Folding-based Electronic Biosensors

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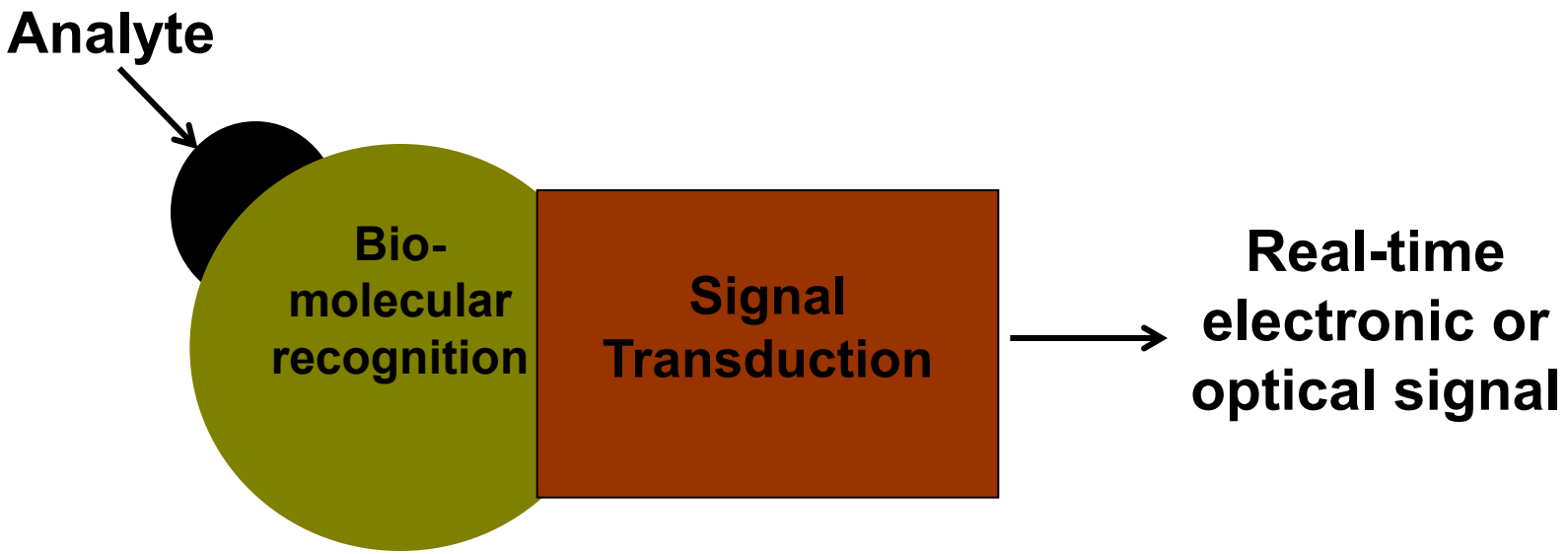
Why Biology-based Sensors?

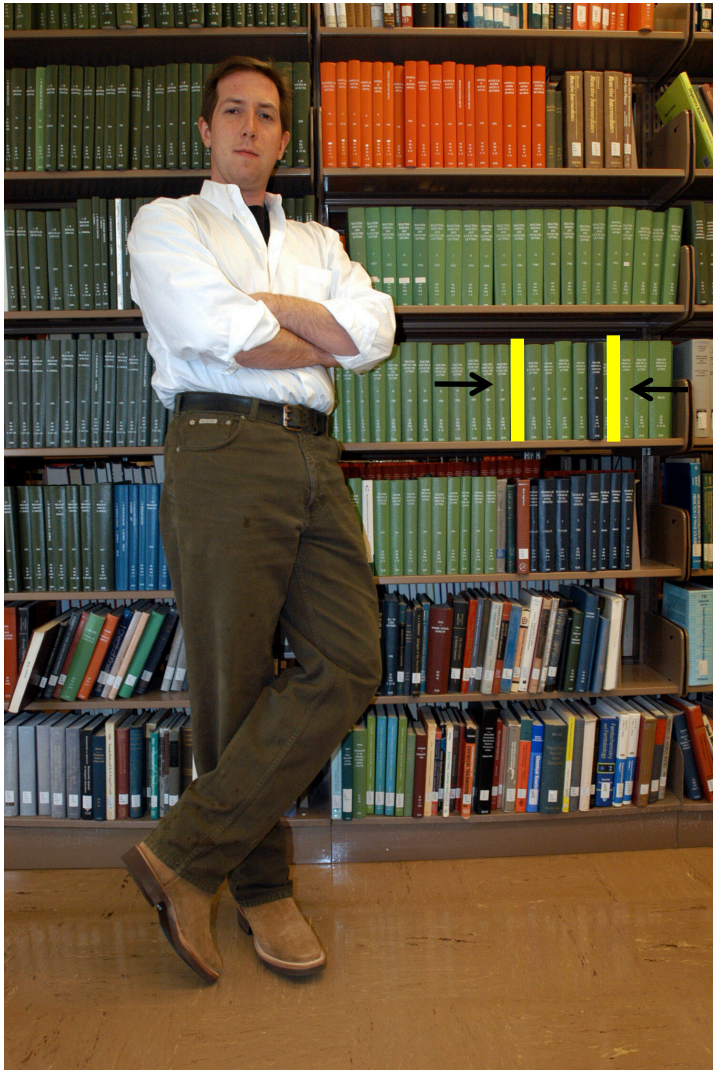
- **General: virtually any water-soluble target**
- **Sensitive: affinities approaching 10^{-18} M**
- **Specific: single residue/base discrimination**

What is a Biosensor?



A sensor that exploits the specificity of biological recognition, such as performed by enzymes, antibodies, nucleic acids or cells.

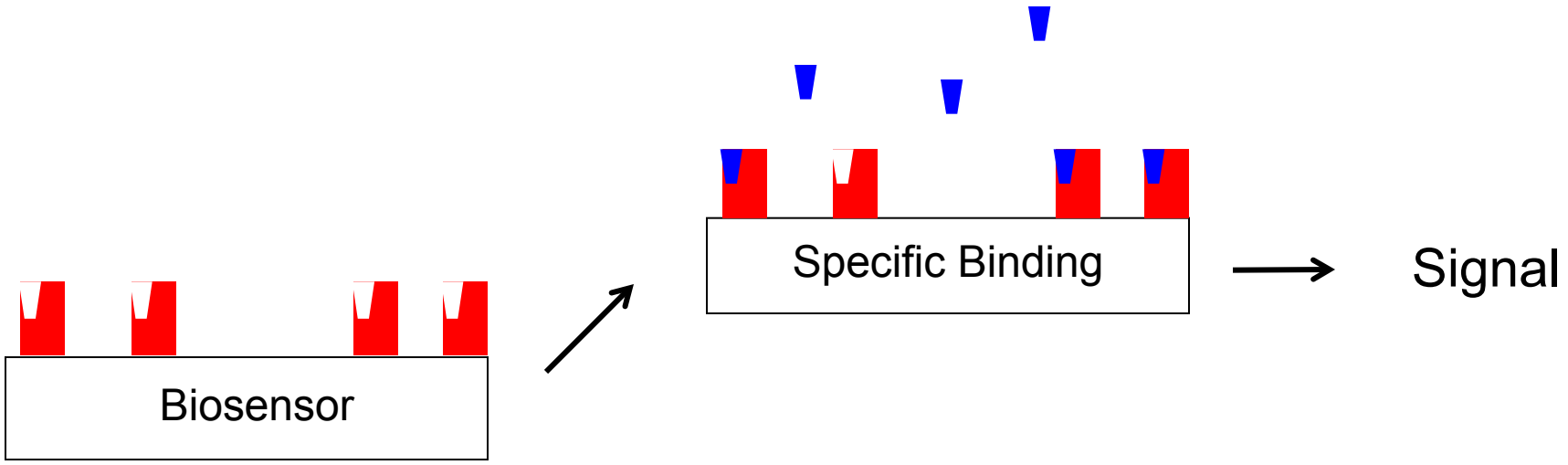
The “Biosensor Gap”



>300 papers/year are published with key words “Biosensor” and “Rapid”

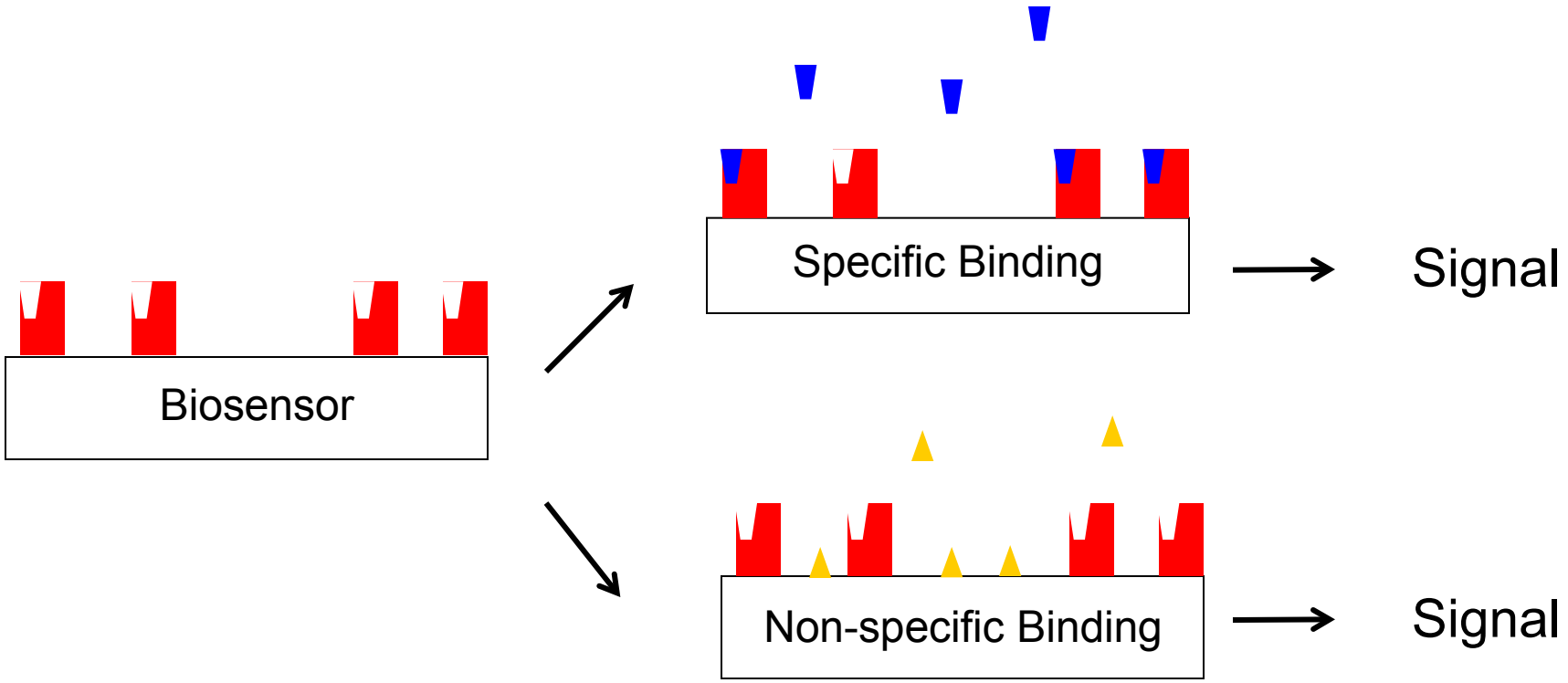
Yet there is only a single real-time biosensor on the market today

“Traditional” Biosensor



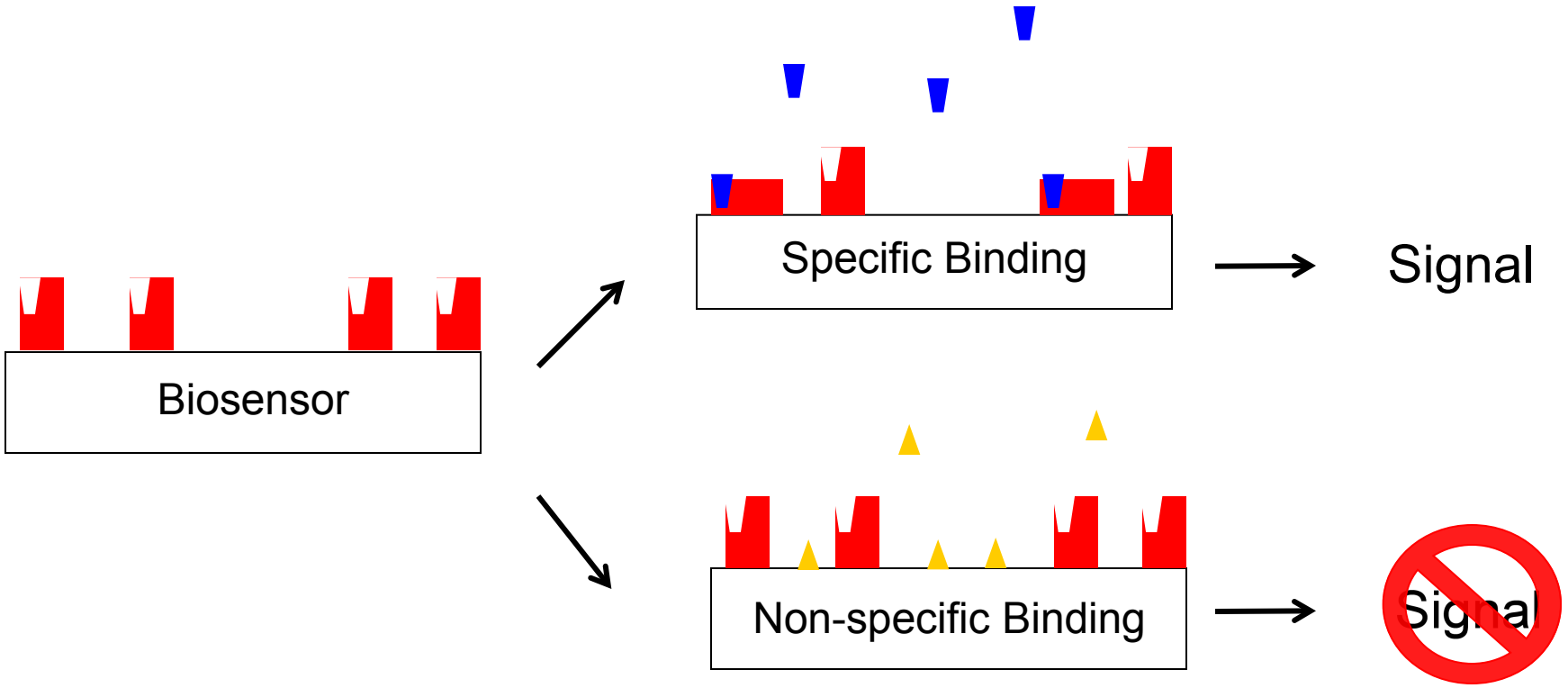
Measure changes in adsorbed mass, polarizability, sterics or charge

Achilles' Heel



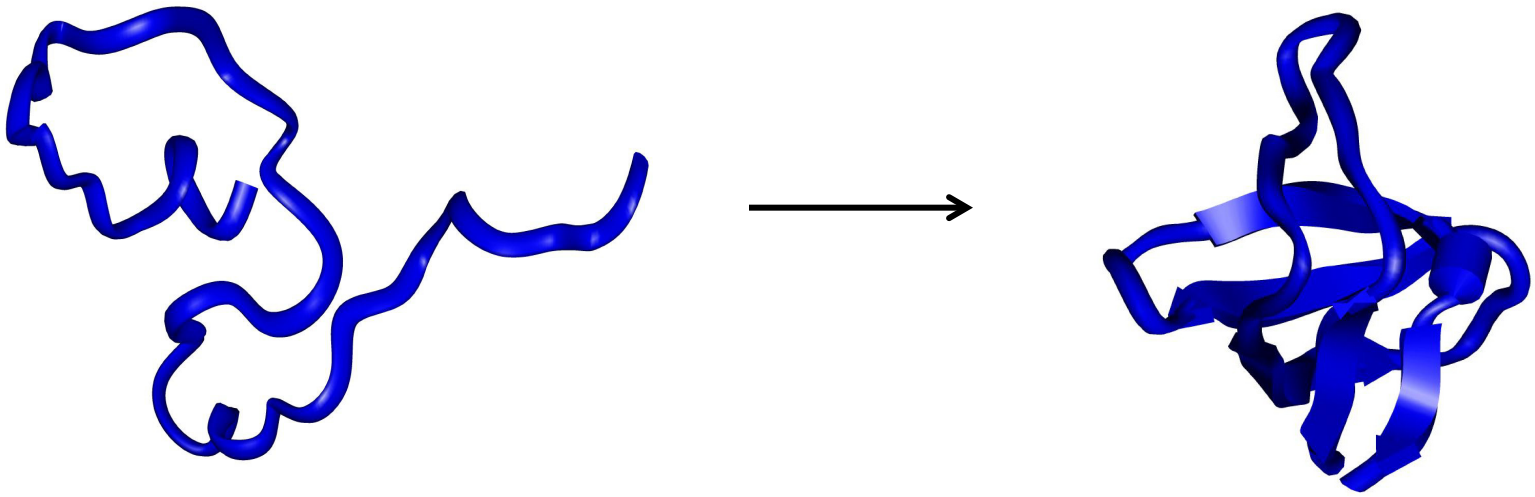
A critical, and to date unavoidable, failure mode of traditional biosensor is signals arising from the non-specific binding of contaminants.

Signal Transduction

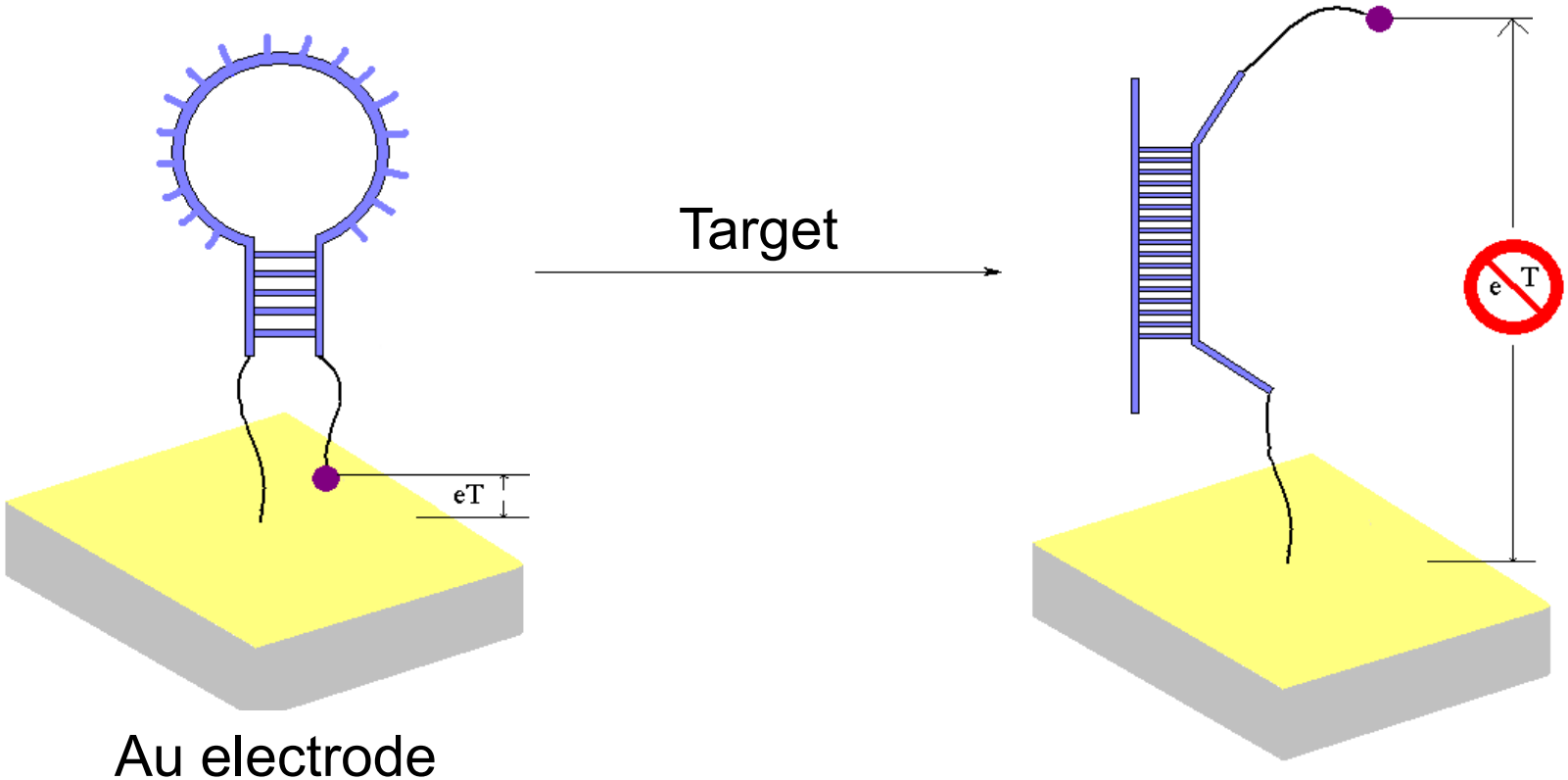


Signaling linked to a binding-specific change in the physical properties of the biopolymer

Folding

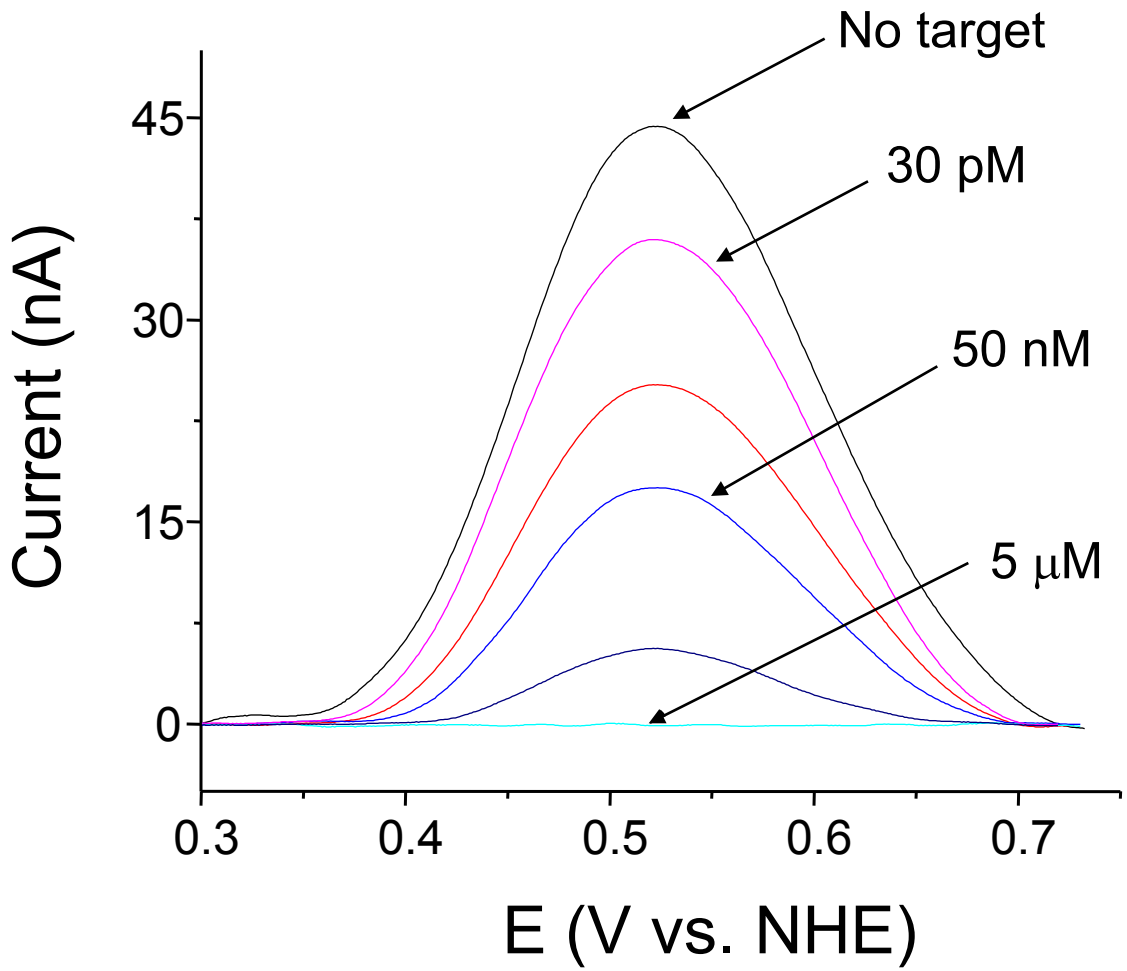


E-DNA

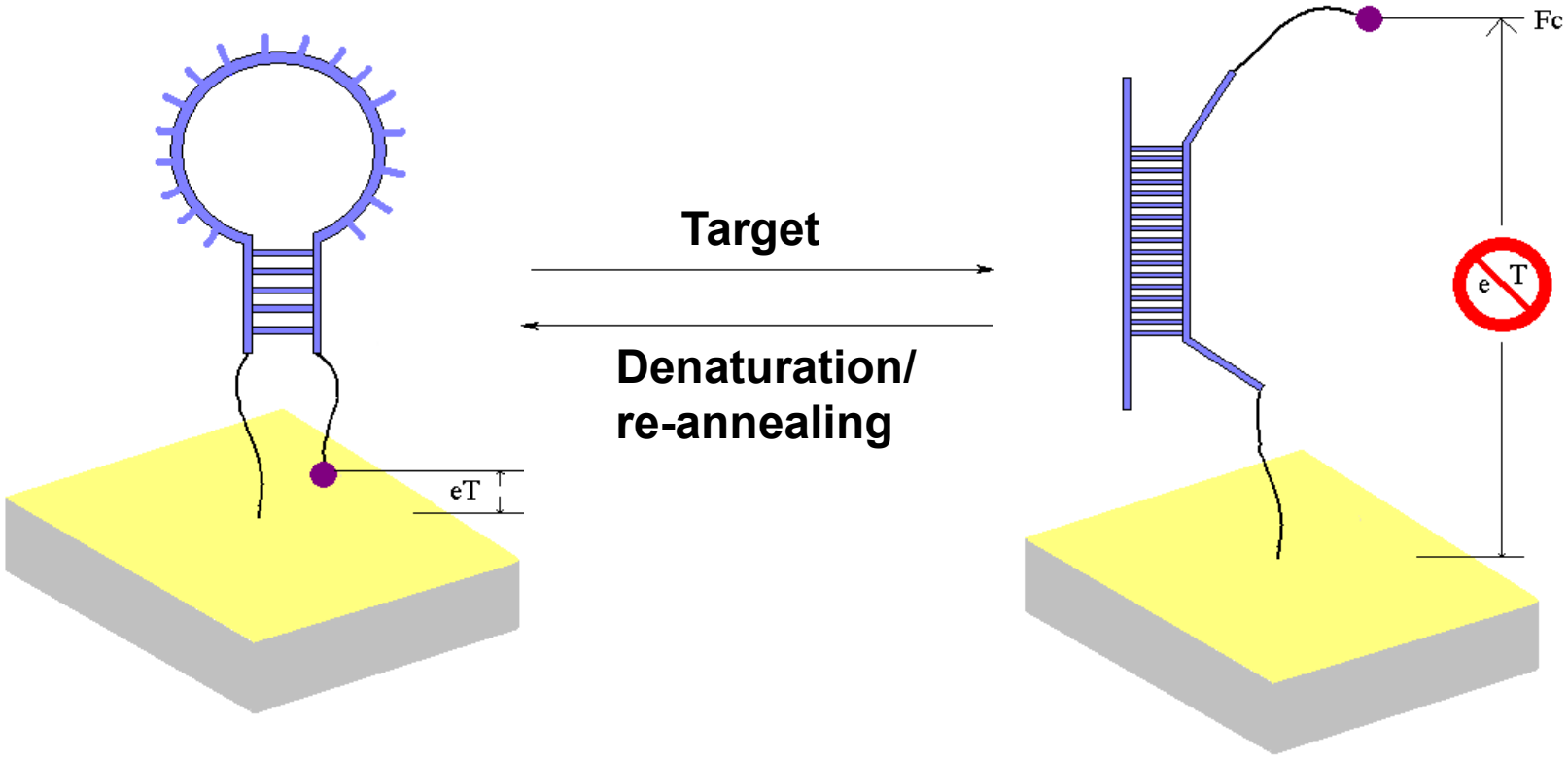


Au electrode

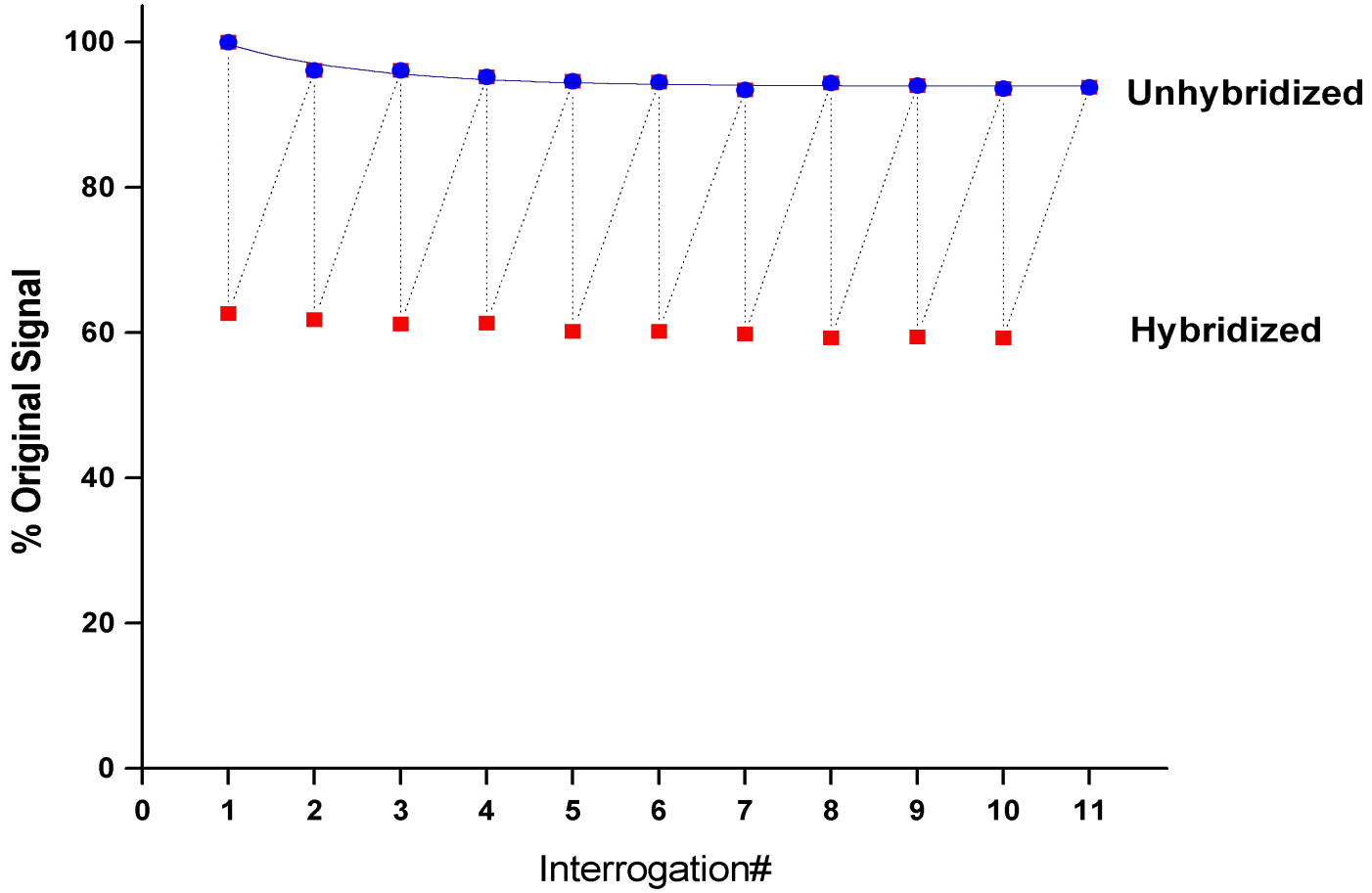
Sensitive


No target
30 pM
50 nM
5 μM
45
30
15
0
Current (nA)
0.3
0.4
0.5
0.6
0.7
E (V vs. NHE)

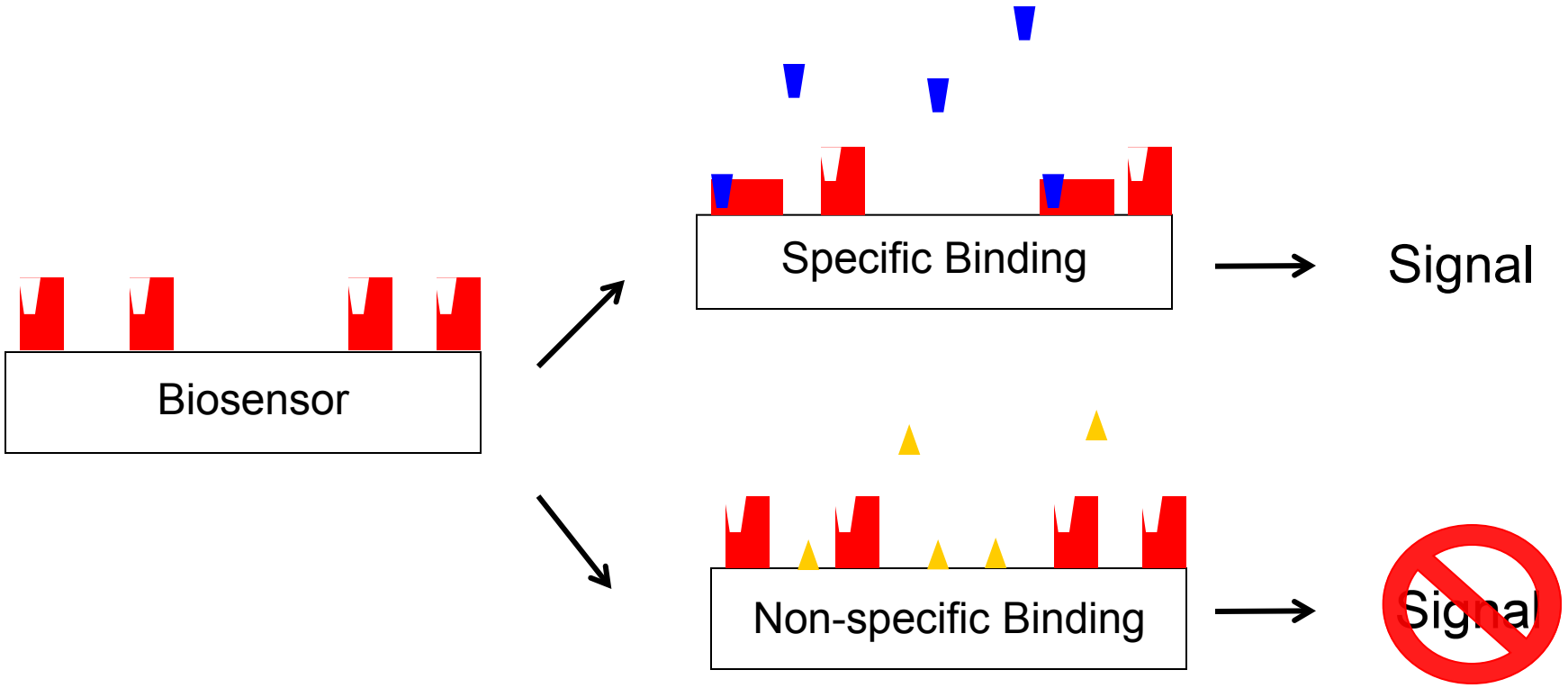
Reagentless, …



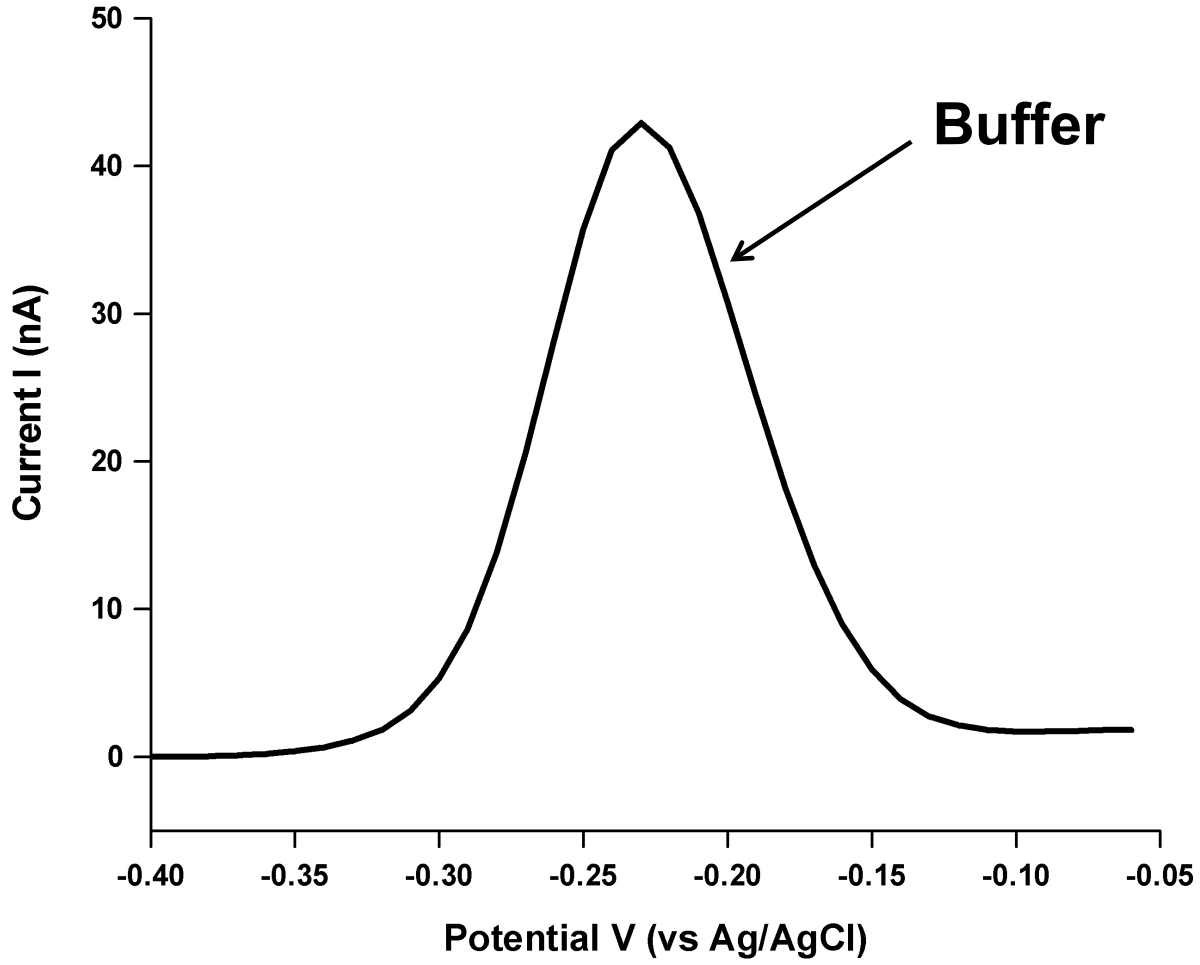
…Reusable, Reproducible

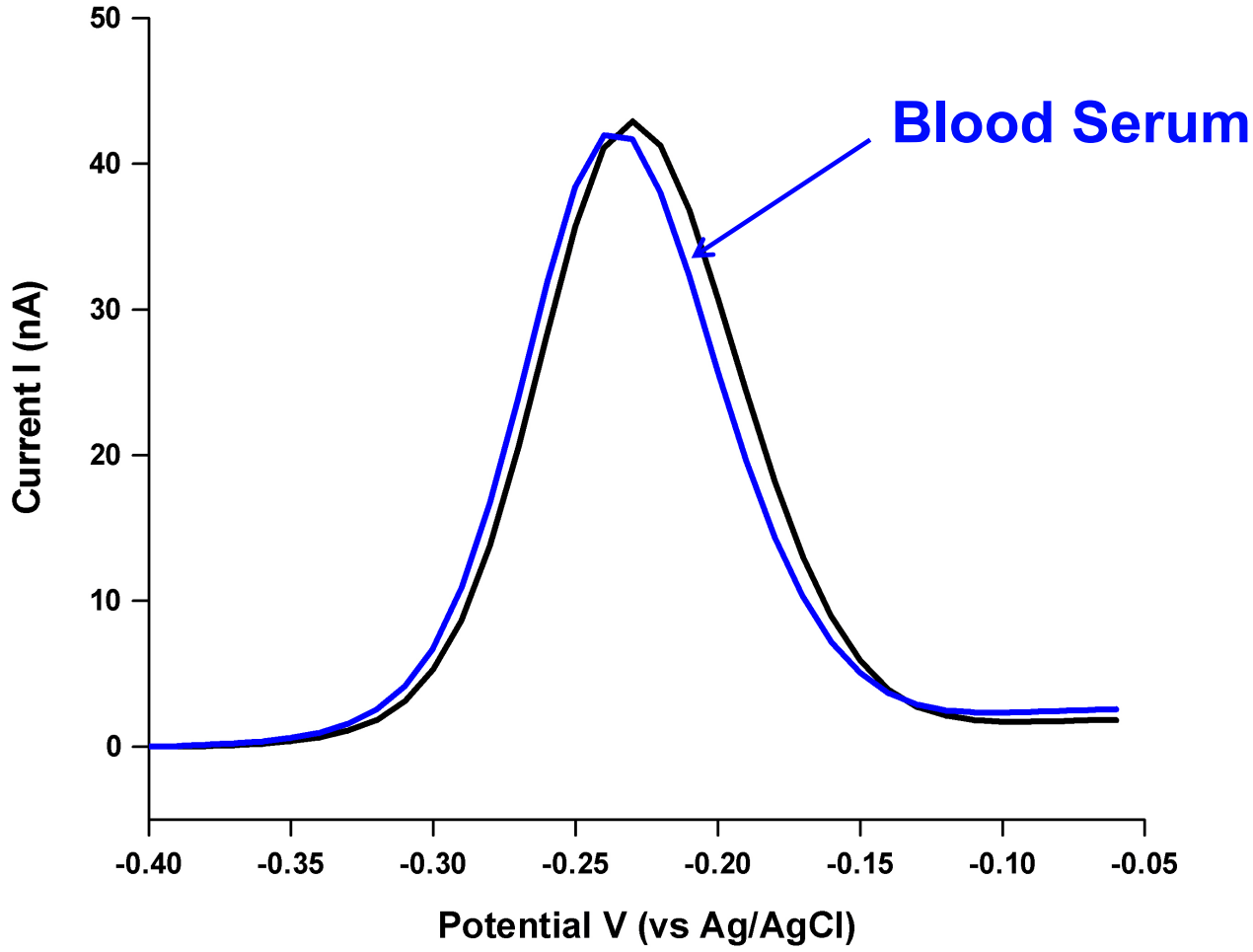


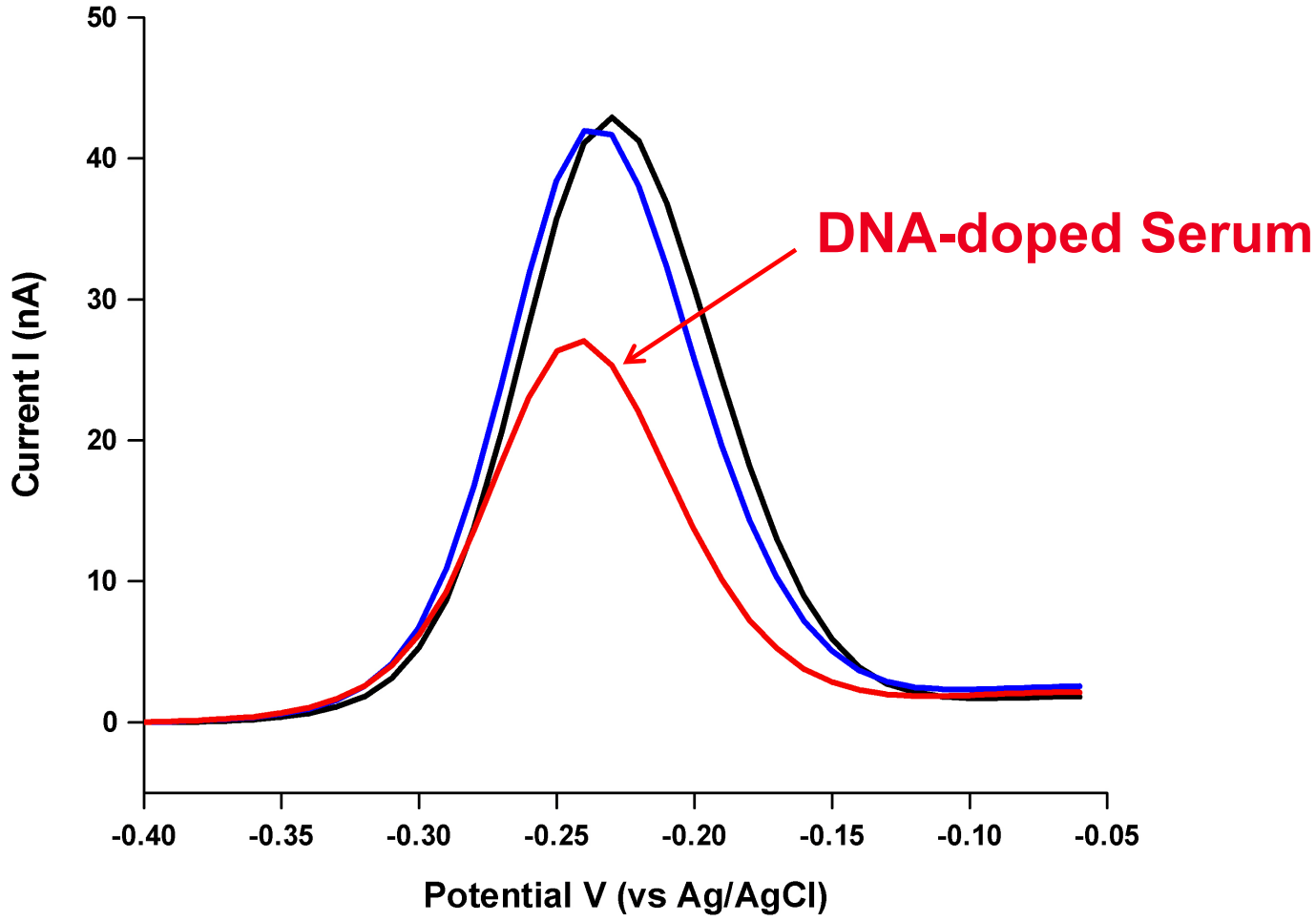
Selective

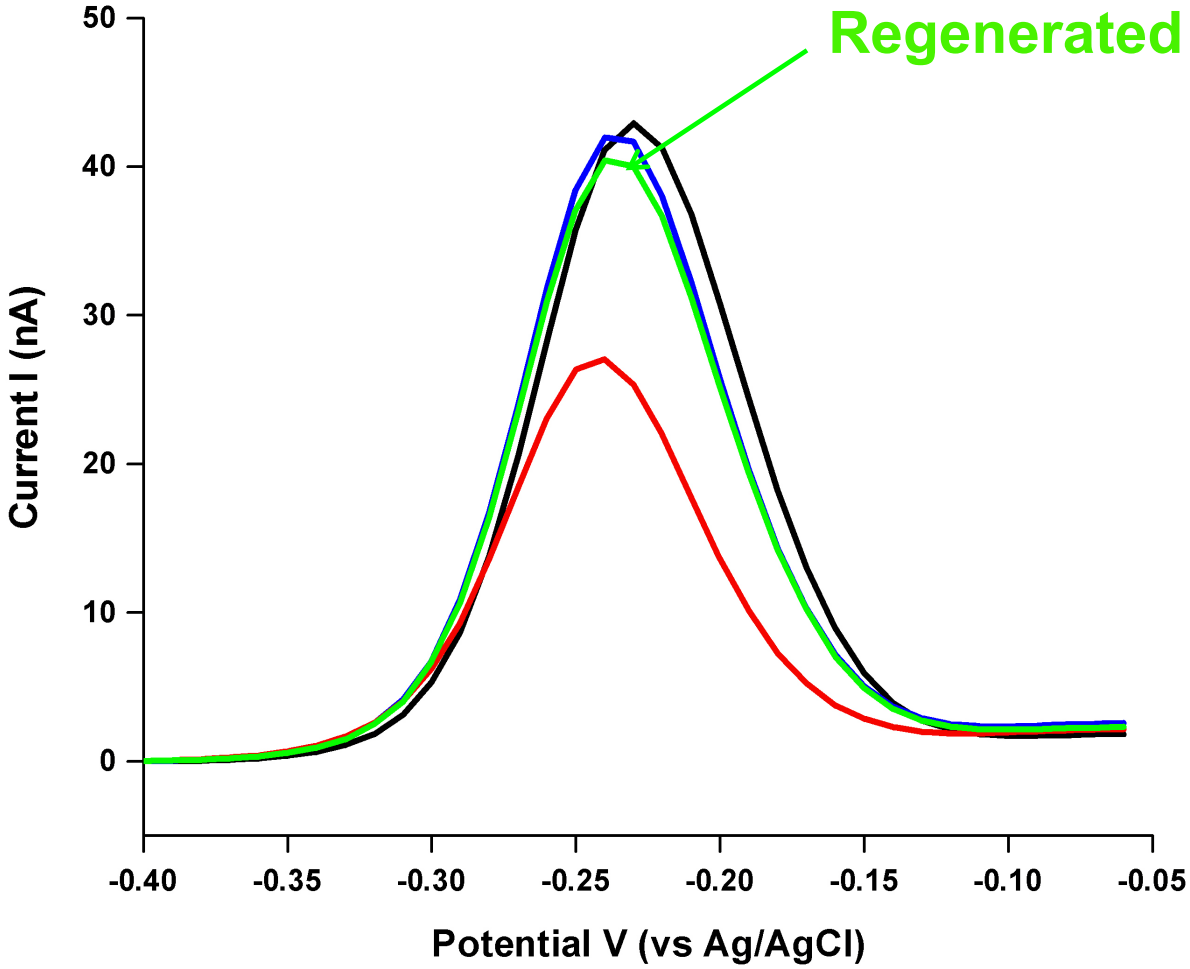


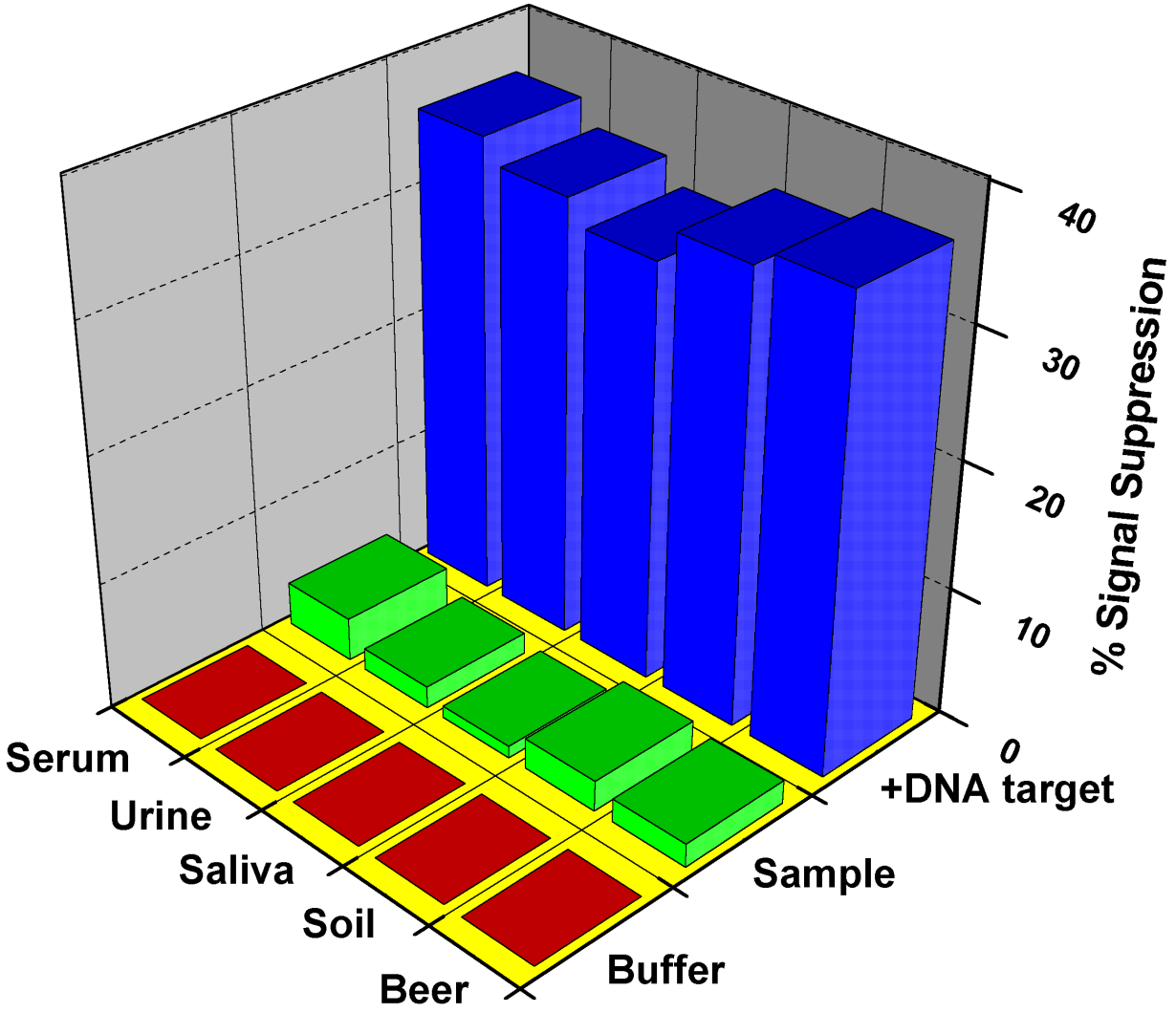
Signaling linked to a binding-specific change in the physical properties of the biopolymer

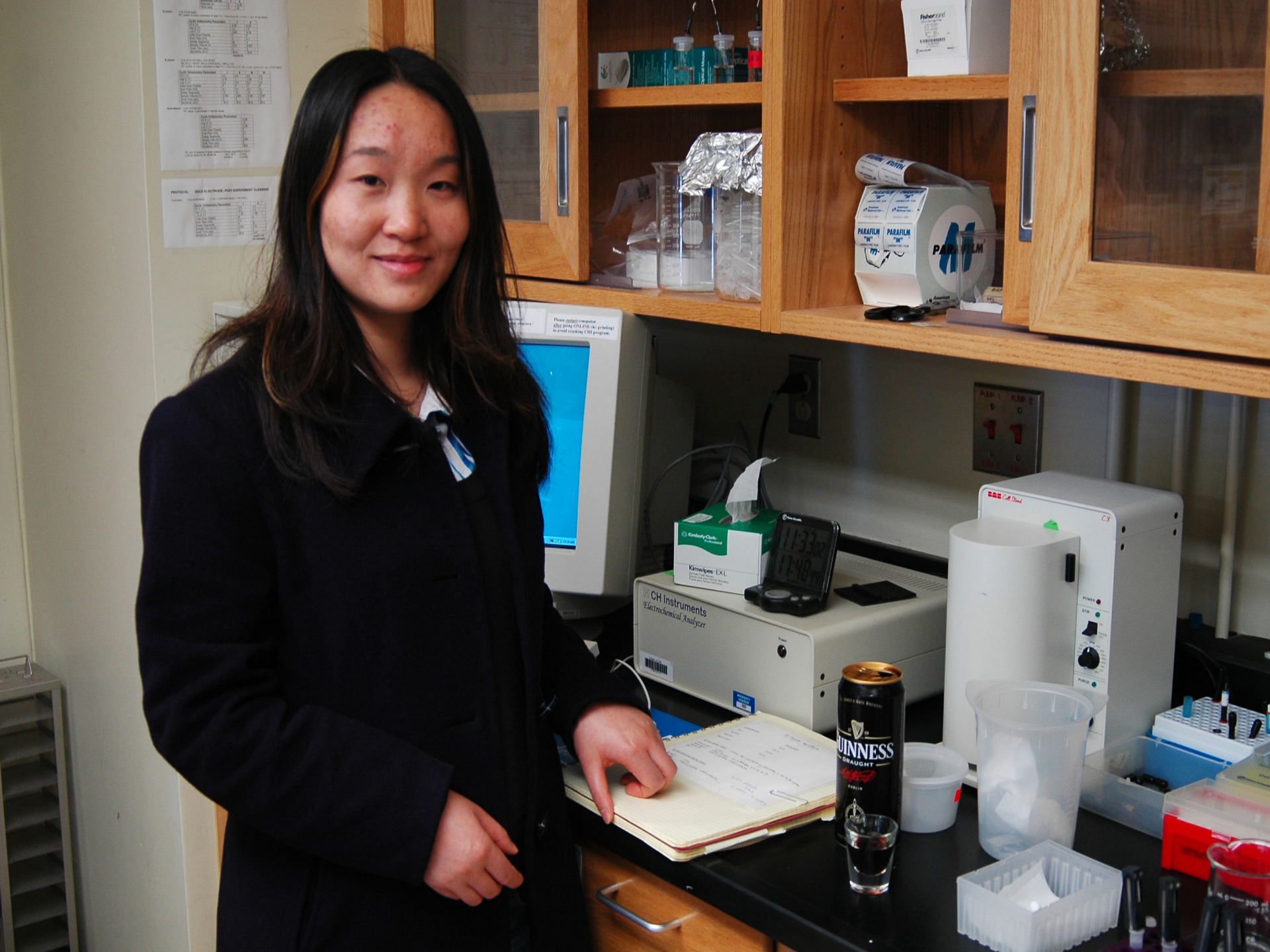

Buffer
Current I (nA)
50
40
30
20
10
0
-0.40
-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
Potential V (vs Ag/AgCl)


Blood Serum
Current I (nA)
50
40
30
20
10
0
-0.40
-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
Potential V (vs Ag/AgCl)

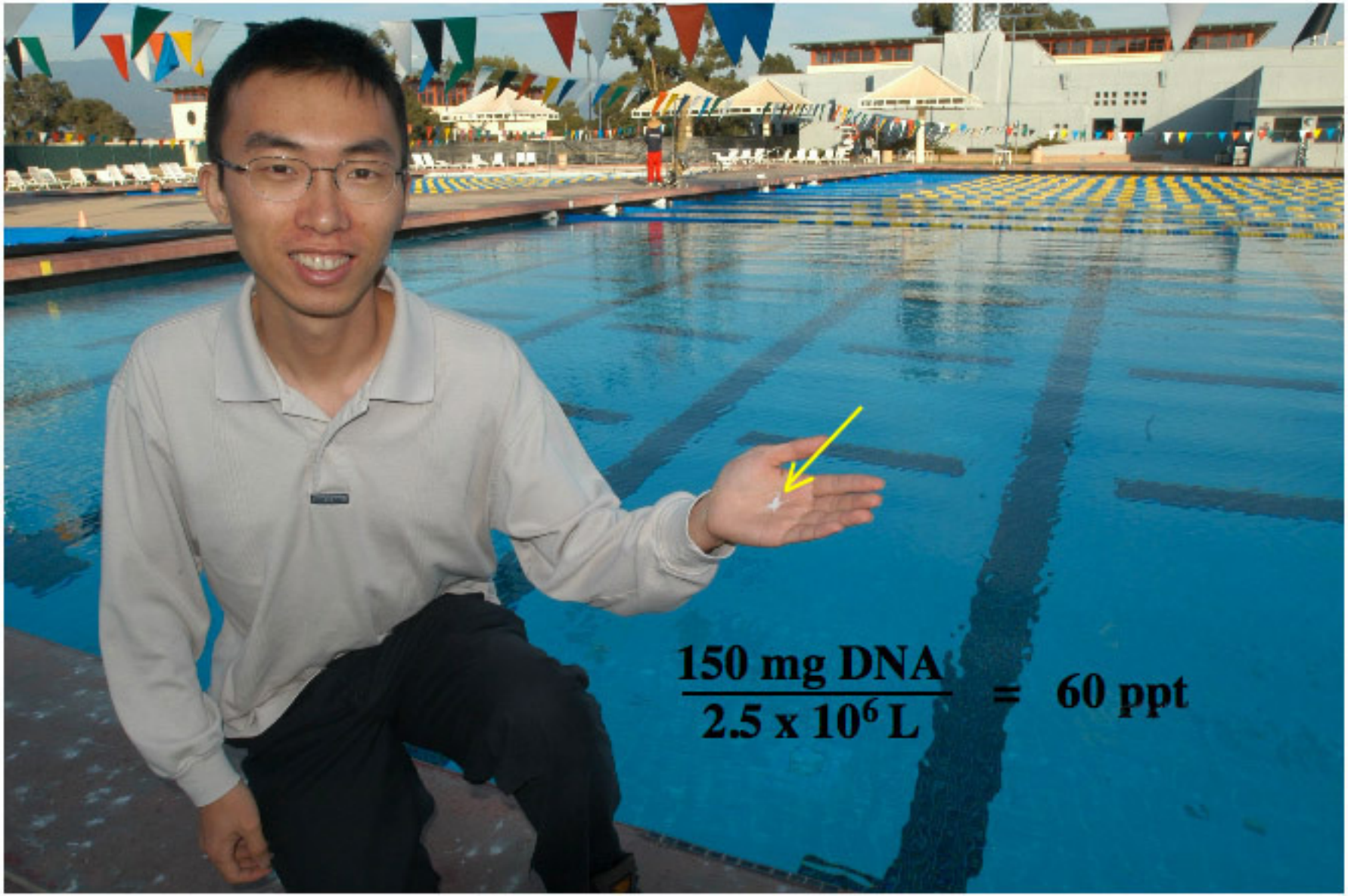

DNA-doped Serum
Current I (nA)
50
40
30
20
10
0
-0.40
-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
Potential V (vs Ag/AgCl)


Regenerated
50
40
30
20
10
0
Current I (nA)
-0.40
-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
Potential V (vs Ag/AgCl)

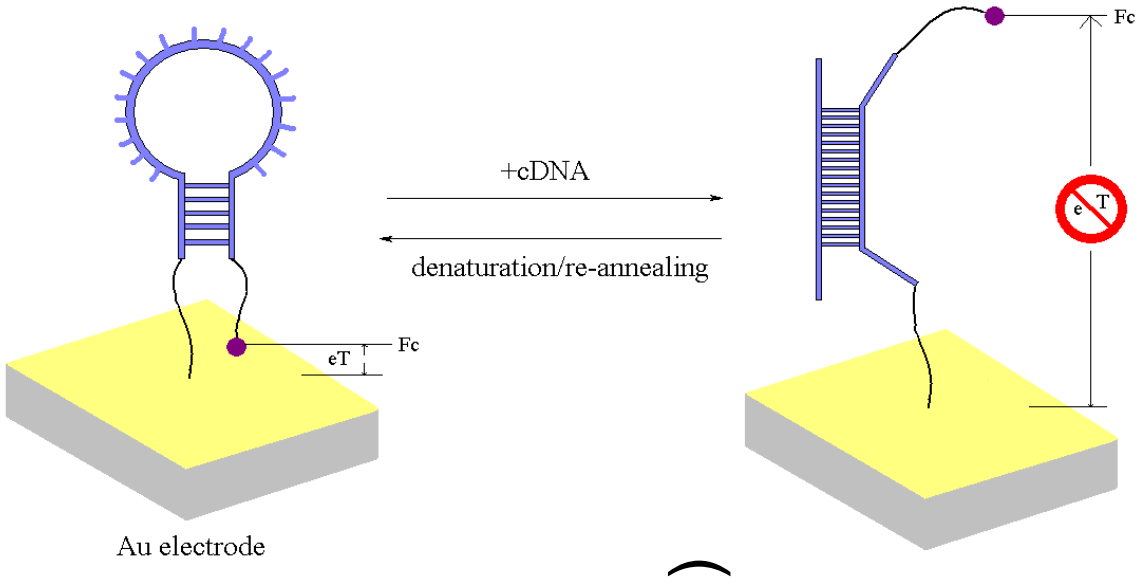

40
30
20
10
0
% Signal Suppression
Serum
Urine
Saliva
Soil
Beer
Buffer
Sample
+DNA target

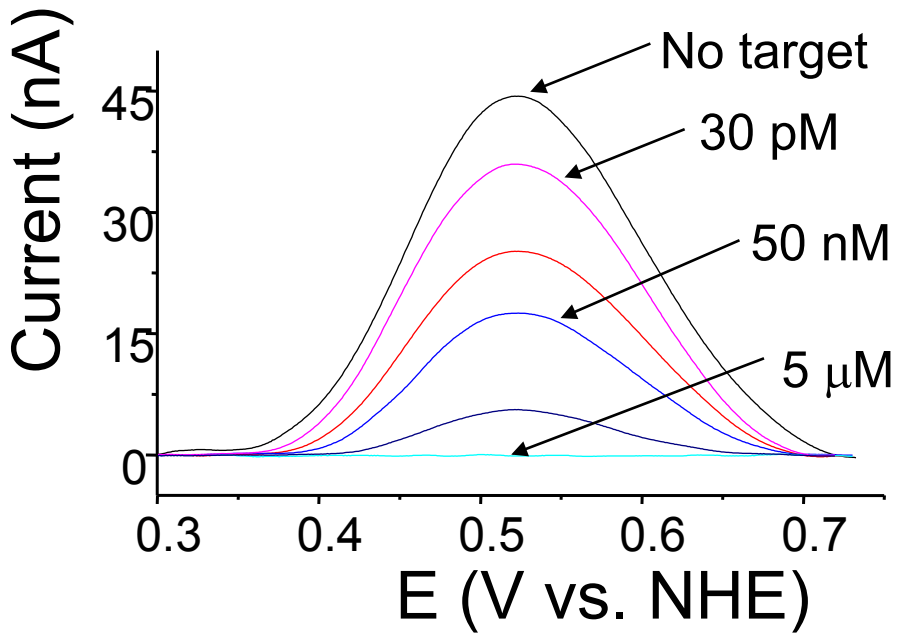

PARAFILM
CH Instruments
Electrochemical Analyzer
Kimwipes EXL
GUINNESS
DRAUGHT

10 pM

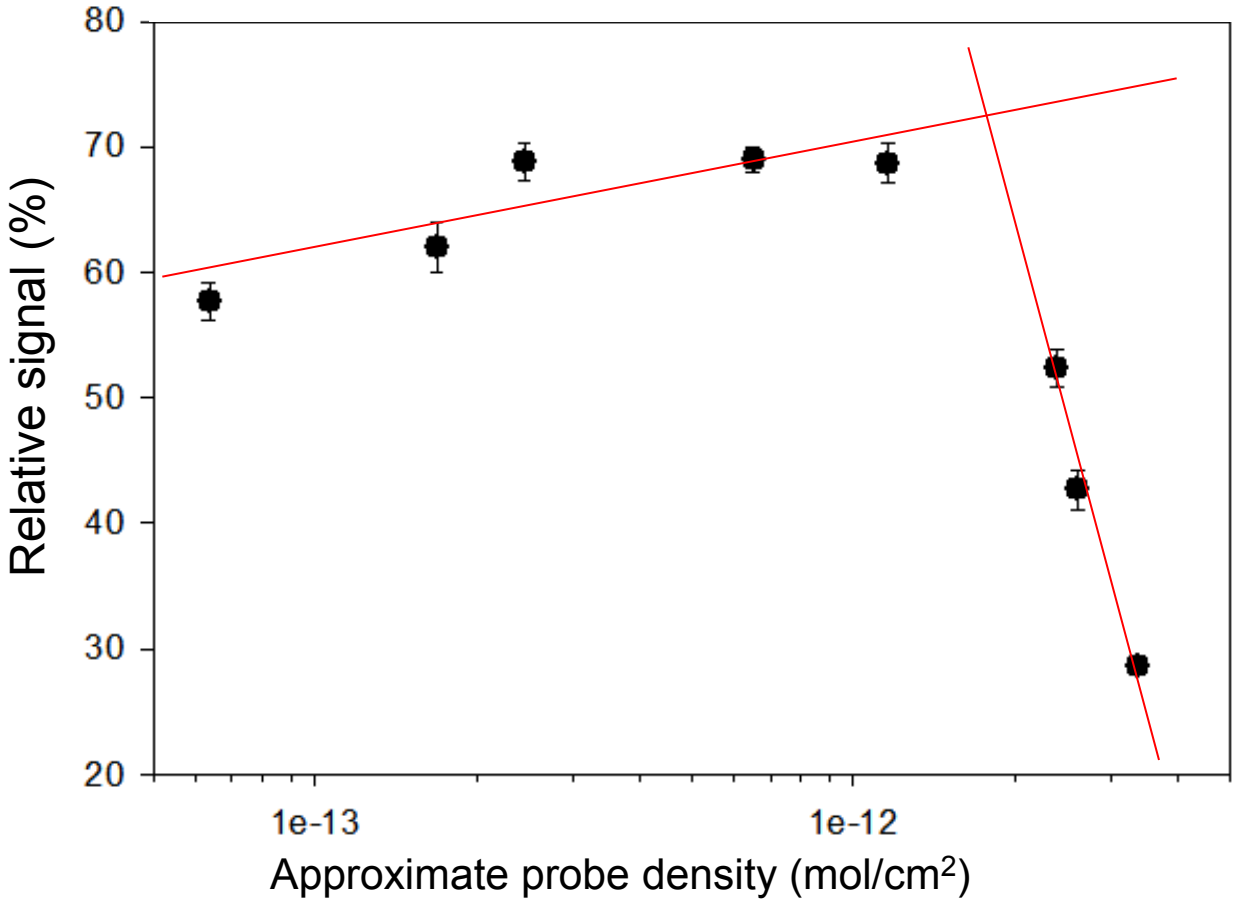


Signal-Off

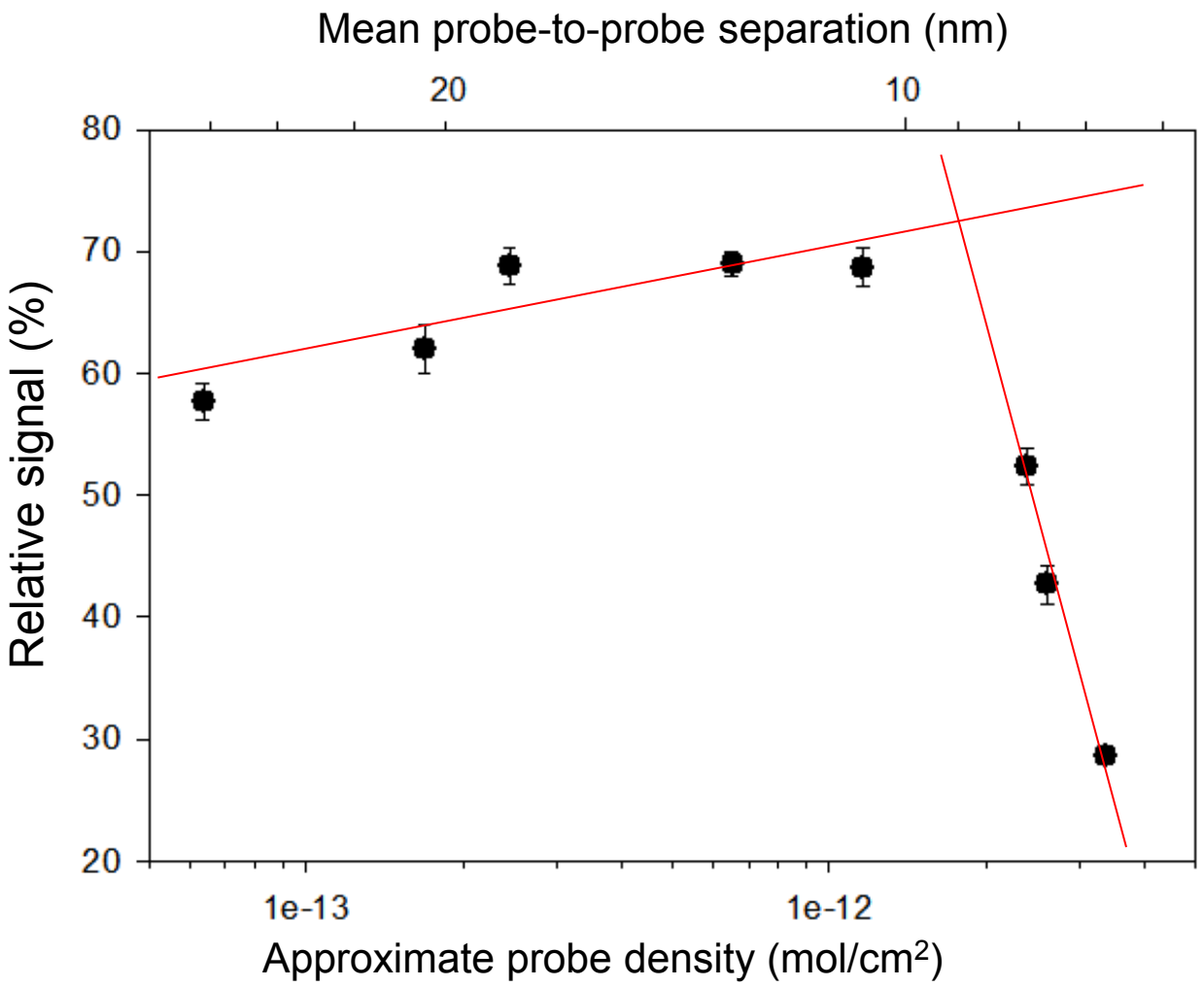

+cDNA
denaturation/re-annealing
Fc
eT
Au electrode
Fc
e
T

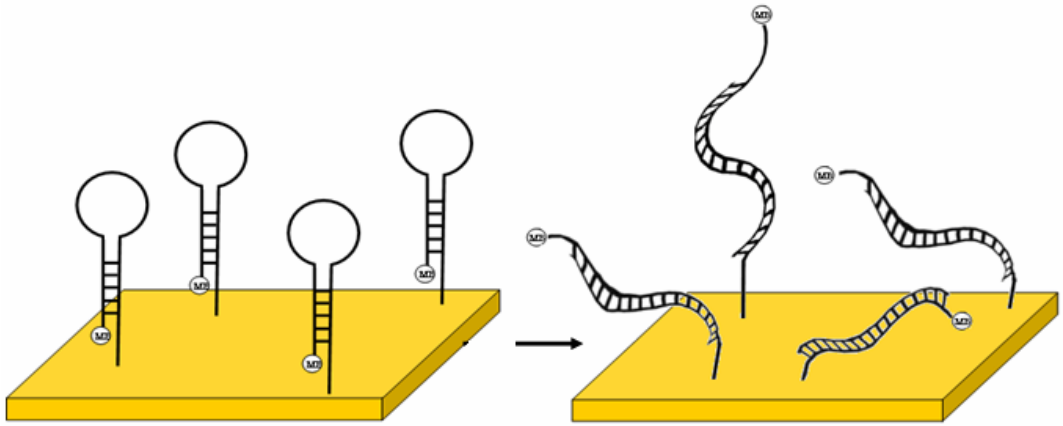

Current (nA)
45
30
15
0
0.3
0.4
0.5
0.6
0.7
E (V vs. NHE)
No target
30 pM
50 nM
5 μM

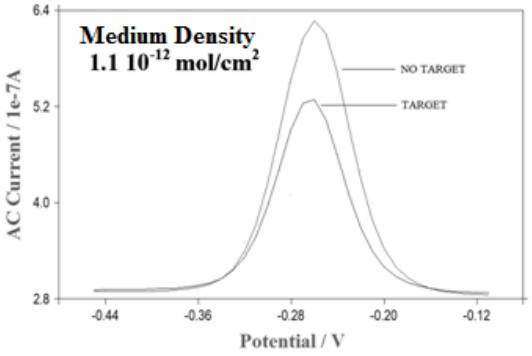
Signaling Mechanism

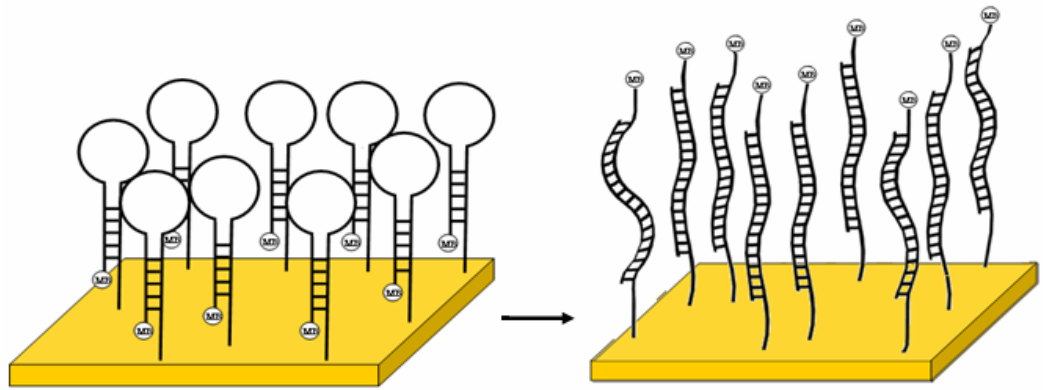


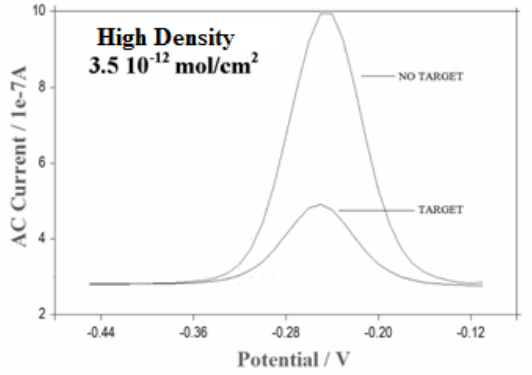
Signaling Mechanism

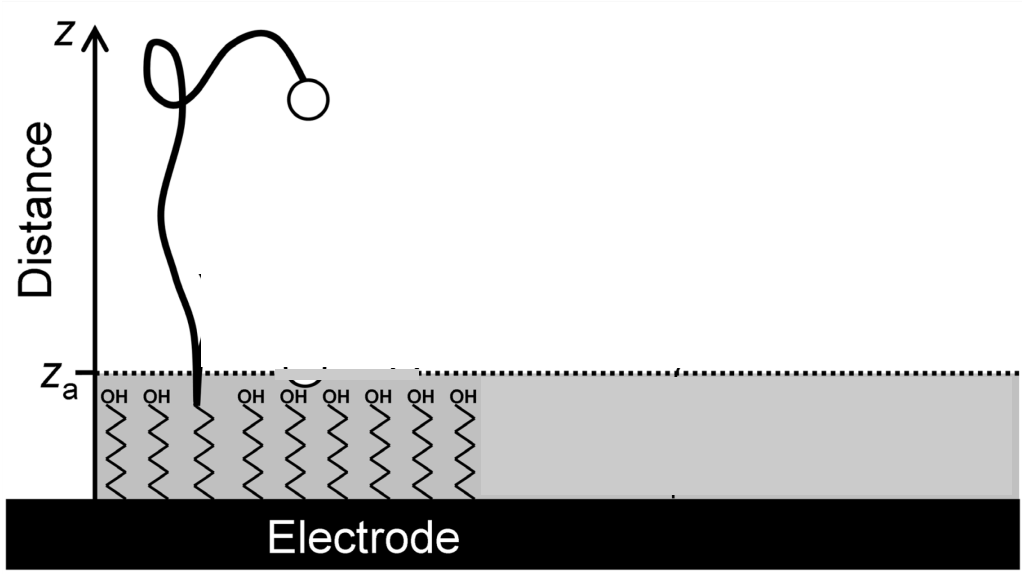


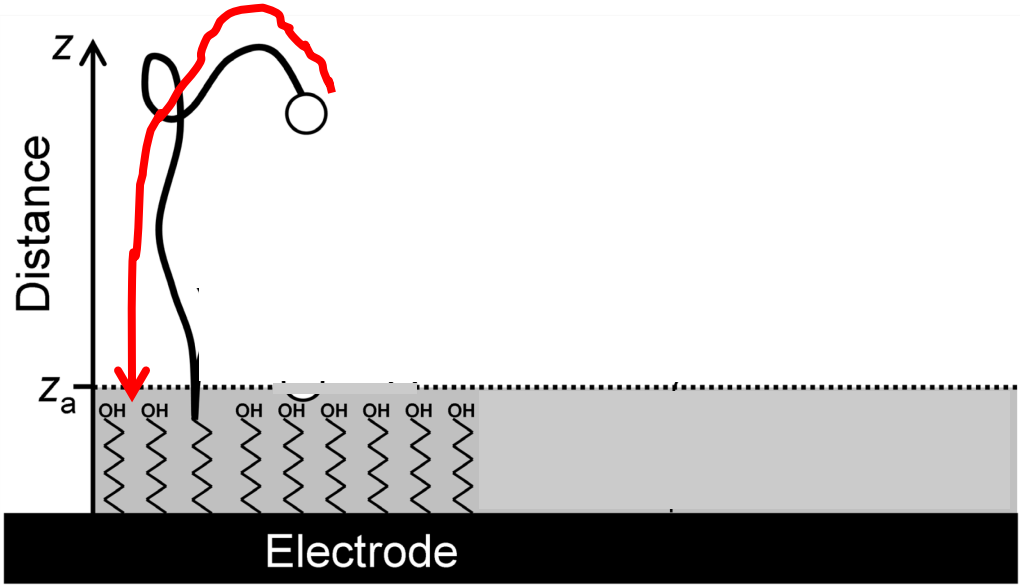



Medium Density
1.1 10-12 mol/cm2
NO TARGET
TARGET
AC Current / 1e-7A
6.4
5.2
4.0
2.8
-0.44
-0.36
-0.28
-0.20
-0.12
Potential / V



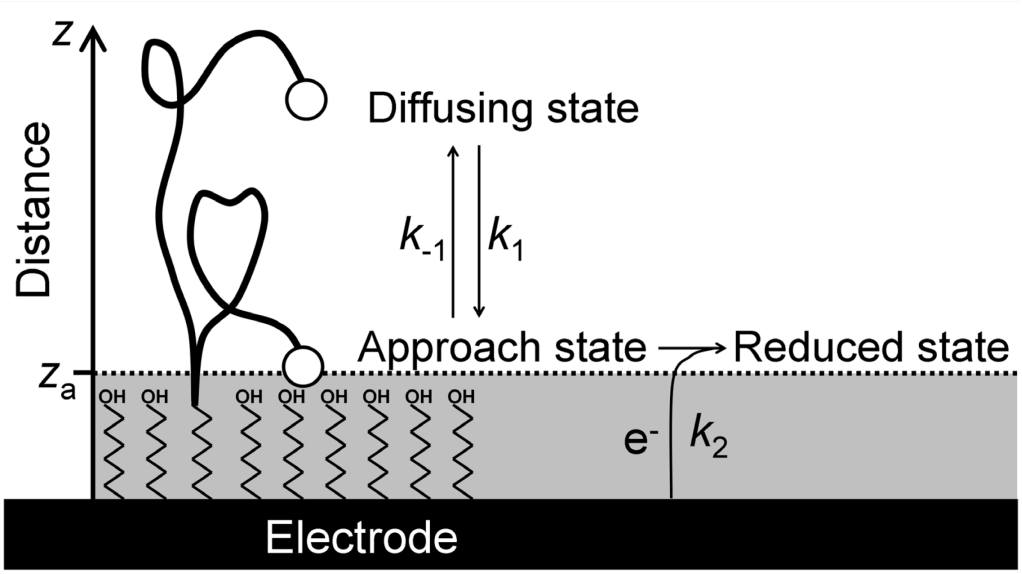

High Density
3.5 10-12 mol/cm2
NO TARGET
TARGET
AC Current / 1e-7A
10
8
6
4
2
-0.44
-0.36
-0.28
-0.20
-0.12
Potential / V


z
Distance
z_a
OH OH OH OH OH OH OH OH
Electrode



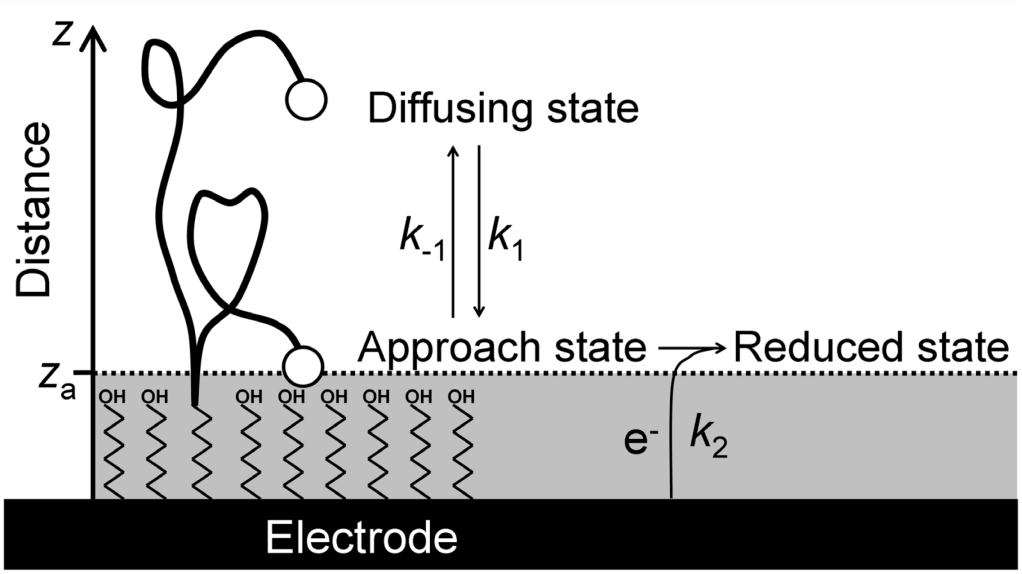
If *through-chain* Electron *Transfer* Dominates

$$k_{app} \propto e^{-N\beta}$$



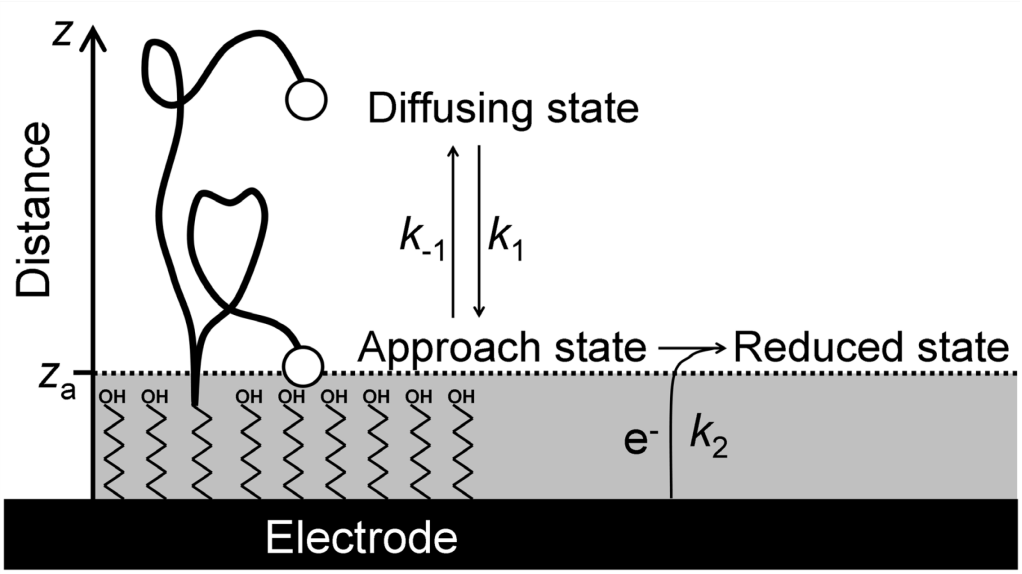
If $k_1 < k_2$ Chain Dynamics Dominate

$$k_{app} \propto N^{-2}$$



If $k_1 > k_2$ Equilibrium Chain Properties Dominate

$$k_{app} = \frac{k_{+1}}{k_{-1}} k_2 \propto N^{-1.2}$$



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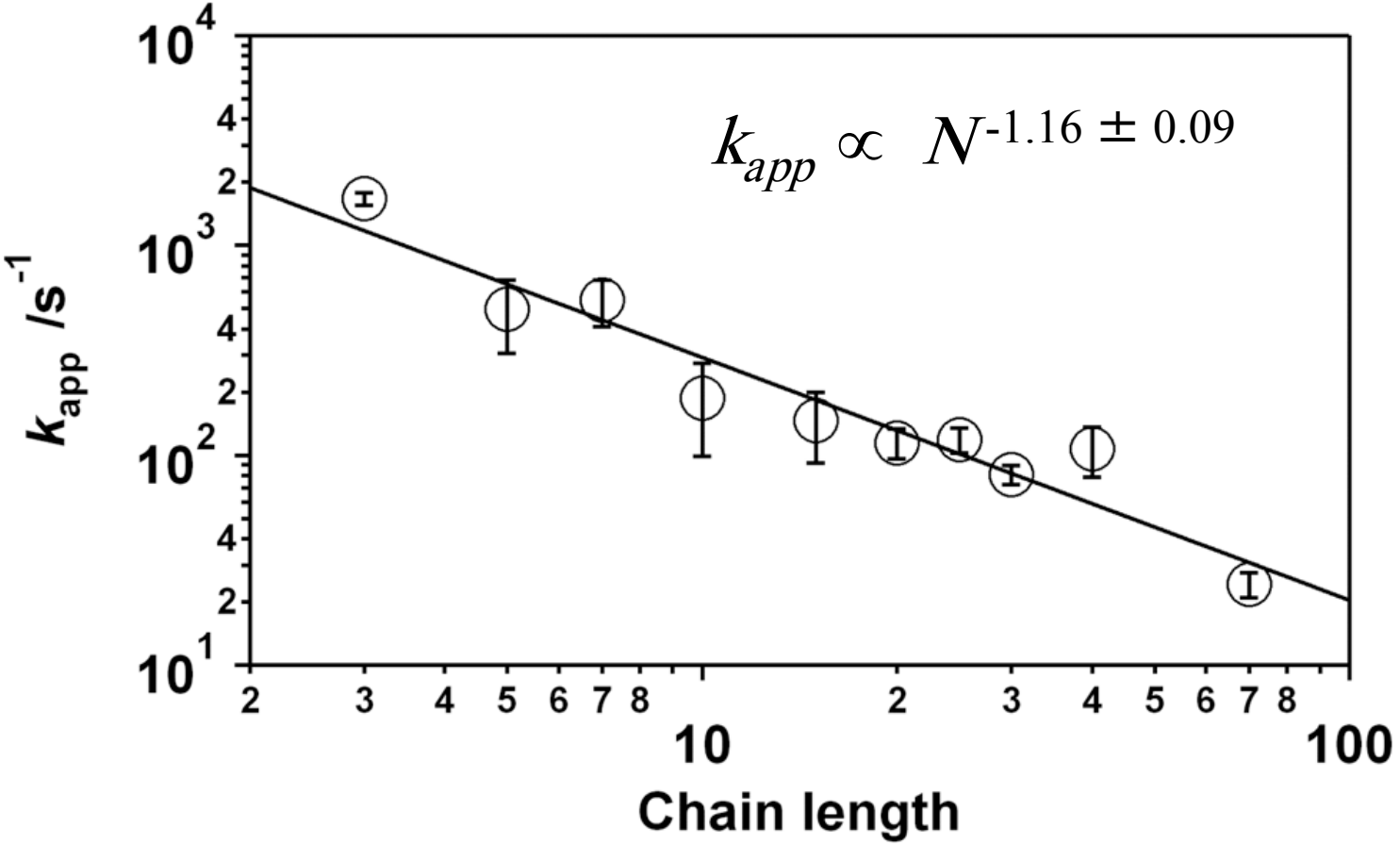
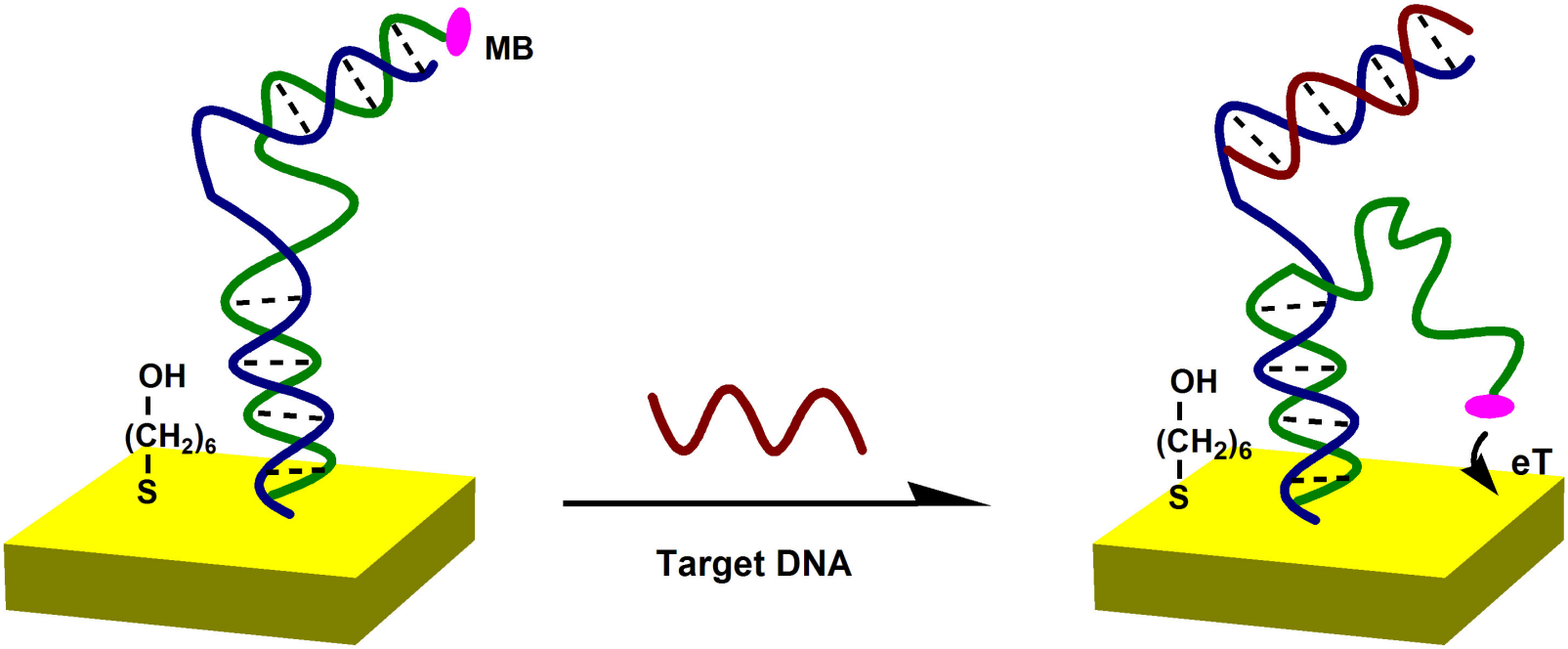
If $k_1 > k_2$ Equilibrium Chain Properties Dominate

$$k_{app} = \frac{k_{+1}}{k_{-1}} k_2 \propto N^{-1.2}$$

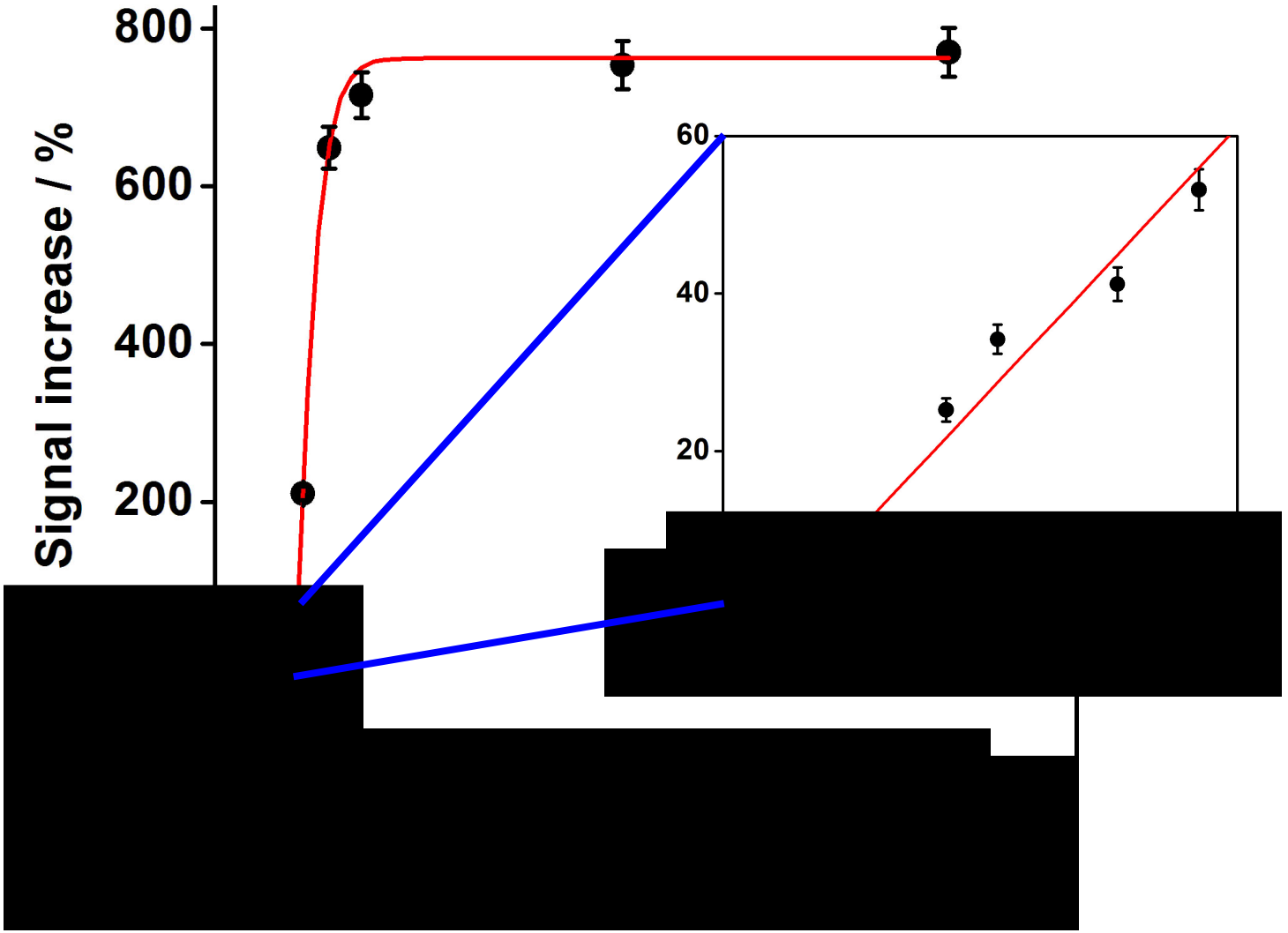
Rates versus Chain Length



Signal-On E-DNA



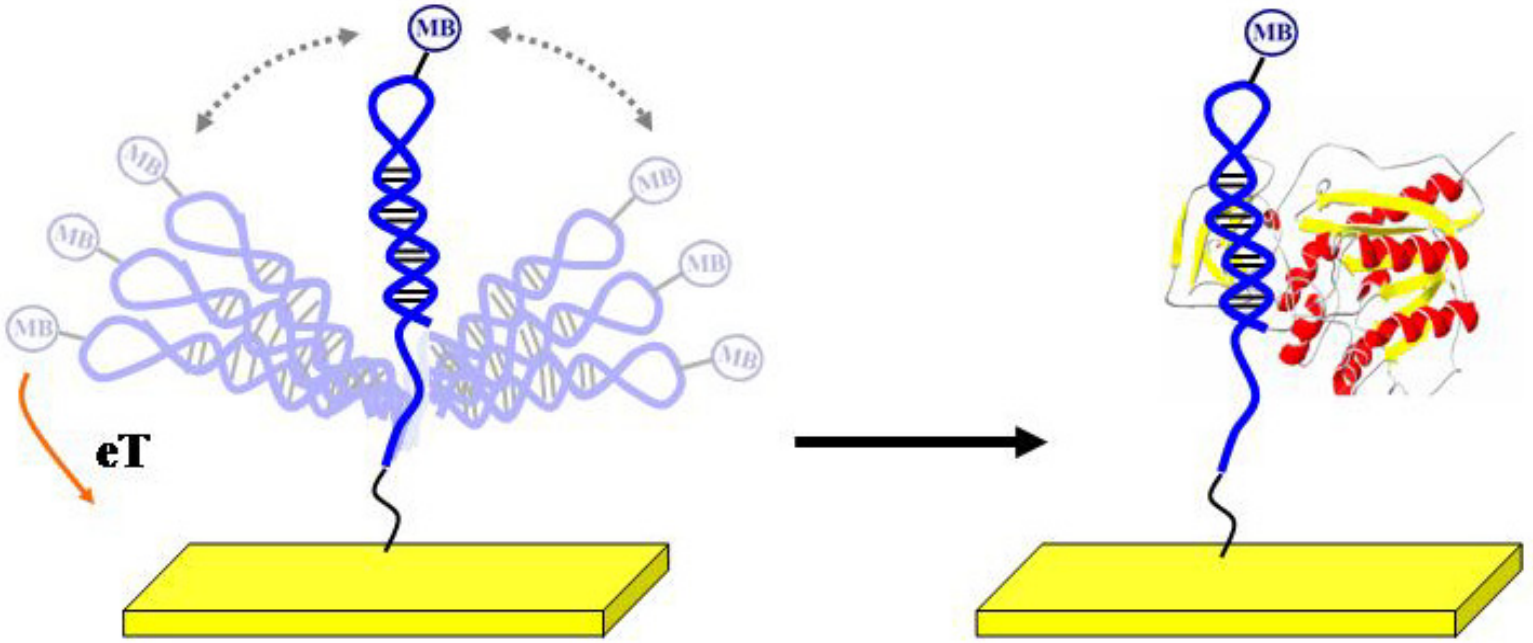
Femtomolar Detection



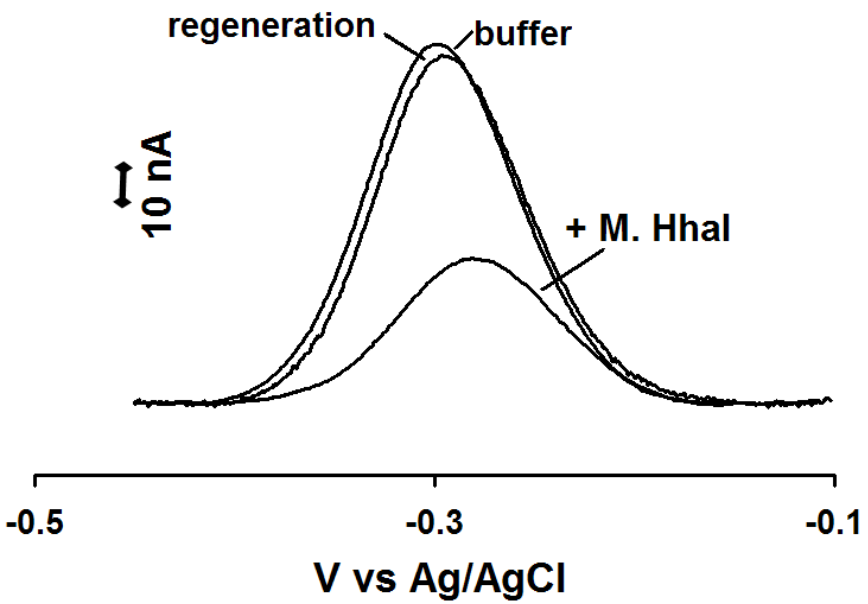
100 fM

$$\frac{1.5 \text{ mg DNA}}{2.5 \times 10^6 \text{ L}} = 600 \text{ ppq}$$

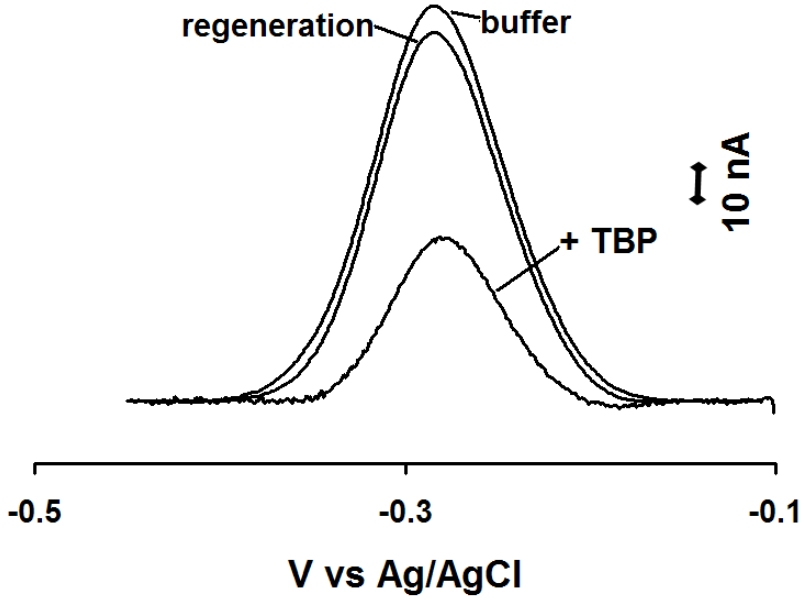
Detection of DNA-binding Proteins



M. Hhal

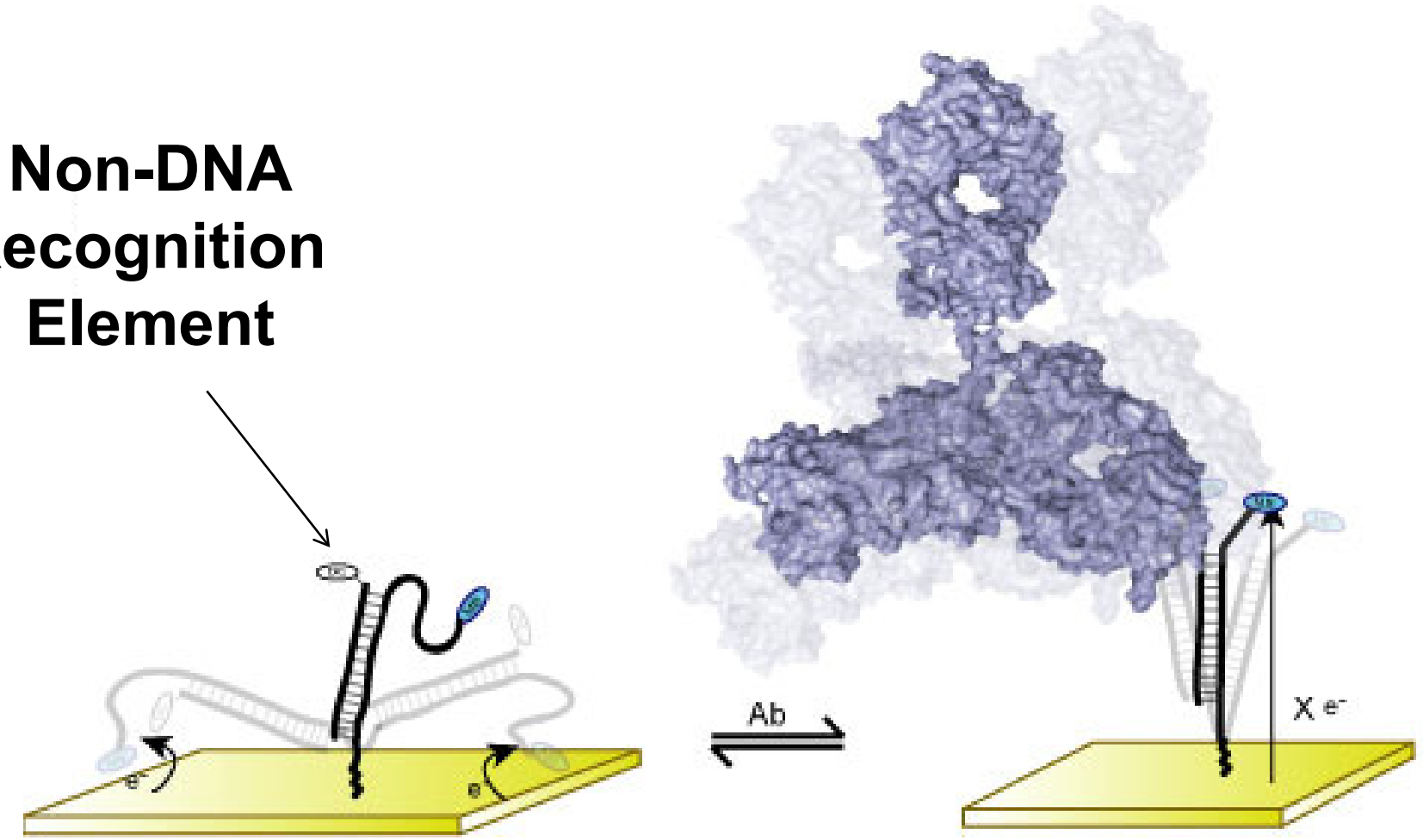

regeneration
buffer
10 nA
+ M. Hhal
-0.5
-0.3
-0.1
V vs Ag/AgCl

TBP

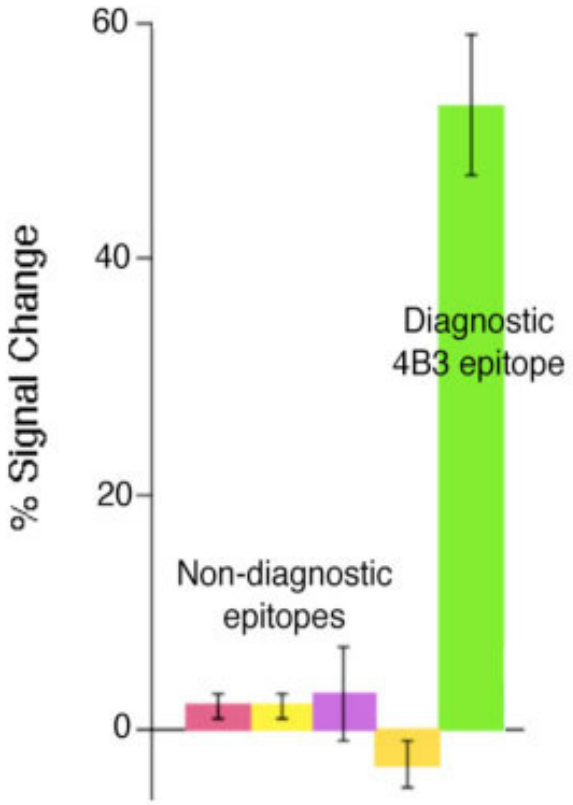

regeneration
buffer
10 nA
+ TBP
-0.5
-0.3
-0.1
V vs Ag/AgCl

DNA as Scaffold

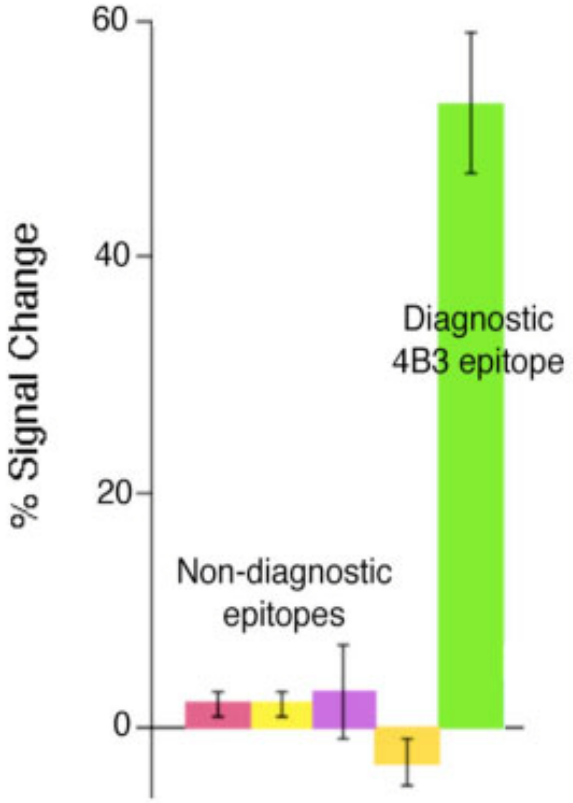
Non-DNA Recognition Element

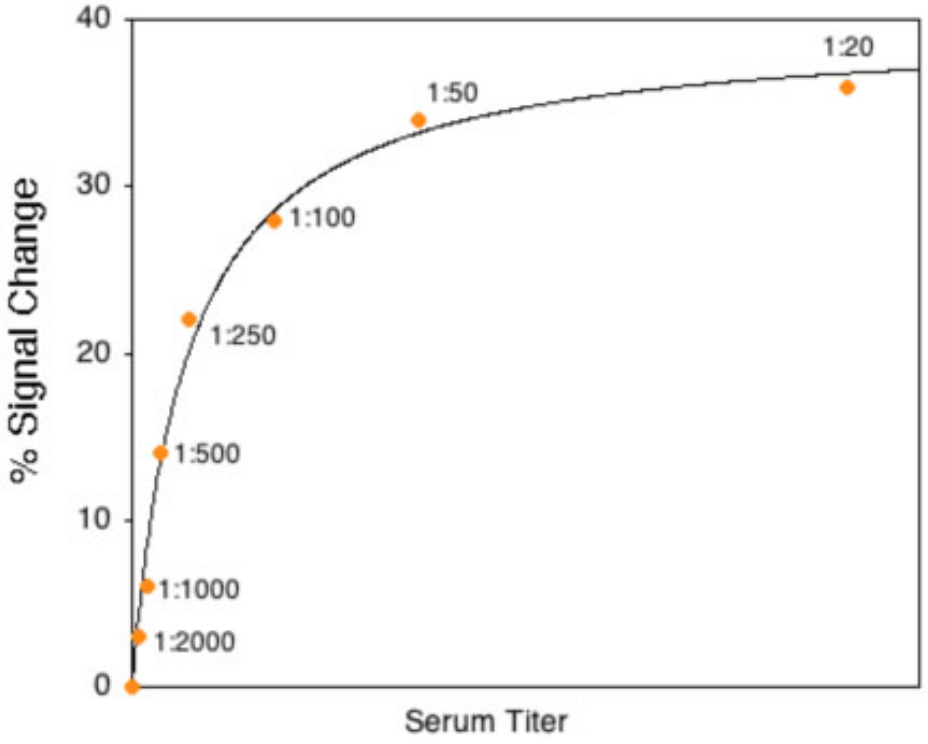


Anti-HIV Antibody Detection



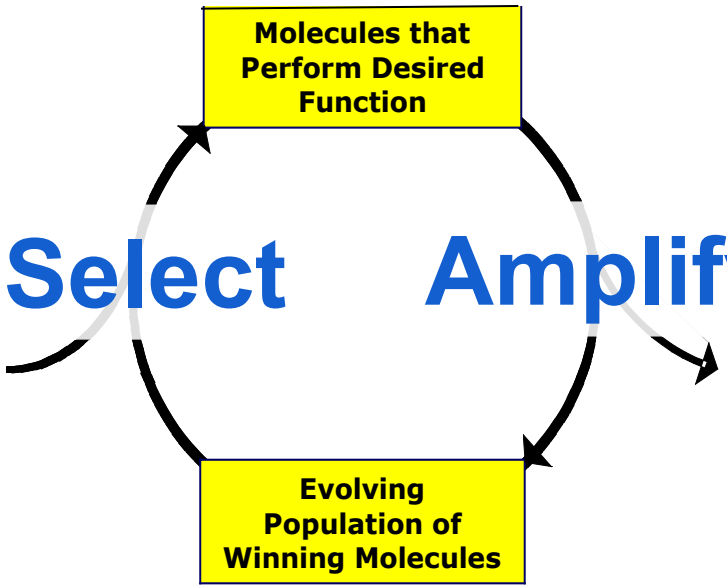
Anti-HIV Antibody Detection



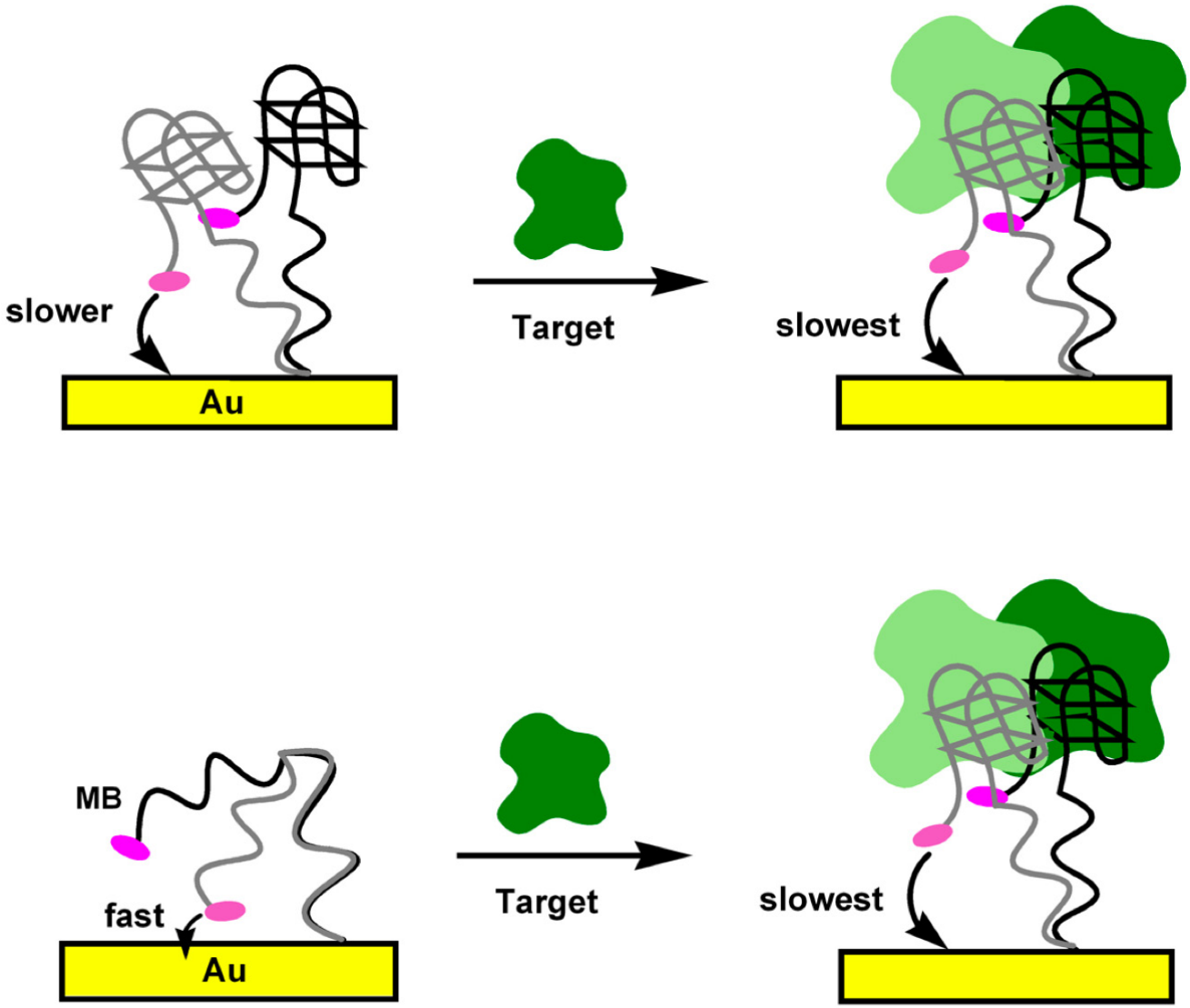


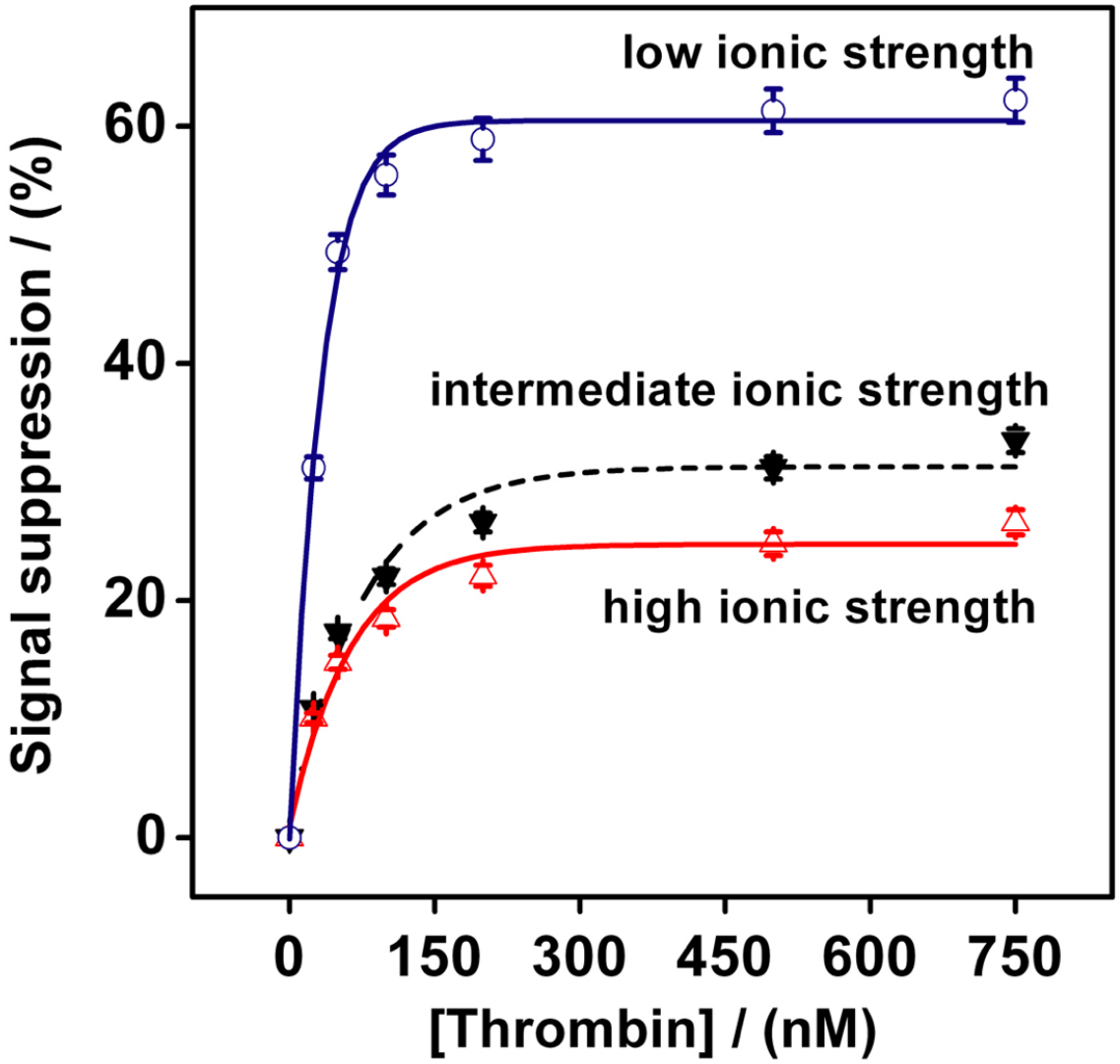
Aptamers

Random library of 10^{14} unique DNA sequences



High Affinity Aptamer

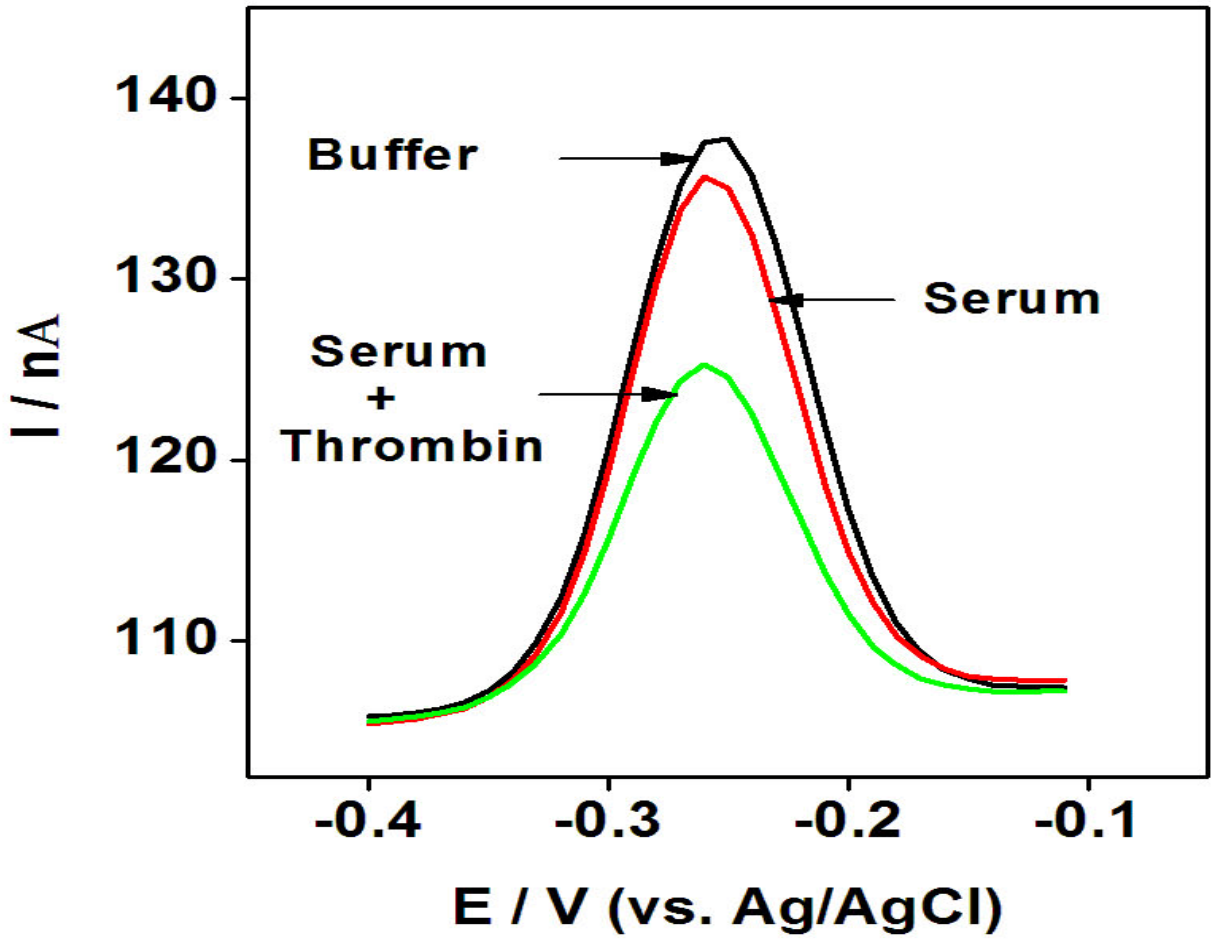

slower
Au
Target
slowest
MB
fast
Au
Target
slowest



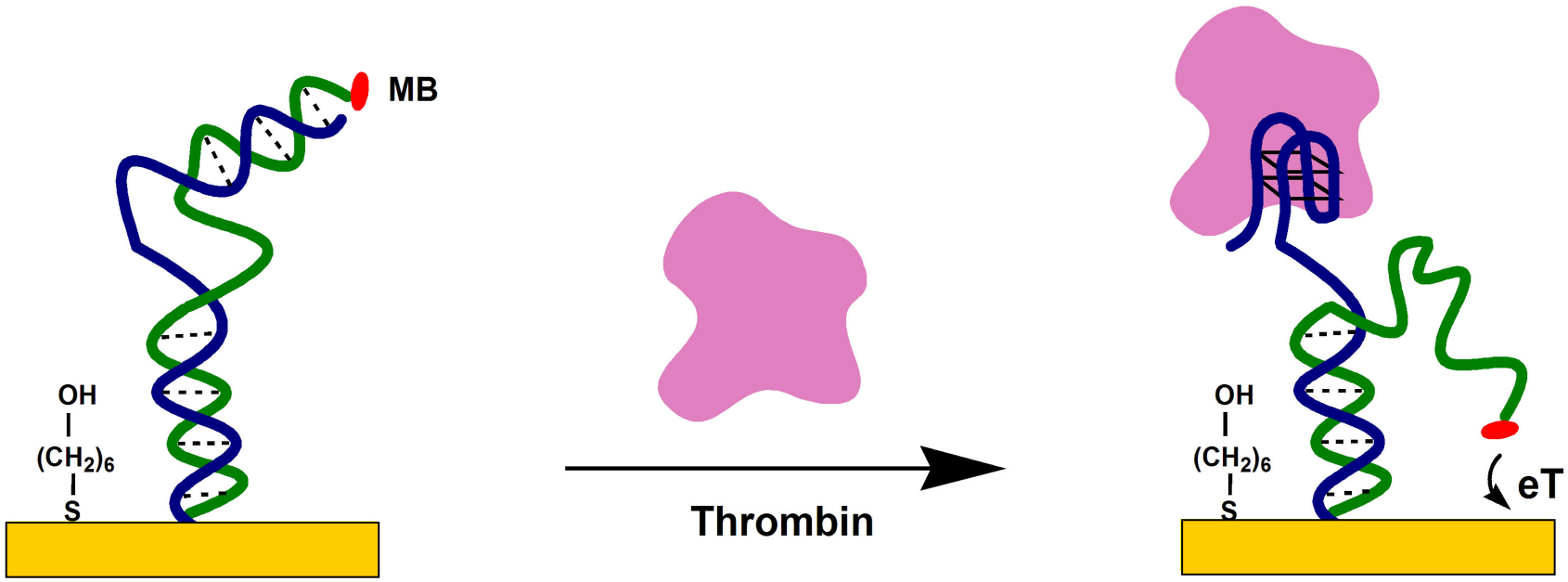
Binding and folding

Binding only

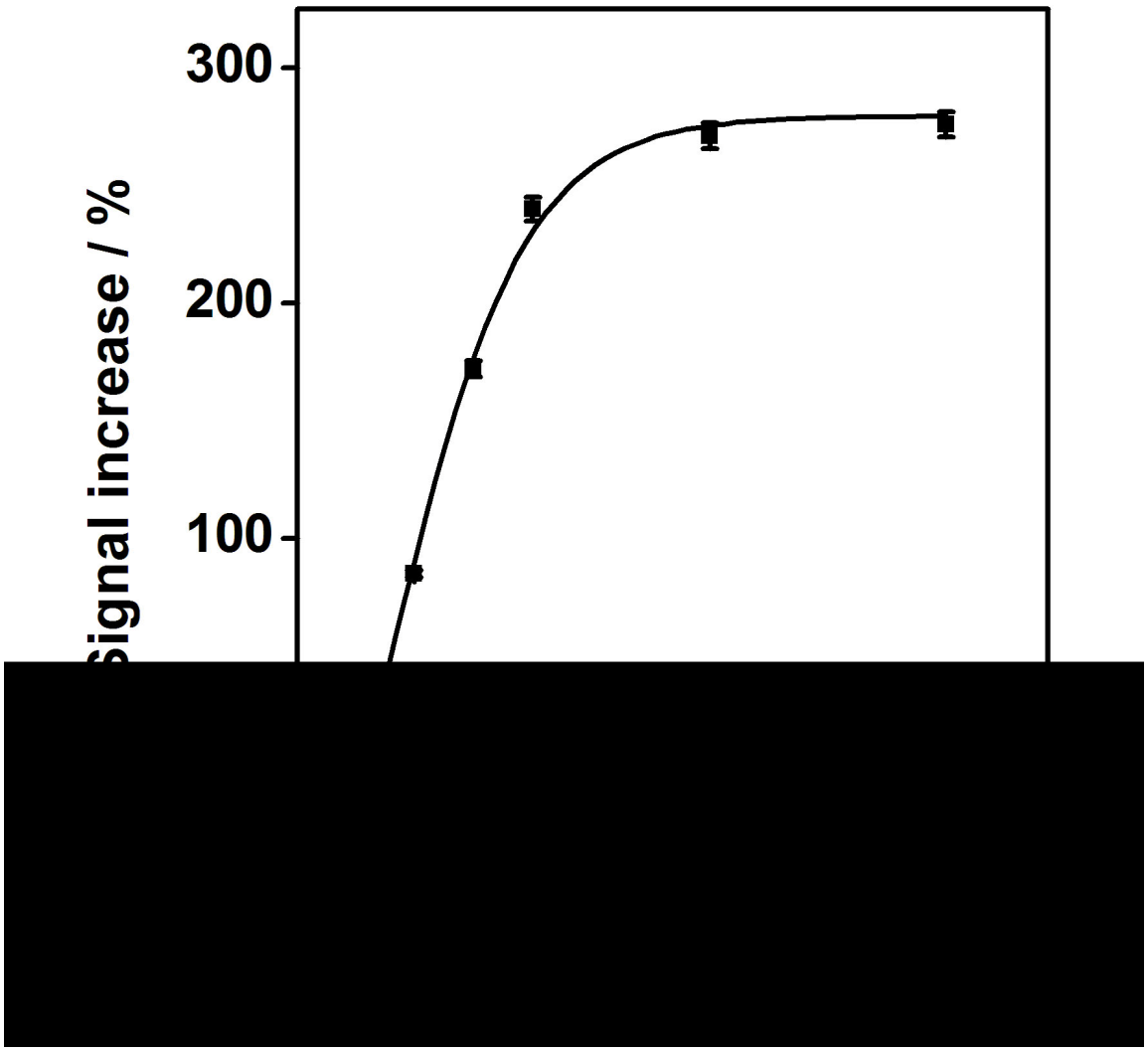
Thrombin Detection



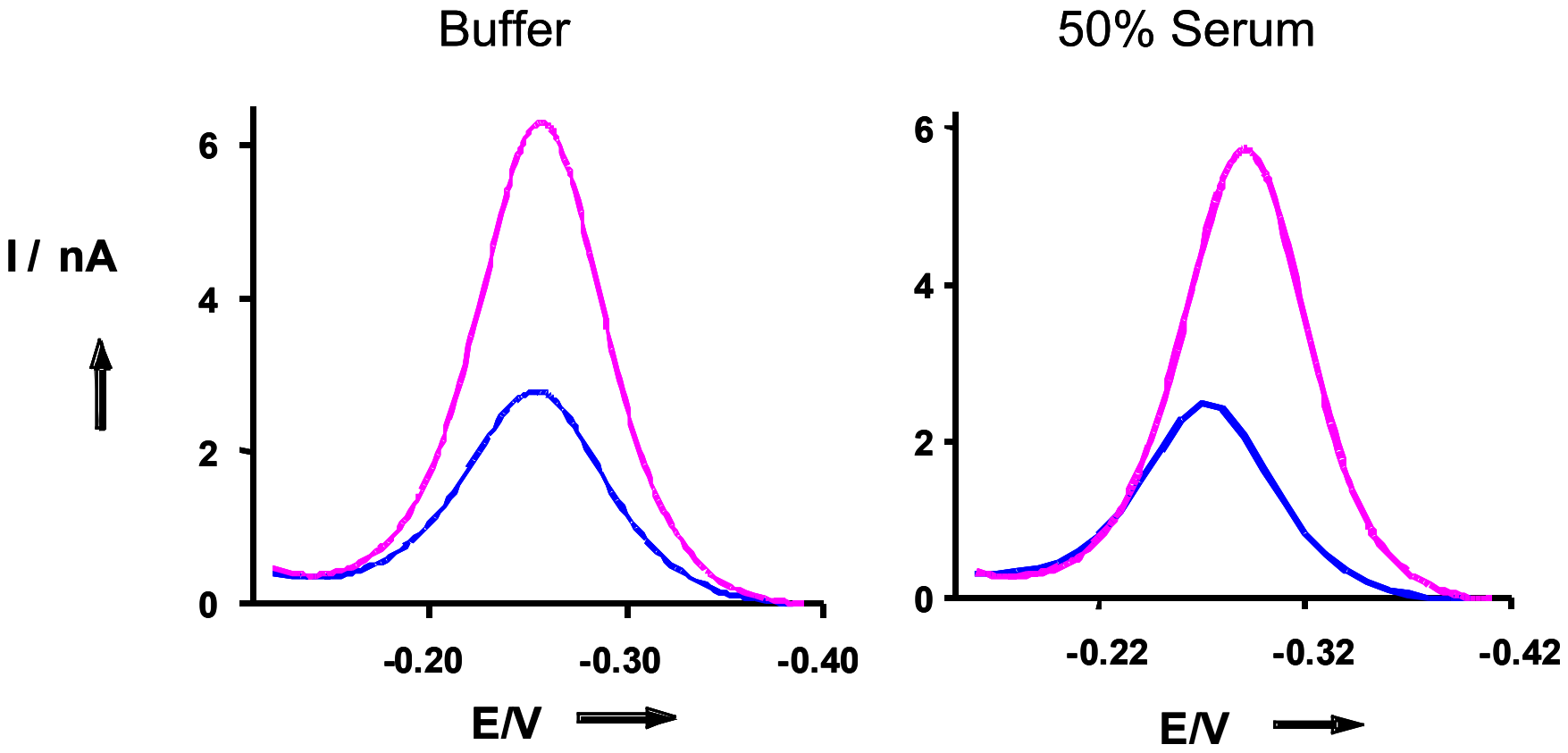
Signal-on E-AB Sensor



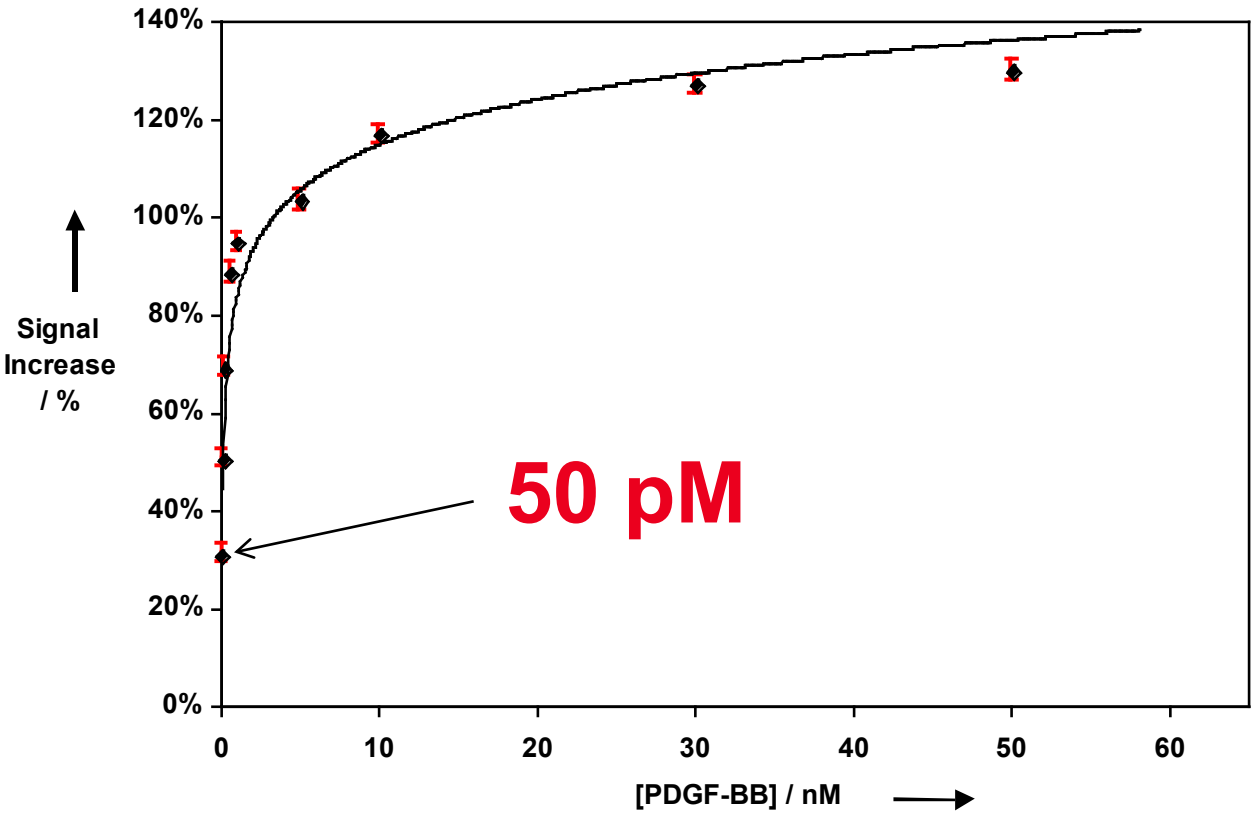
Signal-on E-AB Sensor



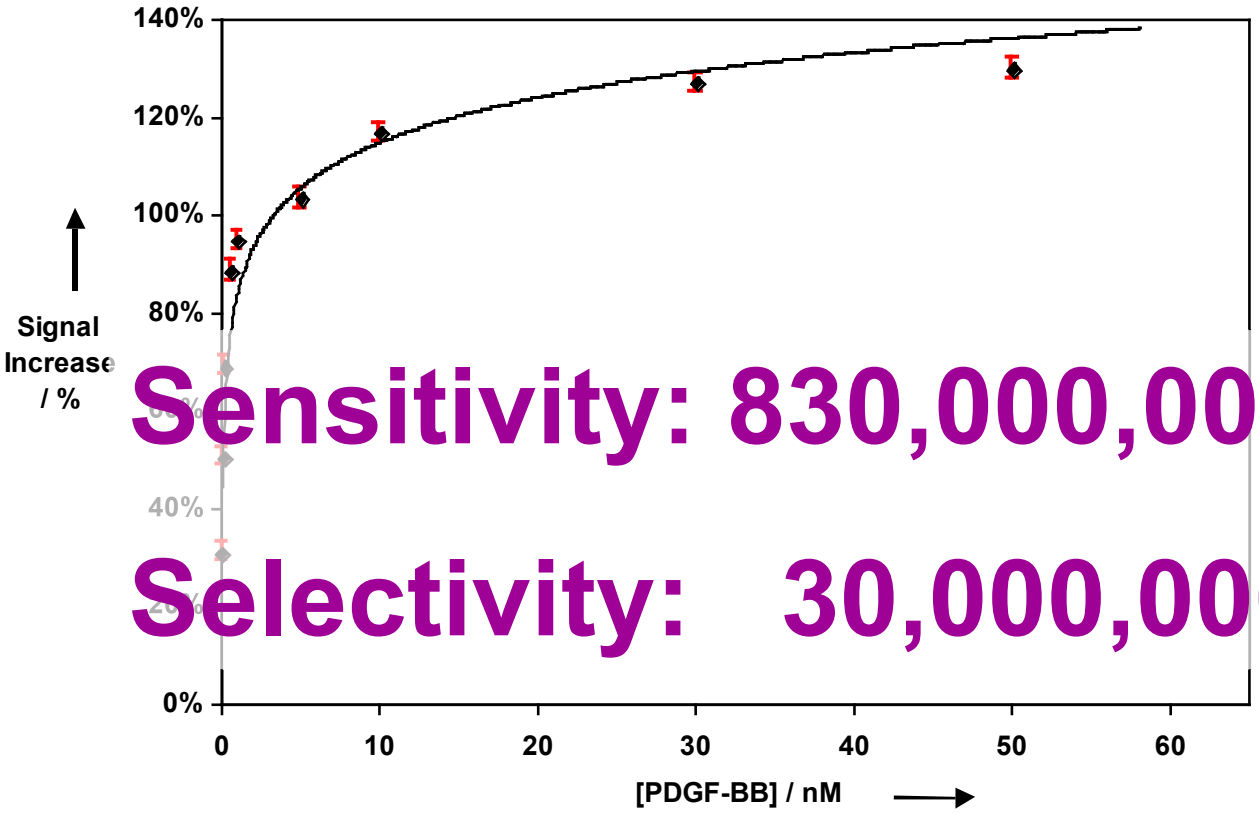
PDGF Detection in Blood



PDGF Detection in Blood



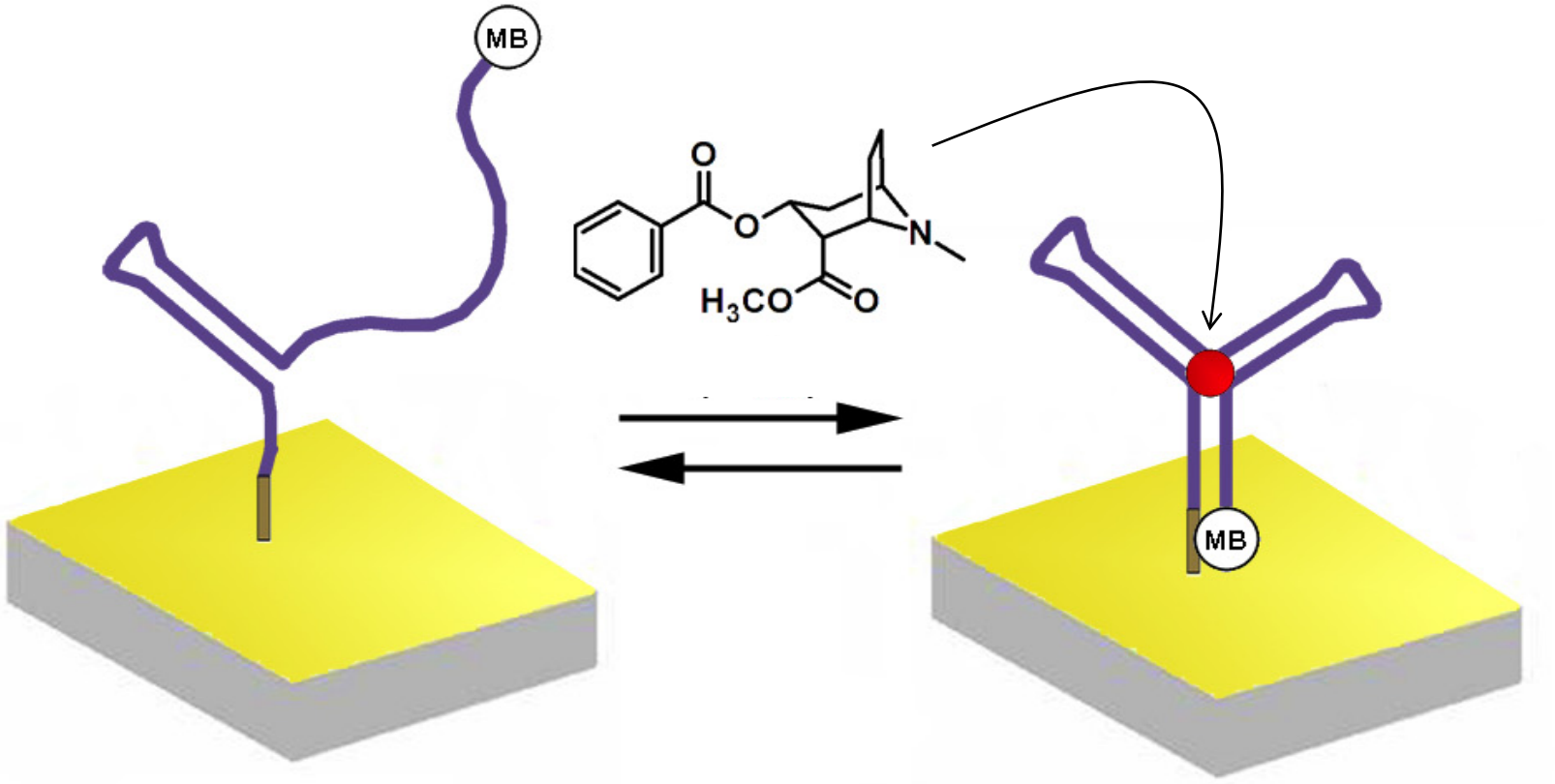
PDGF Detection in Blood



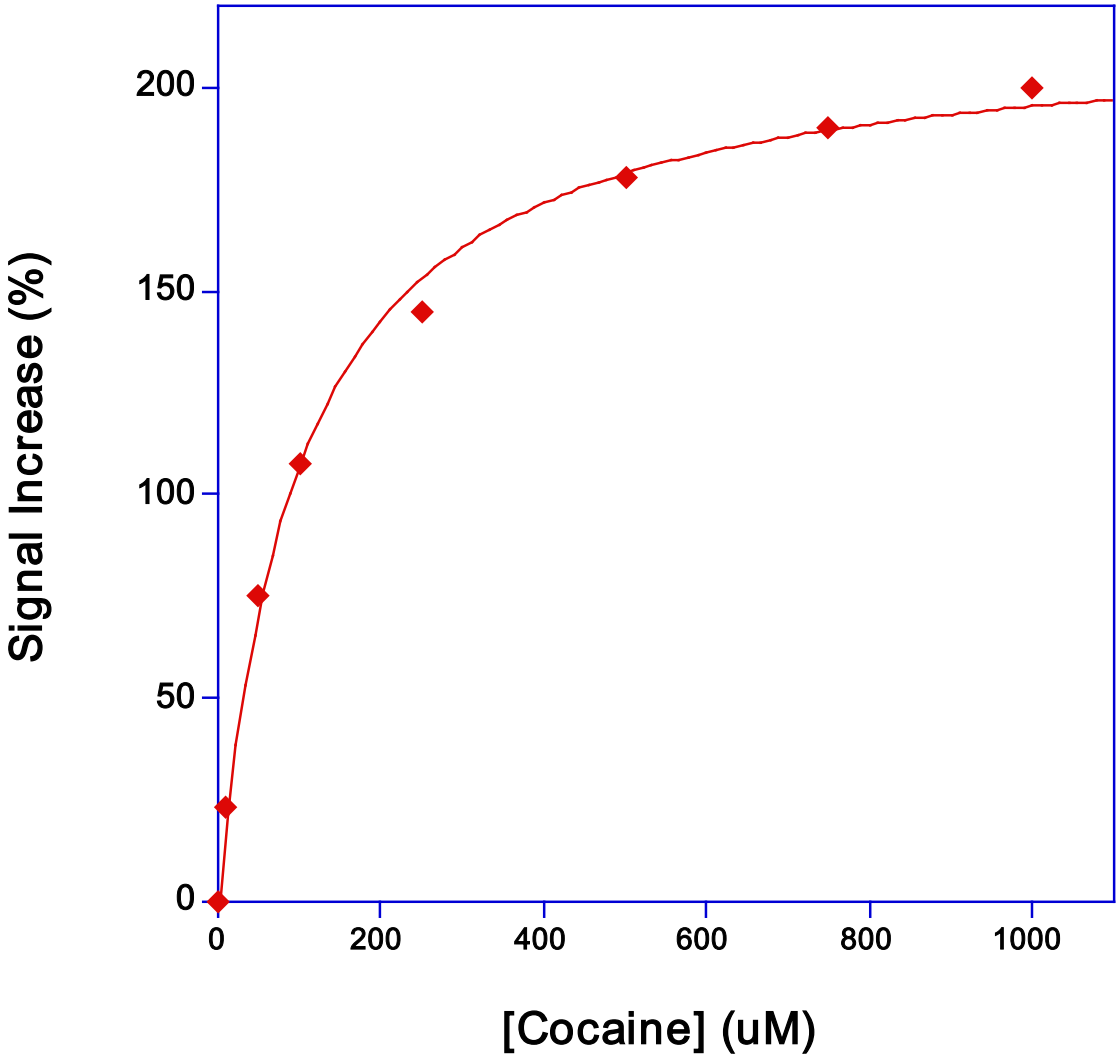
Sensitivity: 830,000,000:1

Selectivity: 30,000,000:1

Small Molecule Detection



Cocaine in Blood Serum

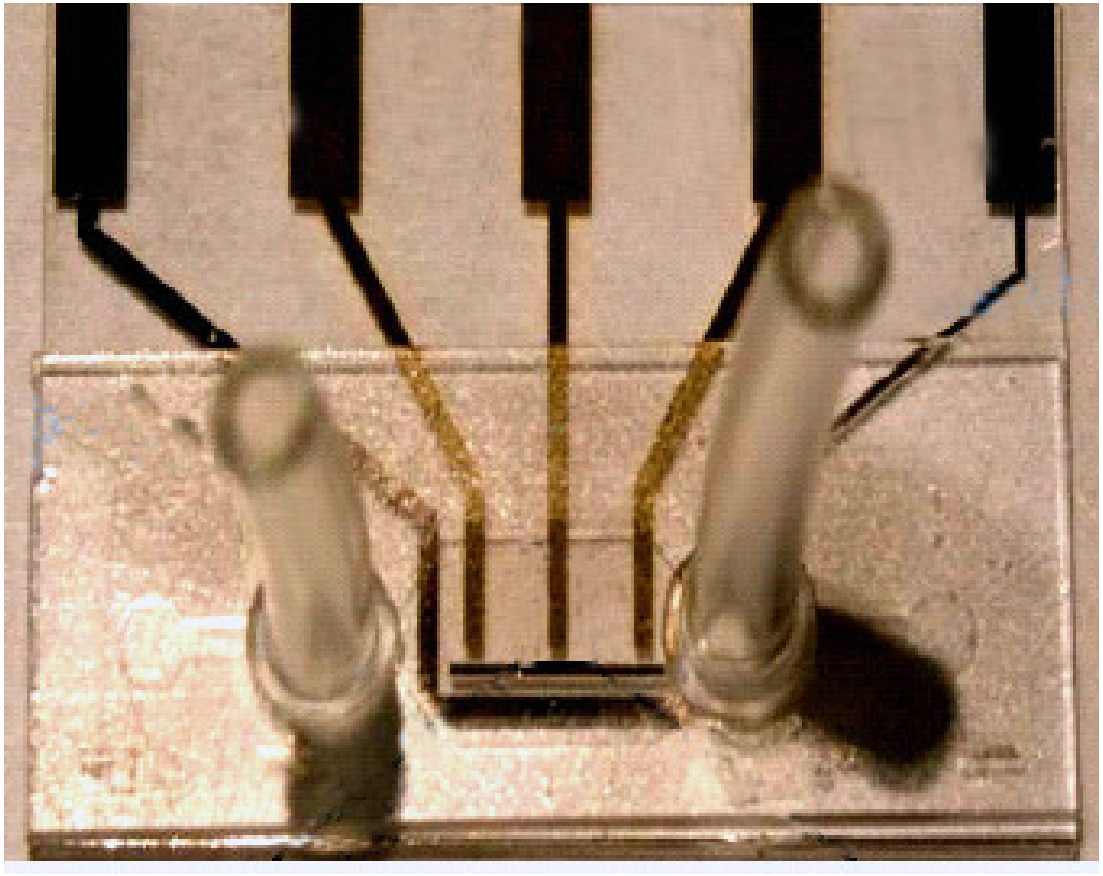



$1\ \mu M = \frac{\sim 1\ kg}{2.5 \times 10^6\ L} = 400\ ppb$
End

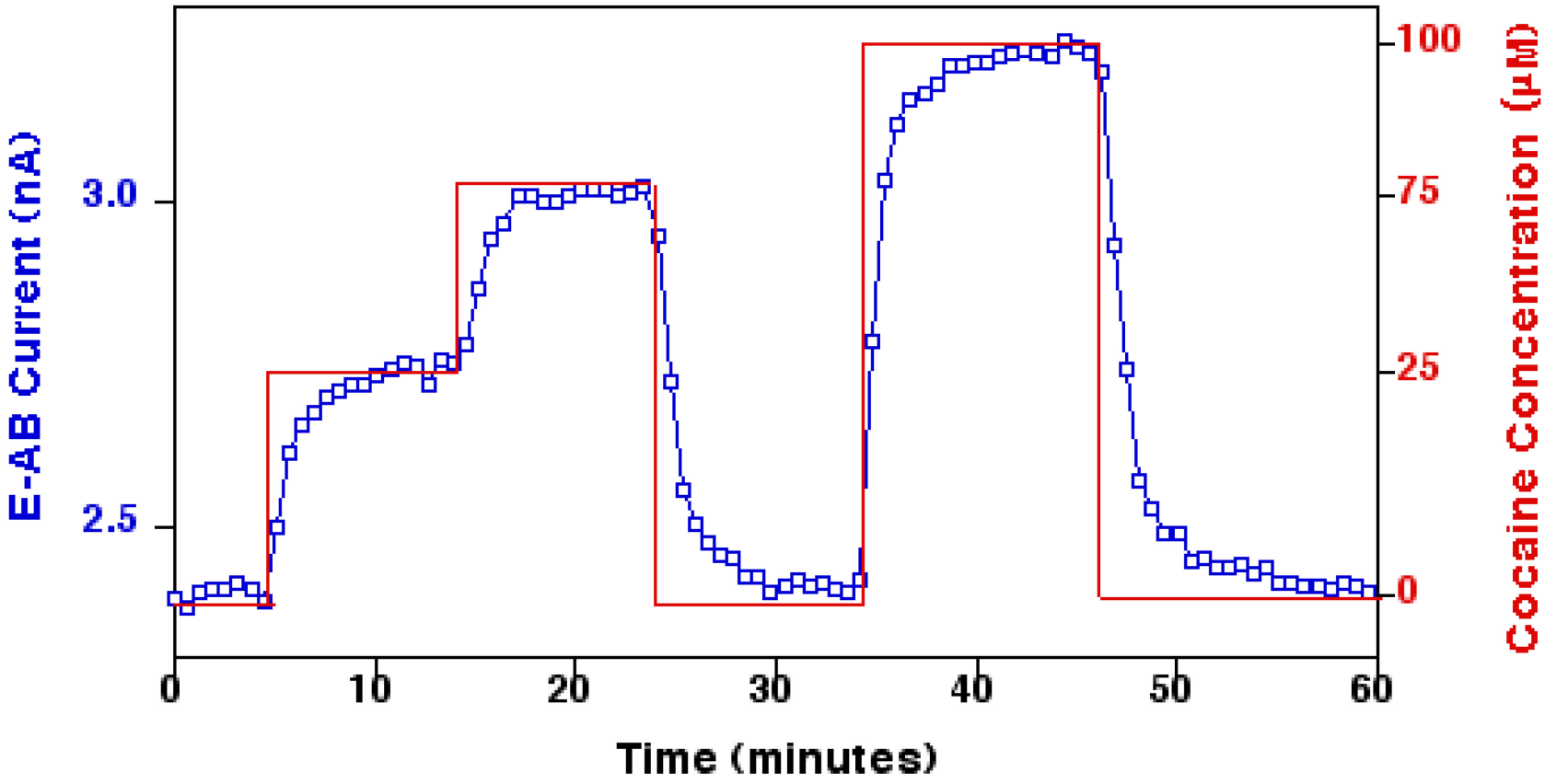
E-DNA/E-AB Sensors

- DNA/RNA
- TBP
- M-HAHA
- SS-BP
- Anti-TNT antibodies
- Anti-Dig antibodies
- Anti-HIV antibodies
- Thrombin
- PDGF
- IgE
- Cocaine
- ATP
- Aminoglycosides
- Theophyline
- K^+
- Pb^{2+}
- Hg^{2+}
- C nanotubes

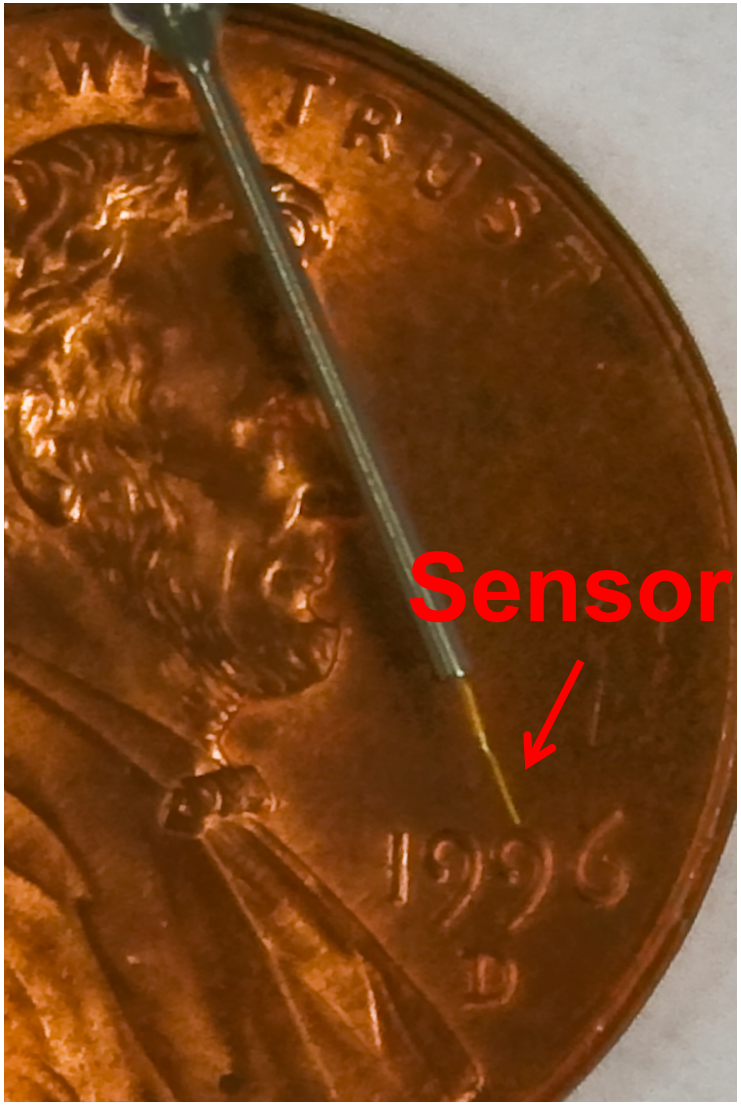
Device Integration

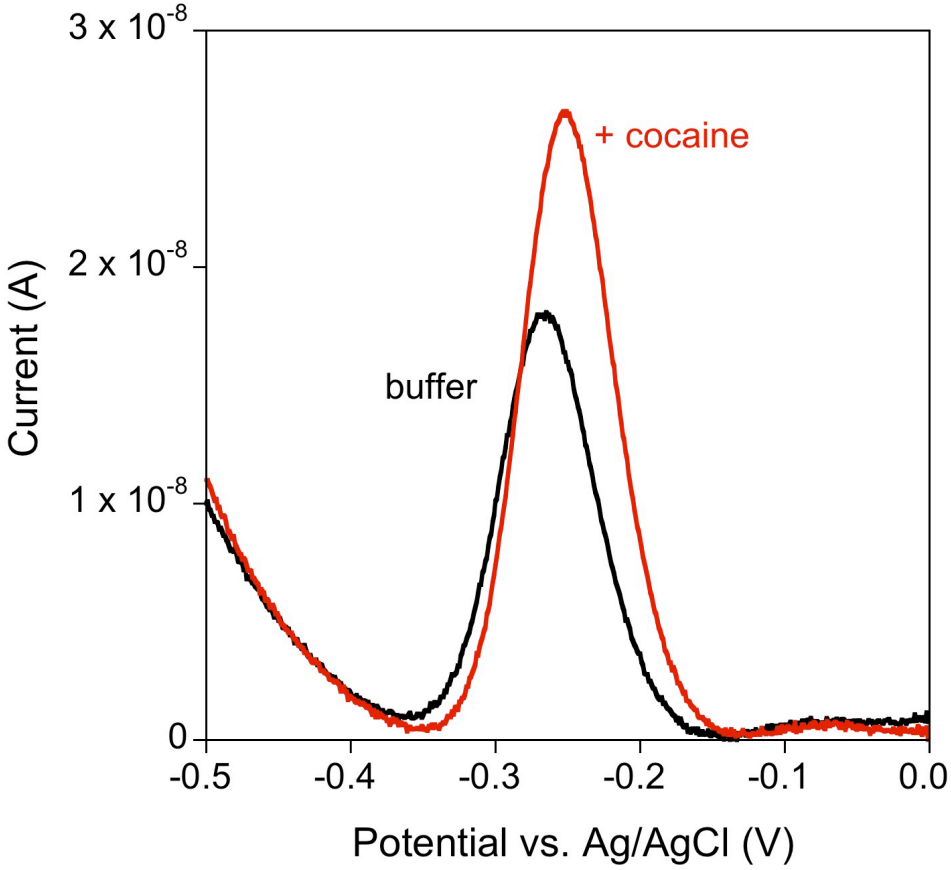


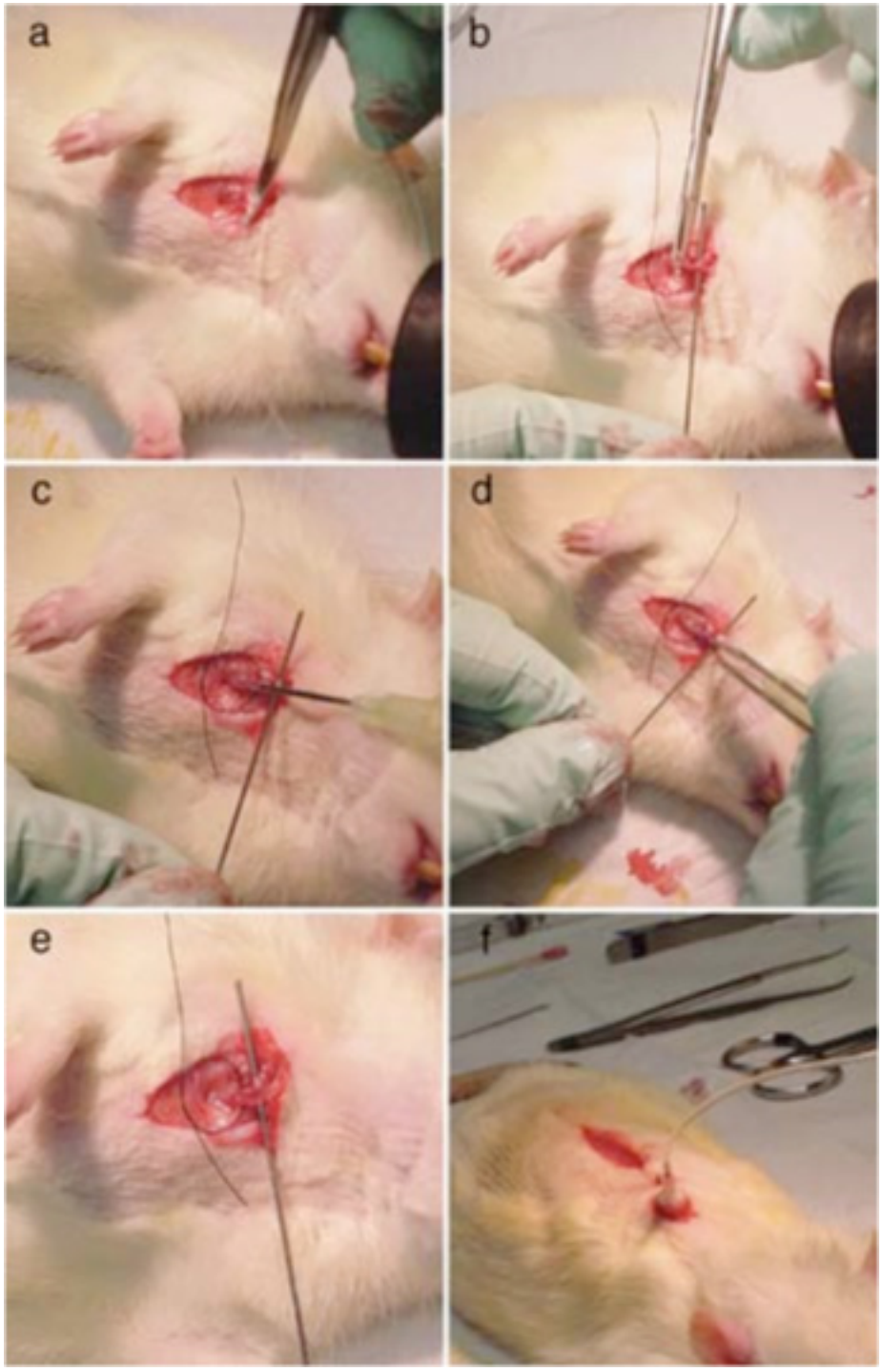
Real-time Cocaine Detection in Flowing Blood Serum



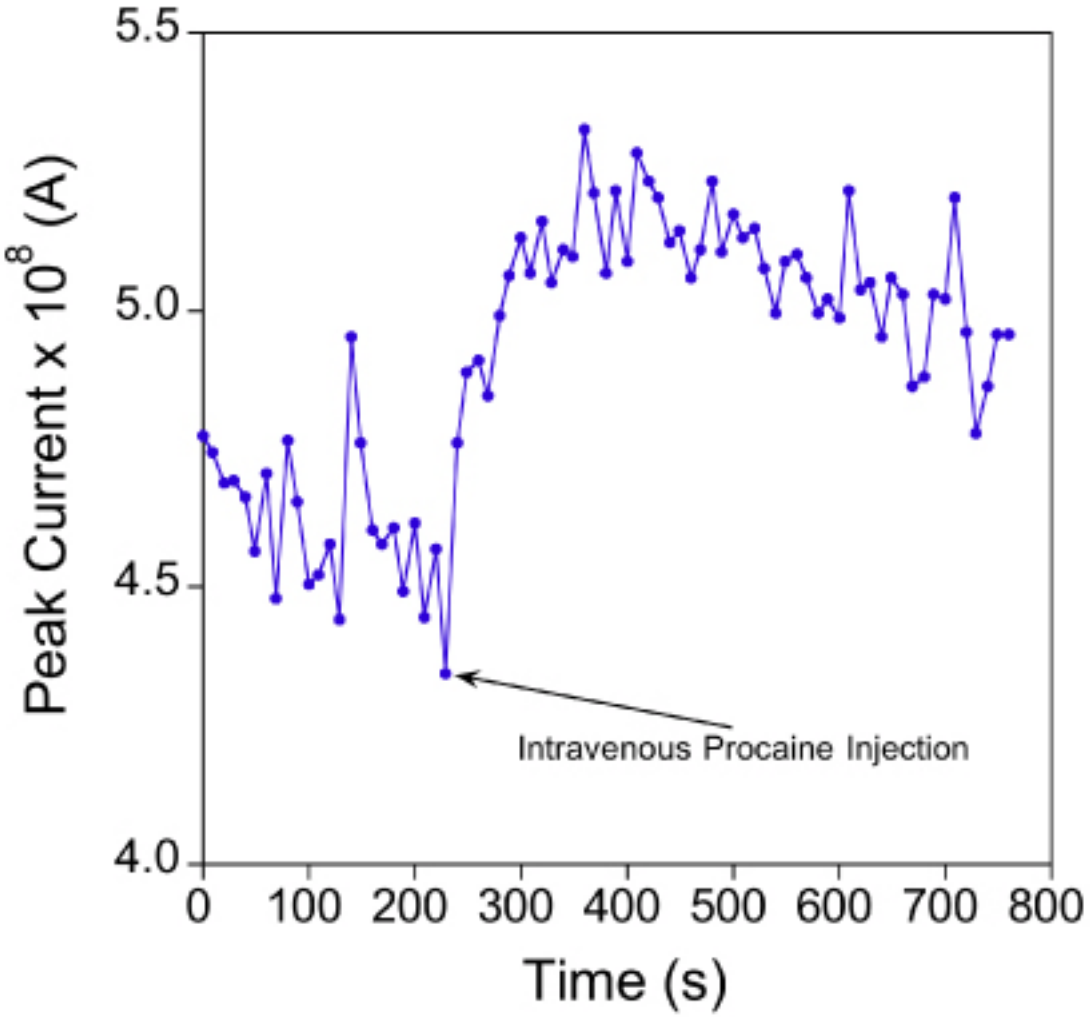
In vivo Devices






a
b
c
d
e
f

In vivo, In Real Time Detection



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