Derivation of Hill's Equations from Scale Invariance

Andres Ortiz

Department of Mathematical Sciences
University of Texas at El Paso
El Paso, Texas 79968, USA
aortiz19@miners.utep.edu

supervised by Vladik Kreinovich
vladik@utep.edu

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1. Molecular Binding in Biochemistry

- Many biochemical reactions involve binding of a smaller molecule L (called *ligand*) to a large macromolecule P:

$$L + P \leftrightarrow LP.$$

- Examples:
  - oxygen binds to haemoglobin: this is one of the most important biochemical reactions;
  - acid content in the stomach regulated by histamine binding to histamine receptor (special protein);
  - human serum albumin, protein in human blood plasma, carries nutrients as ligands.
- It is desirable to predict the proportion of the bound macromolecules $\theta \overset{\text{def}}{=} \dfrac{[LP]}{[P] + [LP]}$.

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2. Hill's Equation: Description and Challenge

- *Reminder:* it is desirable to predict the proportion θ of the bound macromolecules:

$$\theta \stackrel{\text{def}}{=} \frac{[LP]}{[P]+[LP]}.$$

- In many cases, this proportion is described by a formula (called *Hill's equation*)

$$\theta = \frac{[L]^n}{K_d + [L]^n}.$$

- In this formula, K_d and n are empirical parameters.
- Since its invention in 1910, Hill's equation remains a semi-empirical formula.
- It is desirable to provide a theoretical explanation for this formula.

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3. Chemical Kinetics: Reminder

- The quantitative results of chemical reactions are usually described by equations of chemical kinetics (CK).
- In CK, the reaction rate is proportional to the product of the concentrations $[c]$ of all reactants c.
- Examples:
  - for the reaction $A + B \to C$, the reaction rate is proportional to the product $[A] \cdot [B]$:

$$\frac{d[A]}{dt} = -k\cdot[A]\cdot[B]; \quad \frac{d[B]}{dt} = -k\cdot[A]\cdot[B]; \quad \frac{d[C]}{dt} = k\cdot[A]\cdot[B].$$

  - for the reaction $2A + B \to C$, the reaction rate is proportional to $[A] \cdot [A] \cdot [B]$.
- These formulas explain specific cases of Hill's equation, corresponding to the case when n is an integer.

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4. Chemical Kinetics and the $n = 1$ Case of Hill's Equation

- We have two reactions: $L + P \xrightarrow{k_a} LP$ and $LP \xrightarrow{k_d} L + P$.
- Thus, equilibrium is when

$$\frac{d[L]}{dt} = -k_a \cdot [L] \cdot [P] + k_d \cdot [LP] = 0.$$

- So, $k_a \cdot [L] \cdot [P] = k_d \cdot [LP]$ and $[LP] = \dfrac{k_a}{k_d} \cdot [L] \cdot [P]$.
- Here, $[P] + [LP] = \left(1 + \dfrac{k_a}{k_d} \cdot [L]\right) \cdot [P]$, hence

$$\theta = \frac{[LP]}{[P] + [LP]} = \frac{\dfrac{k_a}{k_d} \cdot [L]}{1 + \dfrac{k_a}{k_d} \cdot [L]}.$$

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5. Chemical Kinetics and the $n = 1$ Case of Hill's Equation (cont-d)

- Reminder: chemical kinetics implies that
$$\theta = \frac{\dfrac{k_a}{k_d} \cdot [L]}{1 + \dfrac{k_a}{k_d} \cdot [L]}.$$
- Multiplying both numerator and denominator by $K_d \stackrel{\text{def}}{=} \dfrac{k_d}{k_a}$, we get $\theta = \dfrac{[L]}{K_d + [L]}$.
- This is Hill's equation for $n = 1$.
- Reactions like $L + 2P \to LP + P$ can explain $n = 2$ and other cases when n is integer.
- In practice, we often observe non-integer values n.
- Such values are difficult to explain by chemical kinetics.

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6. Towards Generalization of Chemical Kinetics

- In the traditional chemical kinetics, the rate r of the reaction $A + B \to C$ is $r = \text{const} \cdot [A] \cdot [B]$.
- This formula only explains the $n = 1, 2, \ldots$ cases.
- To explain the general case of Hill's equation, we need to consider a more general formula $r = f([A], [B])$.
- Idea: the numerical value of a quantity depends on the choice of a measuring unit; e.g., 2 m = 200 cm.
- If we replace a unit for $[A]$ by a λ_A times smaller one, we get a new numerical value $[A]' = \lambda_A \cdot [A]$.
- Similarly, for B, we get $[B]' = \lambda_B \cdot [B]$.
- It makes sense to require that the dependence is the same in the new unit if we appropriately re-scale r.
- So, for every $\lambda_A > 0$ and $\lambda_B > 0$, there exists a μ s.t. if $r = f([A], [B])$, then $\mu(\lambda_A, \lambda_B) \cdot r = f(\lambda_A \cdot [A], \lambda_B \cdot [B])$.

7. Mathematical Analysis of Scale Invariance

- *Reminder:* the dependence $f([A],[B])$ is such that for every λ_A and λ_B, there exists a μ for which:
  - if $r = f([A],[B])$ then $r' = f([A]',[B]')$
  - where $[A]' = \lambda_A \cdot [A]$, $[B]' = \lambda_B \cdot [B]$, and $r' = \mu \cdot r$.
- *In math. terms:* $f(\lambda_A \cdot x, \lambda_B \cdot y) = \mu(\lambda_A, \lambda_B) \cdot f(x,y)$.
- *Natural assumption:* $f([A],[B])$ is differentiable.
- For $\lambda_B = 1$, diff. w.r.t λ_A and taking $\lambda_A = 1$, we get $x \cdot f'(x,y) = \alpha \cdot f(x,y)$, i.e., $x \cdot \dfrac{df}{dx} = \alpha \cdot f$, w/ $\alpha \stackrel{\text{def}}{=} \mu'(1)$.
- Separating the variables, we get $\dfrac{df}{f} = \alpha \cdot \dfrac{dx}{x}$.
- Integrating, we get $\ln(f(x,y)) = \alpha \cdot \ln(x) + c_1(y)$, so $f(x,y) = \exp(\ln(f(x,y))) = c_2(y) \cdot x^\alpha$, w/ $c_2 = \exp(c_1)$.
- Similarly, $f(x,y) = c_3(x) \cdot y^\beta$, so $c_2(y) = \text{const} \cdot y^\beta$ and $f(x,y) = \text{const} \cdot x^\alpha \cdot y^\beta$.

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8. Generalized Chem. Kin. Explains Hill's Eq.

- *Reminder:* for $A + B \to C$, the rate is $k_a \cdot [A]^\alpha \cdot [B]^\beta$.
- *Similarly:* for $C \to A + B$, the scale-invariant reaction rate is $f([C]) = k_d \cdot [C]^\gamma$. Thus, equilibrium is when
$$\frac{d[L]}{dt} = -k_a \cdot [L]^\alpha \cdot [P]^\beta + k_d \cdot [LP]^\gamma = 0.$$
- So, $\frac{k_a}{k_d} \cdot [L]^\alpha \cdot [P]^\beta = [LP]^\gamma$ and $[LP] = C \cdot [L]^n \cdot [P]^{\beta/\gamma}$, with $C = \left(\frac{k_a}{k_d}\right)^{1/\gamma}$ and $n = \alpha/\gamma$.
- When $\beta = \gamma$, we have $[P] + [LP] = (1 + C \cdot [L]^n) \cdot [P]$, hence
$$\theta = \frac{[LP]}{[P] + [LP]} = \frac{C \cdot [L]^n}{1 + C \cdot [L]^n}.$$
- Dividing both numerator and denominator by C, we get Hill's equation $\theta = \frac{[L]^n}{K_d + [L]^n}$, with $K_d \stackrel{\text{def}}{=} 1/C$.

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- In biochemistry, the proportion of the bounded macromolecules is often described by Hill's eq. $\theta = \dfrac{[L]^n}{K_d + [L]^n}$.
- When n is an integer, this eq. can be explained by chem. kin., where the rate of $A + B \to C$ is $k \cdot [A] \cdot [B]$.
- However, in practice, n is often not an integer, and so the chemical kinetics explanation is not applicable.
- We assume that the reaction rate $f([A], [B])$ is scale-invariant but can be more general than the product.
- As a result, we get a family of formulas that include Hill's equation as a particular case.
- Thus, we get a theoretical explanation for Hill's equation.
- We also get a more general formula that may be useful to explain possible deviation from Hill's equation.

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