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The Core Mathematical Error of PROTEIN LIGAND BINDING Expression

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A protein in solution exists in two forms: bound and unbound. Depending on a specific protein's affinity for ligand, a proportion of the protein may become bound to ligands, with the remainder being unbound. If the protein ligand binding is reversible, then a chemical equilibrium will exist between the bound and unbound states, such that:

P (protein) + L (ligand) ↔ PL (protein - ligand complex)

The dissociation constant for this reaction is,

$$K = [P]\,[L]\,/\,[PL]$$

In this equation $[P] = [P]_T – [PL]$ and $[L] = [L]_T – [PL]$ where $[P]_T$ and $[L]_T$ are the initial total concentrations of the protein and ligand, respectively. The dissociation constant K is a useful way to present the affinity of a protein for its ligand. This is because the number K quickly tells us the concentration of protein that is required to yield a significant amount of interaction with the target ligand. Specifically, when protein concentration equals K, the 50% of the target ligand will exist in the protein ligand complex and 50% of the ligand will remain in the free form [L]. (This holds true under conditions where protein is present in excess relative to ligand). Typically, proteins must display a $K \leq 1 \times 10^{-6}$ M for the interaction with their target ligand. When considering the K for proteins, smaller numbers mean better binding. The higher the K value the protein does not bind well to the ligand. At very high ligand concentrations all the protein will be in the form of PL such that

$$[P] = 0$$

If [P] = 0, then

$$K = 0$$

Using the equilibrium relationship K [PL] = [L] [P] and substituting,

$[P]_T – [P]$ for [PL], $[L]_T – [PL]$ for [L] and $[P]_T – [PL]$ for [P] Gives:

$$K\,\{[P]_T – [P]\} = \{[L]_T – [PL]\}\,\{[P]_T – [PL]\}$$

$$K\,[P]_T – K\,[P] = [L]_T\,[P]_T – [PL]\,[L]_T – [PL]\,[P]_T + [PL]^2 \text{ which on rearranging:}$$

$$K\,[P]_T – [L]_T\,[P]_T + [PL]\,[P]_T = – [PL]\,[L]_T + [PL]^2 + K\,[P]$$

$$[P]_T\,\{K – [L]_T + [PL]\} = [PL]\,\{– [L]_T + [PL]\} + K\,[P]$$

Further, if we substitute $[L]_T = [PL] + [L]$. Then we get

$$[P]_T\,\{K – [PL] – [L] + [PL]\} = [PL]\,\{–[PL] – [L] + [PL]\} + K\,[P]$$

$$[P]_T\,\{K – [L]\} = – [PL]\,[L] + K\,[P] \text{ which is the same as:}$$

$$[P]_T\,\{K – [L]\} = K\,[P] – [PL]\,[L]$$

$$K – [L] = K\,\{[P]/ [P]_T\} – \{[PL]/ [P]_T\}\,[L]$$

Labeling $[P] / [P]_T$ as F_{FP} (fraction of free protein) and $[PL] / [P]_T$ as F_{BP} (fraction of bound protein) then above expression turn into

$$K – [L] = K\,F_{FP} – F_{BP}\,[L]$$

Any equation is valid only if LHS = RHS. Hence

If $F_{FP} = F_{BP}=1$, then the LHS = RHS, and the above Equation is true.

If $F_{FP} = F_{BP} \neq 1$, then the LHS $\neq$ RHS, and the above Equation is invalid.

Let us now check the validity of the condition

$$\text{“}F_{FP} = F_{BP} = 1\text{”.}$$

As per the protein conservation law,

$$[P]_T = [PL] + [P]$$

From this it follows that

$$1 = F_{BP} + F_{FP}$$

If we assume $F_{BP} = F_{FP} = 1$, we get:

$$1 = 2$$

The condition $F_{FP} = F_{BP} = 1$ is invalid, since 1 doesn’t = 2. In fact, the only way it can happen that K – [L] = K – [L] is if both $F_{FP} = F_{BP} = 1$. Since $F_{FP} = F_{BP} \neq 1$, Equation $K - [L] = K F_{FP} - F_{BP} [L]$ does not therefore hold well.

CONCLUSION: Using the equilibrium relationship K [PL] = [L] [P] and substituting $[P]_T - [P]$ for [PL], $[L]_T - [PL]$ for [L], $[P]_T - [PL]$ for [P] and simplifying we get the wrong result:

$$K - [L] = K F_{FP} - F_{BP} [L]$$

REFERENCES

- Protein-Ligand Binding by MK Gilson.