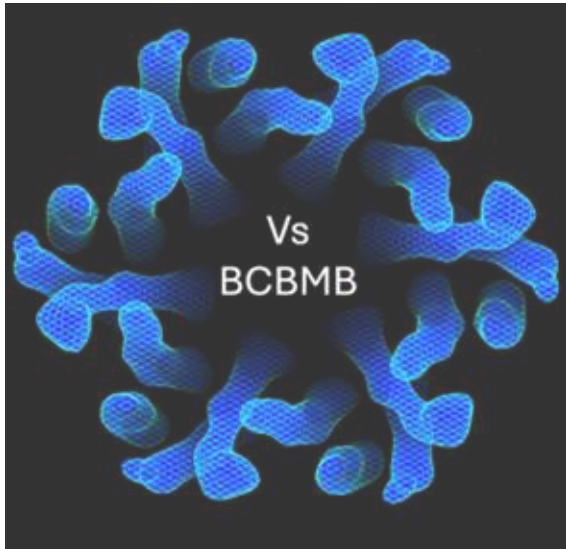
Complementarity

Specificity

The significance of this diagram lies in its simple message:

if it doesn't fit, it doesn't interact.

(eg a pair of glasses won't fit your knee).



If you found this short tutorial helpful – recommend it to friends and consider downloading other chapters.

Comments and Suggestions for Improving This Tutorial Are Welcome

pdf-comments@vsbcbmbstudy.com