Guanine mediated adsorption of DNA repair enzymes

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Short Abstract — We model the stochastic dynamics of guanine radical mediated deposition of repair enzymes on DNA. We use a Broadwell model to describe the coherent motion of an electron released by a bound repair enzyme. This electron can back-scatter (by heterogeneities in the DNA) to the repair enzyme and destabilize it, causing it to desorb; or it can be absorbed by nearby guanine radicals. First, we compute first passage times to find the statistics of repair enzyme binding and desorption rates along an infinite DNA strand. Then, we use a mean-field approach to describe the dynamics of electrons, guanine radicals and repair enzymes through a set of coupled Partial Differential Equations.

***Keywords* — Base Excision Repair, Enzyme adsorption, Broadwell Model, Stochastics, Mean Field.**

I. Purpose

THE genome of all living things are constantly under attack by mutagenic agents such as reactive oxygen species and ionizing radiation. Such agents can damage bases or nucleotides giving rise to lesions in the DNA [1]. One of the cell's defense mechanisms against lesions is the Base Excision Repair (BER) pathway. BER enzymes maintain the integrity of the DNA by locating and repairing damage, generally keeping miscoded proteins to a minimum. However, the mechanism through which repair enzymes locate lesions in DNA is generally not well understood.

One proposed explanation is that BER enzymes cooperate to scan to scan the DNA more rapidly through a charge transport (CT) mechanism [2]. This mechanism was suggested as a possible basis for efficient scanning by MutY, a particular type of repair enzyme. MutY is known to contain an Iron-Sulfur cluster which plays a key role in the CT mechanism. The cluster can take one of two forms: $[4Fe\text{-}4S]^{2+}$ and $[4Fe\text{-}4S]^{3+}$. When the BER enzyme contains the $[4Fe\text{-}4S]^{3+}$ cluster, it has a higher binding affinity to DNA; hence MutY in its $[4Fe\text{-}4S]^{2+}$ form preferentially adsorbs to DNA, oxidizing the cluster and emitting an electron along the DNA. The electron is emitted on either side of the enzyme with equal probability. If the electron back-scatters and returns to the original MutY, the MutY self-desorbs. If the electron is absorbed by a repair enzyme further along the DNA, the MutY remains on the DNA and the distant repair enzyme is destabilized and desorbs.

Furthermore, it is also throught that Guanine radicals play an important role in the CT mechanism. The radicals absorb electrons released by repair enzymes, converting to "normal" guanine bases in the process [3]. Therefore, the presence of guanine radicals promotes the adsorption and accumulation of repair enzymes.

The presence of a lesion prevents the passage of electrons between two BER enzymes [2, 3]. It is thought that the disruption of the CT mechanism results in an aggregation of enzymes near the lesion but quantifying the improved behavior has so far been restricted to simple scaling arguments [4].

In this work, we investigate the kinetics of MutY BER enzymes on DNA by using a stochastic Broadwell model [5] to describe the electron motion. We derive desorption rates and statistics in terms of electron flip rates, velocities and guanine density. We also find expected search times for MutY to locate lesions. Finally, we describe the interaction of repair enzymes, electrons and guanine radicals through a mean field approach. By solving a set of coupled Partial Differential Equations, we find the distribution of BER enzymes near lesions and quantify their aggregation rate.

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