Cooperative kinetics of ligand binding to polymers

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Ligands change the chemical and mechanical properties of polymers. In particular, single strand binding protein (SSB) non-specifically bounds to single-stranded DNA (ssDNA), modifying the ssDNA stiffness and the DNA replication rate, as recently measured with single-molecule techniques. SSB is a large ligand presenting cooperativity in some of its binding modes.

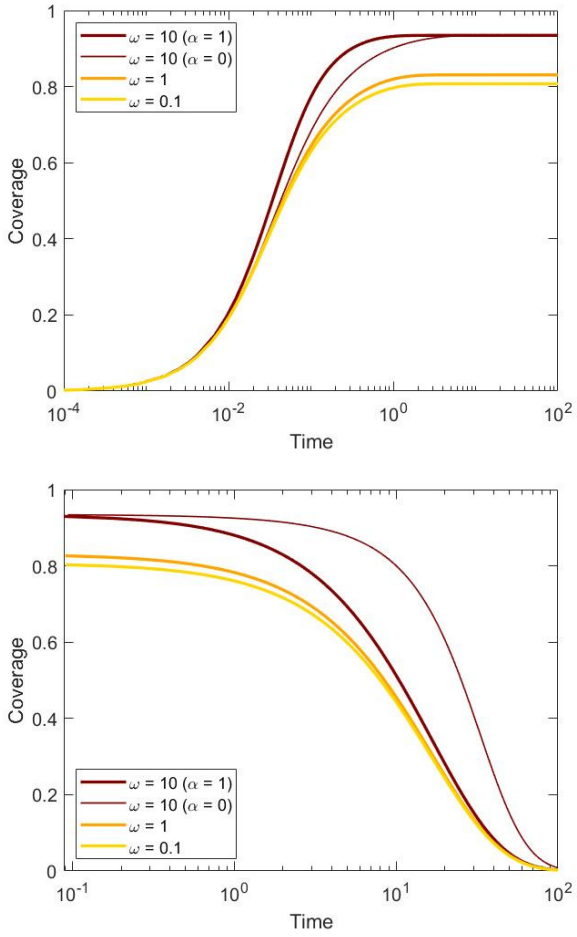

Fig. 1. Polymer coverage as a function of time compared for non-cooperative ($\omega = 1$) and cooperative ($\omega \neq 1$) cases. (Up) Starting with a naked polymer, ligands binding to 30 sites, binding rate $k_b = 0.8\,s^{-1}$, and release rate $k_r = 0.06\,s^{-1}$. (Down) Starting with the previous equilibrium coverages the detachment dynamics is induced setting $k_b = 0$. The cooperativity parameter ω is the equilibrium constant for the process of moving a bound ligand to a location with an additional neighboring bound ligand. ω is determined by the interaction energy between bound ligands. The activation state parameter α measures the impact of cooperativity on the activation energy of the binding process. In the limiting case $\alpha = 1$ cooperativity only enhances binding, while for $\alpha = 0$ only inhibits release.

We aim to develop an accurate kinetic model for the cooperative binding kinetics of large ligands [1, 2]. Cooperativity accounts for the changes in the affinity of a ligand to the polymer due to the presence of another bound ligand. Large ligands, attaching to several binding sites, require a detailed counting of the available binding possibilities. This counting has been done by McGhee and von Hippel to obtain the equilibrium state of the ligands-polymer complex. The same procedure allows to obtain the kinetic equations for the cooperative binding of ligands to long polymers, for all ligand sizes (see Fig. 1).

We also derive approximate cooperative kinetic equations in the large ligand limit, at the leading and next-to-leading orders. We found cooperativity is negligible at the leading-order, and appears at the next-to-leading order. Positive cooperativity can be originated by increased binding affinity or by decreased release affinity, implying different kinetics. Nevertheless, the equilibrium state is independent of the origin of cooperativity and only depends on the overall increase in affinity. Next-to-leading approximation is found to be accurate, particularly for small cooperativity (see Fig. 2).

These results allow to understand and characterize relevant ligand binding processes, as the binding kinetics of SSB to ssDNA, which has been reported to affect the DNA replication rate for several SSB-polymerase pairs.

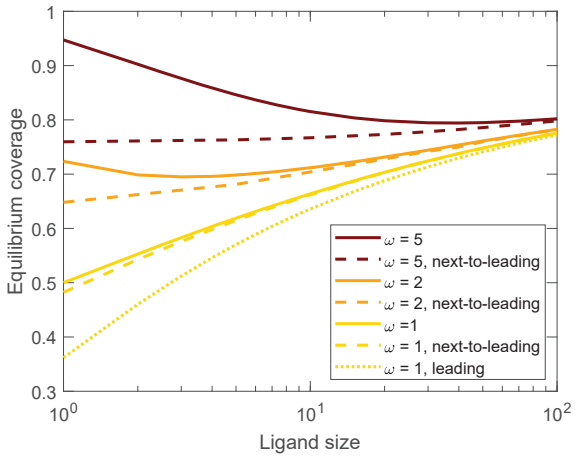

Fig. 2. Comparison of exact and large ligand-size approximation results. Equilibrium coverages as a function of the ligand size.

[1] Juan P.G. Villaluega, and Francisco Javier Cao-García, *Cooperative kinetics of ligand binding to linear polymers*, Comput. Struct. Biotechnol. J. **20**, 521 (2022).

[2] J.P.G. Villaluega, J. Vidal, and F.J. Cao-García, *Noncooperative thermodynamics and kinetic models of ligand binding to polymers: Connecting McGhee – von Hippel model with the Tonks gas model*, Phys. Rev. E **102**, 12407 (2020).