Text S2: Detailed description of the operators.

The implementation of the DynaDom approach is based on the definition of three basic operator functions, which are combined in the final prediction pipeline, which is discussed in the main text. Her we provide a detailed description of these functions.

General objective function for the rigid body optimization operators: All rigid body operators (RMZ, RAT, and RAR) operate on a selection s_i, which is transformed relatively to an additional part of the system defined as context c_i. For the evaluation of the objective function only non-bonded interactions between atoms of the s_i and of the remaining context c_i are taken into account. Internal non-bonded interactions within the selected rigid body are not computed, as they remain constant during rigid body operations. The contribution of the objective function e_i is computed as follows:

$$e_{RXX,i} = \sum_{a \in s_i} \sum_{\substack{b \in c_i \\ b \notin s_i}} (E_{vdW}(a,b) + E_{Coul}(a,b)) \qquad (1)$$

In the context of the above described example: let w_1 and w_2 be atoms of the Vβ domain chain B, and w_3 and w_4 atoms of the Vα domain chain A. Then, $\{w_1, w_{2\}} \subseteq s_{TV\beta}$ is the selection and $\{w_1, w_2, w_3, w_4\} \subseteq c_{TV\beta}$ is the context, the intra-selection interactions (w_1, w_2) are ignored, whereas the inter-domain interactions (w_1, w_3), (w_1, w_4), (w_2, w_3), and (w_2, w_4) are taken into account.

The rigid body rotation and translation operator (RMZ) is based on the work of Mirzaei *et al.,* who recently introduced an algorithm focusing on the RBEM problem for molecular docking [2]. To minimize the interaction energy between two molecules, this algorithm rotates one molecule around a center (usually the center of mass), whereby this center is concurrently slightly translated to an optimum position. Their implementation makes use of the limited memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) Newton-Raphson method [3] and of a transformation of the force field gradient based on the Rodrigues formula. The approach was shown to outperform other RBEM methods by an order of magnitude in time [2].
The operator takes the non-bonded interactions between the flexible rigid body and the defined context c_i (without s_i) of the system into account, according to Equation 1. The operator simultaneously modifies three parameters for the rotation and three parameters for the translation of the rigid body. The gradient evaluation is discussed in detail in ref. [2]. We extended this method to allow for the simultaneous structural optimization of multiple rigid bodies. In the context of the TCRpMHC modeling, both the Vβ domain and the pMHC ligand are translated and rotated in one step.

The rigid body axis operators RAT and RAR: These operators define the separate translation along (RAT) or the rotation around (RAR) an axis according to the forces between the treated rigid body (s_i) and the remaining context c_i without s_i. The objective function e_i is computed according to Equation 1 of the main text.
To compute the gradient for the RAT operator, the non-bonded forces are projected on a predefined normalized axis ($\vec{A}$) as:

$$\overrightarrow{F_{RAT,i}} = \sum_{a \in s_i} \sum_{\substack{b \in c_i \\ b \notin s_i}} (\overrightarrow{F_{vdW}(a,b)} + \overrightarrow{F_{Coul}(a,b)}) \qquad \text{(S1)},$$

$$g_{RAT,i} = -\overrightarrow{F_{RAT,i}} \cdot \vec{A} \qquad \text{(S2)}$$

For the RAR operator the gradient is computed as the one-dimensional tangential force gradient:

$$F_t(s_i, c_i, \vec{A}, \vec{R}) = \sum_{a \in s_i} \sum_{\substack{b \in c_i \\ b \notin s_i}} \overrightarrow{T^r_{ab}} \cdot (1,0,0) \cdot \overrightarrow{D^r_a} \cdot (0,1,0) \qquad \text{(S3)}$$

$$g_{RAR,i} = -F_t(s_i, c_i, \vec{A}, \vec{R}) \quad \text{(S4)}$$

where s_i denotes the atoms of the treated rigid body, and where c_i is the remaining context to interact with. $\vec{R}$ is the coordinate vector of a predefined center of rotation and $\vec{A}$ defines the normalized rotation axis. F_t is the one dimensional tangential force vector with respect to the rotation axis $\vec{A}$ for all atoms a of the selection s_i interacting with all atoms b of the context c_i. The vector $\overrightarrow{T_{ab}^r}$ is the transformed projected force based on the objective function e_i, and $\overrightarrow{D_a^r}$ is the transformed distance vector of atom a with respect with respect to the origin.

The glutamine and asparagine carboxamide group rotation operator (AQR) defines the rotation of a glutamine or asparagine carboxamide group around an axis defined in the direction of the bond between two adjacent side chain atoms (*i.e.* Cβ-Cγ and Cγ-Cδ for an asparagine and a glutamine residue, respectively). The selection s_i ($s_i \subseteq c_i$) contains all atoms of the carboxamide group and the context is usually either the whole remaining protein or all atoms sharing the domain with the carboxamide group. The objective function contribution e_i is computed as follows:

$$e_{AQR,i} = \sum_{a \in s_i} \sum_{\substack{b \in c_i \\ b \neq a}} (E_{vdW}(a,b) + E_{Coul}(a,b) + E_{bonded}(a,b)) \quad \text{(S5)}$$

The evaluation of the tangential force gradient for the AQR operator is based on Equations S3 and S4, but differs from the RAR evaluation in two aspects: First, for the RAR operator, interactions within the selection are not taken into account, whereas for the AQR these interactions are computed and second, also bonded interactions are considered.

Rigid body position restraints (RPS and RPC): To avoid unfavorable large translational moves, we implemented two types of restraint operators, which can be combined with the rigid body operators RAT and RMZ. The restraint operators allow for a certain tolerance of deviation and add distance dependent restraints to the translational gradients and to the objective function. The first type of restraint operator (RPS) restrains the coordinates of one single atom contained in the rigid body to be around a defined position. The second type (RPC) restrains the geometric center of a set of atoms contained in the rigid body to be around a defined position.
For both cases harmonic restraints are used and are computed as follows:

$$e_{rest} = \begin{cases} 0, & if\ d \leq t \\ \frac{k}{2} \cdot (d-t)^2 & \end{cases} \quad \text{(S6)}$$

where t is the threshold, d is the distance between the desired reference position of the rigid body ($\vec{R}$) and the actual position of the rigid body ($\vec{P}$) and k an adjustable force constant (here, k = 100.000 kJ mol^{-1} nm^{-2}).
To restrain the position of the TCR Vβ domain, the RPS restraint operator is used. For this purpose, the reference position $\vec{R}$ is set to the Center of Rotation defined in ref. [1], the actual position $\vec{P}$ is defined as the coordinates of the C_β-atom of the CoR_β Q residue, and the threshold is set to 0.75 nm.
To restrain the pMHC position, the RPC operator is used. As stated above, a conserved residue at the CoR_μ could not be found and the CoR_μ is located close to the center of the bound peptide. Due to the lack of a conserved residue, we define the actual position $\vec{P}$ of the rigid body pMHC as the geometric center between the C- and N-terminal C_α-atoms of the bound peptide. The reference position $\vec{R}$ is set to the

CoR_{μ}, and a threshold of 2.7 nm and 1.3 nm is used for the preplacement pipeline step and the main pipeline step, respectively (see below for the pipeline).

References

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