The Tie That Binds: Optimal Design of Equilibrium Spectrophotometric Titrations

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Introduction

- Binding constants are crucial numbers for many areas of chemistry.
- Applications in self-assembly: molecular fabrication of nanostructures.
- UV-vis titrations provide an inexpensive way to probe solution binding behavior.
- However, the existing literature does not provide guidelines for designing effective titrations regardless of the size of the binding constant.
- This work derives new formulas for helping chemists to design optimally-accurate titrations for 1:1 equilibrium systems.

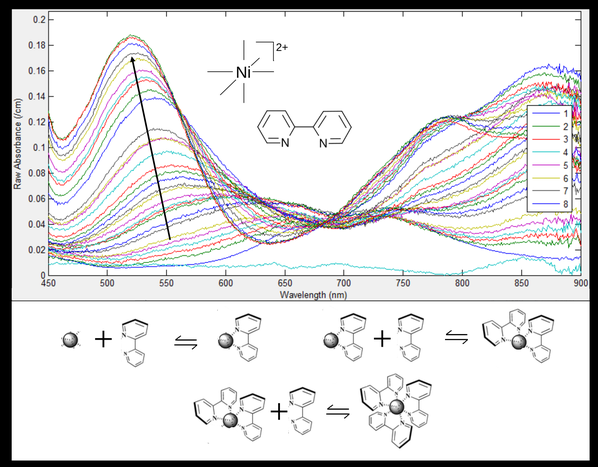

Figure 1: *Example spectrophotometric titration data.*

The Binding Isotherm

- This plot shows how 1:1 equilibrium complexes are formed as the analyte (host) is titrated with guest molecules.

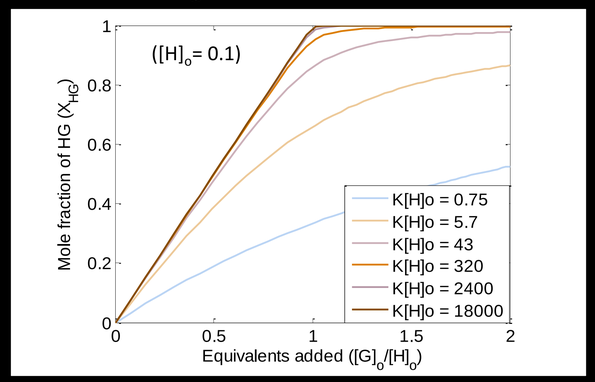

Figure 2: ***B****inding isotherms for varying binding regime strengths (as quantified by* $K[H]_0$*).*

Results and Discussion

Mathematical Derivation

- Starting with a reparameterized form of the 1:1 equilibrium constant expression, the mole fraction of the 1:1 complex can be found.

$$X_{HG} = \frac{[HG]}{[H]_0} \qquad E = \frac{[G]_0}{[H]_0} \qquad B = K_a[H]_0$$

$$X_{HG} = \frac{1}{2}\left[1 + E + \frac{1}{B} - \sqrt{\left(1 + E + \frac{1}{B}\right)^2 - 4E}\right] \quad \text{(eq. 1)}$$

- The following derivative shows how much the data changes with the equilibrium constant.

$$\frac{dX_{HG}}{dB} = \frac{1}{2B^2}\left[\frac{1 + E + \frac{1}{B}}{\sqrt{\left(1 + E + \frac{1}{B}\right)^2 - 4E}} - 1\right] \quad \text{(eq. 2)}$$

- The location of the max of the derivative plot in Figure 2 can be expressed as a function of the binding constant parameter (eq. 3).

$$\frac{[G]_0}{[H]_0} = 1 + \frac{1}{K[H]_0} \quad \text{(eq. 3)}$$

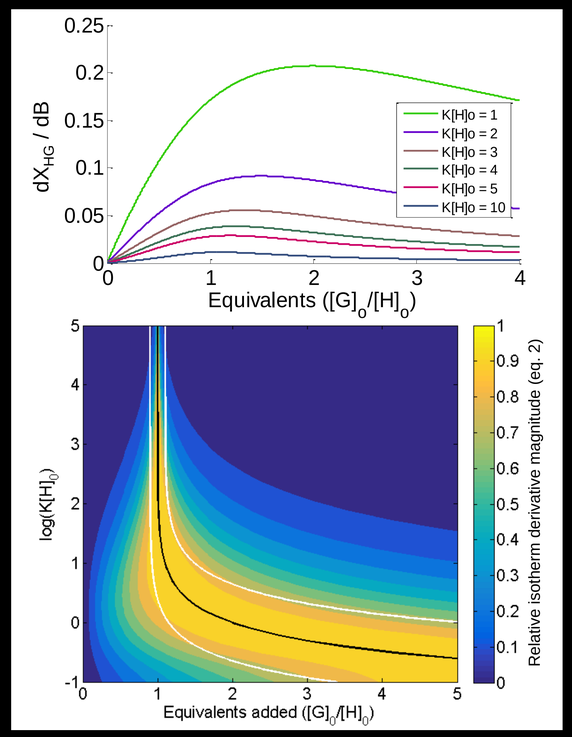

Figure 3: *Derivative of the binding isotherm with respect to the strength of the binding regime. Lower contour plot represents the normalized concatenation of individual traces in the line plot.*

- While eq. 3 represents the single best (most sensitive) solution in the titration, this derivation also leads to an optimal envelope of equivalents for the titration (eq. 4).

$$(1 - C) + \frac{1}{4K[H]_0} < \frac{[G]_0}{[H]_0} < (1 + C) + \frac{4}{K[H]_0} \quad \text{(eq. 4)}$$

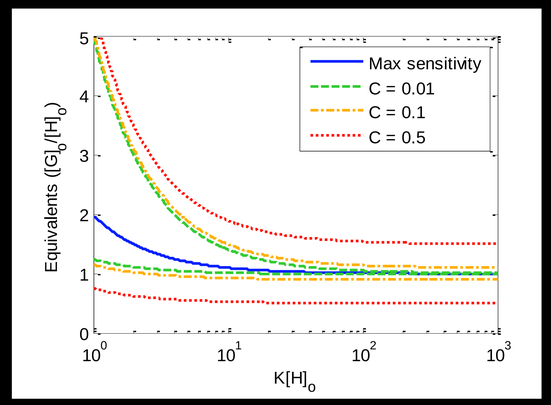

Figure 4: *Sensitivity envelopes according to eq. 4.*

Three Targeting Strategies

a) Control: 0 to 1.2 × $\left((1 + C) + \frac{4}{K[H]_0}\right)$ or 2 equivalents (whichever is larger).

b) Envelope: all solutions in eq. 4 range.

c) Telescope: reserves 11 of 51 solutions to cover range outside of envelope.

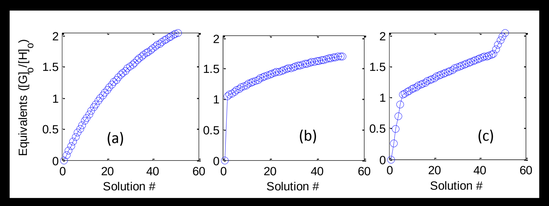

Figure 5: *Titrations generated by the targeting strategies for* $\Delta G° = -10.0$ *kJ/mol,* $[H]_0 = 0.1$ *M, C = 0.*

Computational Validation

- Monte Carlo simulation: computer runs the data analysis procedure thousands of times.
- As the binding regime becomes stronger, uncertainty increases.
- $K[H]_0$ cutoff: when $\sigma(\Delta G°)$ exceeds 1 kJ/mol. As the cutoff increases, accuracy increases.
- Table 1 shows that the telescope strategy is more effective than the standard "control" design in strong binding regimes.

C	Mild Error			Harsh Error		
	Control	Envelope	Telescope	Control	Envelope	Telescope
0.5	3.6×10^4	4.8×10^4	4.8×10^4	5.3×10^3	6.9×10^3	6.9×10^3
0.25	2.8×10^4	8.3×10^4	8.3×10^4	5.3×10^3	1.2×10^4	9.1×10^3
0.1	3.6×10^4	1.5×10^5	1.5×10^5	5.3×10^3	1.2×10^4	1.6×10^4
0.01	3.6×10^4	4.4×10^2	3.3×10^5	5.3×10^3	83	2.1×10^4
0	3.6×10^4	1.9×10^2	5.8×10^5	5.3×10^3	63	2.8×10^4

Table 1: *Monte Carlo* $K[H]_0$ *cutoff values for the two targeting strategies and the control.*

Conclusions

- Not all points along a titration yield insight into the binding interaction occurring.
- We have mathematically derived a novel way of constructing titrations so that the binding isotherm exhibits maximum sensitivity.
- Computational studies suggest this technique should reduce the amount of error in the calculated binding constant.
- Analyses following the new protocol should increase reliable information regarding solution-phase chemical equilibria.

References

Hirose, K. Determination of Binding Constants. In *Analytical Methods in Supramolecular Chemistry*, 1st Ed.; Schalley, C. A., Ed.; Wiley-VCH: Weinheim, 2007, pp 17-54.

Thordarson, P. Determining Association Constants from Titration Experiments in Supramolecular Chemistry. *Chem. Soc. Rev.* **2011**, *40*, 1305–1323.

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