Competitive qTMDD: Exact Formula of Total Quasi-Steady State Approximation in Competitive Target-Mediated Drug Disposition

Kim, Taehong (School: Korea Science Academy of KAIST)
Cha, Jaeyun (School: Korea Science Academy of KAIST)

Competitive target-mediated drug disposition (competitive TMDD) has been used to describe the behavior of two different types of ligands competing for a common receptor. Due to the complexity of these systems, several reduction methods using quasi-steady state approximation (QSSA) have been attempted, such as standard quasi-steady state approximation (sQSSA) and total quasi-steady state approximation (tQSSA). Although sQSSA yields a system of linear equations with an exact formula, its accuracy significantly drops in conditions with high receptor concentrations, making it challenging to apply to a wide variety of systems. On the other hand, while tQSSA is known to be accurate for all conditions, its exact formula was largely unknown due to the cubic equations involved. In this work, we derived an exact formula of tQSSA in competitive TMDD (competitive qTMDD) by leveraging the properties of cubic equations and complex numbers. Competitive qTMDD provides an accurate approximation of competitive TMDD which is at most 34.7 times more efficient than the alternative methods previously used. Moreover, we have shown that competitive qTMDD can be used for unbiased and efficient drug parameter estimation, with potential applications in a range of competitive interaction scenarios.

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