COMPUTATIONAL RESEARCH in BOSTON and BEYOND SEMINAR

Population-specific design of de-immunized protein biotherapeutics

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ABSTRACT:

Immunogenicity is a major problem during the development of biotherapeutics since it can lead to rapid clearance of the drug and adverse reactions. The challenge for biotherapeutic design is therefore to identify mutants of the protein sequence that minimize immunogenicity in a target population whilst retaining pharmaceutical activity and structural stability. Current approaches are moderately successful in designing sequences with reduced immunogenicity, do not account for the genetic variation of the immune system in a specific population, and require costly experimental post-screening to guarantee structural and functional integrity.

Here, we will present a novel computational approach for de-immunization design using multi-objective combinatorial optimization that simultaneously optimizes the likelihood of a functional protein sequence at the same time as minimizing its immunogenicity tailored to a target population. We bypass the need for three-dimensional protein structure and molecular simulations to identify functional designs by generating sequences using a probabilistic model that has been used previously for mutation effect and structure prediction. We will demonstrate the method's potential based on initial results of a proof-of-principle study in which we redesigned Factor VIII, a replacement therapeutic used to treat hemophilia A.

FRIDAY, MAY 5, 2017
12:00 PM – 1:00 PM
Building 32, Room 155
(STATA)

Pizza and beverages will be provided.

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