MULTI-SCALE SIMULATIONS OF CELL-MATRIX INTERACTIONS IN TUMORS

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INTRODUCTION:

Cells reside in a complex, dynamic and heterogeneous environment known as the extra-cellular matrix. Interactions with the extra-cellular matrix regulate fundamental cellular processes such as signaling, adhesion, migration and affect sub-cellular mechano-chemical architecture. Alterations in cell-matrix interactions can result in a variety of life threatening consequences including cancer, neurological disorders and bone defects. In this paper, we develop a multi-scale approach to quantify the force of adhesion between cells and the extra-cellular matrix using a mean field approach. Our approach allows for quantification of adhesion forces as a function of molecular level events including mutations and changes in molecular structure.

METHODS:

Our model is rooted in a mean field approach to calculate spatial dependent equilibrium free energies of the system containing receptor, ligand and the solvent (1-3). The adhesion force is calculated from these spatially dependent free energies. The method and the equations to quantify the free energy of the system are similar to previous studies. By varying the distance "*d*" between the cell membrane and the substrate, our method allows us to compute free energies at varying distances. After calculating free energies at various distances, we apply the thermodynamic relation to derive the adhesion force from free energy. Assuming a canonical ensemble we have:

$$dA = -SdT - f\,dz + \sum_i \mu_i\, dN_i \qquad (1)$$

The temperature of our system is assumed to be constant. And since the number of each of the species (receptor, ligand and solvent) remains unchanged. Therefore:

$$f = -\left(\frac{\partial A}{\partial z}\right)_{T,\{N_i\}} \qquad (2)$$

Eq. 2 allows us to calculate adhesion force strength at the cell-matrix interface. Since the force here depends on the free energy of interaction, that is dependent upon receptor, ligand and solvent properties, our model is able to predict bulk behavior as a function of molecular parameters and conformations, something that has traditionally been beyond the scope of models aiming to quantify forces of the cell.

RESULTS AND DISCUSSION: To test our model, we calculate adhesion forces under three receptor surface coverages: 10^3 /μm^2, 10^4 /μm^2 and $2*10^4$ /μm^2. We first calculate the free energy at varying distances "*d*" and use Eq. 2 to calculate the adhesion force. Fig. 1 shows the force versus distance for the three surface coverages. At distances shorter than 6nm, forces are of significantly higher magnitude. At lower receptor/ligand coverages, we see a competition of entropic repulsions and energetic interactions. Our results suggest that, at a separation of 10nm from the substrate, with an area around 1μm^2 the total force of adhesion would be around 520pN for receptor coverage 10^3 /μm^2, $1.2*10^4$pN for 10^4 /μm^2 and $3.9*10^4$pN for $2*10^4$ /μm^2.

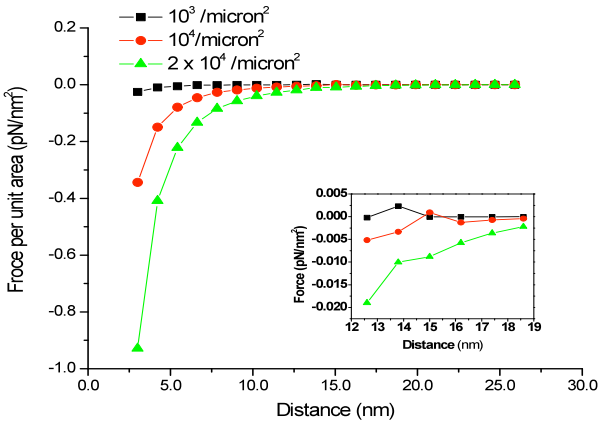

Fig 1 The dependence of force on separation.

Conclusions: Our model can easily be extended to study adhesion of the entire cell-matrix interface. In addition, our method allows for further quantification of cell-adhesion forces with the use of more fine-grained simulations to study mutations and the effects of molecular identities of receptors and ligands. This molecular level detail can not be included in most continuum level models. Such details will provide valuable information on how changes in molecular structure and conformations can lead to alterations in adhesion forces and migration and will allow for a better connection between molecular and cellular biophysical studies of cell adhesion and migration.

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