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 signifi-
cant 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 formul-
ation 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 beha-
viors 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 excipi-
ents: 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 hy-
drophobic 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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