43b Molecular Recognition in Model DNA Microarrays: a Computer Simulation Study

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DNA microarrays have been widely adopted by the scientific community for a variety of applications - to identify genes that are preferentially expressed by cells, to reconstruct the metabolic pathways for cell operation, to identify genes that are differentially expressed in healthy versus diseased cells, enabling disease diagnosis, etc. We study the thermodynamics and the kinetics of hybridization of singlestranded "target" genes in solution with complimentary immobilized "probe" DNA molecules on a microarray surface using a coarse-grained lattice model. The target molecules in our system contain 48 statistical segments and the probes tethered on a hard surface contain 8 to 24 segments. The segments on the probe and target are distinct, i.e., instead of having each segment represent one of the four types of nucleotides A, T, G, C, the segments represent a sequence of nucleotides. Therefore each segment along the probe interacts exclusively with its unique "complement" segment on the target molecule with a single interaction (hybridization) energy; all other interactions are zero. We use lattice Monte Carlo simulations to examine how the following parameters affect the extent of hybridization of the target molecule: (1) the probe length, (2) temperature or interaction (hybridization) energy, (3) the position of the complimentary probe sequence with respect to the target sequence, (4) the grafting density of the probes (number of probes per surface area) and (6) the presence, number and distribution of mismatches on the probe. We also study how each of these factors affects the kinetics of the hybridization process. For systems containing single probe and single target molecules, the results indicate that as the probe length increases the enthalpic gain in binding all of the probe segments to the target is not high enough to overcome the entropic loss upon binding which increases dramatically with increasing probe length. As the hybridization energy increases, the longer probes are able to bind all their segments to the target since the enthalpic gain can overcome the entropic loss of binding. This work should give a fairly broad physical picture of molecular recognition in DNA microarrays and eventually provide a set of general guidelines for maximizing microarray sensitivity and specificity.