Simulation framework for chromatin architecture post UVC irradiation

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1 The simulation framework

We follow *in-silico* the dynamics of DNA and nucleosome signal loss from a circular region of interest (ROI) up to 15 minutes post UV-C irradiation followed by a period post repair. To examine the re-organization of the chromatin post UV-C, we compare the polymer configuration before UV-C and at the end of repair stage. Simulations are performed for UV-C dosage u ranging from 0 to 120 msec exposure.

The UV beam is consider to affect each horizontal slice of the nucleus in a similar manner [1]. Therefore, we perform two-dimensional simulations in spherical domain with reflecting boundaries. Our simulation capture the UV damage micro-environment and not the entire nucleus.

1.1 The polymer model

We use a randomly cross-linked Rouse chain of N monomers connected by harmonic springs [2] to represent a coarse-grained model of the chromatin. Springs connecting adjacent monomers in the linear chain are allowed to contract to a minimal length $L_0 > 0$. Cross-links are represented by harmonic springs connecting a subset of $M \leq N$ non nearest-neighbor (NN), who allowed to contract to a minimal length $L_C > 0$. The position R_n of the nth monomer of the chain is represented by the equation

$$\frac{\partial R_n}{\partial t}(t) = \sum_m H_{nm} \left(-\frac{\partial U_0}{\partial R_m(t)} + g_m(t) \right) - \sum_m \hat{H}_{nm} \frac{\partial U_{L_c}}{\partial R_m(t)} \qquad (1)$$

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where $H_{nm} = \frac{\delta_{nm}}{\zeta}$ is the mobility tensor of the linear chain, and

$$\hat{H}_{nm} = \begin{cases} \frac{1}{\zeta}, & \text{if monomer } n \text{ and } m \text{ are connected } (n \neq m) \\ 0, & \text{else} \end{cases} \tag{2}$$

is the mobility tensor for the cross-linked monomers. The terms g_m are white noise with zero mean and std equals $2\zeta k_B T$, with ζ the friction constant, k_B is the Boltzmann constant, and T the temperature.

The spring potential energy with minimal length L is defined by

$$U_L = \frac{3k_B T}{2b^2} \sum_{n=1}^{N} (||R_n - R_{n+1}||^2 - L)^2 \tag{3}$$

with $b > L$ the std of spring length.

The measure of cross-linking is given by the percentage $0 \leq \alpha \leq 100$ of non-NN monomers connected out of the total.

For each realization of the polymer, cross-links are added between pairs of monomers chosen uniformly at random. The dynamics of the cross-linked polymer is then simulated up to its relaxation time, determined by be the slowest mode of the linear chain [2].

1.2 UV irradiation

At the end of relaxation steps an instantaneous UV beam is shot with its focal point placed at the polymer's center-of-mass (CM). Small fluctuations of monomers are not of interest at the scale of our simulation, therefore the diffusion force acting on the polymer is stopped at this point. Damages caused by UV are restricted to be contained within a fixed two-dimensional circular region of area A_0 centered at laser's focal point. [EXPLAIN ABOUT THE DAMAGES]

Damages to DNA are represented by monomers labeled as damaged. For each UV dose u, damages caused by UV are uniformly distributed between monomers in A_0 at the time of beam shot. With increase of UV dose, we increase the probability of damages linearly as $k_t u$, with k_t in units of $bp/msec$.

1.2.1 The repair stage

To simulate the affect of repair proteins crowding at sites of DNA damage, a circular exclusion region is centered at each damaged monomer. An elastic pushing force originating from the damaged monomer and having affect

radius r_p is applied on any monomers entering the exclusion region. In addition, all cross-links from and to damaged monomers are removed to simulate chromatin de-compaction caused by the activity of chromatin remodlers and repair proteins [3].

The polymer will evolve into a new steady spatial configuration which represents the chromatin 15 minutes post UV-C. At which point, the region of interest (ROI) is defined as the circle in the x-y plane containing 90% of the damaged monomers projected position and centered at their CM. The ROI remains a fixed region used to track the number of damaged and undamaged monomers within it. Measurements are done off-line, such that the ROI's position is retrospectively updated to be centered at the CM of the monomers tagged damaged.
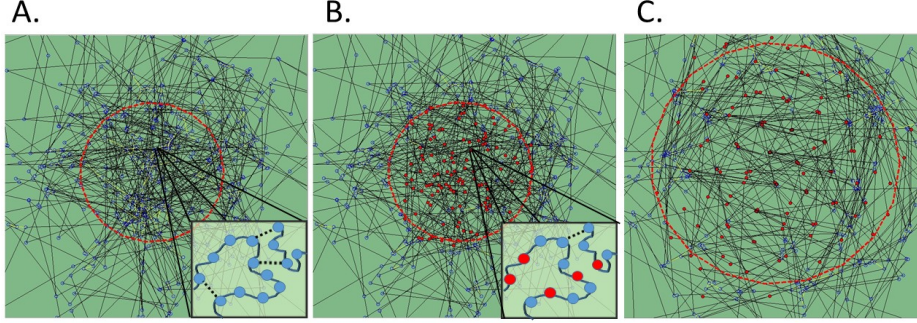
Figure 1: **Stages in the Simulation of chromatin spatial organization post UV-C irradiation**. **A.** a Rouse chain of 500 monomers (circles) connected by harmonic spring (black lines) with a minimal length L0 is crossed-linked by harmonic springs (dashed lines in box) is simulated up to relaxation time, at which point a UV-C beam is vertically shot through a circular damage region (red dashed circle) around the polymers center-of-mass. **B.** damaged monomers (red circles) are set to be distributed uniformly for each UV dose. Following UV-C irradiation, cross-links (dashed lines in box) to and from damaged monomers are removed. **C.** crowding of repair proteins is simulated by regions of exclusion centered around each damaged monomer. An elastic pushing force is applied to surrounding monomers with a maximal affect radius of rp. As a result, the damage region expands until reaching its maximal size 15 minutes post UV-C. The Region of Interest (ROI) is then determined as the circles containing 90% of the damaged monomers (dashed red circle).

1.3   Post repair stage

Fifteen minutes post UV-C we remove the exclusion region around damaged monomers. Cross-links are reintroduced by linking any two monomers located within an encounter distance of ϵ from one another. Cross-links post repair are allowed to be added up to the initial cross-linking percentage α.

1.4 Measuring structural similarity

A measure of similarity between the polymer spatial organization before UV and post repair is based on the comparison of their encounter probability matrices. The polymer's encounter matrix just prior the onset of UV-irradiation is compared to that at end simulation time. The similarity values is given by the mean square error between matrices.

1.5 Parameter estimation

We model a circular region of 3 μm^2 around the UVC laser's focal point. This area is represented by the Rouse polymer's gyration radius given by $R_g = \sqrt{N/6}b$. To estimate b we then substitute $N = 500, R_g = 3\mu m$ to obtain $b = 0.32$.

References

[1] Salomé Adam, Juliette Dabin, Siau-Kun Bai, and Sophie E Polo. Imaging local deposition of newly synthesized histones in uvc-damaged chromatin. *Chromatin Protocols*, pages 337–347, 2015.

[2] Masao Doi and Sam F Edwards. *The theory of polymer dynamics*, volume 73. oxford university press, 1988.

[3] Hélène Gaillard, Daniel J Fitzgerald, Corey L Smith, Craig L Peterson, Timothy J Richmond, and Fritz Thoma. Chromatin remodeling activities act on uv-damaged nucleosomes and modulate dna damage accessibility to photolyase. *Journal of Biological Chemistry*, 278(20):17655–17663, 2003.