DIVERSITY of CHEMORECEPTORS:

Organisms evolved diverse receptors. Say $r_1 \dots r_N \equiv N$ receptors

- each ligand L_i binds each receptor with $\neq$ affinity
- this is useful as a way of encoding odor identity:
  e.g. in rodents, the list of receptor activation codes odor identity (mathematically each odor is defined by vector of activities $a_1 \dots a_N$) $\quad a_i = 0$ or 1 (say binary)
- If each receptor binds odor independently (say binary) N of receptors can encode up to 2^N odor identities.

  → so with 1000 receptors you can potentially encode for $2^{1000} \sim 10^{300}$ odors (a lot!)

  $\log_{10}(2^{1000}) = 1000 \underbrace{\log_{10} 2}_{0,3} \simeq 300$

- 1000 receptors may code for already many odors
- it looks like many organisms evolved a diversity of receptors

  Assuming diversity is good, how can you generate it?

  (1) Mutations / selection → need 1 gene per receptor

  (2) Assembly of receptor from subunits

  → few genes generate many receptors

- NOTE For this to work a_i should not be function of $a_{j \neq i}$

  → in this sense it's important that assembly subunits generates "true" diversity (mathematically: $a_{\alpha i + \beta j} \neq \alpha a_i + \beta a_j$)

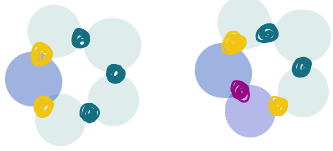
- HOW LARGE IS THE **POTENTIAL DIVERSITY** of OCTOPUS CHEMORECTORS?

If all 26 subunits can be combined at will, then you have:

26 homo-pentamers ;

+ 26 × 25 hetero-pentamers with 2 distinct subunits

×2 { in proportion 4 to 1
   = 3 to 2



+ 26 × 25 × 24 heteropentamers w 3 ≠ subunits in proportions

×2 { ◦ 1-2-2
   ◦ 1-1-3

+ 26 × 25 × 24 × 23 heteropentamers w 4 ≠ subunits (1-1-1-2)

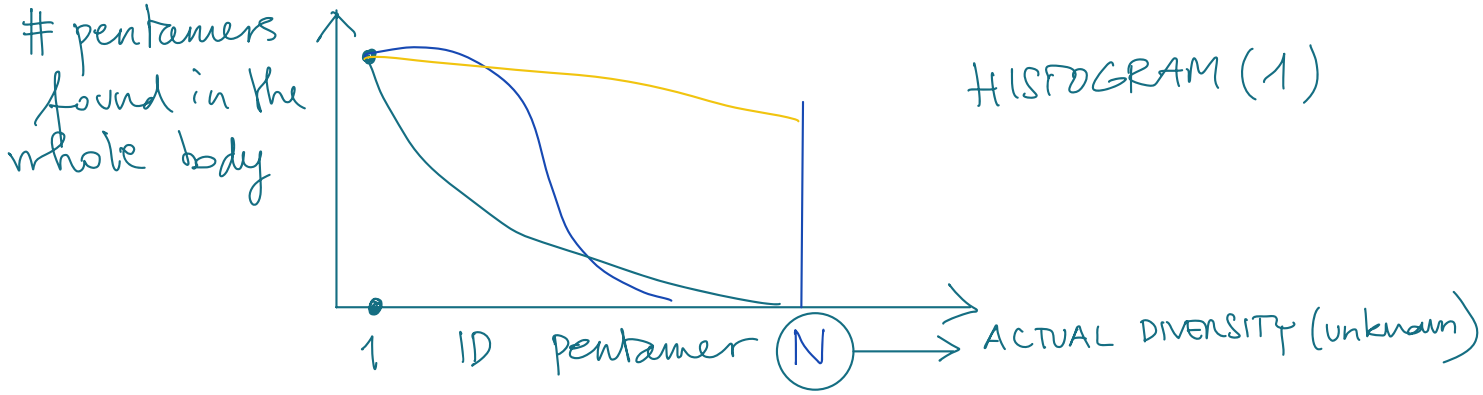
+ 26 × 25 × 24 × 23 × 22 heteropentam. w 5 ≠ subunits

= **GRAND TOTAL = 8 · 284 · 926** (compare with cows ~ 4k)

- WHAT IS THE **ACTUAL DIVERSITY** we can infer from data?

Suppose that you can sequence each single pentamer in an individual, & then ID the pentamer from the most abundant (ID = 1) to the least abundant (ID = N)

Then their histogram may look like any of these:



HISTOGRAM (1)

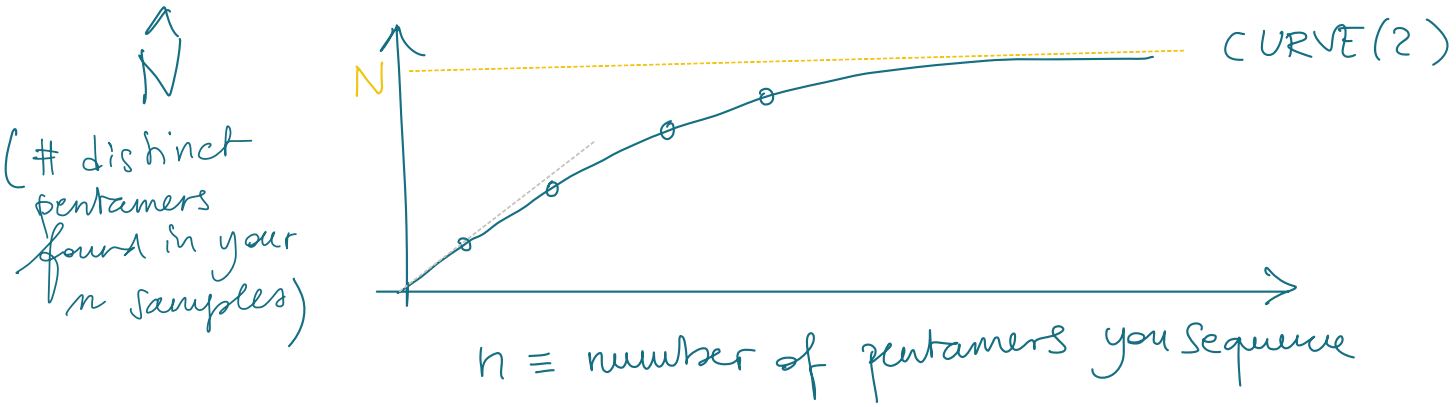
- If you sequence n random pentamers from the whole animal, you'll find a $\hat{N}$ distinct pentamers:

$\hat{N}$ ↗ grows with n, when n is small

↘ cannot be larger than the total # N in the animal

So the curve for sample diversity $\hat{N}$ as a function of how many receptors you sequence will look like this:

PABLO: can you plot this?



If you sample more & more pentamers, we may be able to see CURVE(2) bend, and infer where it saturates, which provides an estimate of N.

NOTE: The estimate will be affected by error, because we don't know how HISTOGRAM(1) looks like

• DOES heterogeneity functionally create diversity?

× Molecularly, for homopentamers we know binding site is @ the interface between two subunits
→ suggests that combining ≠ subunits will modify the binding site hence the binding activities.

PABLO: is there a way to confirm with heteropentamers that binding site is @ interface?

× Computationally.

TO DO: write Monod-Wyman-Changeux model of allostery for receptor with 5 binding sites

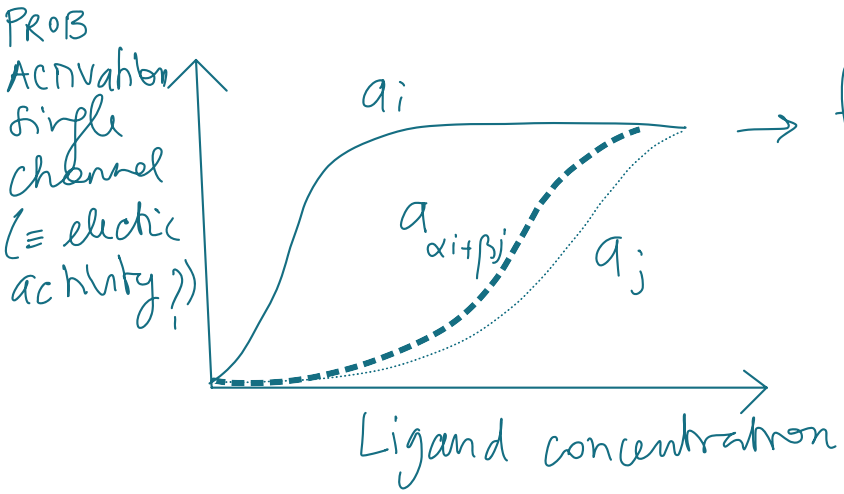
GOAL: make a prediction for null model, where assembly of ≠ subunits does not contribute diversity:

activation homopentamer with 5 subunits of kind i

no diversity from assembly of ≠ subunits $\leftrightarrow$ $a_{\alpha i + \beta j} \propto \alpha a_i + \beta a_j$

activation of hetero-pentamer with α subunits of type i & + β // // // j

activation heteropent. with 5 subunits of type j



→ fit α, β, then use to check for other ligands!

PABLO, if you give us the dose-response curve for your 5 ligands, we can see if they are diverse.