

# CBST/CMET Seminar



**DATE:**

**July 25, 2017**

**TIME:**

**2:00 p.m.**

**LOCATION:**

**366 Colburn Lab**

## **Dr. Francesco Piazza**

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### ***“Ultra-coarse-grained Models to Simulate Ligand-receptor Kinetics of Complex Multivalent Molecules: Fundamentals and Applications to the Design of Novel Agents for Immunotherapy”***

Complex, multivalent and multispecific molecules, such as hinge-engineered antibodies (Ab), multi-Fab chimeric antibodies and similar supramolecular constructs, are receiving increasing attention in biotechnology and biomedicine in the quest for novel more potent agents for cancer and viral immunotherapy. As it is the case for simple antibodies, their considerable structural flexibility [Bongini2004] is a major dynamical determinant of the antigen-ligand kinetics in different natural and laboratory situations [DeMichele2016; Galanti2016; Calero-Rubio 2016]. More generally, it appears crucial to control intramolecular dynamics of complex Abs and derived molecules as a means to design multivalent, multispecific agents with optimum potency and positive cooperativity (avidity).

In this talk I will first trace the contours of a decade-long story of investigation of the structural and dynamical determinants of antigen-antibody interactions, which led us to conceive an ultra-coarse-grained model of Ab parameterized on cryo-EM data. Recently, we have employed this model to simulate the binding dynamics of many Abs to antigens adsorbed on a surface at increasing densities. Our combined computational and theoretical framework is in excellent agreement with SPR data and allowed us to establish and quantify a number of important results. (i) Internal flexibility is key to maximize bivalent binding (avidity). (ii) The large size of Abs is instrumental to keep neighboring molecules at a certain distance (surface repulsion), which helps make epitopes within reach of the second Fab unoccupied on average. (iii) Thermodynamic and geometric factors that regulate the binding equilibrium cannot be condensed into a unique effective parameter. The key geometrical parameters, besides excluded-volume repulsion, describe the screening of free haptens by neighboring bound antibodies. We prove that the thermodynamic parameters govern the low-hapten-concentration regime, while surface screening and repulsion only affect the binding at high hapten densities.

I will finish by briefly describing how we are adapting similar ideas to the computational design of novel multivalent, multispecific agents for HIV and cancer immunotherapy, which we call polybodies (PB), against specific antigen configurations. PB molecules are synthesized by joining different single-domain antibodies (also referred to as nanobodies or VHH) through custom-designed linking architectures realized via DNA-origami, with the aim of boosting the agents' avidity and potency. As an important example, we would like to direct our theoretical framework to design multivalent agents with specific linking architectures able to circumvent the ability of certain viruses, such as HIV, to evade antibodies' avidity [Klein2010].