Computational Modeling of T Cell Receptor Interaction Geometry: <u>SM DeVoe</u> (Ph.D., GS) and S Dai, Department of Immunology and Microbiology, University of Colorado Anschutz, Aurora, CO.

How a T cell receptor (TCR) recognizes its antigen greatly affects the quality of signal and level activation received by the T cell, subsequently dictating the following immune response. Traditionally, the interaction geometry has been defined by two lines: a regression fit of the MHC binding groove and the line formed from the centroids of conserved disulfide bonds in the TCR alpha (TRA) and beta (TRB) chains. The current model fails to take into account several aspects of TCR structure and interaction properties with peptide-major histocompatibility complexes (pMHC). These interactions are facilitated by 3 complementary determining regions (CDR) on each TCR chain. Additionally, the TCR is a complex, dynamic structure where the alpha and beta chains can move independently of one another. We have created an extension of the conventional model to account for these shortcomings where the TCR, TRA chain, and TRB chain are represented by planes. These planes are calculated using the center of mass of the TCR (or corresponding chain) in addition to a linear regression of the coordinates of the atoms within the CDR loops. Furthermore, we have extended our model to identify the impact of CDR3 on interaction geometry by comparing to planes where only germline encoded CDRs are used to model the angle of interaction. From the known structures, an average of a -5.18 degree shift occurs when the CDR3 atoms are included in the model. Using nearest neighbor community detection clustering algorithms, we determined 4 defined clusters of TCR-pMHC interaction geometry exist among the known class I and class II structures. The rigid clustering of our plane-based modelling suggests TCR-PMHC interaction geometry is defined by certain "rules" which dictate a range of orientations that a TCR may take.