

S2 Text. Interactions in the non-specific reservoir

The possibility remains that transcription factors and RNAP can interact with each other when both are bound to non-specific sites on the DNA. These interactions have thus far not been taken into account, since the local concentration of RNAP and transcription factor is low, due to the large number of non-specific sites. Here we will show how to include these interactions explicitly, and in which circumstances it is justified to neglect them.

We consider a single isolated non-specific site in a grand-canonical ensemble. The binding energies of RNAP and transcription factor are set to 0 as before. The grand-canonical partition function is then given by

$$\Xi_{\text{ns}} = 1 + \lambda_P + \lambda_A + \lambda_P \lambda_A x_{\text{AP}}, \quad (\text{S.7})$$

where we have λ_P, λ_A the fugacities of RNAP and activator respectively, and $x_{\text{AP}} = \exp(-\beta\epsilon_{\text{AP}})$ the glue-like interaction between RNAP and activator when both bound adjacent to each other. Note that, since the binding mode of transcription factors to non-specific DNA may be different to the binding mode to specific sites, conformational changes in the protein may also cause x_{AP} to be different from the activator-RNAP interaction on specific sites.

We calculate the occupation number of RNAP and activator on non-specific sites. For activators, this becomes

$$\theta_A^{\text{ns}} = \frac{\lambda_A(1 + \lambda_P x_{\text{AP}})}{1 + \lambda_P + \lambda_A + \lambda_P \lambda_A x_{\text{AP}}} \simeq \lambda_A(1 + \lambda_P x_{\text{AP}}), \quad (\lambda_P, \lambda_A \ll 1) \quad (\text{S.8})$$

When deriving eq. (29), we assumed that $\lambda_P x_P x_{\text{AP}} \ll 1$. Since the binding energy of RNAP to specific sites is more favourable than to non-specific sites, $x_P > 1$, the assumption $\lambda_P x_{\text{AP}} \ll 1$ is already taken care of (provided x_{AP} is not significantly different on non-specific sites than on specific sites). In that case, we have $\theta_A^{\text{ns}} = \lambda_A$ as before.

For RNAP, the occupation number becomes

$$\theta_P^{\text{ns}} = \frac{\lambda_P(1 + \lambda_A x_{\text{AP}})}{1 + \lambda_A + \lambda_P + \lambda_P \lambda_A x_{\text{AP}}} \simeq \lambda_P(1 + \lambda_A x_{\text{AP}}), \quad (\lambda_P, \lambda_A \ll 1) \quad (\text{S.9})$$

In this situation, eq. (S.5) becomes

$$\lambda_P = \frac{P}{N \frac{(1 + \lambda_A x_A x_{\text{AP}})}{1 + \lambda_A x_A} x_P + N_{\text{ns}}(1 + \lambda_A x_{\text{AP}})}, \quad (\text{activation}) \quad (\text{S.10})$$

The zeroth order term in the series expansion of λ_P/λ_P^0 , eq. (S.6), now does not become unity, rather, it becomes $(1 + \lambda_A x_{\text{AP}})^{-1}$. Usually, $\lambda_A \ll 1$, but on specific sites, ϵ_{AP} can be as high as $-5k_B T$, leading to $x_{\text{AP}} \sim 200$. In the situation that λ_A is comparatively high on the order of $\sim 10^{-3}$, which is the case when thousands of activators are present in the cell, we can not make the assumption $\lambda_A x_{\text{AP}} \ll 1$ anymore and we have to explicitly take into account that $\lambda_P/\lambda_P^0 \simeq (1 + \lambda_A x_{\text{AP}})^{-1}$.