# Reply to Douglass and Spiegel: A suite of mathematical solutions to describe ternary complex formation and their application to targeted protein degredation by heterobifunctional ligands

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Calculating equilibrium concentration of a ternary complex for a given total ligand concentration (1, 2) and predicting the ternary complex concentration in equilibrium with a given free ligand concentration (3) are two totally different questions that lead to clearly distinct mathematical solutions. Even though an exact solution to one question can be an approximate answer to the other, the latter approach (3) is consistent with a long-established tradition of analyzing equilibrium behavior of binding reactions: the equilibrium dissociation constants, $K_d$s, that are used in both approaches are defined by the free, not total, ligand concentration at equilibrium, and the universally adopted equation for a bimolecular binding reaction, $B = B_{max} * [L]/([L] + K_d)$, is also a function of free ligand concentration at equilibrium.

The solutions that I offered (3) are: (i) "exact" because the exact ternary complex concentration can be calculated by the provided mathematical equation for any free ligand concentration at equilibrium; (ii) "universal" because the same mathematical equations apply to all ternary complex systems regardless of the value of cooperativity; and (iii) "original" because this is the first time such solutions are reported. Previous reports are either based on total ligand concentration (1, 2) or with an assumption that ligand depletion can be ignored (2). Other important outcomes of my paper include: (i) seamless expansion of the solution to accommodate modified equilibria, as shown in Figure 3 (3); and (ii) intuitive understanding of the complex systems with one set of equations.

*Conflict of interest*—The authors declare that they have no conflicts of interest with the contents of this article.

## References

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