



14. Hill Coefficient and the “Concentration-Effect” Relationship

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In “normal” cases of bimolecular reactions at equilibrium, a one-hundred-fold increase in drug concentration (two logarithmic units) is required for the effect to increase from 10% to 90% of the maximal effect. This general rule applies to any type of effect being evaluated, whether it is an effect measured at the level of an isolated organ response, second-messenger production, inhibition of enzymatic activity, or inhibition of radioligand binding in a competition assay, as predicted by the simple Langmuir-Hill equation, widely discussed in pharmacology textbooks.

In some cases, however, log concentration-effect curves may display a slope different from that expected, which is reflected by the drug effect occurring over a narrower or wider concentration range than normal (see above). In such cases, where the slope of the curve appears atypical, it is recommended to use a more general equation to describe the data, in which an additional parameter, the Hill coefficient, is included. The value of this parameter determines the slope of the curve: if it is less than 1, the curve is less steep; if it is greater than 1, the curve is steeper than normal. Because this aspect is rarely addressed in pharmacology textbooks, it seems appropriate to discuss here the origin, definition, and interpretation of the Hill coefficient, given its widespread use in several areas of pharmacological research, including the screening of new active compounds in the drug discovery process, a topic discussed in a [previous entry of this glossary](#).

Hill coefficient (n_H)

This parameter was introduced in 1910 by Archibald Hill, when he derived the equation now known as the Hill equation (a three-parameter logistic equation, see below), originally to describe the sigmoidal curve of oxygen binding to hemoglobin. With this equation, Hill aimed to provide a more general description of the relationship between drug concentration and binding to its receptor; it was later also used to analyze any type of concentration-effect curve. It is important to emphasize that this equation was originally developed as a phenomenological description of oxygen binding to hemoglobin and is not based on any mechanistic principle of binding, as is sometimes incorrectly extrapolated when a relationship is assumed between the Hill coefficient value and the number of drug binding sites on its receptor. This was yet another contribution to quantitative pharmacology by this mathematics student who became interested in the natural sciences when he began his work in physiology under the supervision of William Langley, the first to propose the existence of receptors.

$$E = \frac{E_{\max} \cdot [D]^n}{EC_{50}^n + [D]^n} \quad \text{Hill Equation}$$



Where: $[D]$ is the drug concentration; E_{\max} is the maximal drug effect; n is the Hill coefficient (n_H); and EC_{50} is the drug concentration required to produce 50% of the maximal effect.

That said, the situations that may give rise to Hill coefficients different from 1 are listed below:

$n_H < 1$:

- Multiplicity of enzymes, receptors, or binding sites for which a drug has different affinities;
- Negative cooperativity between different sites, whether located within the same receptor or on different protomers (in the case of oligomers, such as dimers).

$n_H > 1$ (less frequent):

- Positive cooperativity between different sites;
- Irreversible binding or inhibition;
- Nonspecific phenomena.

References

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