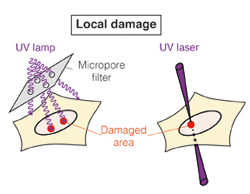
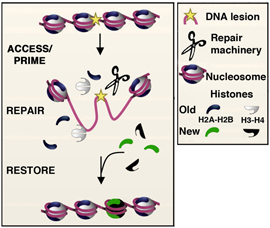
Modelling Chromatin Restoration Post UV Damage Repair.

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**Aim:**

**Background:**

In response to the DNA damage we observe genome stabilization by histones which leads to structure chromatin restoration.

The group of Sophie Polo (Paris Diderot U) have examined the response and coordination of the genome and epigenome in response to an induced local UV damage.

Histones are synthesizes and escorted by histone chaperones in response to the damage and at the site, to stabilize the chromatin structure near the damaged site.

Several histones are excluded from the site of damage, either by being pulled out or by sliding away from the damage site by histone chaperones.

After UV damage, the DNA binding Protein 2 (DDB2) is being recruited to the site of UV damaged and probably plays a role in “pushing” the histones away from the damage site.

The histones close to the damage site carry epigenetic information. What happens to this information after the histones are removed? What happens to the original histones?

In local UV damage experiments, histones can be replaces by labeled histones and be tracked in-vivo by SNAP methods.

DNA density was examined after UV induction and was found to be less compact.

There was found to be no loss of histones in the nucleus in response to UV damage

After the induction of UV damage it was observed that 40% histones were evicted from the site of the damage and 20% loss in DNA density in an observation window around the damage site.

What dynamical phenomena can explain these observations?

**Methods:**

We will construct a 3D simulation framework to address these questions. At first step we will examine whether eviction of 40% histones can account for 20% loss in DNA density in an observation window.

**Modeling the histone-DNA polymer**

We will simulate a beads on strings (Rouse) polymer chain representing the DNA-histone polymer, with beads representing histones and springs representing the DNA chain.

**DNA damage**

Initially, we consider the damage to be in a single position on the DNA chain. Situation where multiple damage site are distributed along the chain will be examined in later stages. We assume that damage to the DNA does not create a double stranded break such that the damaged strand is disconnected.

**The observation window**

We will set our simulation in an open 3D domain in which a 2D circle of radius r will represent the observation window. Examination of the density of DNA inside the observation window will then be calculated as the density of the projection of the 3d image onto the plane containing the observation window.

**DNA density**

Density of DNA will be calculated as total length of the springs contained in the observation window divided by the area of the observation window. DNA density percentages will be relative to the initial DNA density.

**Modelling histone eviction**

This will be explored in two ways:

1. Simulate the system until 40% of the beads are out of the observation window for the first time. In which time, we calculate the density of the DNA. Because in open domain the chain will eventually exit the observation window, if left to diffuse, we have to find a way to correct it such that the chain remains mostly inside the observation window

2. Create a static picture in which 40% of the beads are outside the observation window. Then all possible conformations for which 40% beads are outside will be tested. (I still need to resolve how exactly this will be performed. I might do it with consecutive Brownian bridges)

**Histone sliding on the DNA**

**Single damage case**

After UV damage we need to incorporate a force which draws the histone away from the damage site.

In the case of a single damage site, pushing the histones away from the site can be treated in several ways

1. Shorten the standard deviation of the distance between beads away from the break (the actual shortening function should be defined, as first step we shorten in a linearly decreasing manner from the break site towards polymer ends, such that the springs closest to the break site undergo the most amount of shortening
2. Equivalently, changing spring constants between beads, such that the springs closest to the break site contract the most.
3. Changing allowed angles between springs
4. By active 1D force (to be defined) away from the damage site.

**Multiple damage sites**

In this case damage sites are distributed along the chain. Sliding away from damage sites should now be defined according to the distance of each bead to the closest damage site. Beads are not allowed to cross-over a damage site, and so in the multiple damage sites we will expect to see beads trapped between damage sites.