Understanding histone H1 binding mechanism through model comparison and FRAP experiments

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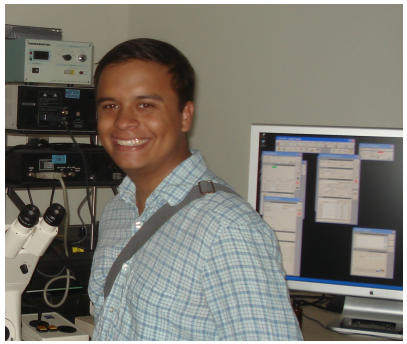
Acknowledgements

- Carlos Contreras (Universidad Simón Bolívar)



- Minalla Villasana (Universidad Simón Bolívar)

- Michael Hendzel (University of Alberta)

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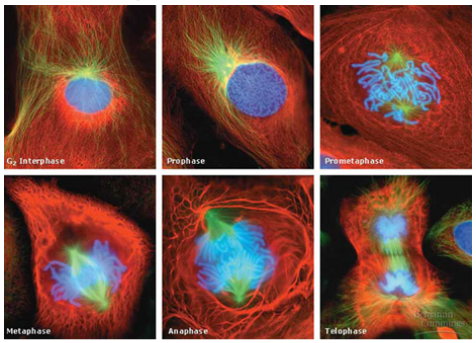
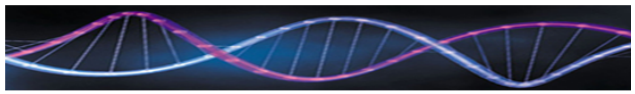
Outline

Histone H1 or Linker Histones

- Length of all DNA in an adult human cell $\sim$ 2 mts



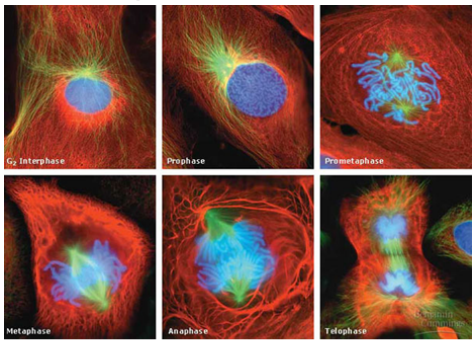
x 1000 times



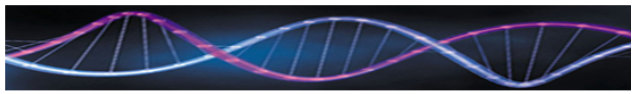
2 kms of DNA

Histone H1 or Linker Histones

- Length of all DNA in an adult human cell $\sim$ 2 mts

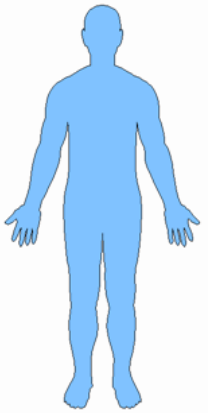


x 1000 times

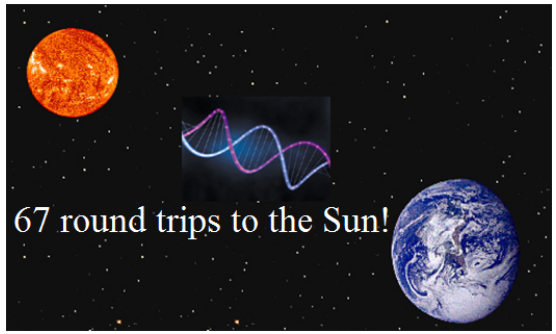


2 kms of DNA

- There are $\sim$ 10 trillion (10×10^{13}) cells in the body



~20 trillion mts. of DNA
in the human body



Histone H1 or Linker Histones

How do 133 AU of DNA fit in our body?

How is the DNA packed and organized in the cells?

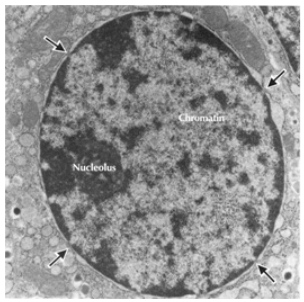
Histone H1 or Linker Histones

How do 133 AU of DNA fit in our body?

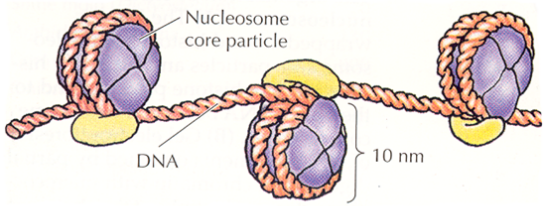
How is the DNA packed and organized in the cells?

With the help of histones!

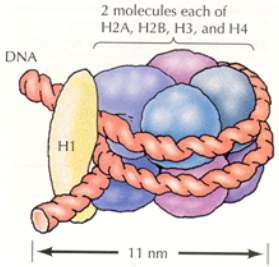
DNA is wrapped around core histones and locked by linker histones.



Chromatin distribution in the nucleus

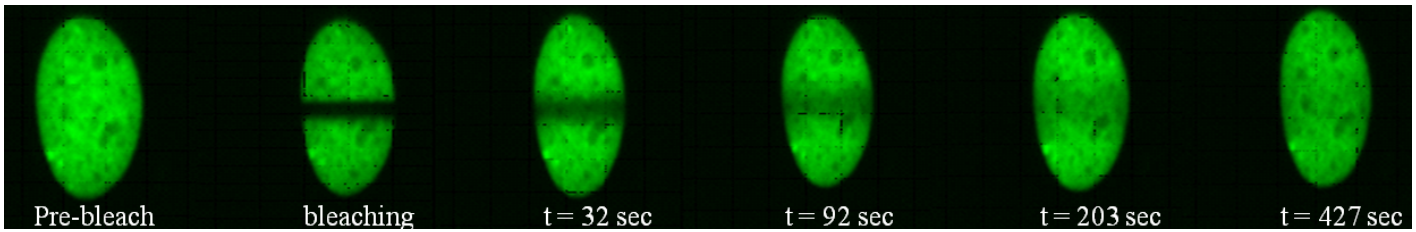


Chromatin: DNA and associated proteins

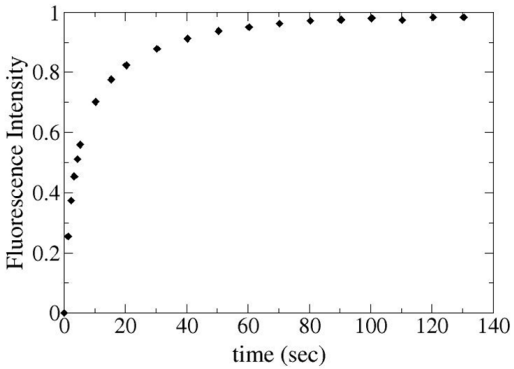


Nucleosome: Core Histones and Linker Histone

FRAP Experiments



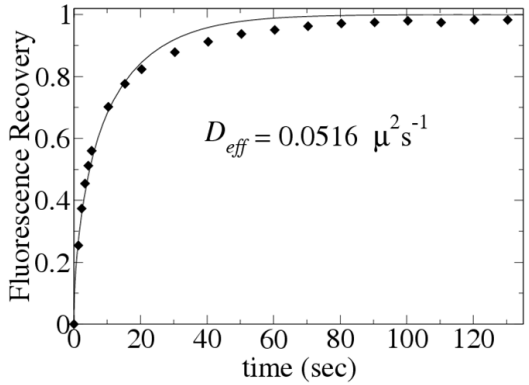
GFP (Green Fluorescence Protein)



$$\frac{\partial}{\partial t}\, u(x,t) = D_{eff}\, \frac{\partial^2}{\partial x^2}\, u(x,t)$$

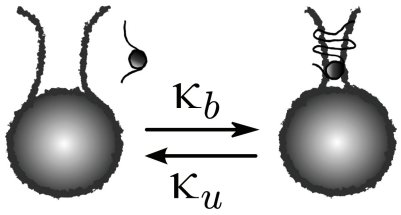
$$R(t; D_{eff}) = \int_{\Lambda} u(x,t)\, dx$$

Λ =photobleached region



Outline

One bound subpopulation model (simple model)



$$\frac{\partial}{\partial t}\,u(x,t) = D\,\frac{\partial^2}{\partial x^2}\,u(x,t) - k_b u(x,t) + k_u v(x,t)\ ,$$

$$\frac{\partial}{\partial t}\,v(x,t) = k_b u(x,t) - k_u v(x,t)$$

I. Variable Diffusion:

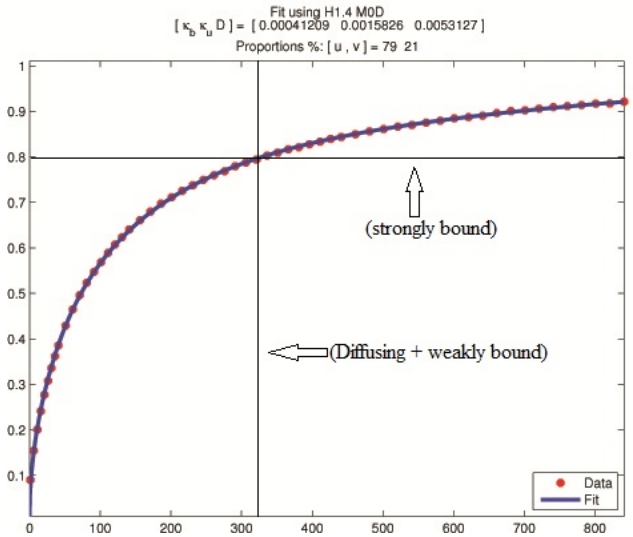
$$R(t; D, k_b, k_u) = \int_\Lambda [u(x,t) + v(x,t)]\,dx$$

Proportion of bound population:

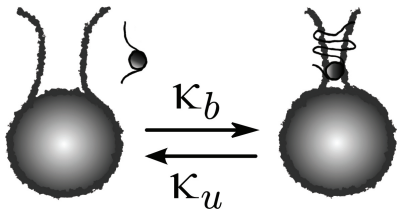
$$P_b = \frac{k_b}{k_b + k_u} \approx 21\%$$

Proportion of unbound population:

$$P_u = \frac{k_u}{k_b + k_u} \approx 79\%$$



One bound subpopulation model (simple model)



$$\frac{\partial}{\partial t}\, u(x,t) = D\, \frac{\partial^2}{\partial x^2}\, u(x,t) - k_b u(x,t) + k_u v(x,t)\ ,$$

$$\frac{\partial}{\partial t}\, v(x,t) = k_b u(x,t) - k_u v(x,t)$$

II. Fixed Diffusion:

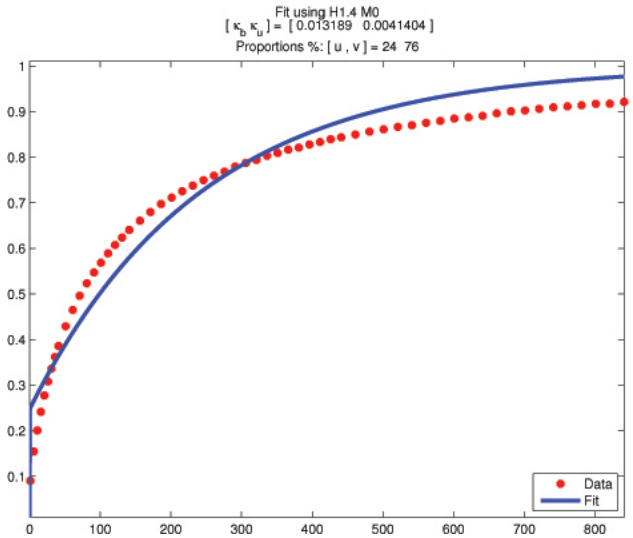
$$R(t; k_b, k_u) = \int_\Lambda [u(x,t) + v(x,t)]\, dx$$

Proportion of bound population:

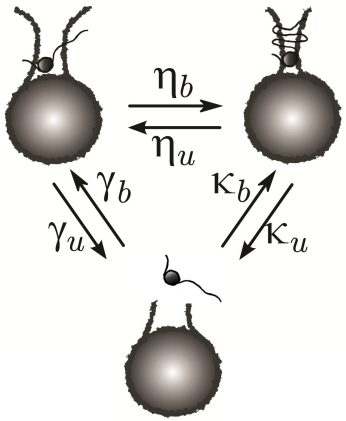
$$P_b = \frac{k_b}{k_b + k_u} \approx 76\%$$

Proportion of unbound population:

$$P_u = \frac{k_u}{k_b + k_u} \approx 24\%$$



Two bound subpopulations model (extended model)



$$\frac{\partial}{\partial t}\,u(x,t) = D\,\frac{\partial^2}{\partial x^2}\,u(x,t) - k_b u(x,t) + k_u v(x,t) - \gamma_b u(x,t) + \gamma_u w(x,t)\ ,$$

$$\frac{\partial}{\partial t}\,v(x,t) = k_b u(x,t) - k_u v(x,t) + \eta_b w(x,t) - \eta_u v(x,t)\ ,$$

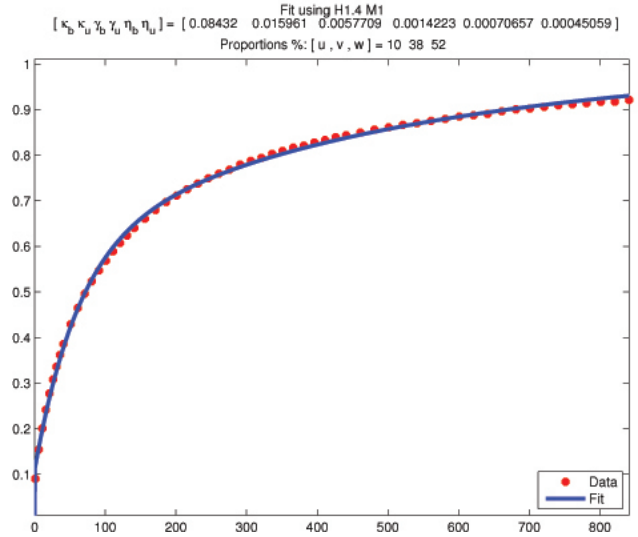
$$\frac{\partial}{\partial t}\,w(x,t) = \gamma_b u(x,t) - \gamma_u w(x,t) - \eta_b w(x,t) + \eta_u v(x,t)\ ,$$

$$R(t; k_b, k_u, \gamma_b, \gamma_u, \eta_b, \eta_u) = \int_\Lambda [u(x,t) + v(x,t) + w(x,t)]\,dx$$

Proportion of strongly bound population: $\sim 52\%$

Proportion of weakly bound population: $\sim 38\%$

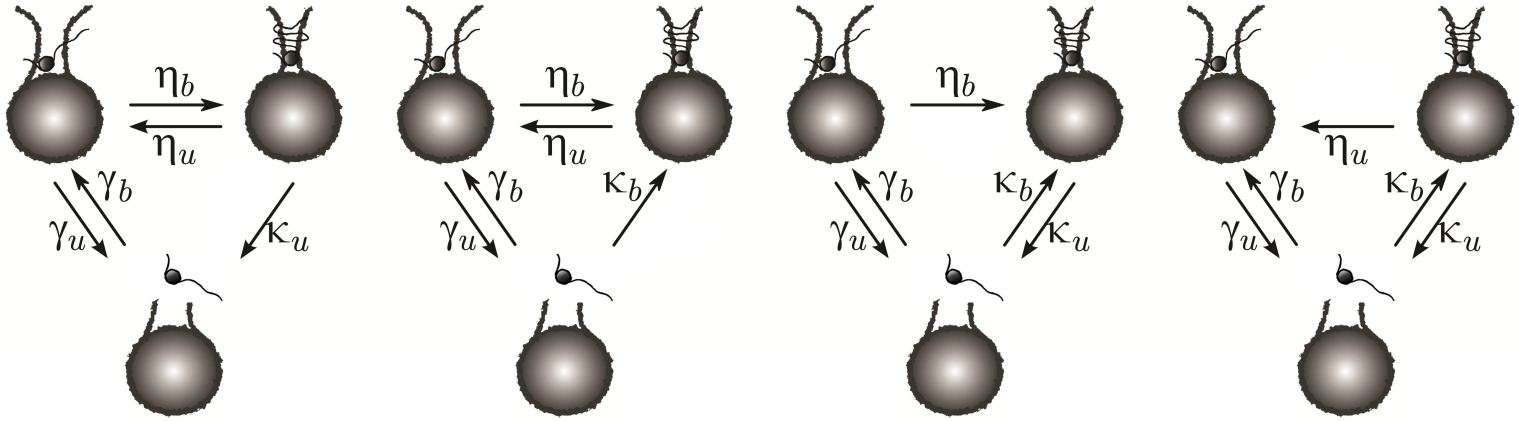
Proportion of unbound population: $\sim 10\%$



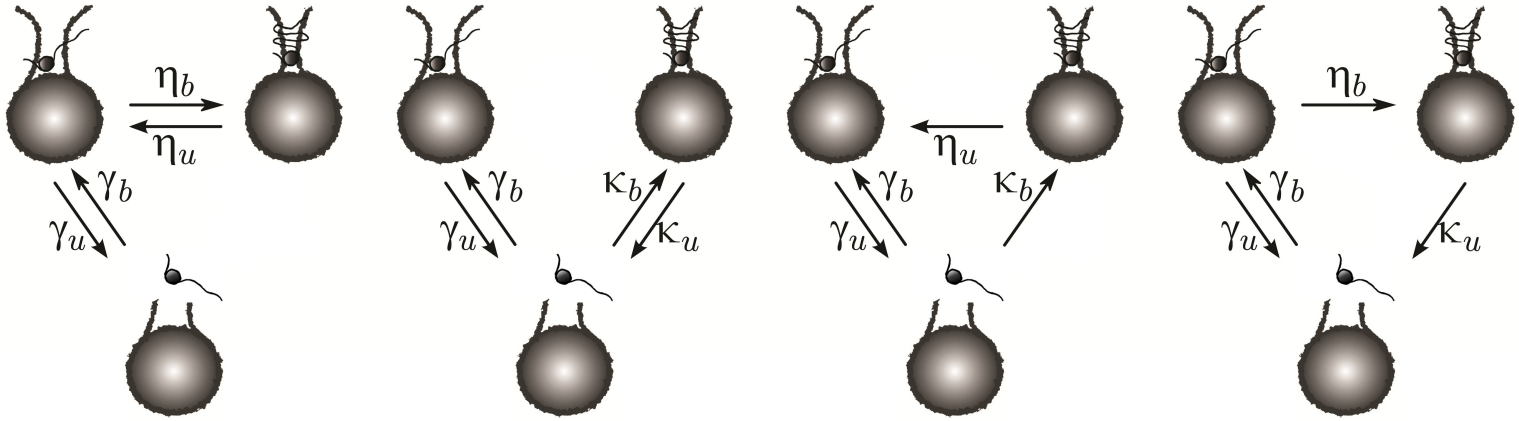
Can we be more specific about the binding mechanism involving weakly and strong interactions?

Nested Models

I. One less interaction:



II. Two less interactions:



Can we favor one of these mechanisms on the basis of FRAP experiments?

Outline

Akaike Information Criterion (AIC)

$$AIC = 2\mathcal{LL}(\hat{p}) - 2n_p \ ;$$

- Used when the models are not nested
- p: *set of parameters*
  n_p: *number of parameters*
  $\mathcal{LL}(\hat{p})$: *log of the likelihood* $\mathcal{L}(p)$
  $\mathcal{L}(p)$: *Likelihood function (probability to find the given data)*
  $\hat{p}$: *maximum likelihood estimator (parameters that maximize* $\mathcal{L}(p)$*)*
- The larger the AIC the better the model

Likelihood Ratio Test (LRT)

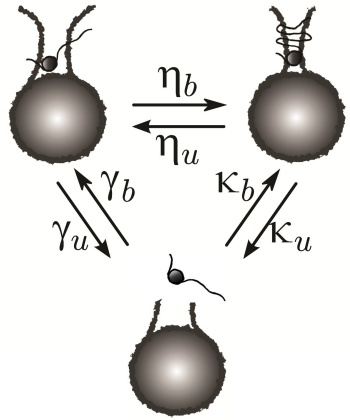
$$H_0: \ M_0 \text{ fits the data well, vs}$$
$$H_1: \ M_1 \text{ fits the data better}$$

- M_0 is nested within the model M_1
- The statistics $\lambda = 2(\mathcal{LL}(M_1) - \mathcal{LL}(M_0))$ is χ^2-distributed
- $\mathcal{LL}(M_1)$ and $\mathcal{LL}(M_2)$: log likelihoods of model M_1 and M_2
- One calculates a χ^2 value given a confidence level and if λ is higher than that value then the null hypothesis is rejected (i.e., M_1 is a better model)

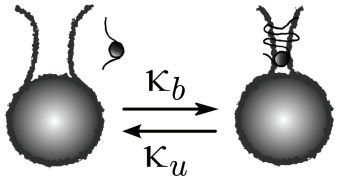
Model Comparison for Nested Models

(general model vs simple model)

M_1:



M_0:

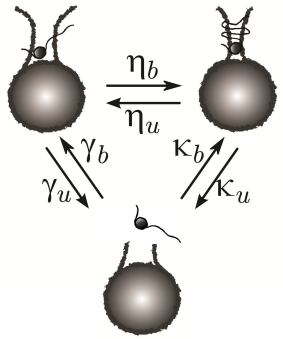


The null hypothesis H_0 is rejected, i.e.,
The general model M_1 is favored using the LRT!

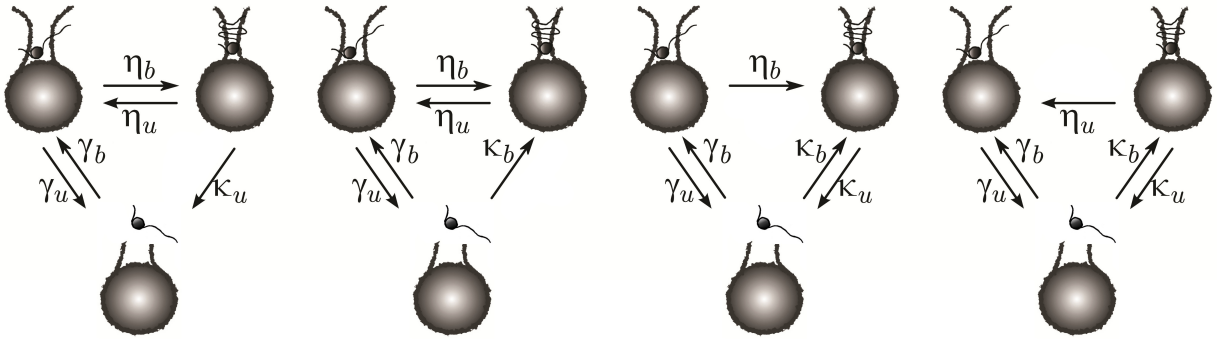
Model Comparison for Nested Models

(general model vs one less interaction models)

M_1:



M_0:

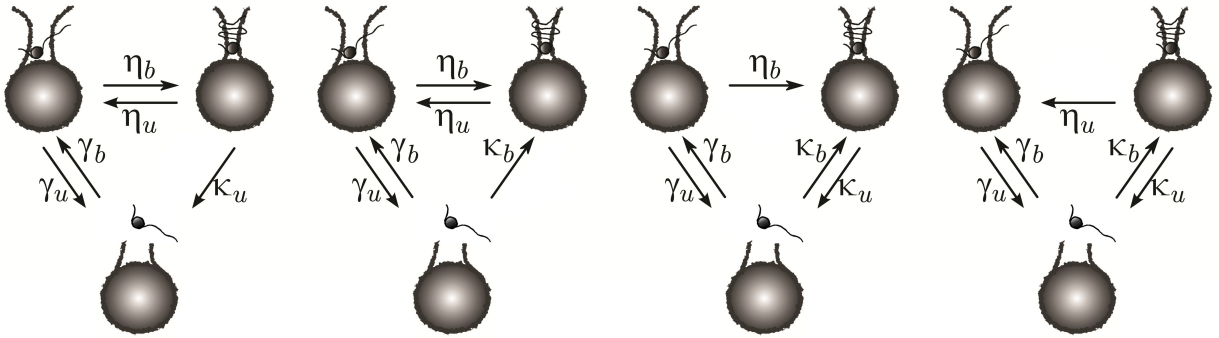


The null hypothesis H_0 cannot be rejected, i.e.,
all nested models M_0 are favored using the LRT!

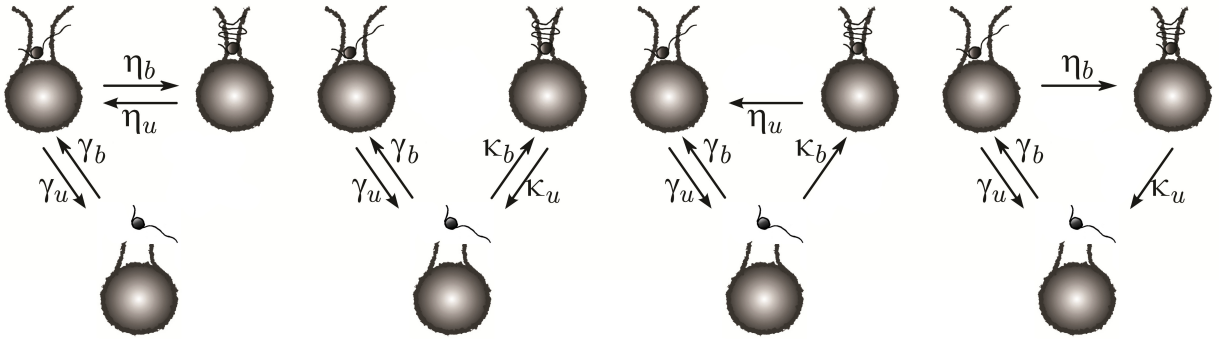
Model Comparison for Nested Models

(one less interaction models vs two less interactions models)

M_1:



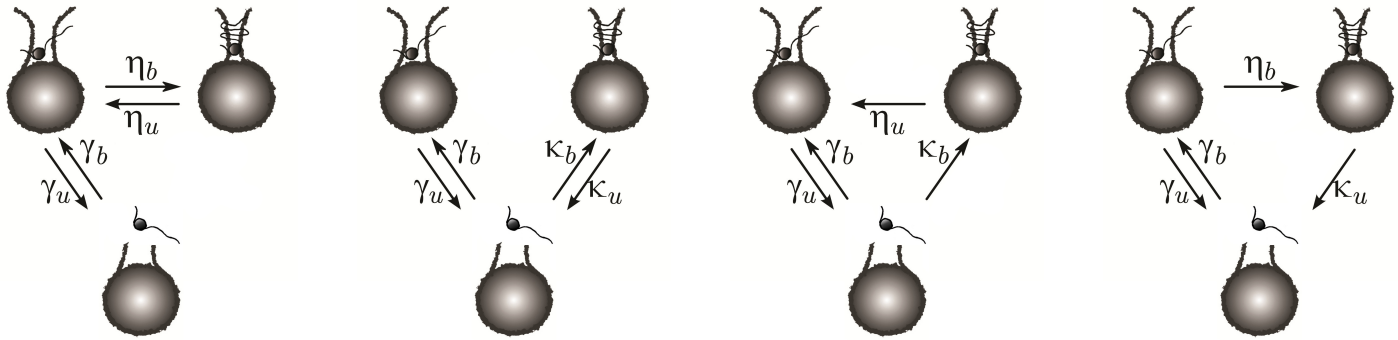
M_0:



The null hypothesis H_0 cannot be rejected, i.e.,
all nested models M_0 with two less interactions are favored using the LRT!

Model Comparison for Non-nested Models

(with two less interactions models)



The Akaike Information Criterion (AIC) is not significantly different in any of these models. Thus, none of these models are favored!

Outline

Discussion and Future Work

- Even though the possibilities for binding mechanisms were reduced, AIC did not allow us to distinguish one final model among the ones considered.
- Suggestions?
- The results require the development of experiments that could validate one of the two less interactions models over the others.
- We plan to use a resulting model (when found) to assess the effect of post-translational modifications on the biding affinity of histone H1 to the chromatin structure.

THANK YOU!