Using the Gillespie algorithm to investigate the role of chromatin geometry in the recruitment of repair proteins to DNA double strand breaks

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The mechanisms by which DNA repair proteins are recruited to DNA double strand breaks (DSBs) remain mostly unknown. Recent Fluorescence Recovery After Photobleaching (FRAP) data has provided accurate measurements of a number of physical parameters related to the dynamics and the interactions between proteins of the RAD52 group homologous recombination proteins (Essers et al. 2002). Analysis of these data is not optimal and it frequently disregards the interactions of these proteins with the chromatin as well as mechanistic models that could account for these observations. Here we describe a new computational method that allows for the incorporation of chromatin structure as well as different mechanistic models of DNA recruitment and repair. Our method is based on a previously published extension of the Gillespie algorithm that includes reaction-diffusion in three-dimensional volumes (Bernstein 2005). Idealized nuclei are divided into microchambers where reaction-diffusion parameters are estimated locally. Using the computer code described in Bernstein (2005) we simulated diffusion and binding of repair proteins to a DSB. Interaction of the proteins with the break was modeled by a simple Michaelis-Menten reaction. Using this system we quantified the number of proteins at the break. For instance, we found that for a single DSB and a K_2 of 0.038 (Essers et al. 2002) the number of Rad52 bound proteins is around 350. This is a small number when compared to a recent study by Lisby et al. where it is proposed that about 600 and 2100 are found at the break. These results are hard to reconcile with the estimated residence times (Essers et al. 2002) but support the model of the formation of repair centers (Lisby et al. 2004).