Quasi-Steady-State Models of Ligand Receptor Binding

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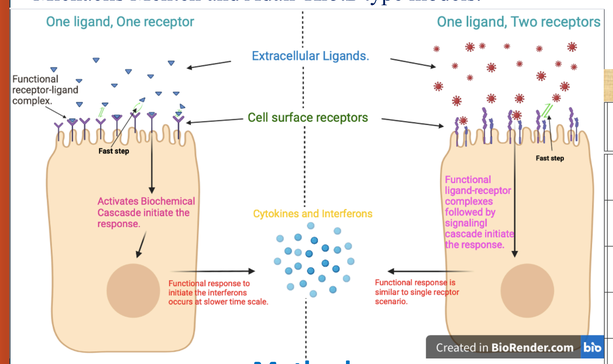
Abstract

Cells use receptors to sense their environment and initiate an appropriate response. While ligand-receptor binding takes minutes or seconds, the cellular response unfolds over hours or days. Hence, receptor ligand binding is often assumed to be at instantaneous equilibrium when modeling the cellular response. That is, a **quasi-steady state assumption** is often employed [1]. The steady-state level of ligand-bound complexes is frequently approximated. In this research, we develop novel models for approximating the steady-state levels of ligand-bound complexes, analyze the accuracy of these models, and compare to the standard Michaelis Menten and Adair-Klotz-type models.



Methods

Case 1: One Receptor, One Ligand

- Receptors and ligands bind in a 1:1 ratio.
- Receptors and ligands are homogeneously distributed in a fixed volume.

This scenario is modeled by the following equation:

- $\frac{d[LR]}{dt} = k_{on}(S^T - [SR])(R^T - [SR]) - k_{off}[SR]$

The exact equilibrium solution can be computed or approximated via a Michaelis-Menten-type model [2].

We propose a novel approximation which:

- Saturates as the concentration of stimulant increases
- Is exact when the concentration of stimulant is zero.
- Is exact when the concentration of stimulant induces half-maximal binding.

Case 2: Two Receptors, One Ligand

Cell surface signaling often takes place in complexes.

- Type I interferon (IFN) signaling is transduced by a complex involving two receptors and one ligand [4].
- Since IFN binds one receptor more readily than the other [4], we assume the binding occurs in sequence, i.e., we assume **cooperative binding**.
- This scenario is modeled by the following system:
- $\frac{dy}{dt} = k_{on}^{y}(x - y)(R_2^T - y) - k_{off}^{y}y$
- $\frac{dx}{dt} = k_{on}^{x}(R_1^T - x)(S^T - x) - k_{off}^{x}(x - y)$

- x : total concentration of receptor-ligand complexes.
- y: concentration of 2:1 receptor-ligand complexes.
- The 2:1 complexes are competent for signaling [4].
- The equilibrium concentration of 2:1 complexes is
  - found numerically (e.g. MATLAB fsolve.m)
  - or approximated using an Adair-Klotz-type model.
- We propose a novel three-point approximation which:
  - is exact in the limit as the concentration of stimulant approaches infinity.
  - is exact when the concentration of stimulant is zero.
  - is exact when the concentration of stimulant induces half-maximal binding.

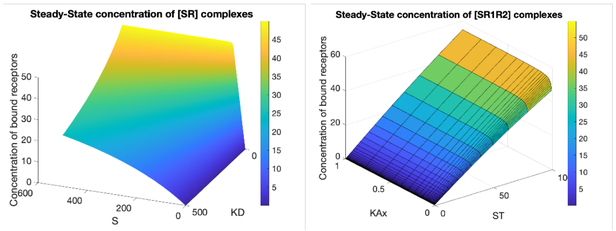
Models

Names	Equations
Exact equilibrium solution (single receptor)	$n(A_2, V, K_{AI}) = \frac{S+R+K_D-\sqrt{(S+R+K_D)^2-4S}}{2}$.
Three-point approximation model (single receptor)	$p_2(A_2^+, V, K_{AI}) = \frac{V}{V+r_1A_2^+ + k_2}$
Michaelis-Menten-type model (single receptor)	$v = \frac{V[S]}{K_M+[S]}$
Three-point approximation model (two receptors)	$Approx = (R_2^T)\frac{S^T}{S^T+S_{half}}$
Adapted Adair-Klotz model (two receptors)	$SR1R2 = R1(1/2)\frac{2(KAy)(KAx)(ST)(R2)}{1+(KAx(ST))+((KAx)(KAy)(ST)(R2))}$

In the above chart, the first three models are for a single-receptor complex while the last two are for a two-receptor complex.

Results

We compute the exact solution and approximations as the substrate concentration and dissociation/association constants vary.



Equilibrium concentration of receptor-ligand complexes for case 1 (left) and 2 (right).

Case 1: One Receptor, One Ligand

- The Michaelis-Menten model suffers from high relative error at low substrate concentrations.
- The relative error of the three-point-approximation model is low to moderate across the parameter space.
- The three-point approximation model is more accurate than the Michaelis Menten model over much of the parameter space (see Figure 2).

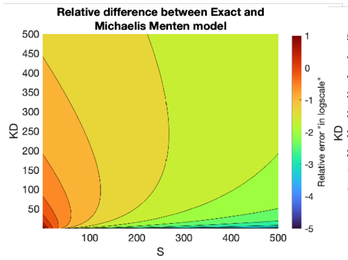


Figure 2a: Relative error in the Michaelis-Menten Model.

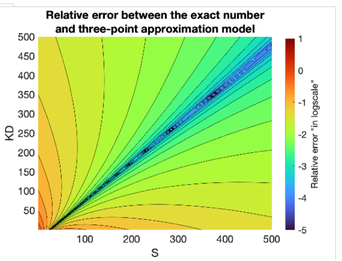


Figure 2b: Relative error in the three-point approximation model.

Case 2: Two receptors, one ligand.

- The Adair-Klotz model suffers from very high relative error.
- At low and moderate substrate concentrations the Adair-Klotz approximation is off by one to two orders of magnitude.
- The three-point approximation model had significant error, but is generally of the correct magnitude.
- The three-point approximation model is approximately ten times more accurate than the Michaelis Menten model across much of the parameter space (see Figure 4).

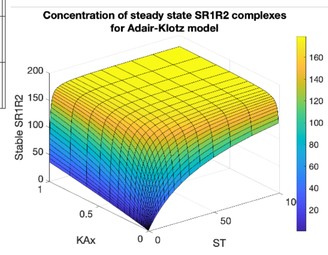


Figure 3a: Adair-Klotz's approximation of 2:1 receptor complexes.

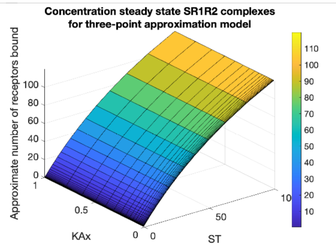


Figure 3b: Three-point approximation of 2:1 receptor-ligand complexes.

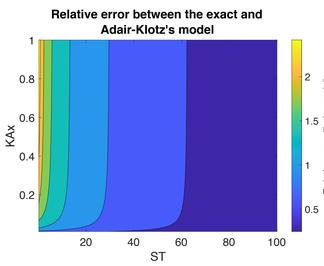


Figure 4 a: Relative error of the Adair-Klotz model*

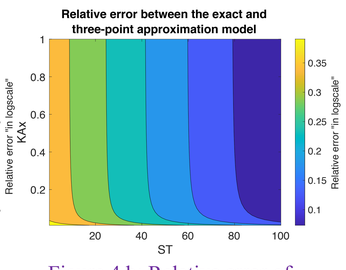


Figure 4 b: Relative error of the three-point approximation model.*

* Note the difference in the color bar scales in Figures 4a and 4b.

Summary/Significance

- We proposed a novel three-point approximation model as an alternative to the well-known Michaelis-Menten and Adair-Klotz equations for approximating the steady-state level of receptor-ligand complexes.
- This novel method of approximation improves on standard methods by accounting for the effect of receptor concentration.
- Our three-point approximation model has several benefits.

Case 1:

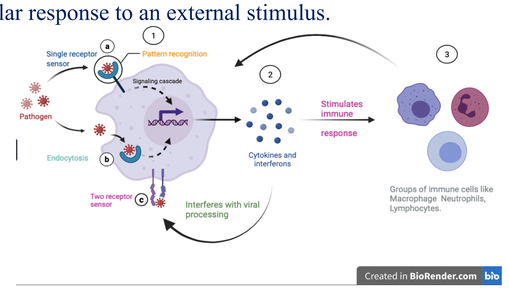
- Our model has a small to moderate relative error over the entire parameter space.
- Our model is significantly more accurate than the Michaelis-Menten model at low substrate concentration.
- Our model is simple to compute.

Case 2:

- Our model is significantly more accurate than the Adair-Klotz equation over the entire parameter space.
- Our model accurately describes the concentration of functional 2:1 receptor-ligand complexes to within an order of magnitude.
- Our model is simple to compute.
- This novel method of approximation can aid biological and pharmaceutical researchers who wish to study systems that are controlled by processes which evolve over disparate time scales [3].
- In such studies, it is beneficial to have a method of approximation that is accurate over a wide range of substrate concentrations, as substrate concentration is likely to vary as the cellular response unfolds.

Future plans

Future work will incorporate the novel three-point approximation model proposed here into a greater tissue-level model of the cellular response to an external stimulus.



References

[1] Diekmann O. and Planqué B., "Exploiting time scale differences: the quasi-steady-state approximation (QSSA)." *Mathematical methods to gain biological insight*. April 16, 2014, 7-23.

[2] Johnson, Kenneth A., and Roger S. Goody. "The original Michaelis constant: translation of the 1913 Michaelis–Menten paper." *Biochemistry* 50.39 (2011): 8264-8269.

[3] Kim, Jae Kyoung. "Analysis of Timeseries Data with Hidden Components." Department of Mathematics Sciences, KAIST, Korea MBI workshop. Department of Mathematics Sciences, KAIST, Korea MBI workshop, 14 July 2021, ZOOM, https://video.mbi.ohio-state.edu/video/player/?id=4893&title=Analysis+of+timeseries+data+with+hidden+components.

[4] Piehler, Jacob, et al. "Structural and dynamic determinants of type I interferon receptor assembly and their functional interpretation." *Immunological reviews* 250.1 (2012): 317-334.

Acknowledgement

We are thankful of **National Science Foundation** for the REU grant #1757493.

We are thankful of **John Ford** and **Anthony Krueger** for providing us their time and assistance throughout this summer research project.