Computational Design of Therapeutic Monoclonal Antibody Formulations

by

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Abstract

Antibody formulation research seeks to move the field from heuristics and rules of thumb to mechanistic approaches. Traditionally, formulations are designed via significant trial and error work after the phase in which molecule discovery and optimization take place. However, this often leads to molecules failing in late development due to an inability to develop a formulation with the desired properties. This thesis aimed to develop a computational formulation design framework that would allow formulation to be addressed during the molecule discovery and optimization steps, allowing molecules able to be formulated to be selected early on. To this end, antibody behaviors with a variety of different formulation excipients were probed via simulation and experiment, and machine learning models of local antibody-excipient interactions were developed.

The behaviors of three antibodies were simulated in the presence of six excipients: sorbitol, sucrose, trehalose, proline, arginine.HCl, and NaCl. Carbohydrates tended to reduce aggregation propensity due to their preferential interactions with exposed aromatic residues. However, their impact on viscosity was highly dependent on the surface characteristics of the antibody, especially on whether charge effects significantly contributed to the antibody viscosity. Proline tended to interact with aromatic residues, reducing the aggregation of antibodies whose aggregation rate was association-limited. Arginine.HCl could interact via charge effects as well as with hydrophobic residues, while NaCl only interacted via charge effects. The overall impact of these excipients in terms of aggregation and viscosity was highly dependent on the surface charge distribution on the variable region.

Finally, these local antibody-excipient interactions were modeled using machine learning techniques. These models were shown to capture the important antibody-excipient interactions that are relevant for understanding the impact on stability. Thus, with the implementation of this tool, antibody formulation design could be implemented efficiently during the molecule optimization step, reducing the cost of follow-up formulation work and reducing the likelihood of molecule failure due to formulation issues.

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