

Principles of Electronic Nanobiosensors

Unit 4: Selectivity

Lecture 4.1: Introduction and Molecular Recognition

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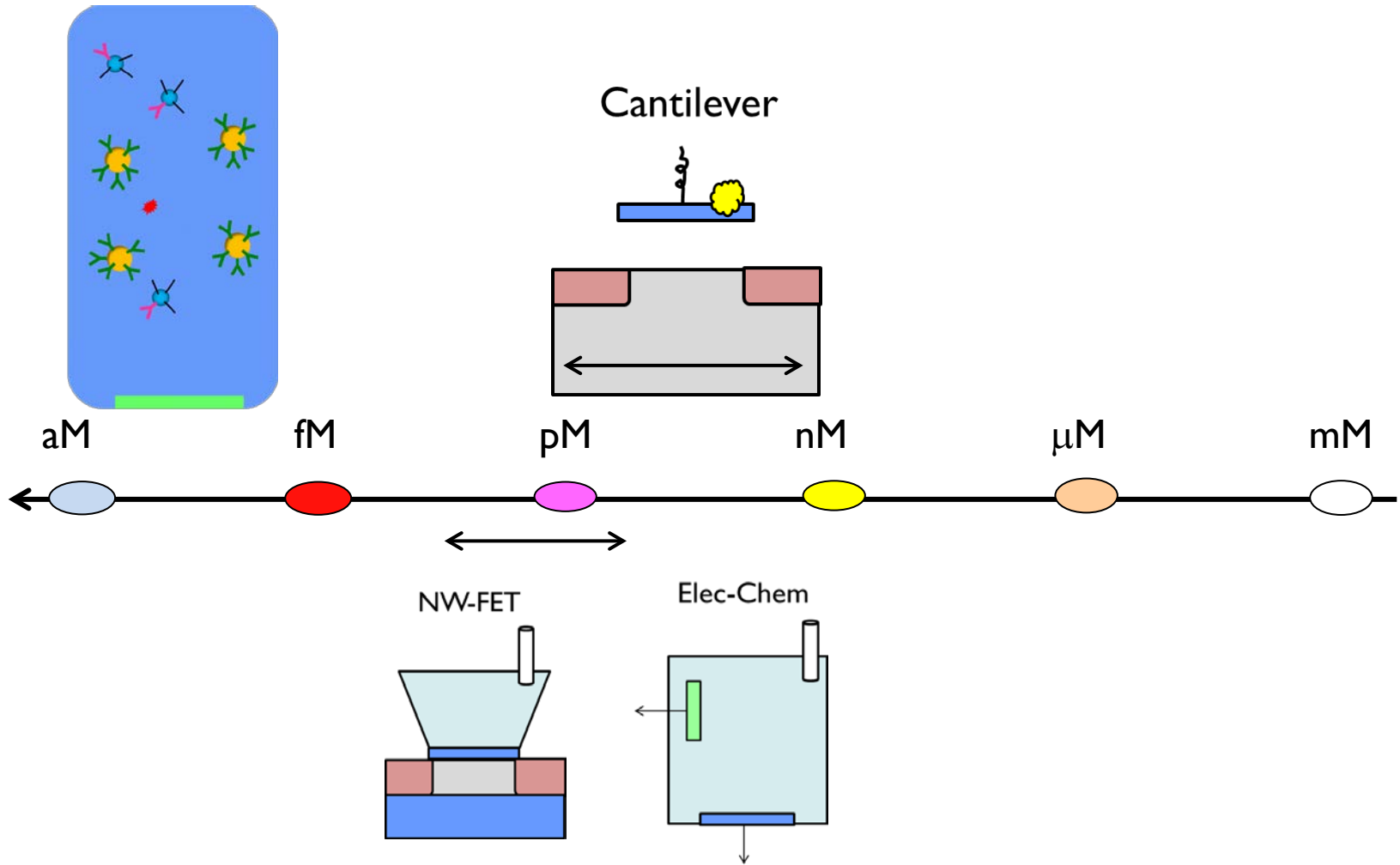
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Outline

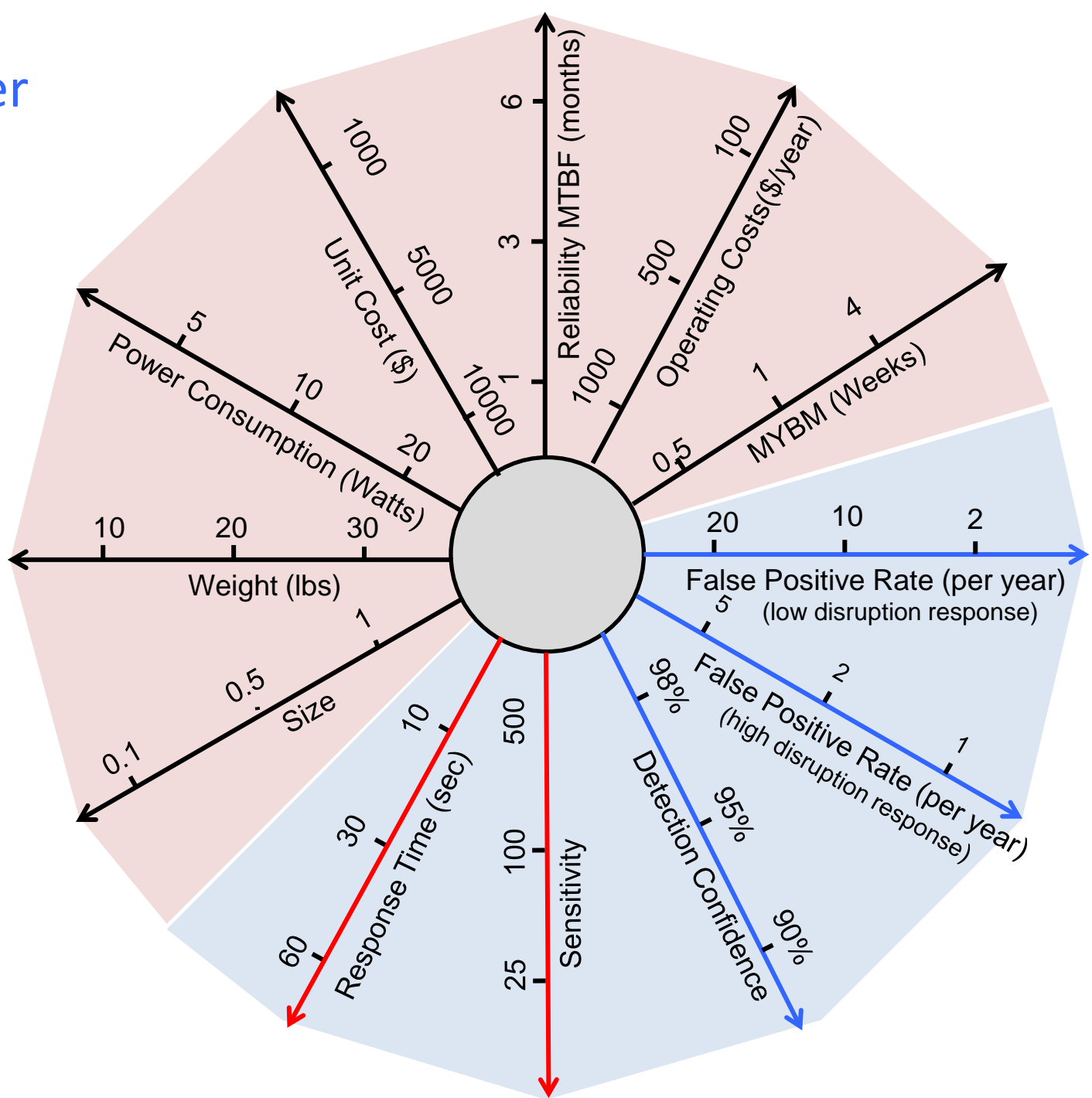
- Introduction and background
- Two types of selectivity issues
 - Binding to the wrong molecule
 - Binding in the empty space
- Theory of selectivity by binding energy
- Conclusion

Response time and sensitivity of sensors

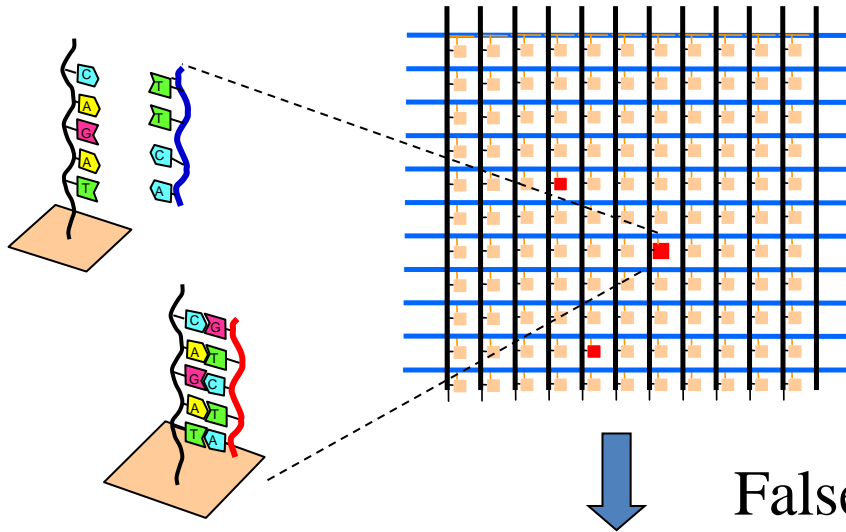


All have nanowire or nanosphere geometry

The Spider Chart Of Sensors



A Matrix definition of selectivity



False Positive: $3\beta = 0.3$

True Positive: $\alpha = 0.7$

Response Sensor Target

$$\begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix}$$

$$\begin{pmatrix} \alpha + \beta \\ \beta \\ \beta \\ \alpha + \beta \end{pmatrix} = \begin{bmatrix} \alpha & \beta & \beta & \beta \\ \beta & \alpha & \beta & \beta \\ \beta & \beta & \alpha & \beta \\ \beta & \beta & \beta & \alpha \end{bmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix}$$

Classical approach to selectivity

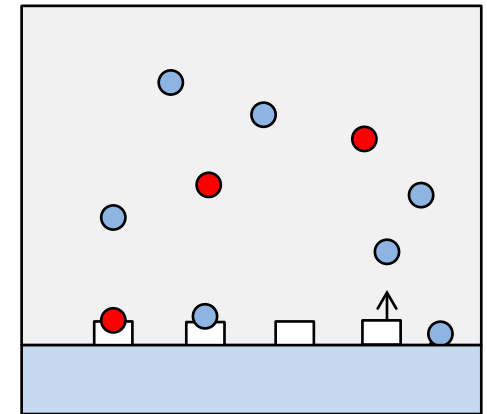
Recall
$$\frac{dN_T}{dt} = k_F (N_0 - N_T) \rho_s - k_R N_T,$$

$$N_T (t \rightarrow \infty) = \frac{k_T N_0 \rho_T}{k_T \rho_T + 1} \Rightarrow N_0$$

$$k_T \equiv \frac{k_F}{k_R} \rightarrow \infty \quad \text{Full absorption}$$

At steady-state

$$D \nabla^2 \rho = 0$$



Competitive binding at steady state

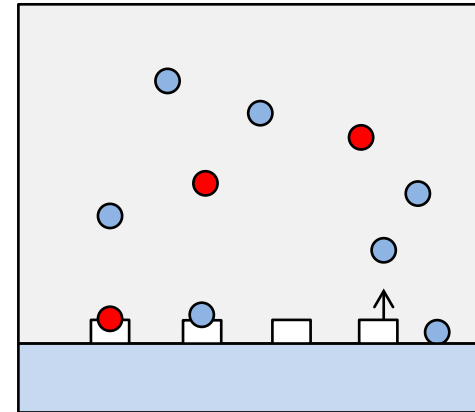
$$N (t \rightarrow \infty) = N_T + N'_T + N_{Geom} = \frac{k_T N_0 \rho_T}{k_T \rho_T + 1} + \frac{k'_T N_0 \rho'_T}{k'_T \rho'_T + 1} + \frac{k_p N_p \rho_p}{k_p \rho_p + 1}.$$

Classical approach to selectivity

Competitive binding at steady state

$$\begin{aligned}
 N(t \rightarrow \infty) &= N_T + N'_T + N_{Geom} \\
 &= \frac{k_T N_0 \rho_T}{k_T \rho_T + 1} + \frac{k'_T N_0 \rho'_T}{k'_T \rho'_T + 1} + \frac{k_p N_p \rho_p}{k_p \rho_p + 1}.
 \end{aligned}$$

$$D\nabla^2 \rho = 0$$



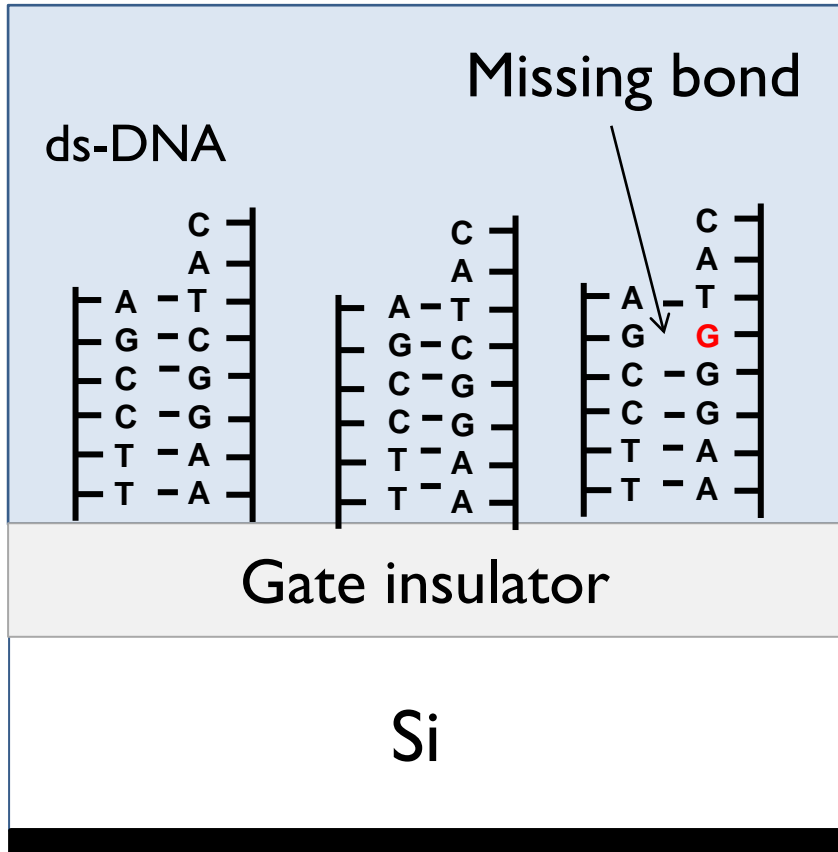
$$\alpha = \frac{N_T}{N_T + N'_T + N_{Geom}}.$$

$$\beta = \frac{N'_T + N_{Geom}}{N_T + N'_T + N_{Geom}}.$$

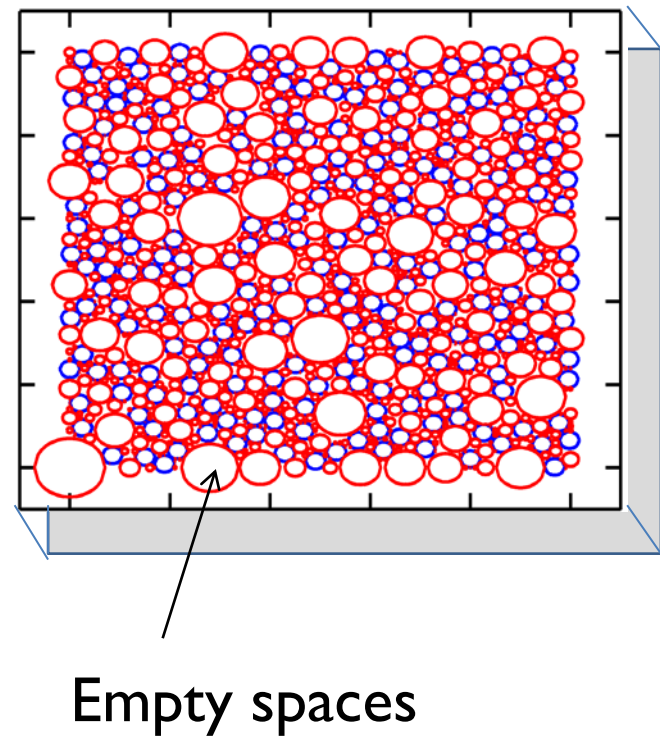
$$\begin{pmatrix} \alpha + \beta \\ \beta \\ \beta \\ \alpha + \beta \end{pmatrix} = \begin{bmatrix} \alpha & \beta & \beta & \beta \\ \beta & \alpha & \beta & \beta \\ \beta & \beta & \alpha & \beta \\ \beta & \beta & \beta & \alpha \end{bmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix}$$

Selectivity classified

Selectivity in Energy



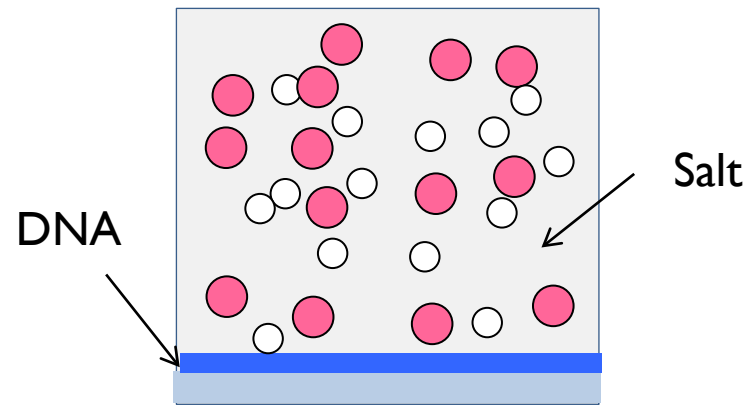
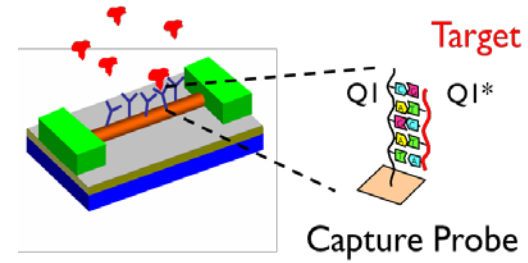
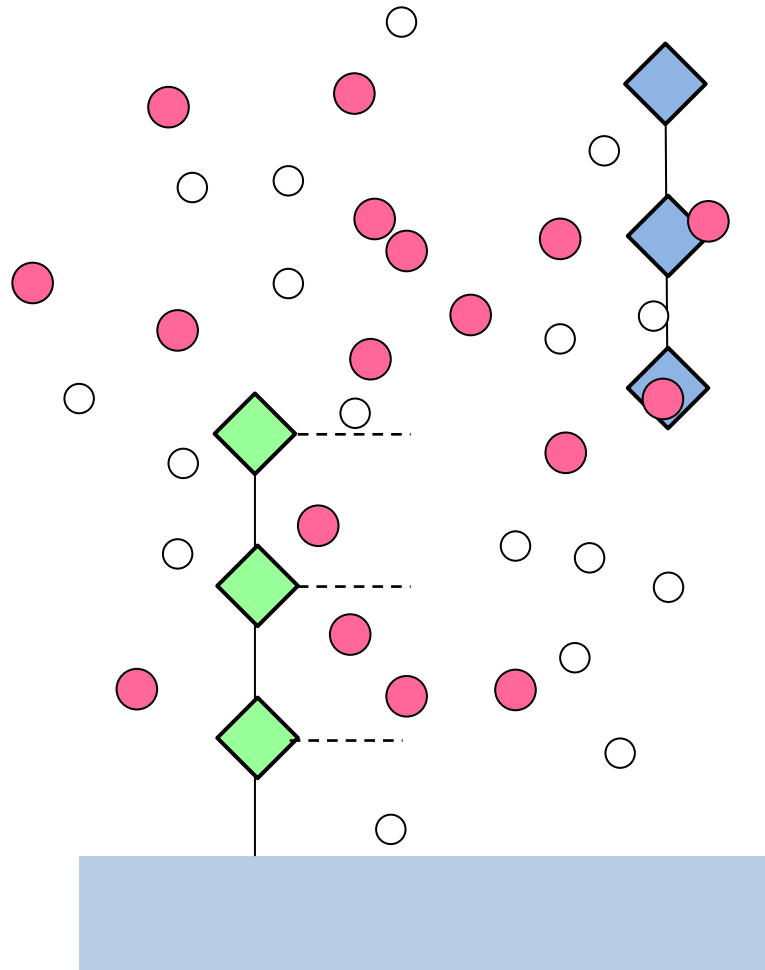
Selectivity in Space



Outline

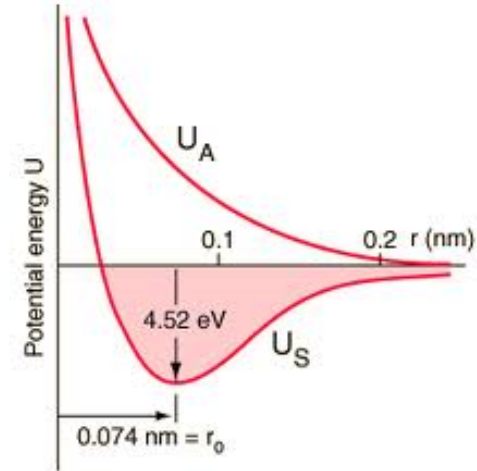
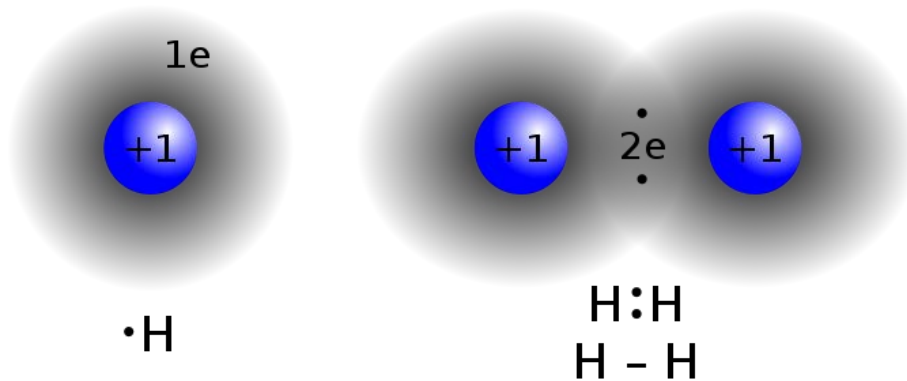
- Background: What is Selectivity
- **Selectivity – Incorrect hybridization**
 - Why and how DNAs hybridize
 - How is incorrect hybridization measured
 - How to improved hybridization selectivity
- Selectivity – Binding in the empty space
- Conclusion

DNA binding and Salt screening



How does H2 stay together

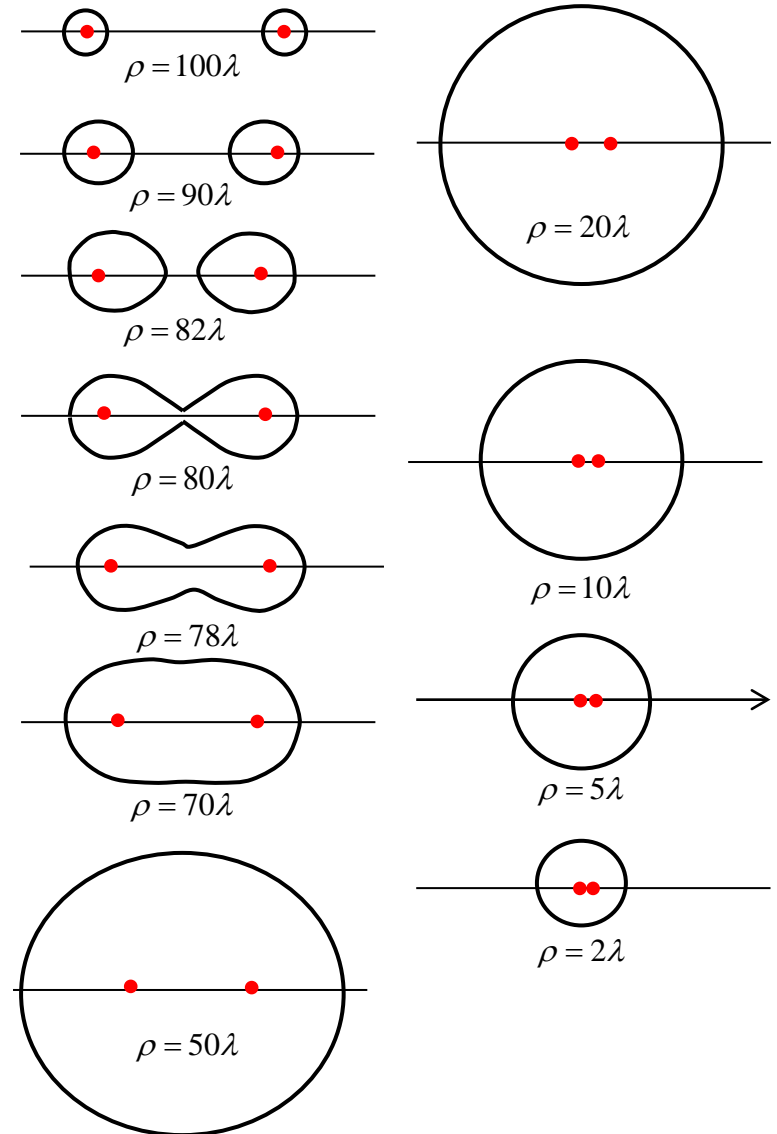
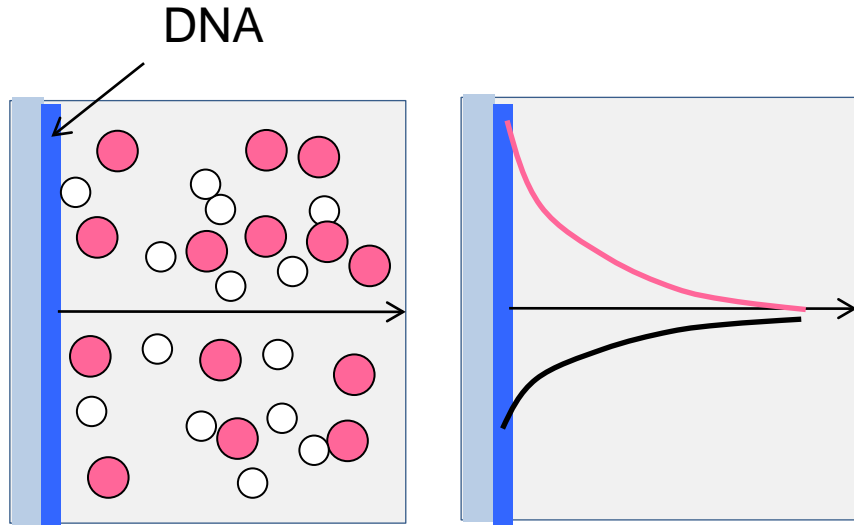
Quantum Physics, Wiley Stephen Gasiorowicz, p. 328



$$U = \frac{q^2}{4\pi\epsilon_0} \left[\underbrace{-\frac{1}{|R_1 - R_2|} - \frac{1}{|r_1 - r_2|}}_{\text{repulsion}} + \sum_{\substack{i=1,2 \\ j=1,2}} \underbrace{\frac{1}{|R_i - r_j|}}_{\text{attraction}} \right]$$

Counter charges help repulsive carriers stay together

Manning theory of DNA bonding



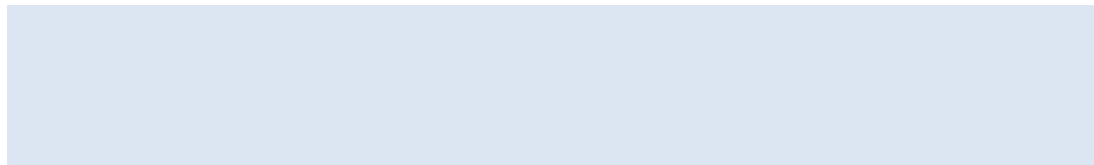
DNA binding energy: compact model

Model 1:

$$\begin{aligned} T_m (^{\circ}C) &= 4 \times (N_C + N_G) + 2 \times (N_A + N_T) \\ &= 2 \times (N_C + N_G) + 2 \times N \quad N < 14, I_0 = 50\text{mM} \end{aligned}$$

Example:

ATCGATCG N=8



DNA binding energy: compact model

Model 2 for $N \gg 14$:

$$T_m (^{\circ}C) = 81.5 + 16.6 \log(I_0) / (1 + 0.7 \log(I_0)) \\ + 41 \times ((N_C + N_G - 16.46) / N) - (\text{Mismatch} / N) \times 100$$

Example: T7 Promoter

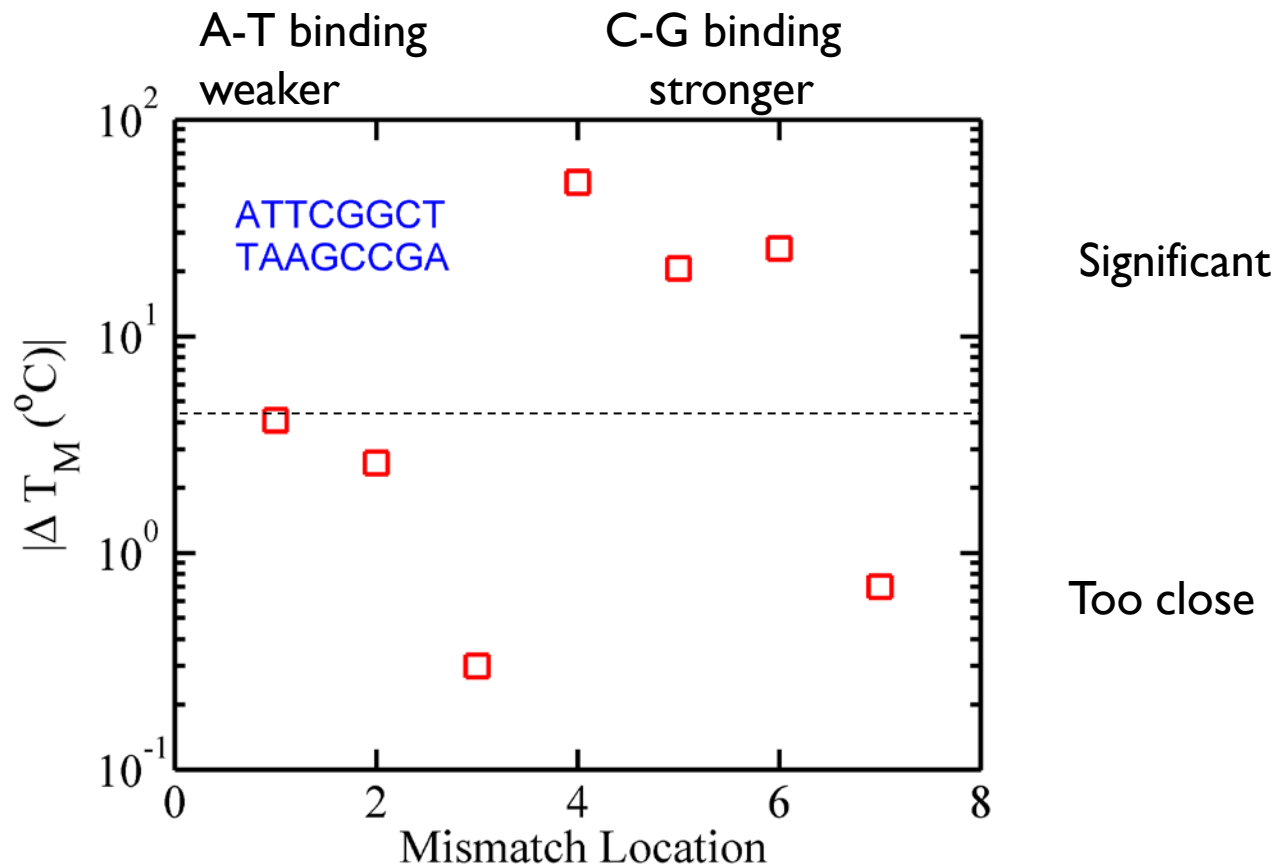
TAATAC**CG**ACT**CA**CTATAG**GGG** N=20

$$T_m (^{\circ}C) = 59.9 + 41 \times (4 + 4 - 16.46) / 20 = 42.5$$

Calculators: http://protein.bio.puc.cl/cardex/servers/melting/sup_mat/servers_list.html

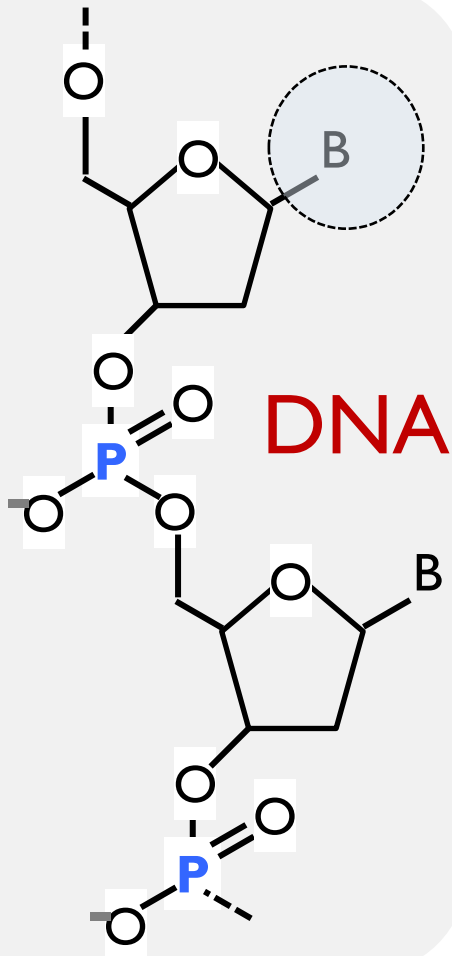
Parasitic binding to host site

Model 1: $T_m (^{\circ}\text{C}) = 4 \times (N_C + N_G) + 2 \times (N_A + N_T) = 24$

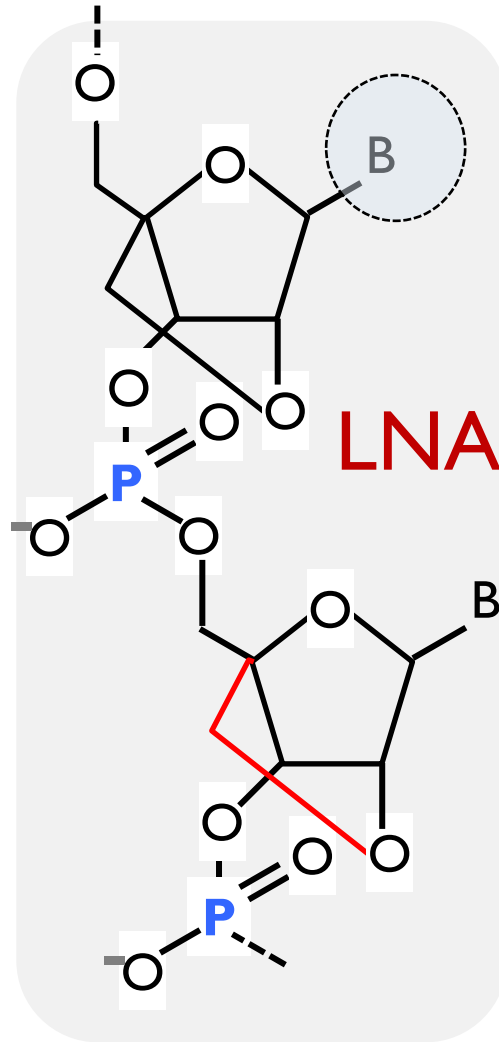


Melting temperature too close, must find ways to make the energy difference more significant

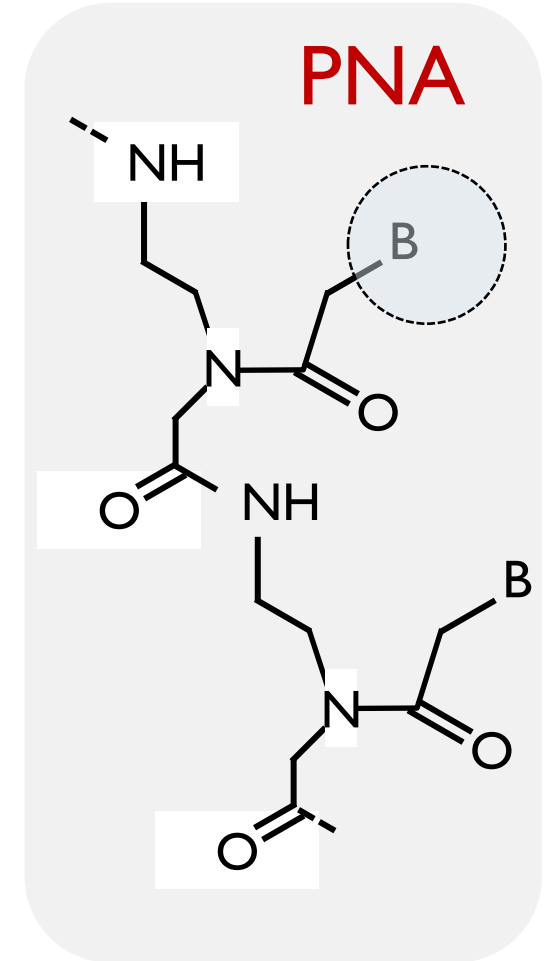
Engineering DNA for better binding



Negative charge,
difficult binding

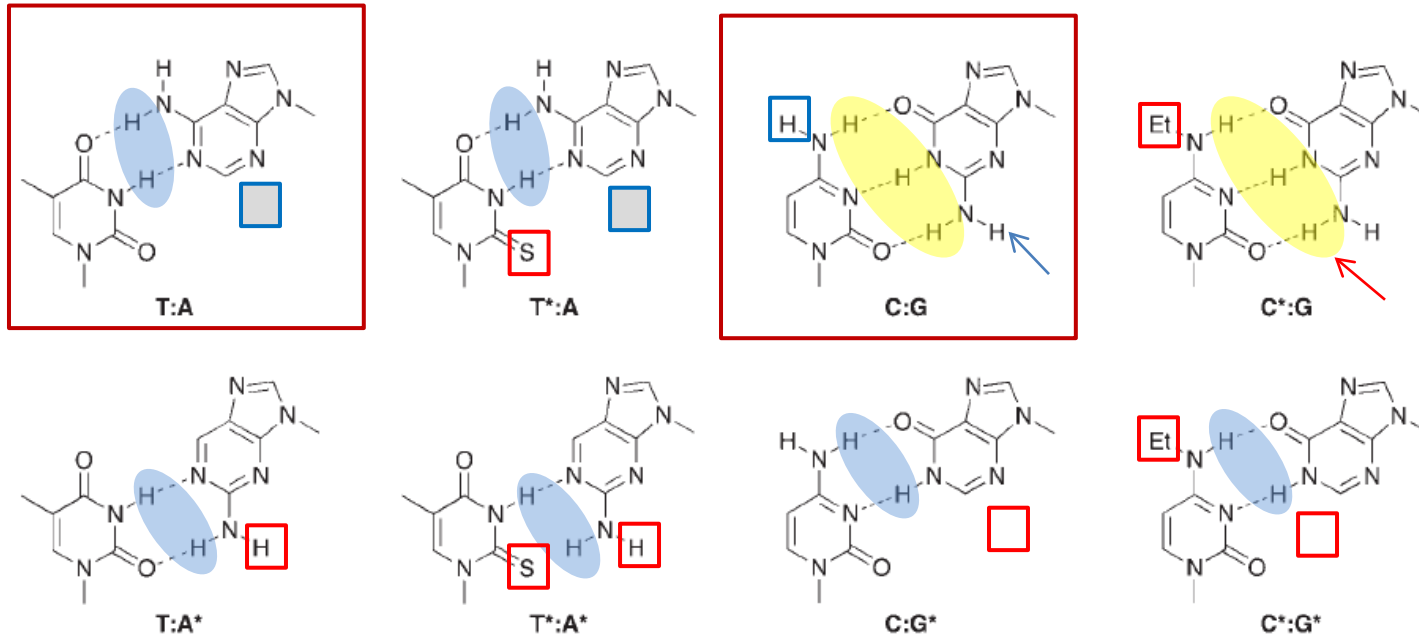


Locked conformation
Stronger, specific binding



No charge at backbone
Stronger, specific binding

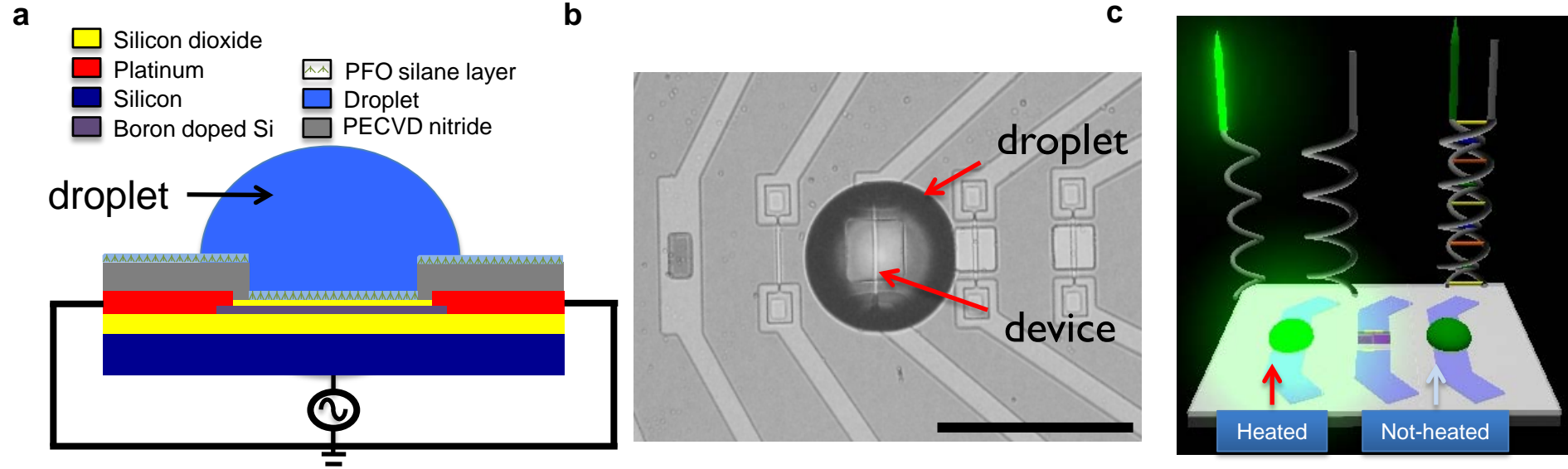
Improved design of probes



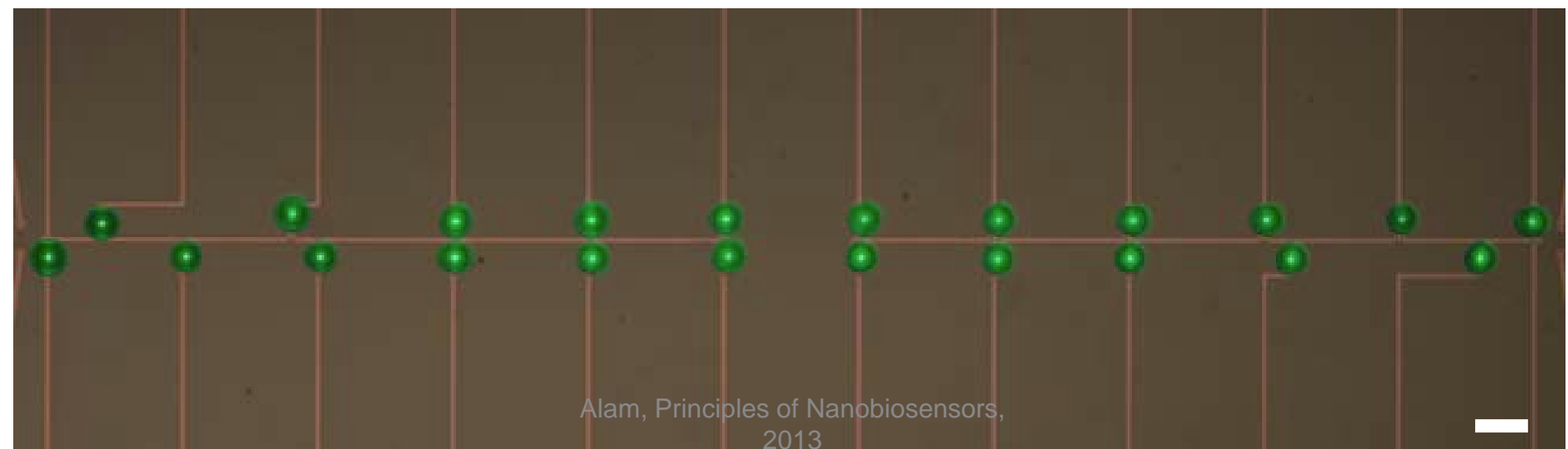
$$T_m (^{\circ}C) = 4 \times (N_C + N_G) + 2 \times (N_A + N_T)$$

Re-engineering the DNA makes binding more symmetric/selective

Differential heating for parasitic desorption



d



Conclusions

- Incorrect binding is a key concern for potentiometric and cantilever-based sensors.
- Incorrect binding does not occur in natural systems because it is chaperoned by zipper-like enzyme that ensures specific binding.
- Selectivity can be improved by new class of DNA that are less floppy and does not contain charged backbone.

References

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- Brown, T. L., et al. "Chemistry: The Central Science. 2003." (DNA hybridization)
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