

# Biosensing Neurochemicals in the Brain

## Lesson 13

MSE 304

Nako Nakatsuka

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December 12<sup>th</sup> 2025



# Exam Schedule (I will leave this open during the break)

Wednesday 21 Jan				Thursday 22 Jan			
Preparation (MXG 032)		Exam (MXG 030)		Preparation (MXG 032)		Exam (MXG 030)	
10:00-10:20	Vladimir	Albitov		9:00-9:20	Pamela Rikako	Matencio	
10:20-10:40	Fragkiski	Auger	Vladimir	9:20-9:40	Annika Selma	Minder	Pamela Rikako
10:40-11:00	Ennio	Beretta	Fragkiski	9:40-10:00	Baptiste	Monet	Annika Selma
11:00-11:20	Louna	Bologna	Ennio	10:00-10:20	Nefeli Jeannine N	Motteu	Baptiste
11:20-11:40	Pablo	Brisson	Louna	10:20-10:40	Victor Florent Thie	Negri	Nefeli Jeannine N
11:40-12:00	Jules Armand Lod	Champion	Pablo	10:40-11:00	Michael Edmond	Nijm	Victor Florent Thierry
12:00-12:20	Jules Charles Flor	Chauvin	Jules Armand Lodoïse	11:00-11:20	Lucas	Pralong	Michael Edmond
12:20-12:40	Killian	Lazzarelli	Jules Charles Florent	11:20-11:40	Victor	Manhe	Lucas
12:45-13:10			Killian	11:40-12:00			Victor
13:10-13:40 LUNCH		LUNCH		12:00-12:40		LUNCH	
13:40-14:00	Axel José	Favre		12:40-13:00	Zina Arinaivo	Randriamanantena	
14:00-14:20	Ozven	Fontani	Axel José	13:00-13:20	Hermine Marie	Malaquin	Zina Arinaivo
14:20-14:40	Maurine	François	Ozven	13:20-13:40	Amira Sophie	Repenning	Hermine Marie
14:40-15:00	Xavi Roméo	Fuentes	Maurine	13:40-14:00	Gabriel Noah Jules	Rondard	Amira Sophie
15:00-15:20	Jamal Jelani Deon	George	Xavi Roméo	14:00-14:20	Loris Nicolas	Santaniello	Gabriel Noah Jules
15:20-15:40	Break		Jamal Jelani Deon	14:20-14:40	Break		Loris Nicolas
15:40-16:00	Scott Pierre	Girardet	Break	14:40-15:00	Andrés Santiago	Ulloa Canizares	Break
16:00-16:20	Laura Garance	Granjou	Scott Pierre	15:00-15:20	Aurélien	Vincent	Andrés Santiago
16:20-16:40	Charline	Delamotte	Laura Garance	15:20-15:40	Jérémie Romain	Viollet	Aurélien
16:40-17:00	Sacha Charles	Razani	Charline	15:40-16:00	Gustav	Widén	Jérémie Romain
17:00-17:20	Riccardo Andrés	Quadri	Sacha Charles	16:00-16:20	Christophe Pascal	Wodiunig	Gustav
17:20-17:40	Maud Charlotte	Studer	Riccardo Andrés	16:20-16:40			Christophe Pascal
17:45-18:10			Maud Charlotte				



# In-Depth Evaluations Open

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We will dedicate 5-10 minutes for you at the start of class to complete the survey next week

Log onto moodle and stay on the home page (dashboard, not the course page)

Click on the arrow to the top right of the screen which will reveal a block that contains the  
entitled “In-depth evaluation” tile

You can then select this course (MSE 304) and complete the feedback

You will also be able to access the course evaluations via the EPFL Campus App



# In-Depth Evaluations – The Importance of Your Participation

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This was the first time we ran this course with 80% new material compared to Prof. Francesco Stellacci's course last year

Any feedback you provide will help us to improve the content for next year!

I am a tenure-track assistant professor (non-permanent position at EPFL) and your evaluations are necessary for my tenure case in the future. So your feedback is very important so I can continue to teach future students, thank you for your cooperation!



# Plan of the Course: Fundamentals, Characterization, and Applications

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1: Intro to Surfaces & Interfaces

2: Surfaces in the Real World - Adsorption

3: Surface Energetics & Interfacial Phenomena

4: Atomic Structure of Real Surfaces

5: Solid-Solid Interfaces

6: From Ideal Planes to Real Materials (Recap)

7: Characterization of Surfaces & Interfaces

8: Surface Chemistry

9: Surface Patterning and Polymer Chemistry

10: Probing Functional Interfaces

11: Surface Phenomena at the Nanoscale

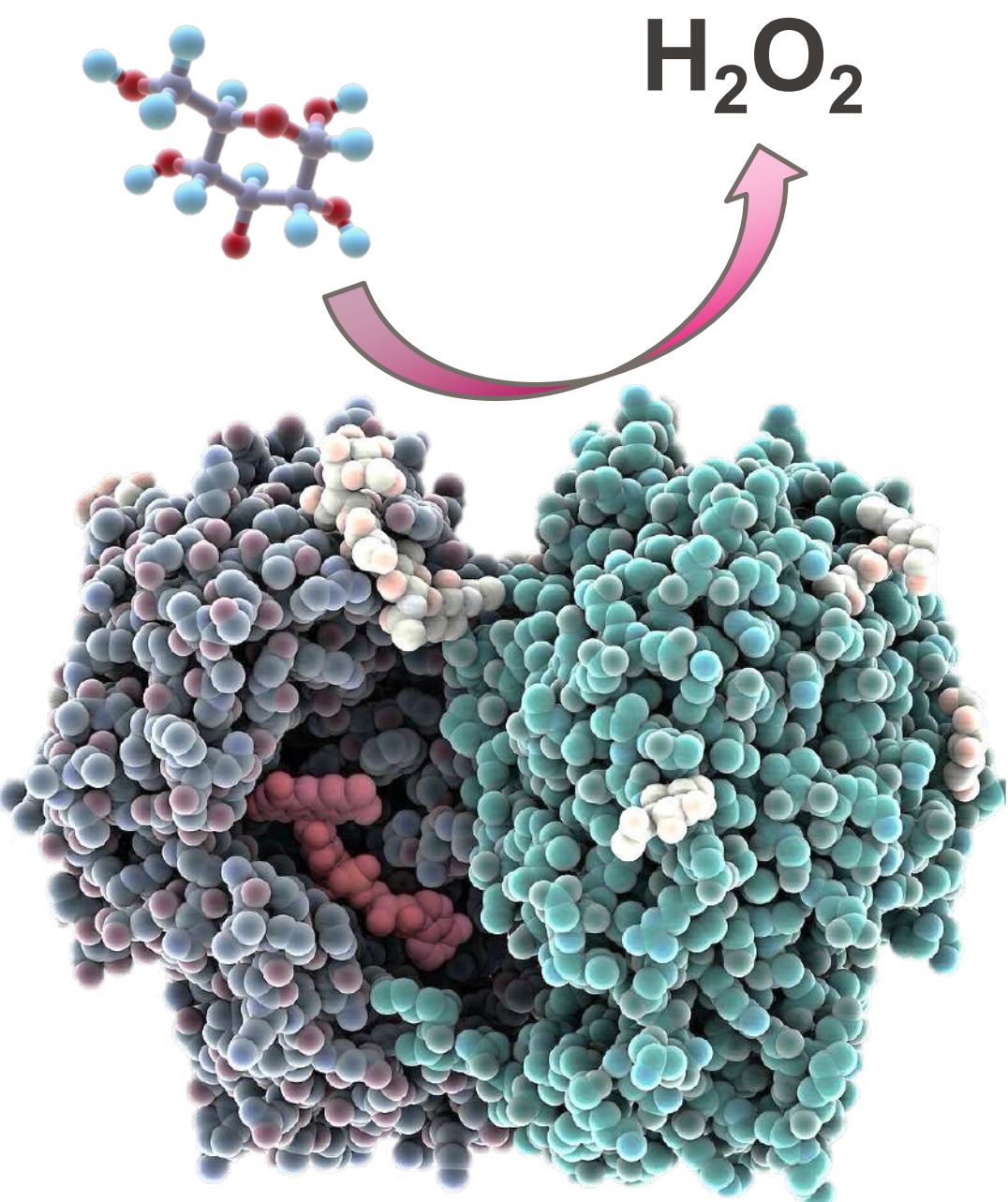
12: Introduction to Biosensing

13: Biosensing Neurochemicals in the Brain

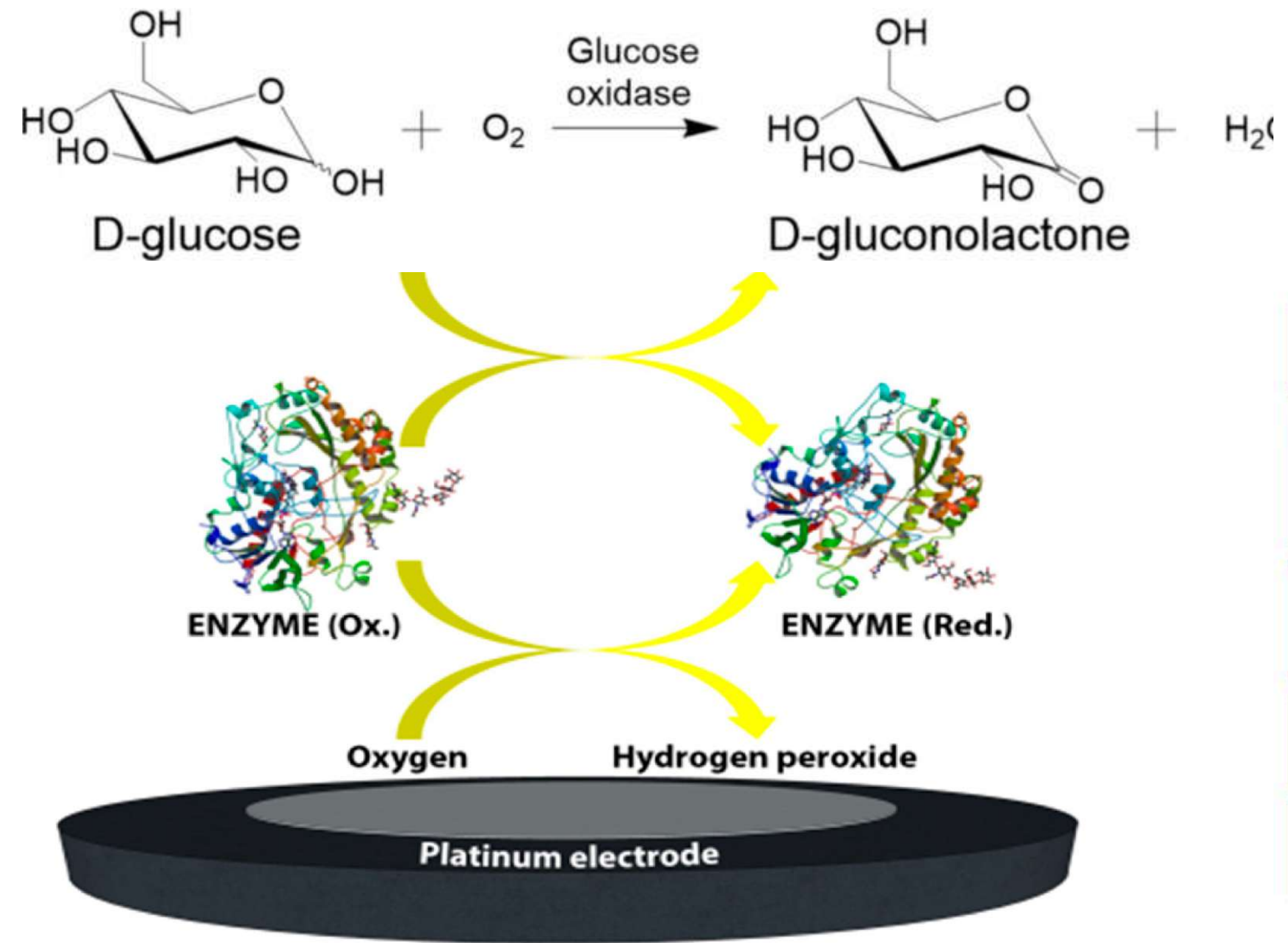
14: Chemistry of Semiconductor Surfaces & Beyond



# Recap: Success of the Glucose Biosensor – Robust System



Highly specific and robust enzyme



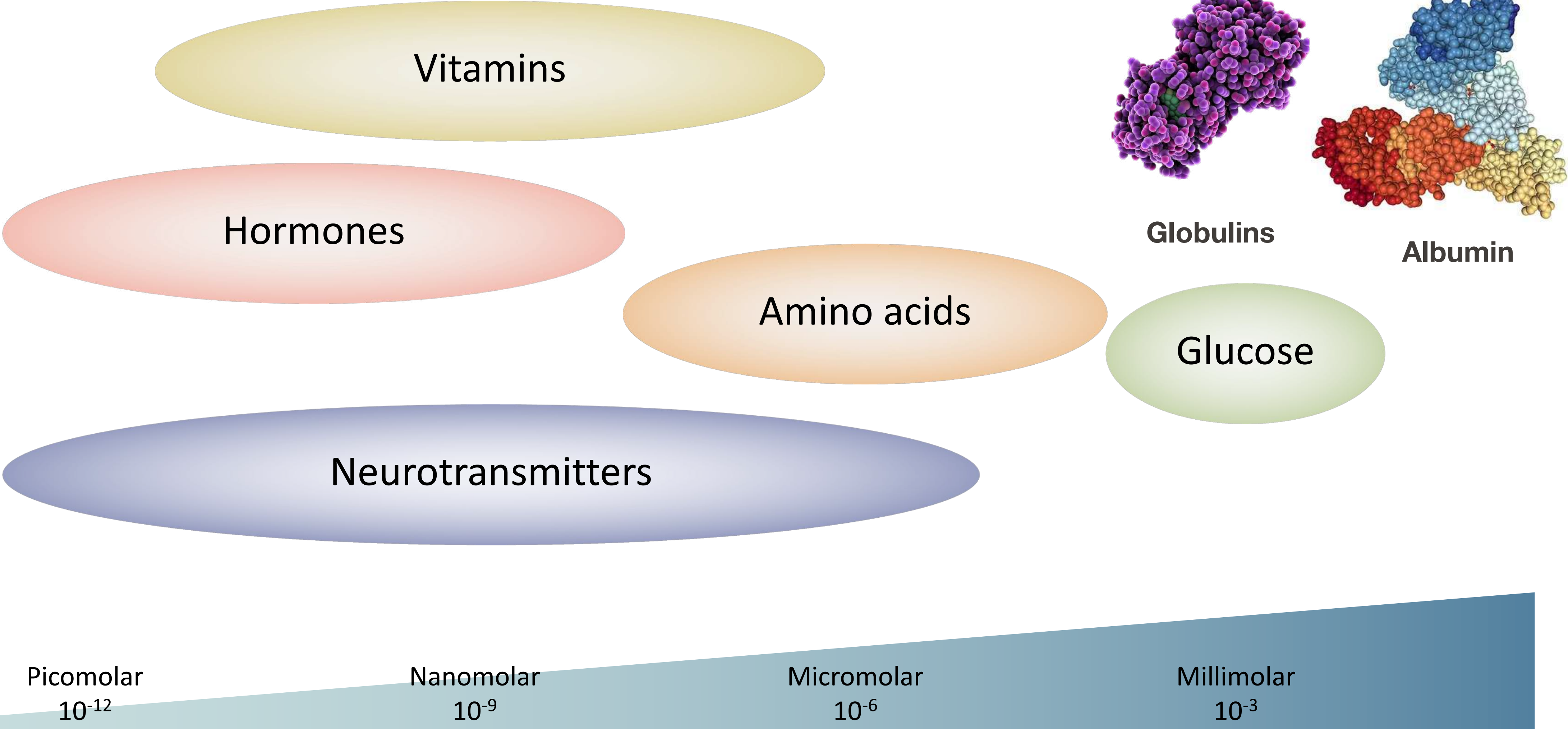
Detection window for H<sub>2</sub>O<sub>2</sub> doesn't overlap with other species in blood

## BLOOD GLUCOSE LEVELS CHART

LEVEL	mg/dl	mmol/L	RISK	SUGGESTED ACTION
DANGER - HIGH	315+	17.4	VERY HIGH	MEDICAL ATTENTION
HIGH	280	15.6	HIGH	MEDICAL ATTENTION
HIGH	250	13.7	HIGH	MEDICAL ATTENTION
HIGH	215	11	HIGH	MEDICAL ATTENTION
BORDERLINE	180	10	MEDIUM	CONSULT DOCTOR
BORDERLINE	150	8.2	MEDIUM	CONSULT DOCTOR
BORDERLINE	120	7	MEDIUM	CONSULT DOCTOR
NORMAL	108	6	NO RISK	NO ACTION NEEDED
NORMAL	72	4	NO RISK	NO ACTION NEEDED
LOW	70	3.9	MEDIUM	CONSULT DOCTOR
DANGER - LOW	50	2.8	HIGH	MEDICAL ATTENTION

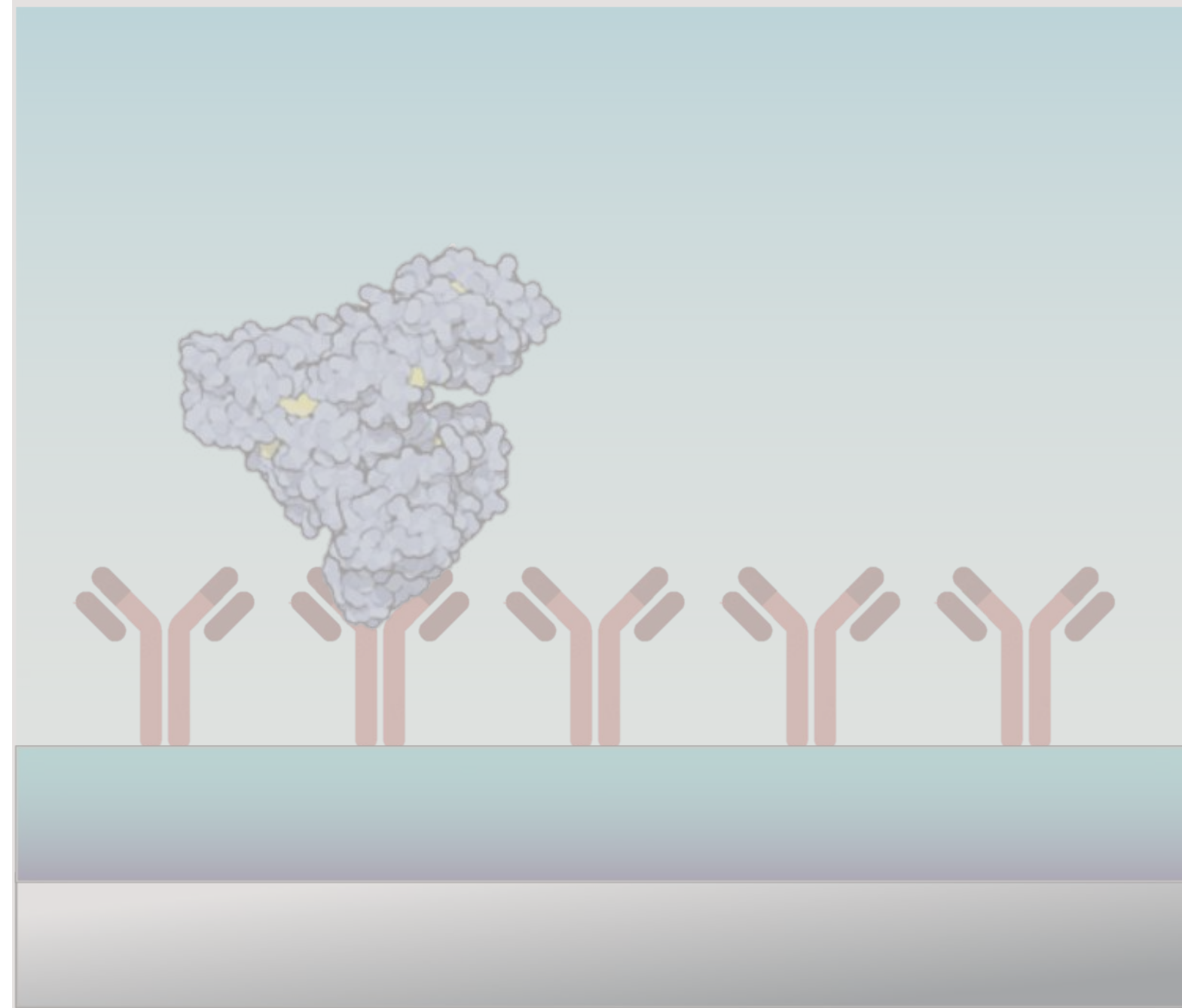
Clear values associated with healthy and disease states (diabetes)

# Recap: Success of the Glucose Biosensor – Concentration Range

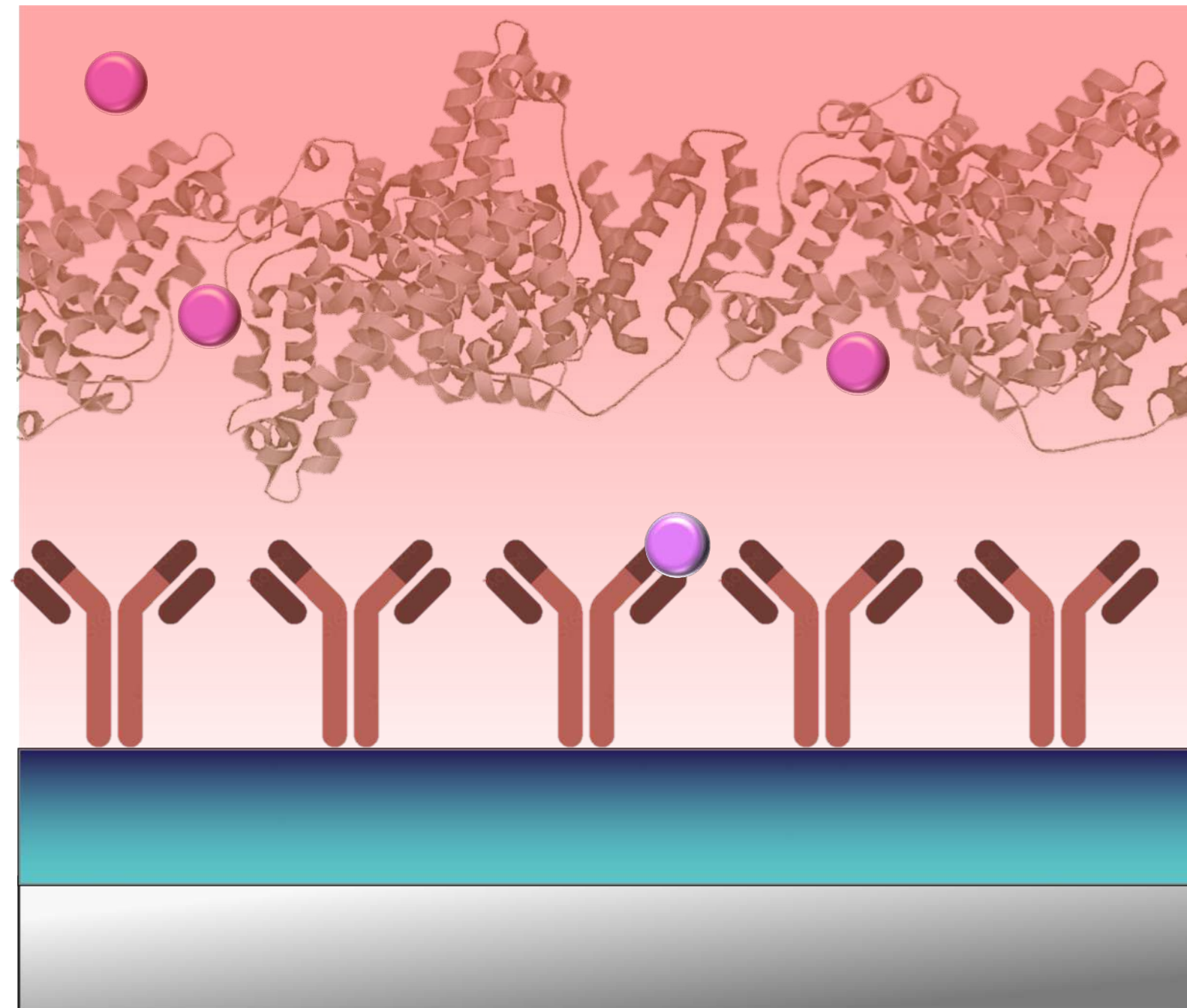


# Topics We Cover in Today's Lecture on Biosensing

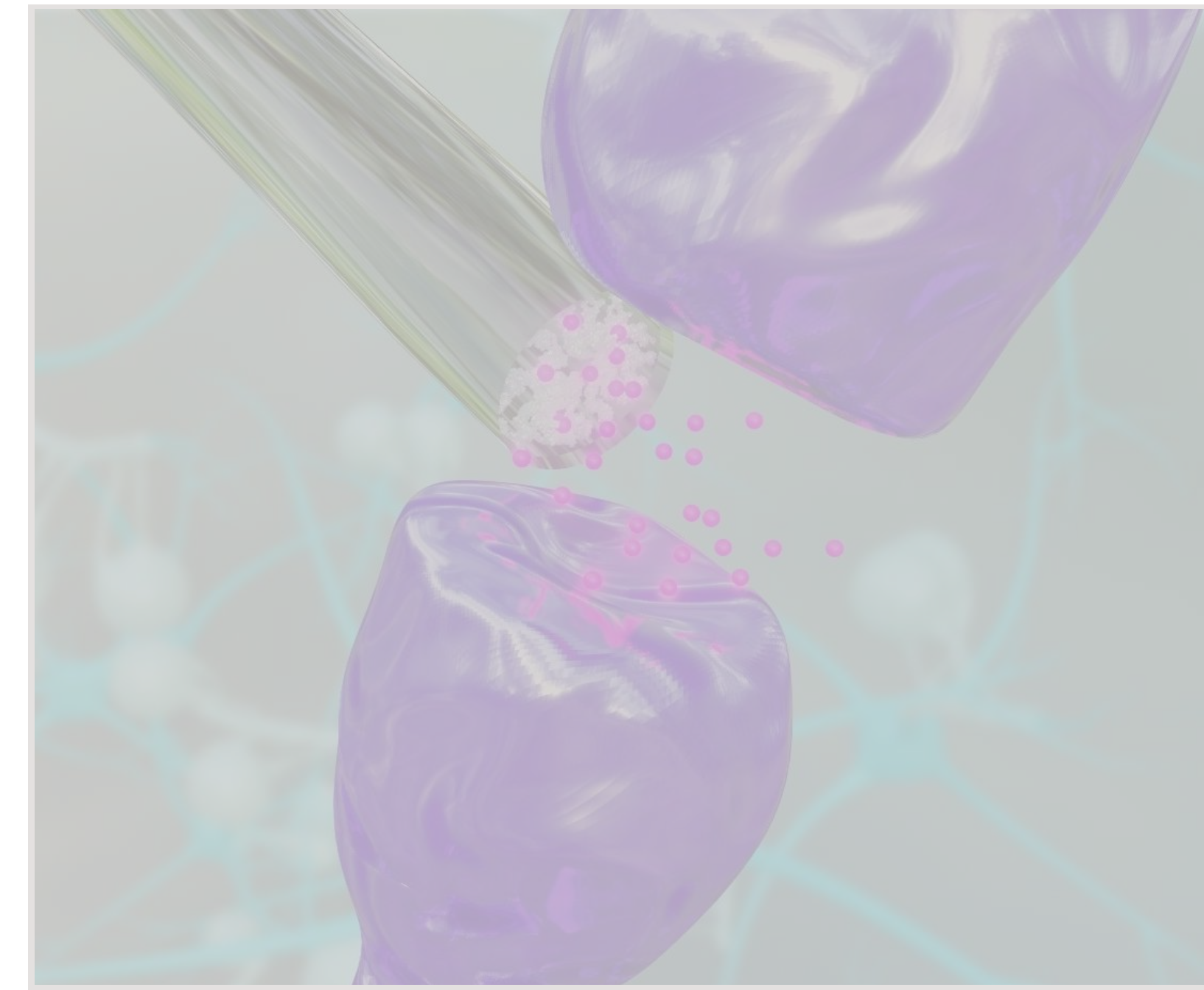
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Fundamentals of Biosensors



Challenges of Biosensing in Complex Environments



DNA-Based Biosensing that Tackle Challenges

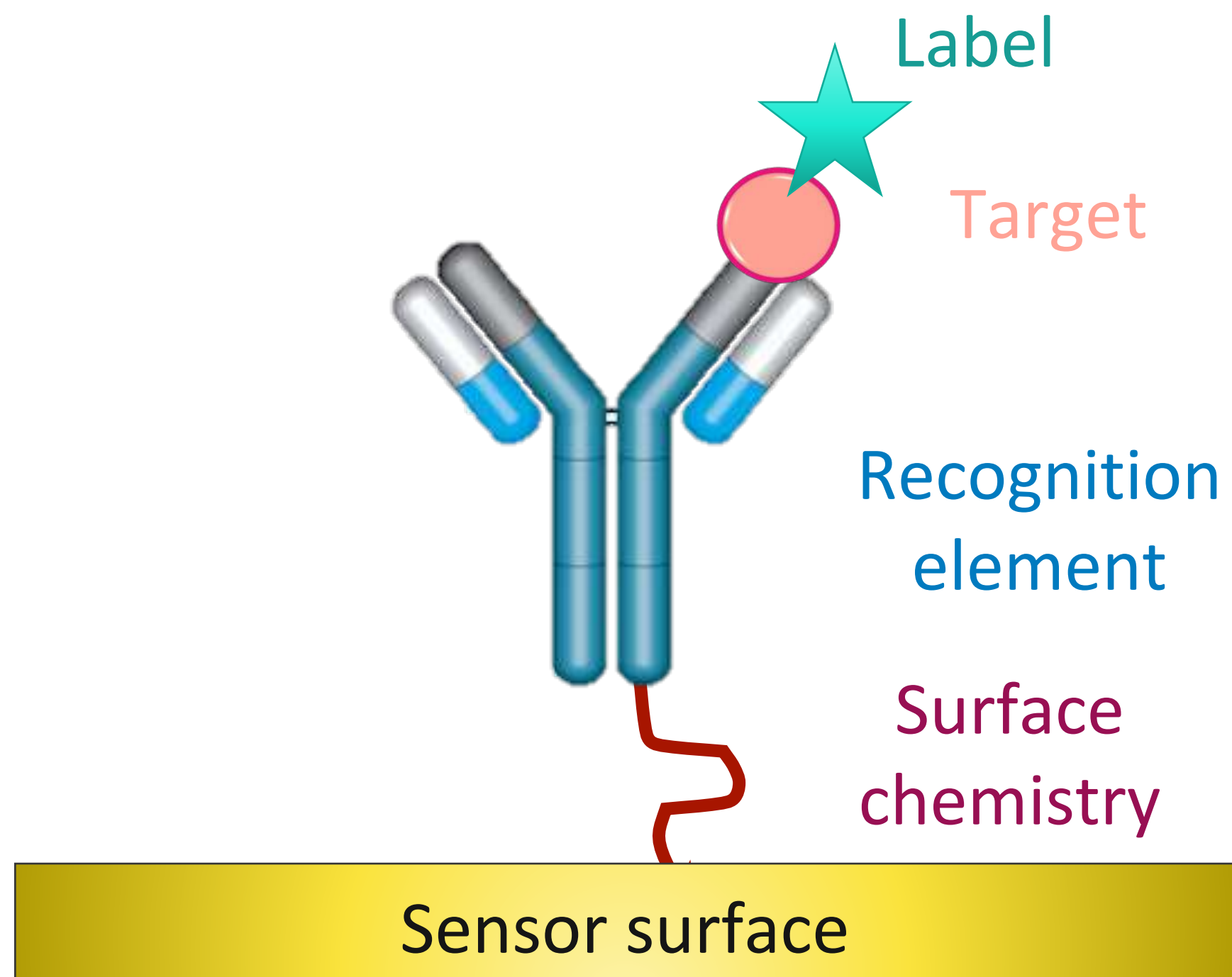
# Various Application Dependent Requirements for a Biosensor



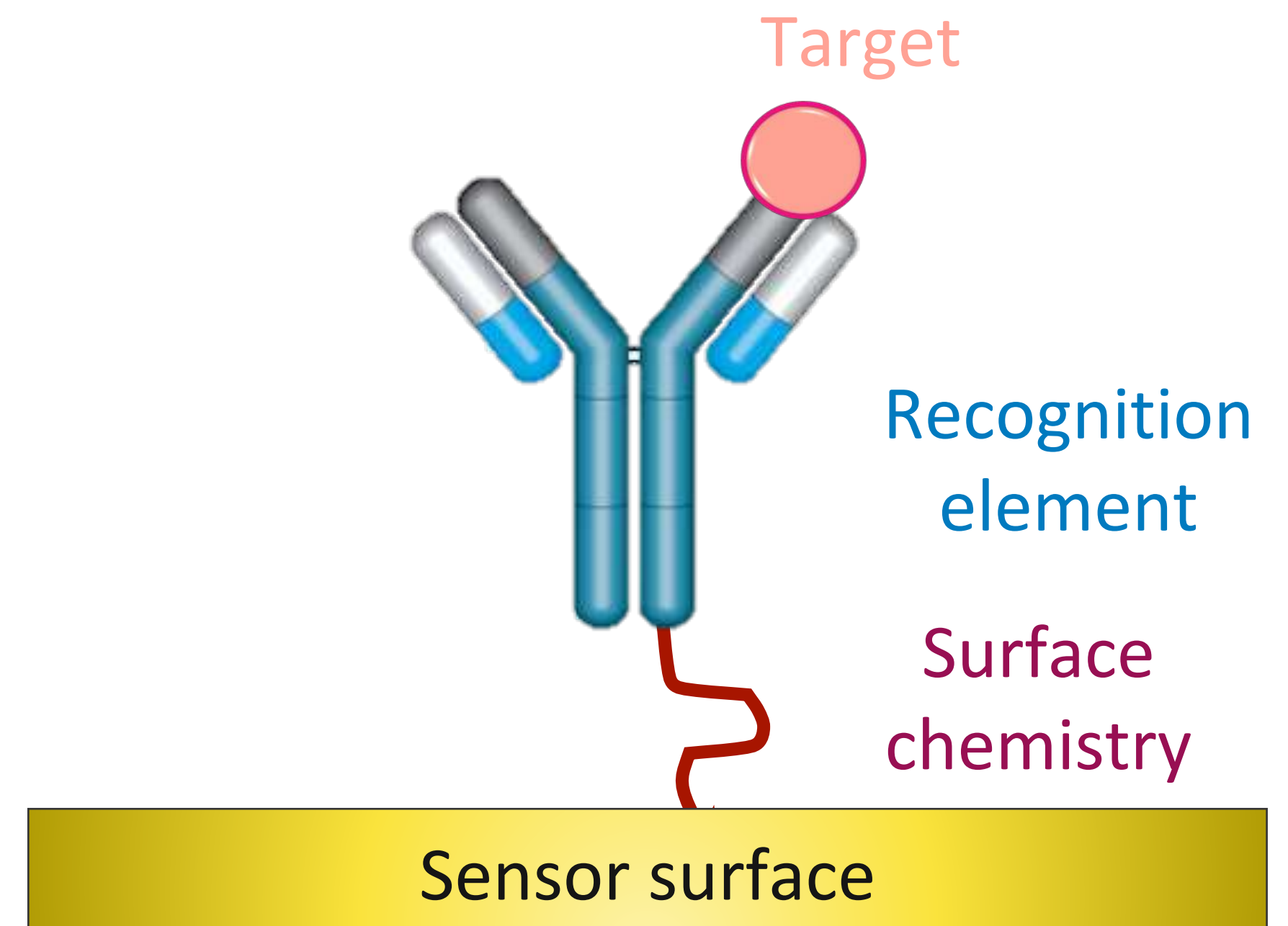
# Need for Label-Free Detection



**Labeled:** detection based on label activity generated from recognition event

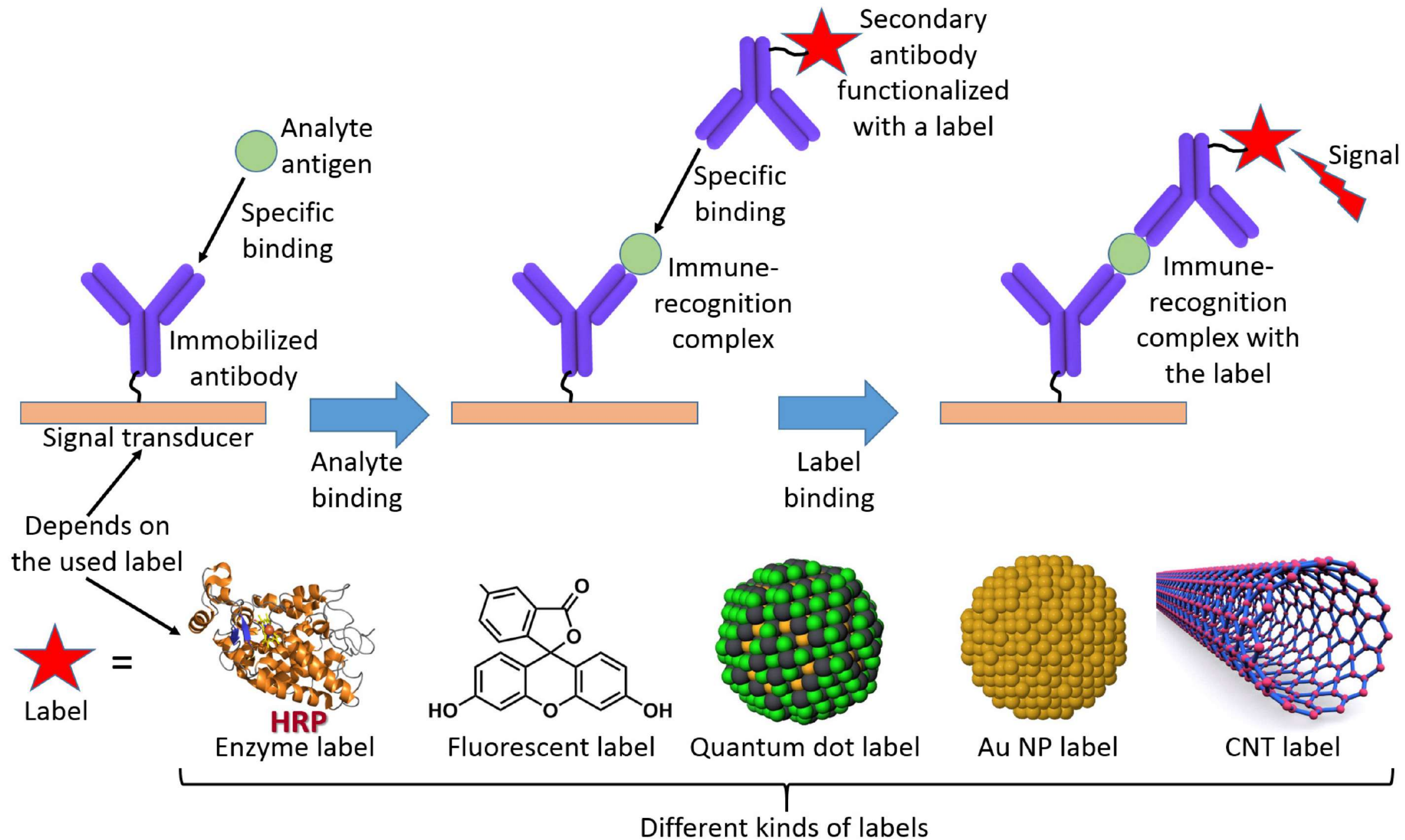
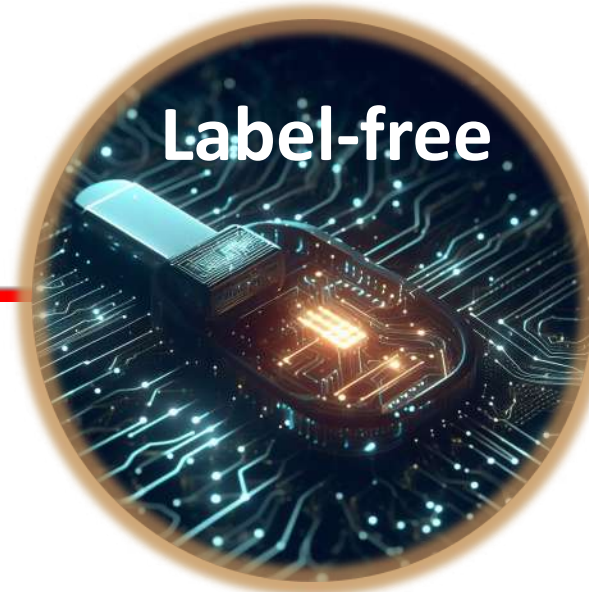


**Label-free:** detection based on solely the recognition event

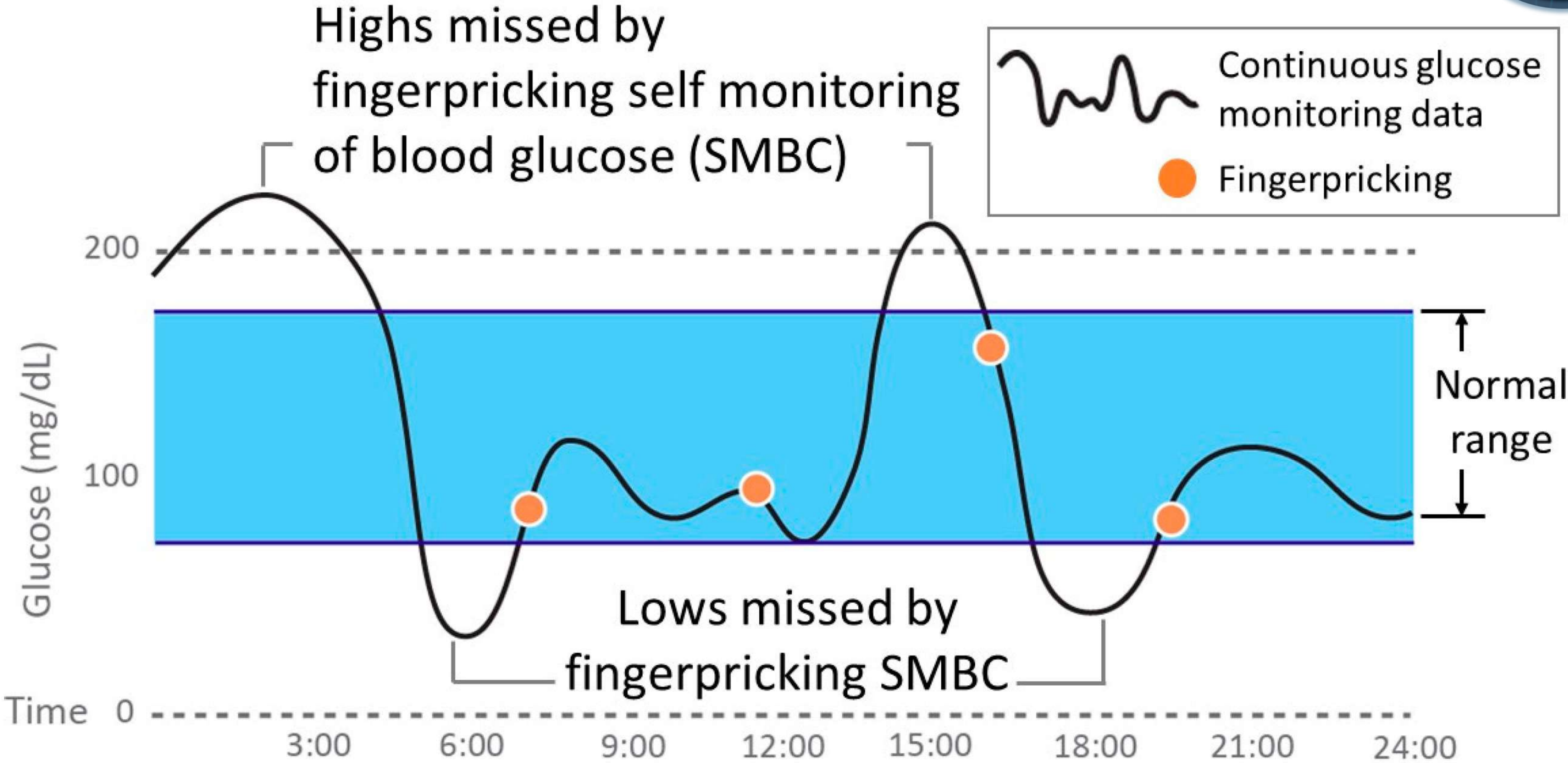


You want to avoid labeling the analyte that you are trying to detect freely in the biological environment

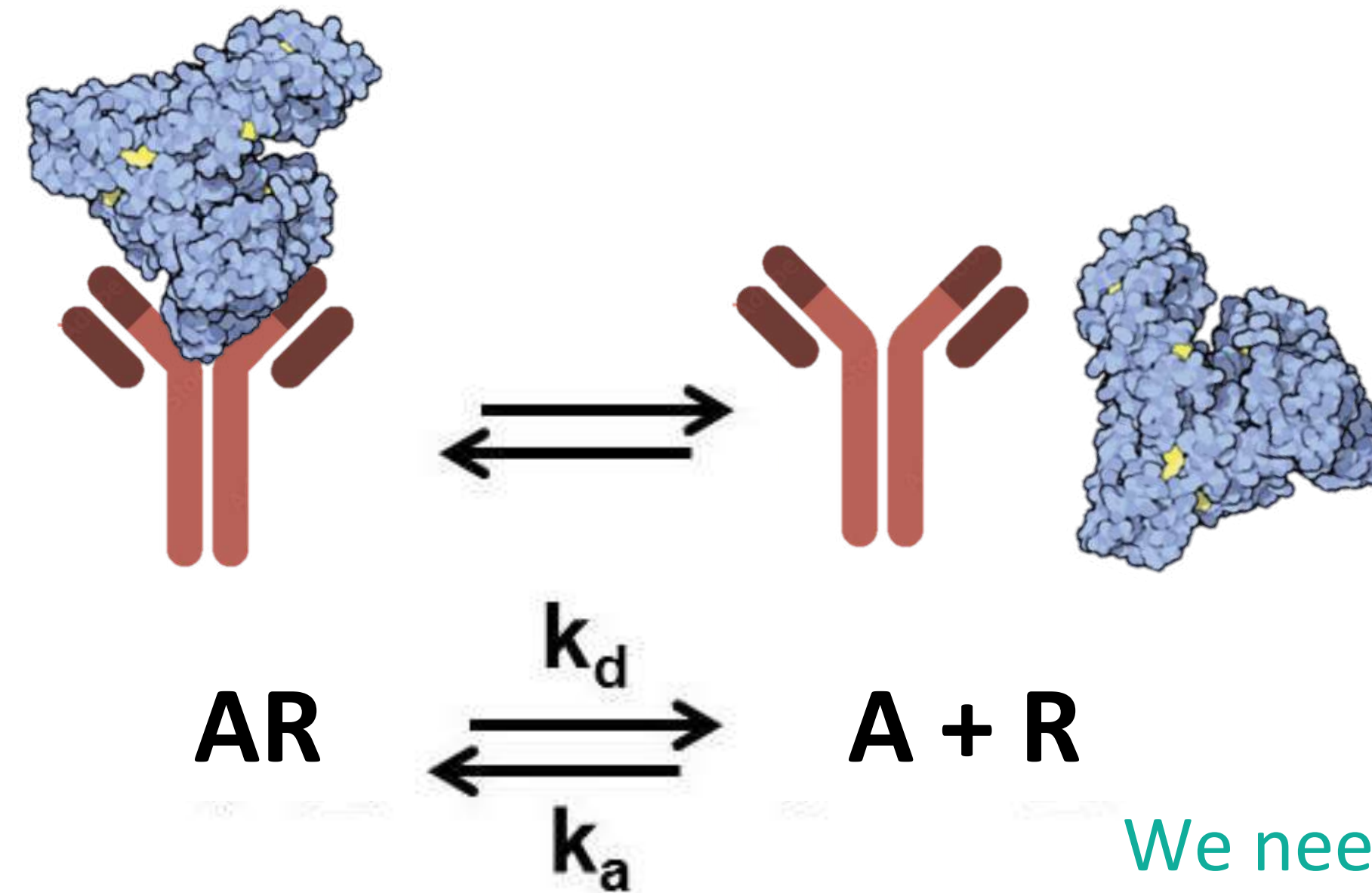
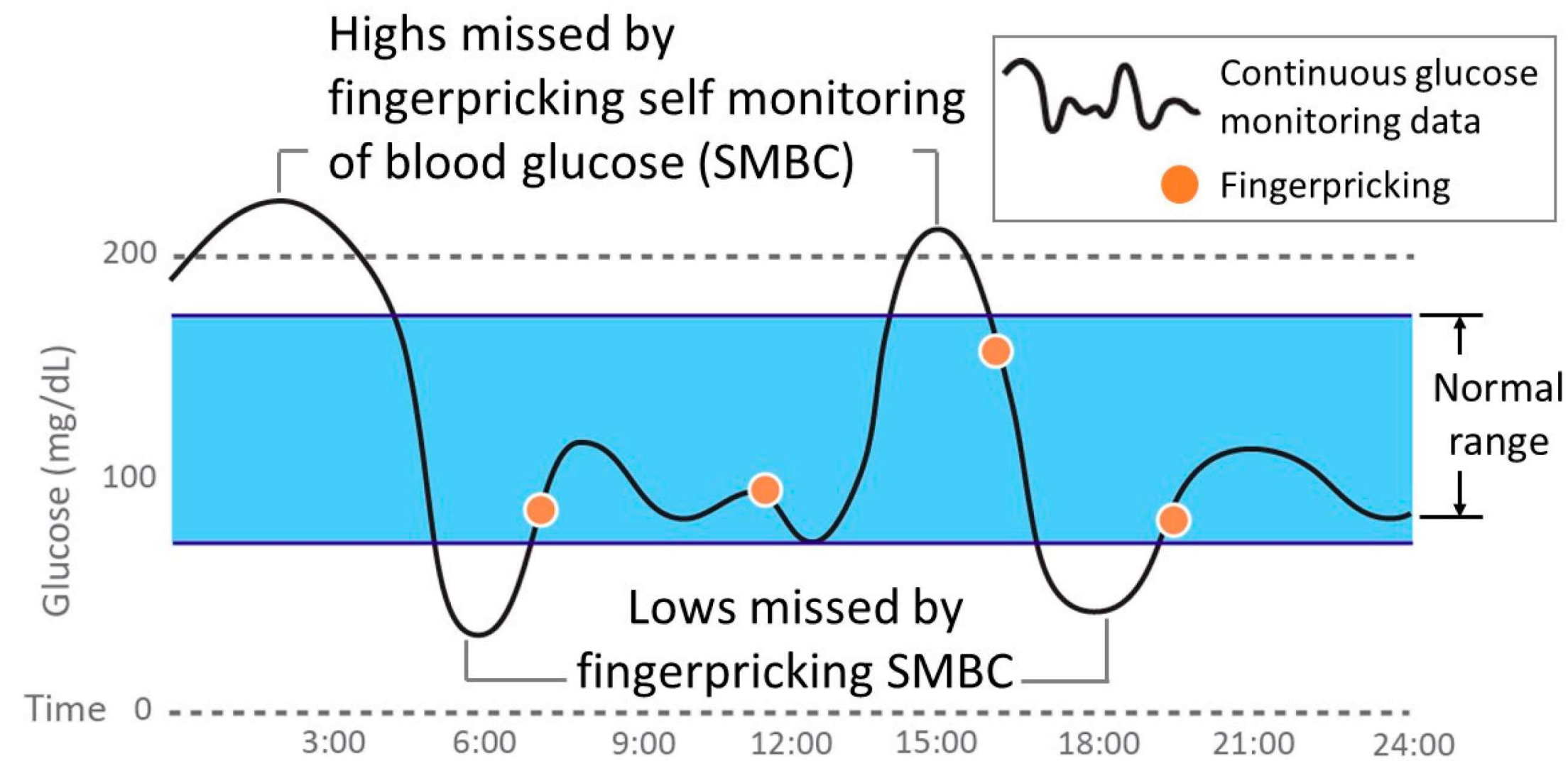
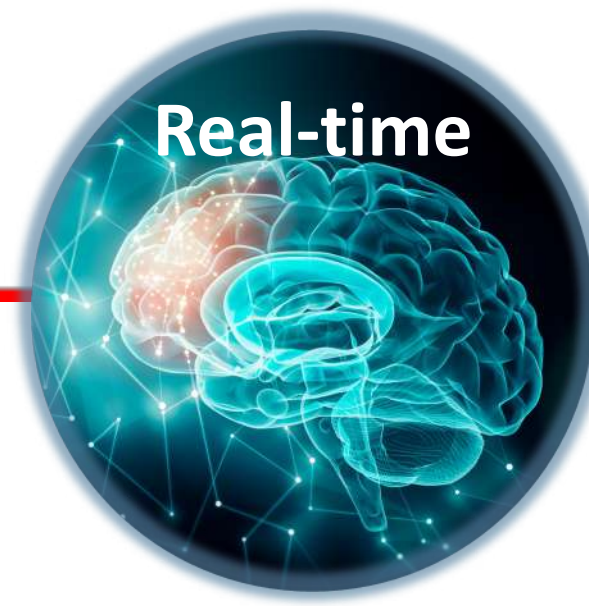
# 1. Need for Label-Free Detection of Molecules



# 2. Challenges of Real-Time Continuous Monitoring



# 2. Continuous Measurements Need Reversible Binding



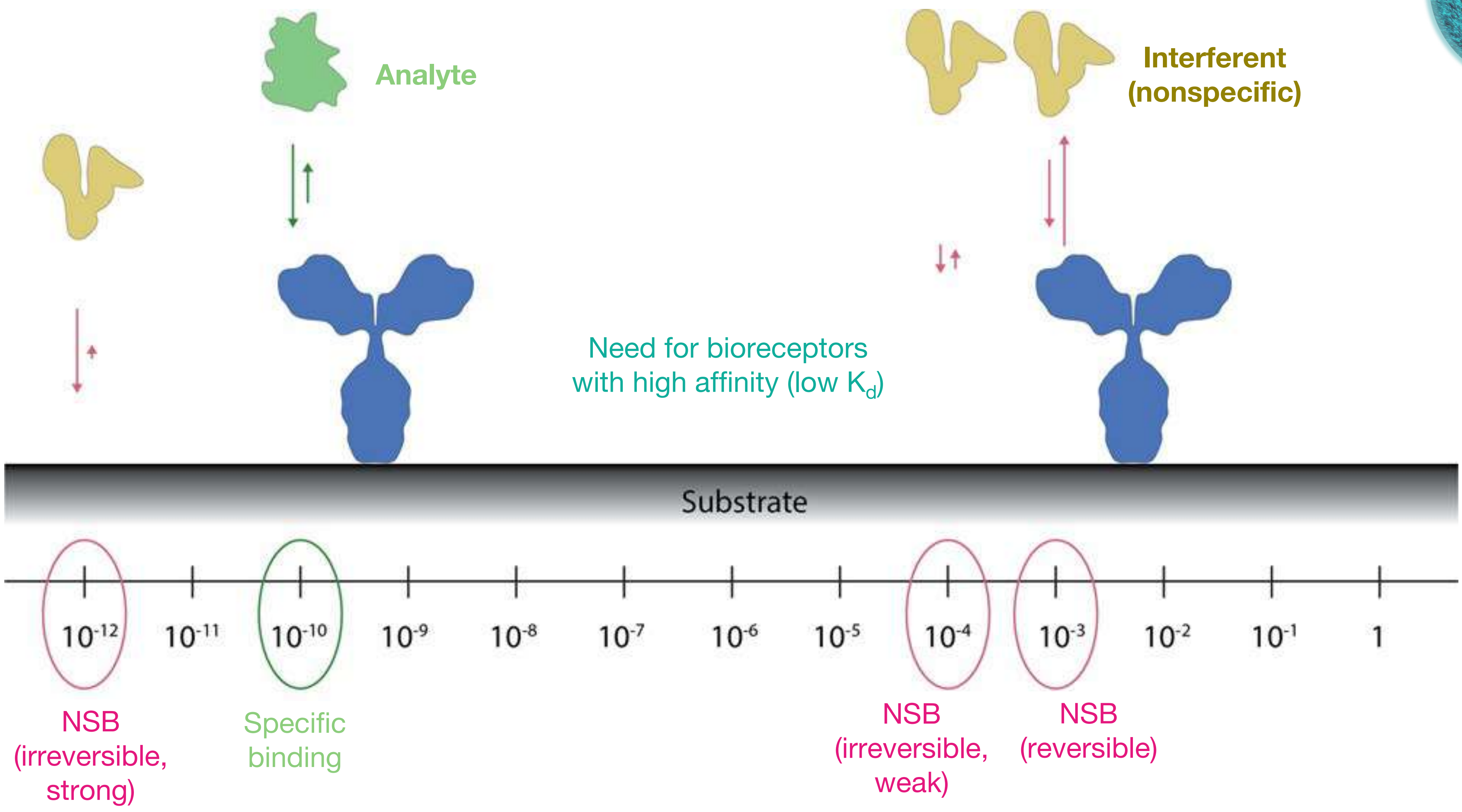
We need strong binding (low  $K_d$ )  
To detect analytes at low concentrations

We need fast kinetics (high  $k_d$ )

$$K_d = \frac{[A][R]}{[AR]} = \frac{k_d}{k_a} = \frac{1}{K_a}$$

We need to engineer/redesign bioreceptors to overcome this mismatch

# 3. Challenges of Bioreceptor Specificity in Addition to NSB



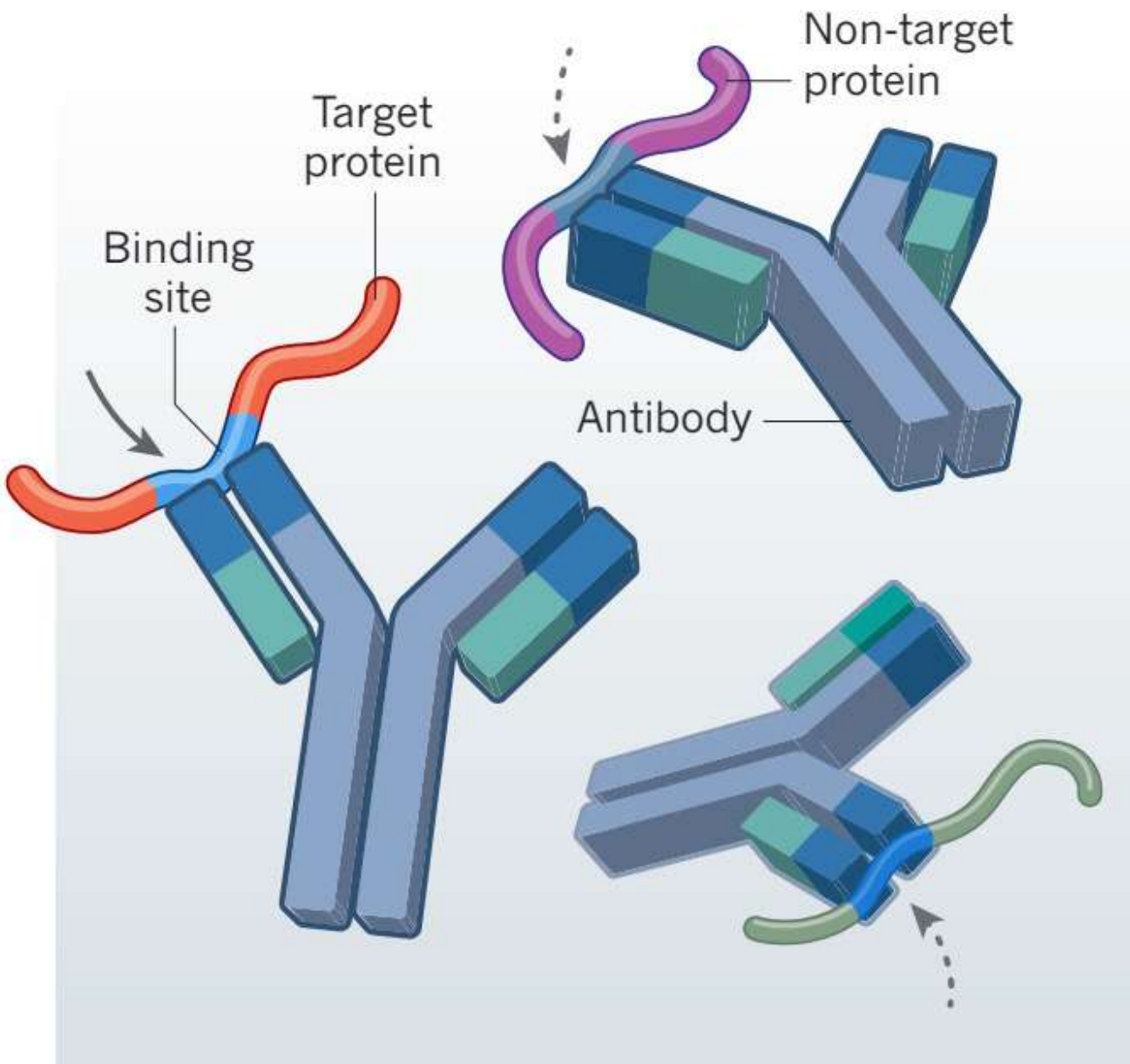


# 3. Cross-Reactivity to Nonspecific Molecules

## Reproducibility crisis: Blame it on the antibodies

[Monya Baker](#)

[Nature](#) 521, 274–276 (2015) | [Cite this article](#)



**Cross-reactivity:**  
binding to other non-targets

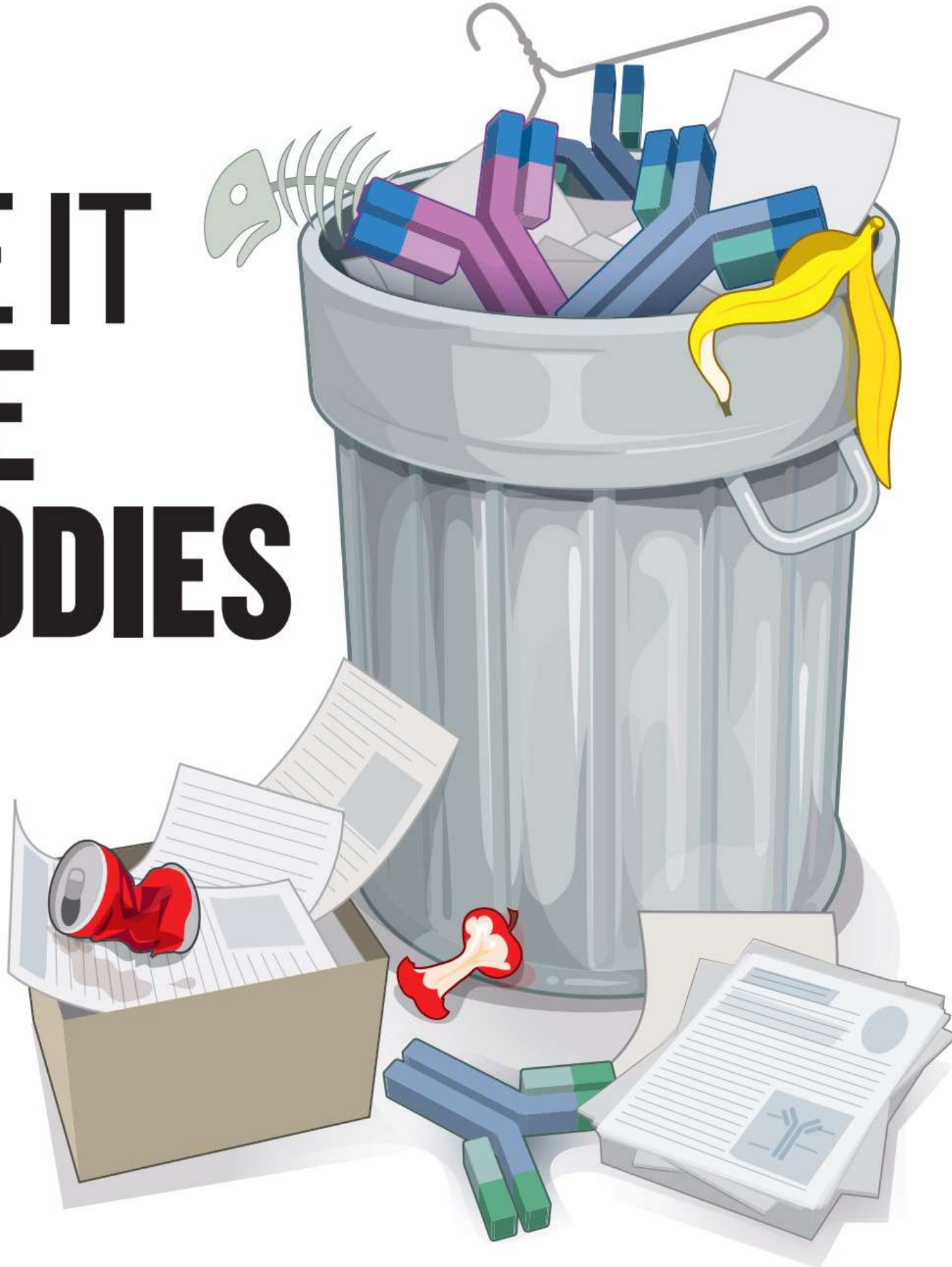
**Batch-to-batch variability**

**Sensitivity** to environment

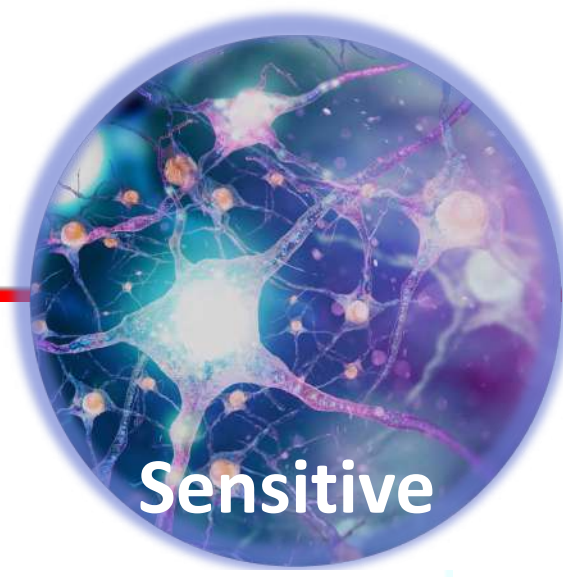
# BLAME IT ON THE ANTIBODIES

*Antibodies are the workhorses of biological experiments, but they are littering the field with false findings. A few evangelists are pushing for change.*

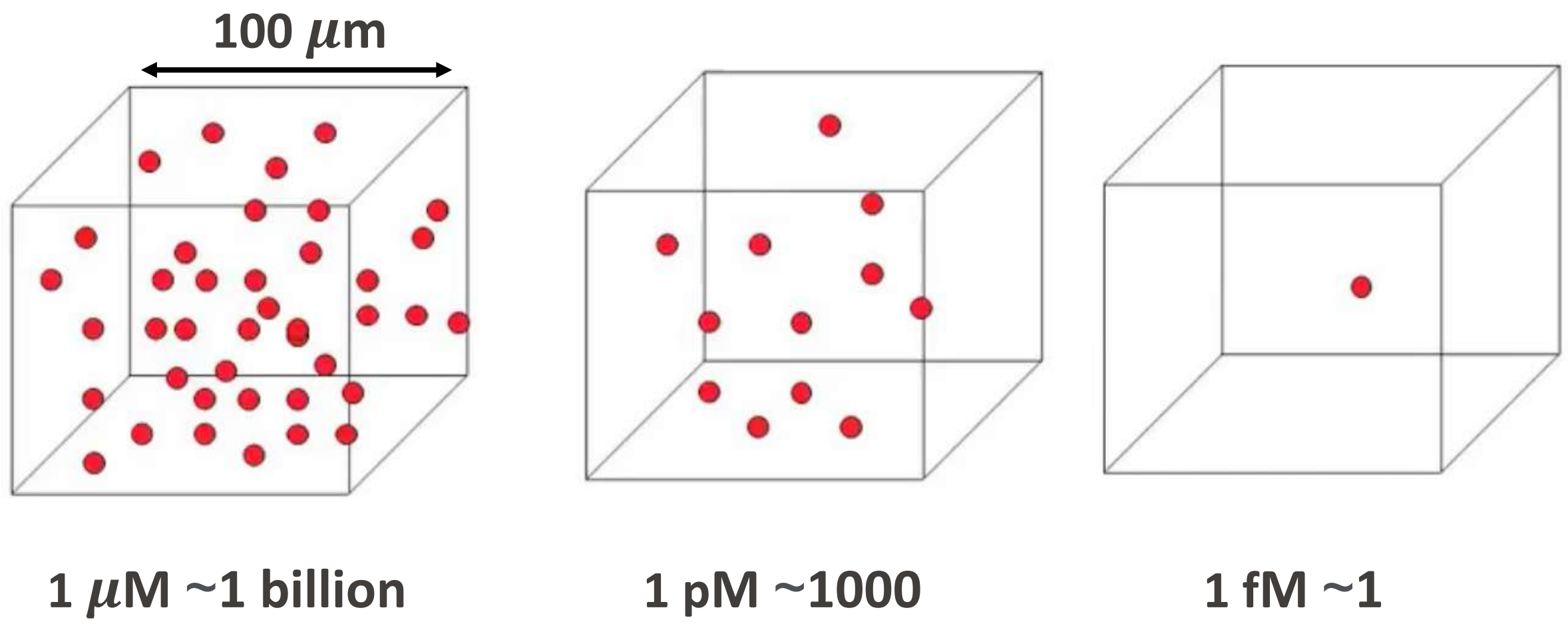
BY MONYA BAKER



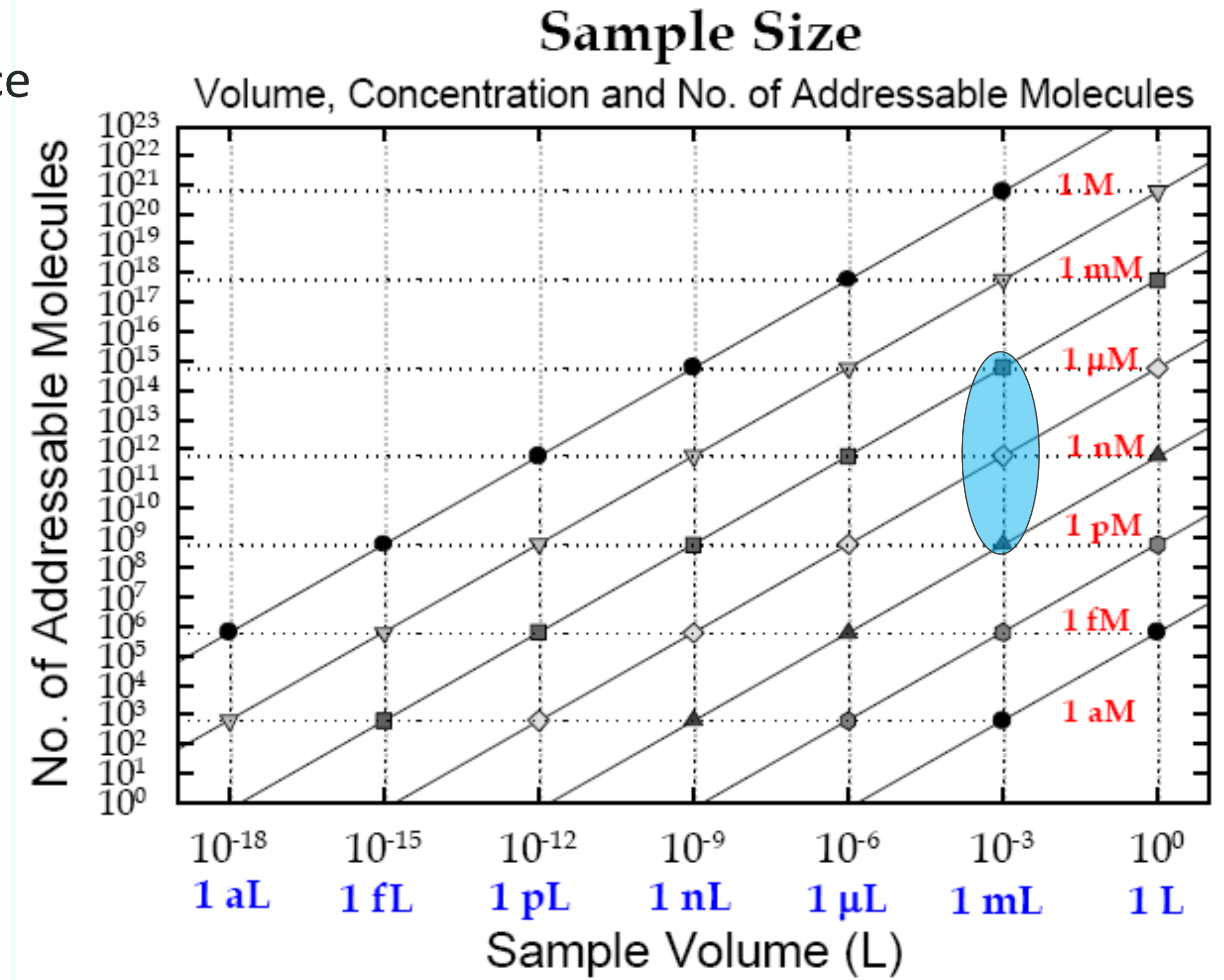
# 4. Very Few Number of Molecules Within Sample Size

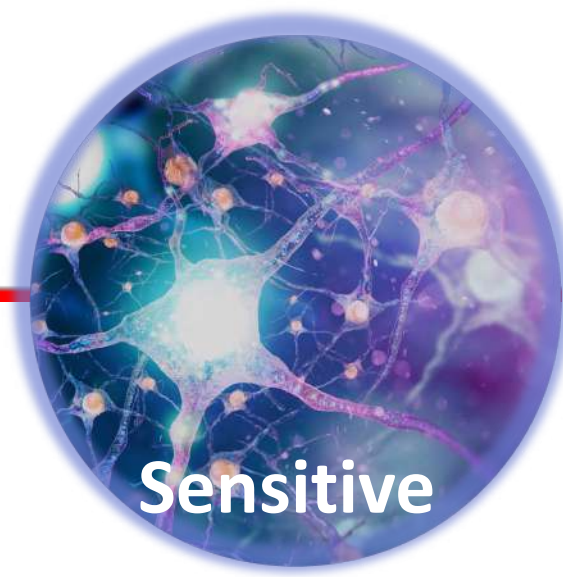


**Stochastic process** – low probability of the biosensor seeing low concentration of target diffusing to the surface



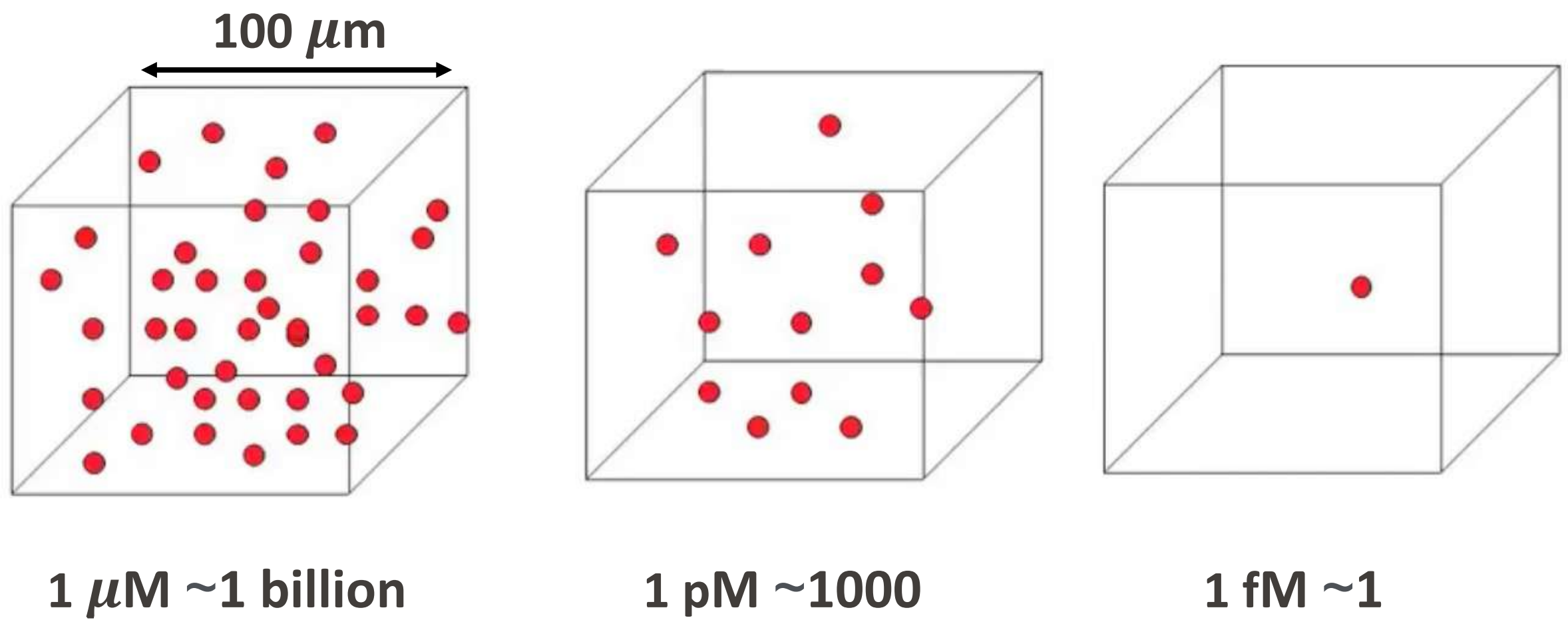
Single molecule of salt in several Olympic-sized swimming pools!





# 4. Diffusion Limitation to the Sensor Surface

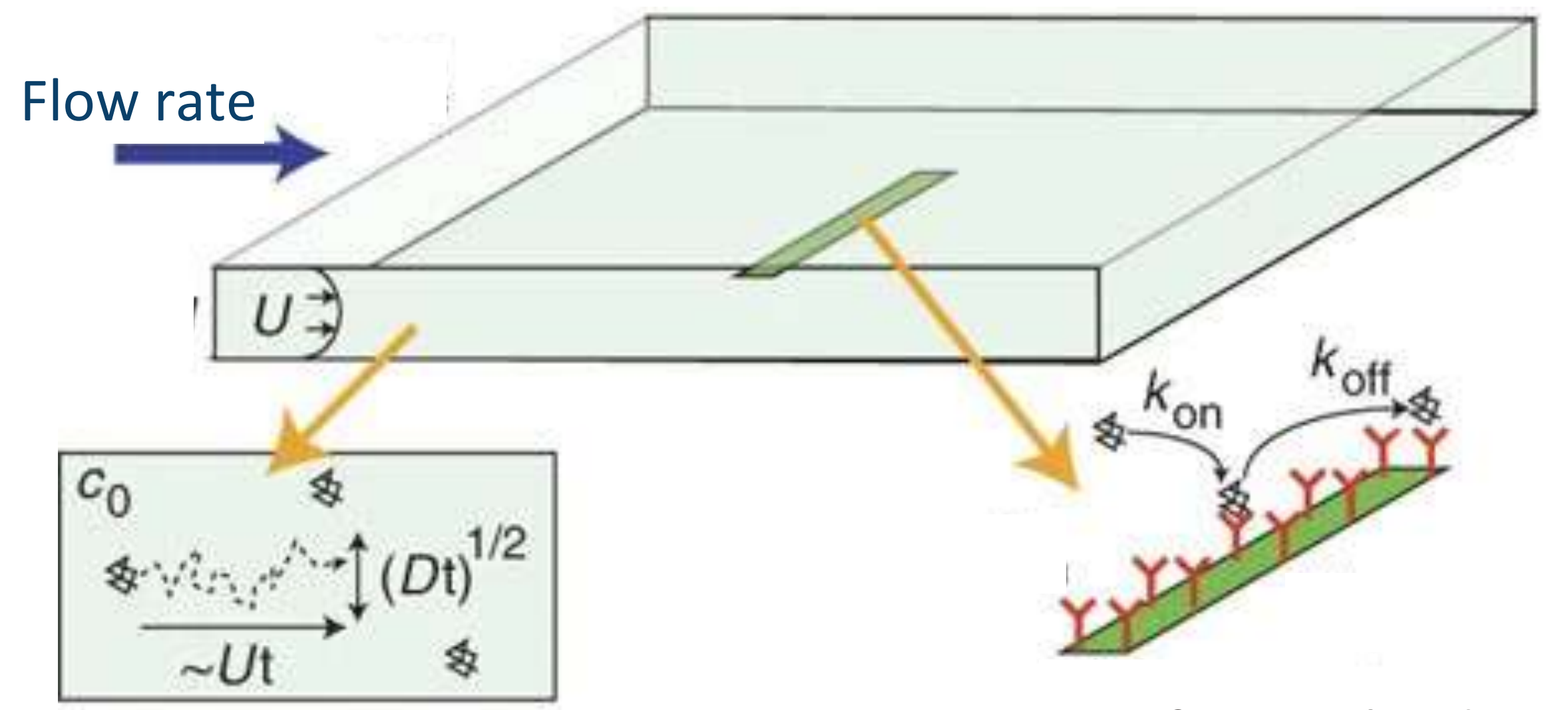
**Stochastic process** – low probability of the biosensor seeing low concentration of target diffusing to the surface



Single molecule of salt in several Olympic-sized swimming pools!

## Making it stick: convection, reaction and diffusion in surface-based biosensors

[Todd M Squires](#), [Robert J Messinger](#) & [Scott R Manalis](#)  
*Nature Biotechnology* 26, 417–426 (2008) | [Cite this article](#)



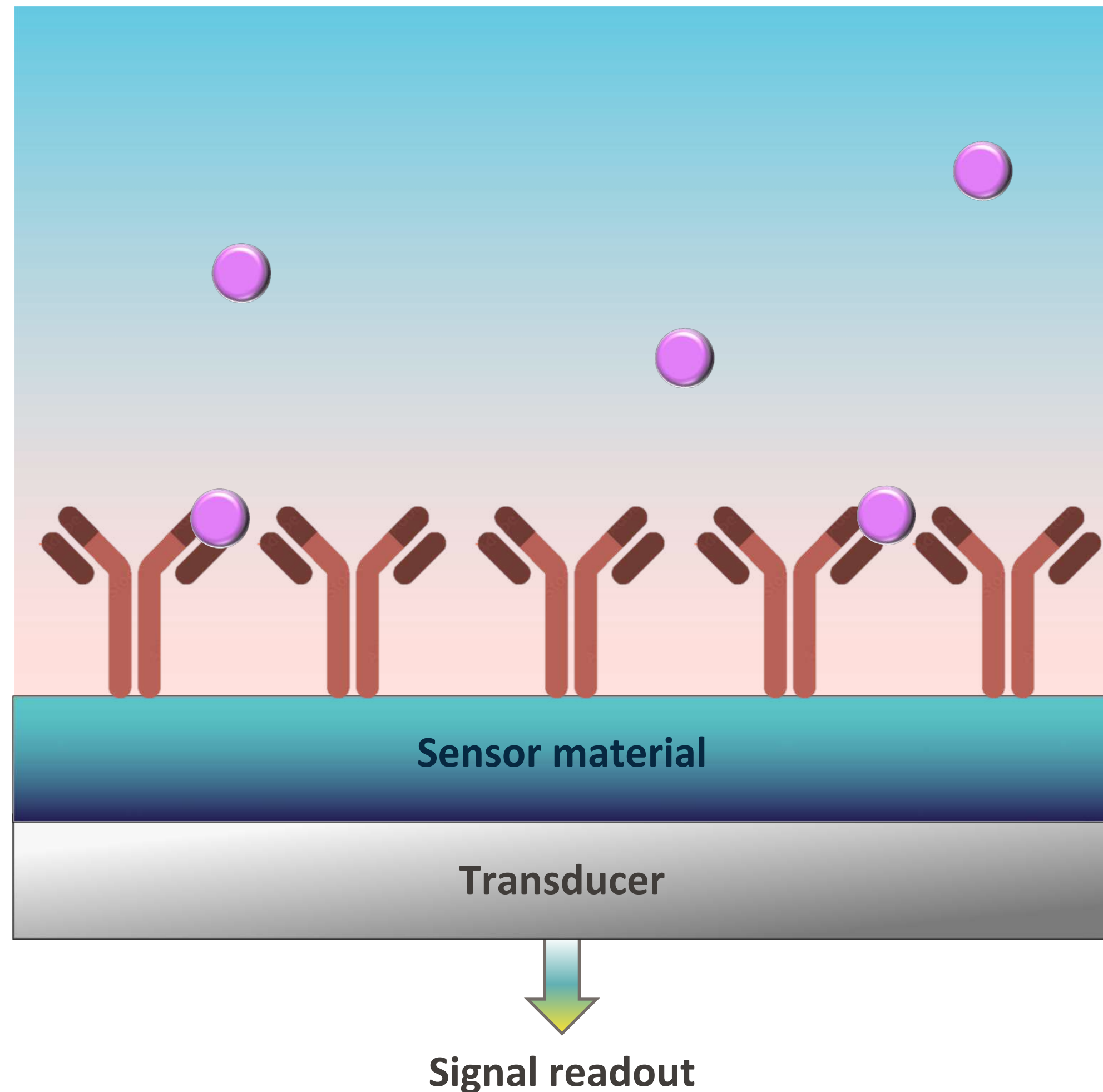
Solution with target concentration ( $c_0$ ) flows with velocity ( $U$ ) through channel based on diffusion ( $D$ )

Kinetics of target binding to bioreceptors

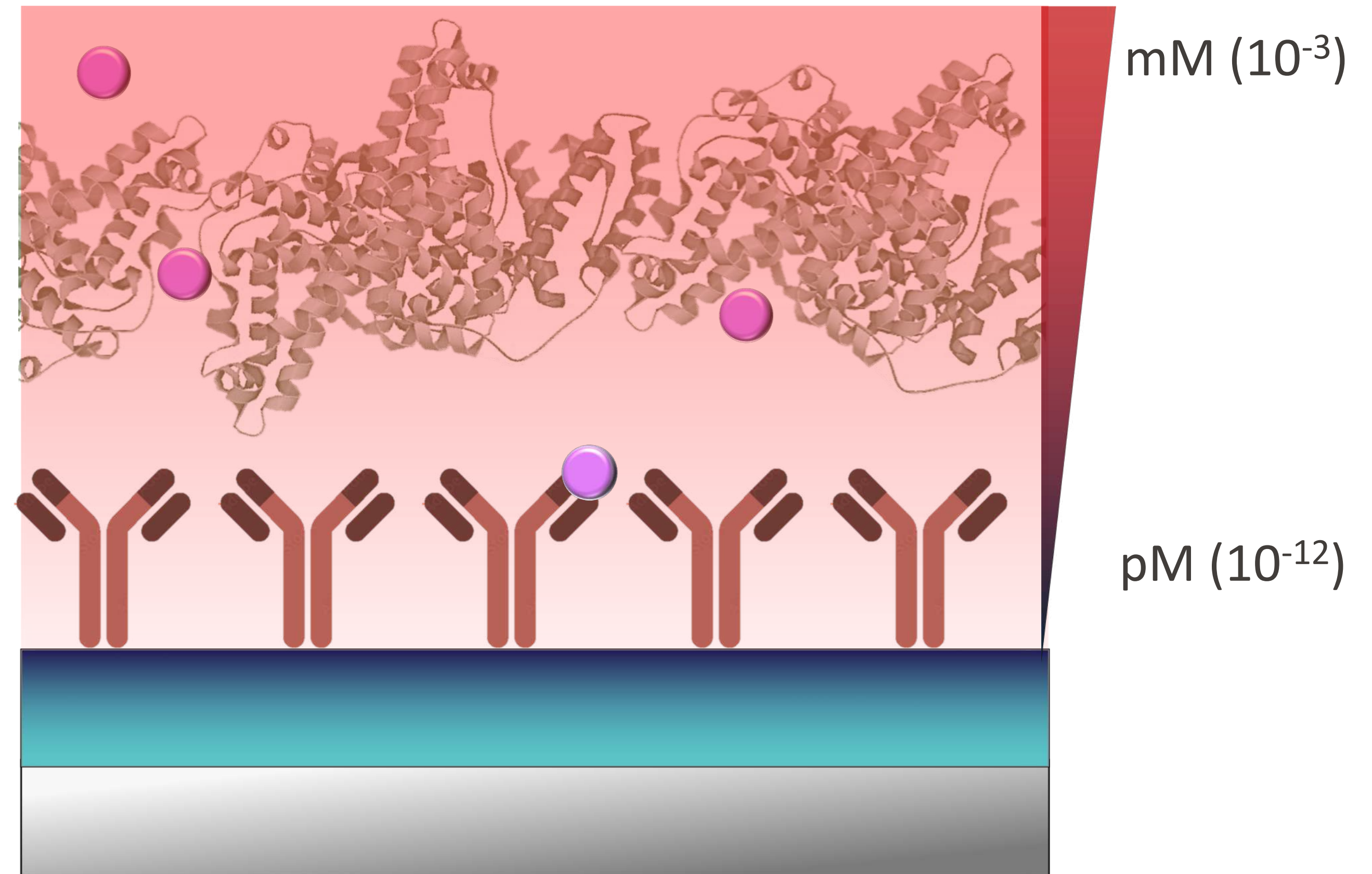
# 5. Nonspecific Binding (NSB) in Complex Environments



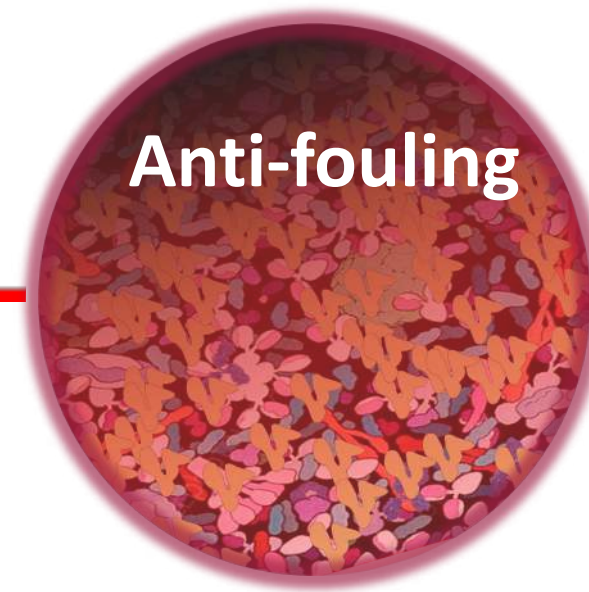
Expectation (phosphate buffered saline)



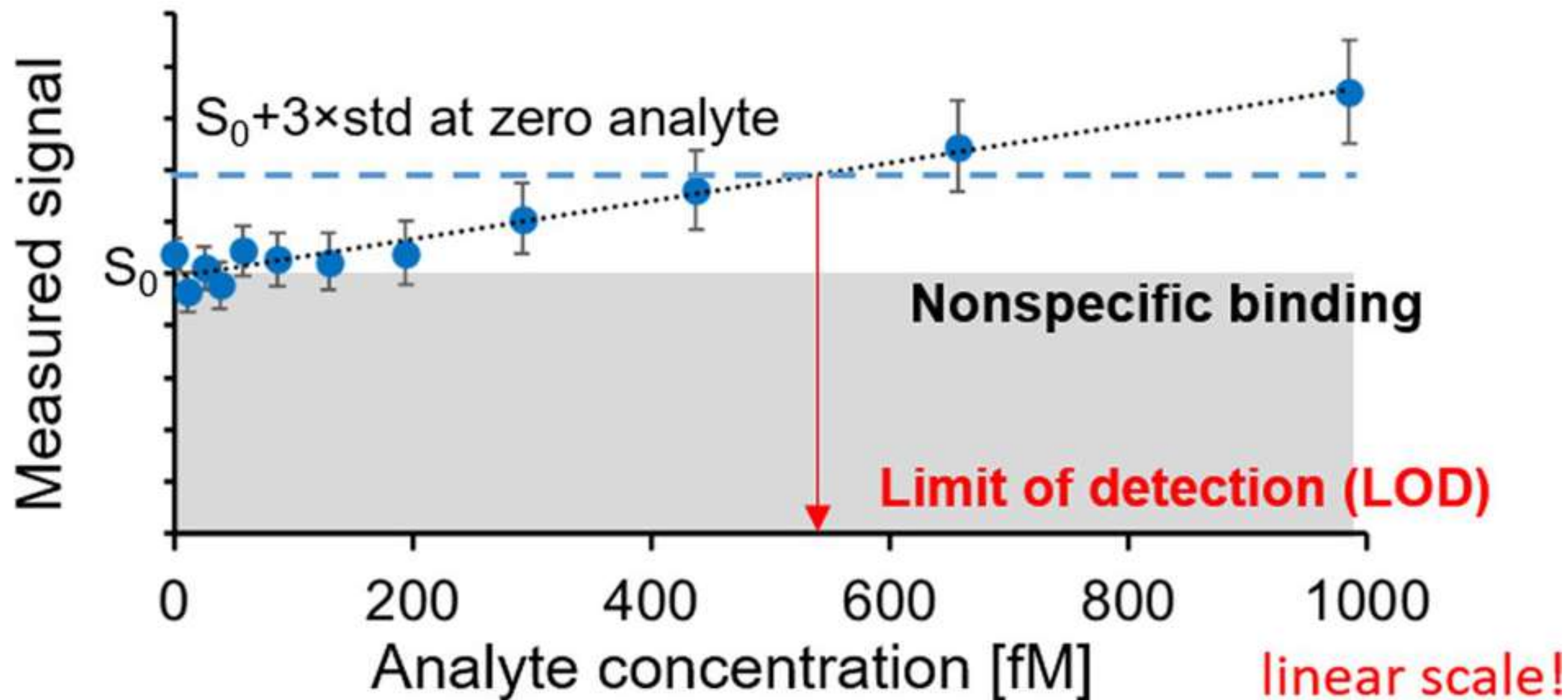
Reality (biofluids such as blood)



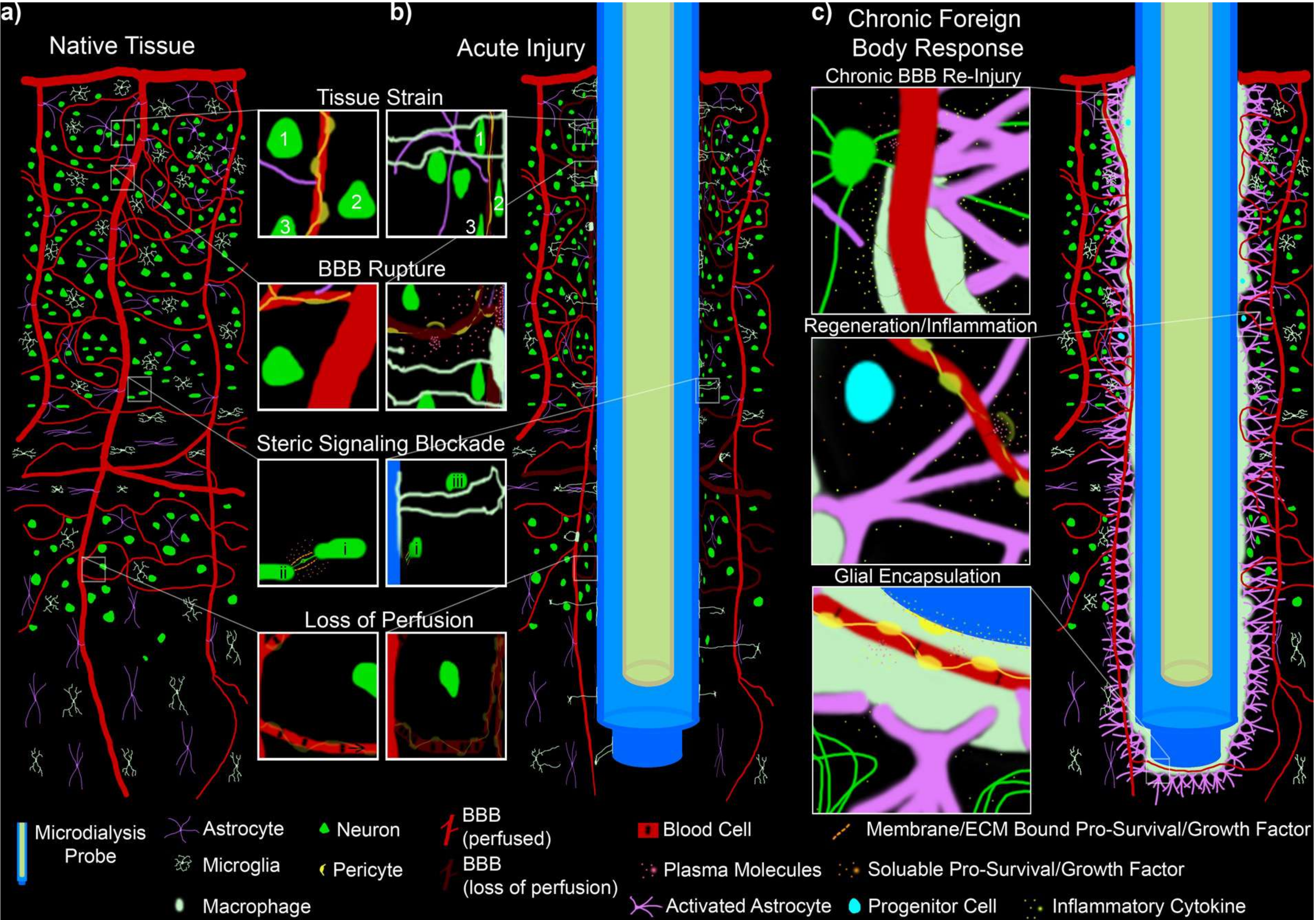
# 5. Most Diagnostics Limited by Nonspecific Binding



Non-specific binding induced noise at low concentrations limits diagnostic biosensors



# 6. Tissue Response to Implanted Sensors

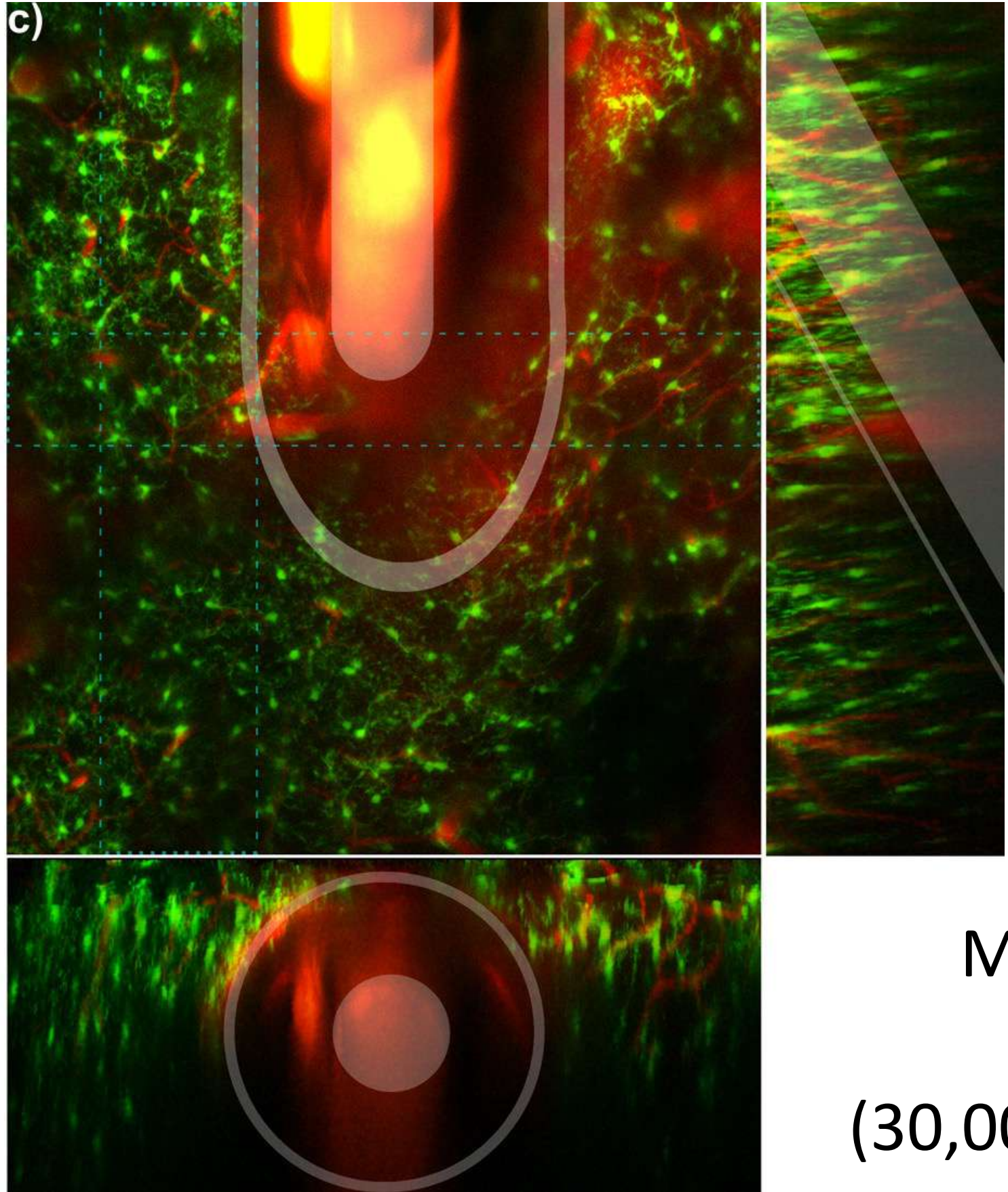
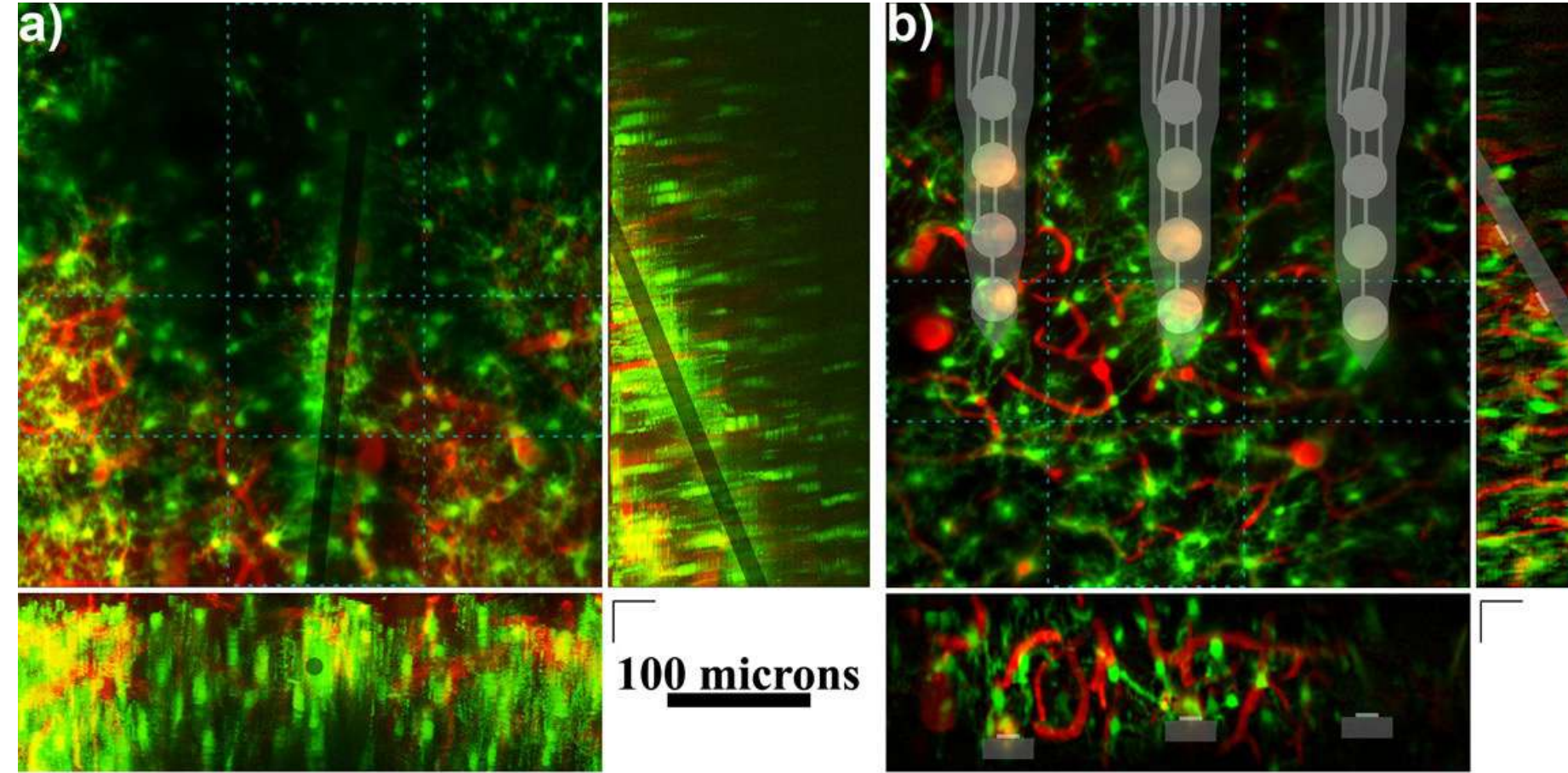




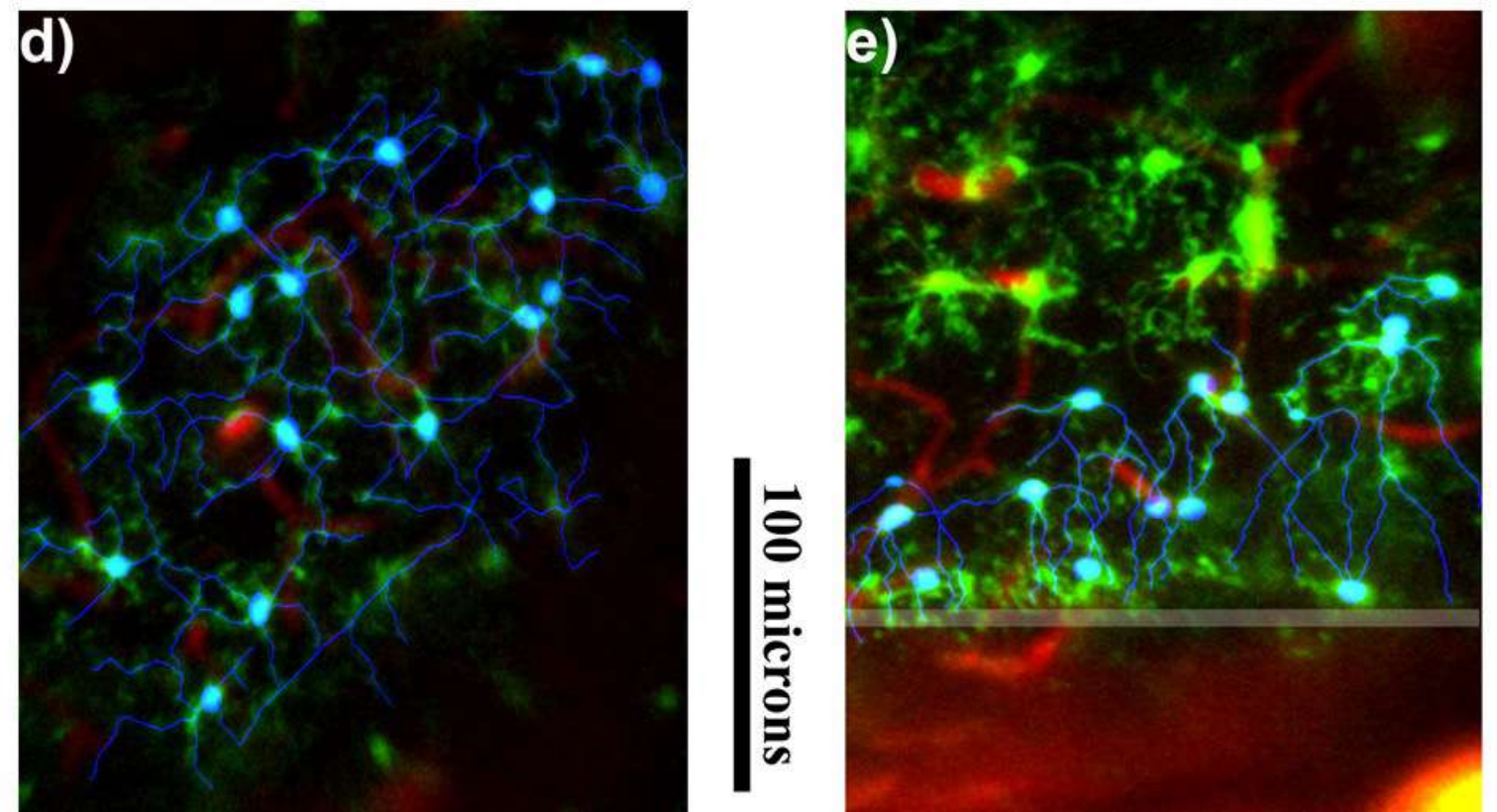
# 6. Size Matters: Miniaturization of Sensors

Microglia activation hours after implantation

Carbon fiber electrodes  
(20-60  $\mu\text{m}^2$ )



Microdialysis probes  
(30,000-70,000  $\mu\text{m}^2$ )



Planar silicon electrodes  
(3000-15,000  $\mu\text{m}^2$ )

# Key Takeaways

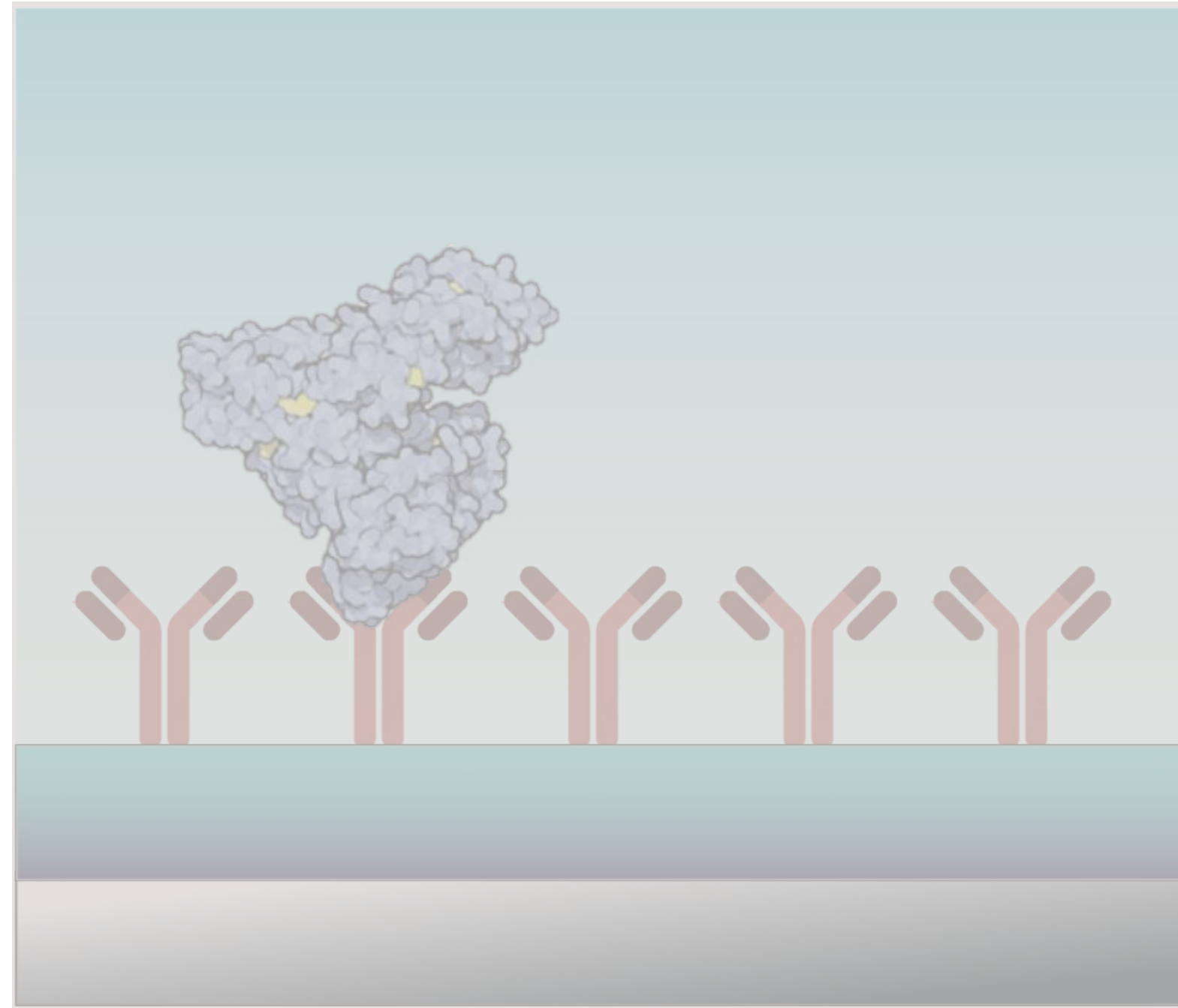
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There are different requirements for biosensors depending on the applications:

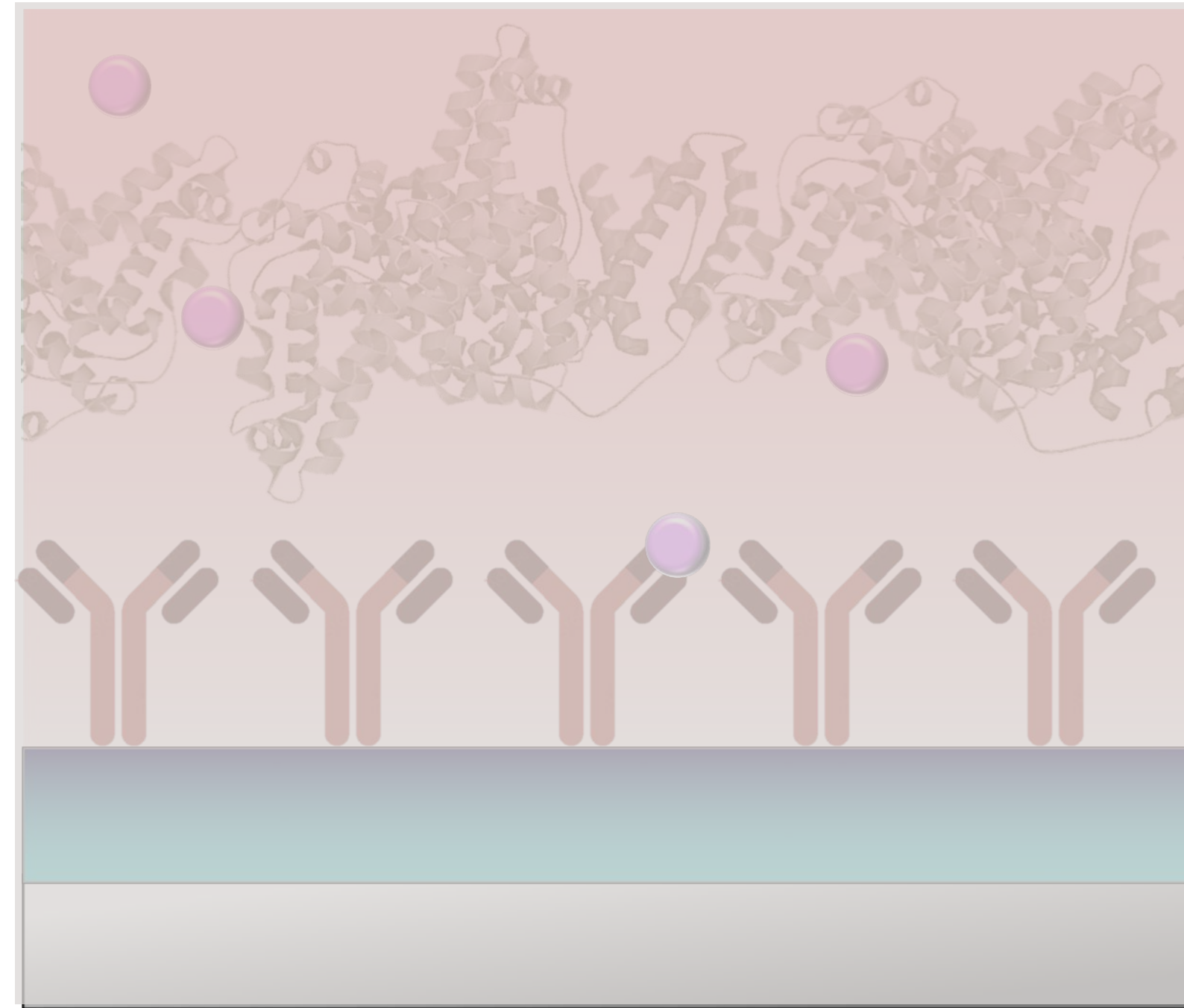
- **Labe-free detection**
- **Real-time continuous monitoring**
- **Selectivity** – differentiating nonspecific molecules
- **Sensitivity** – detection of molecules at low concentrations in vast space
- **Anti-fouling** – mitigating nonspecific binding on surfaces
- **Localized** – size of biosensors define tissue response upon implantation

# Topics We Cover in Today's Lecture on Biosensing

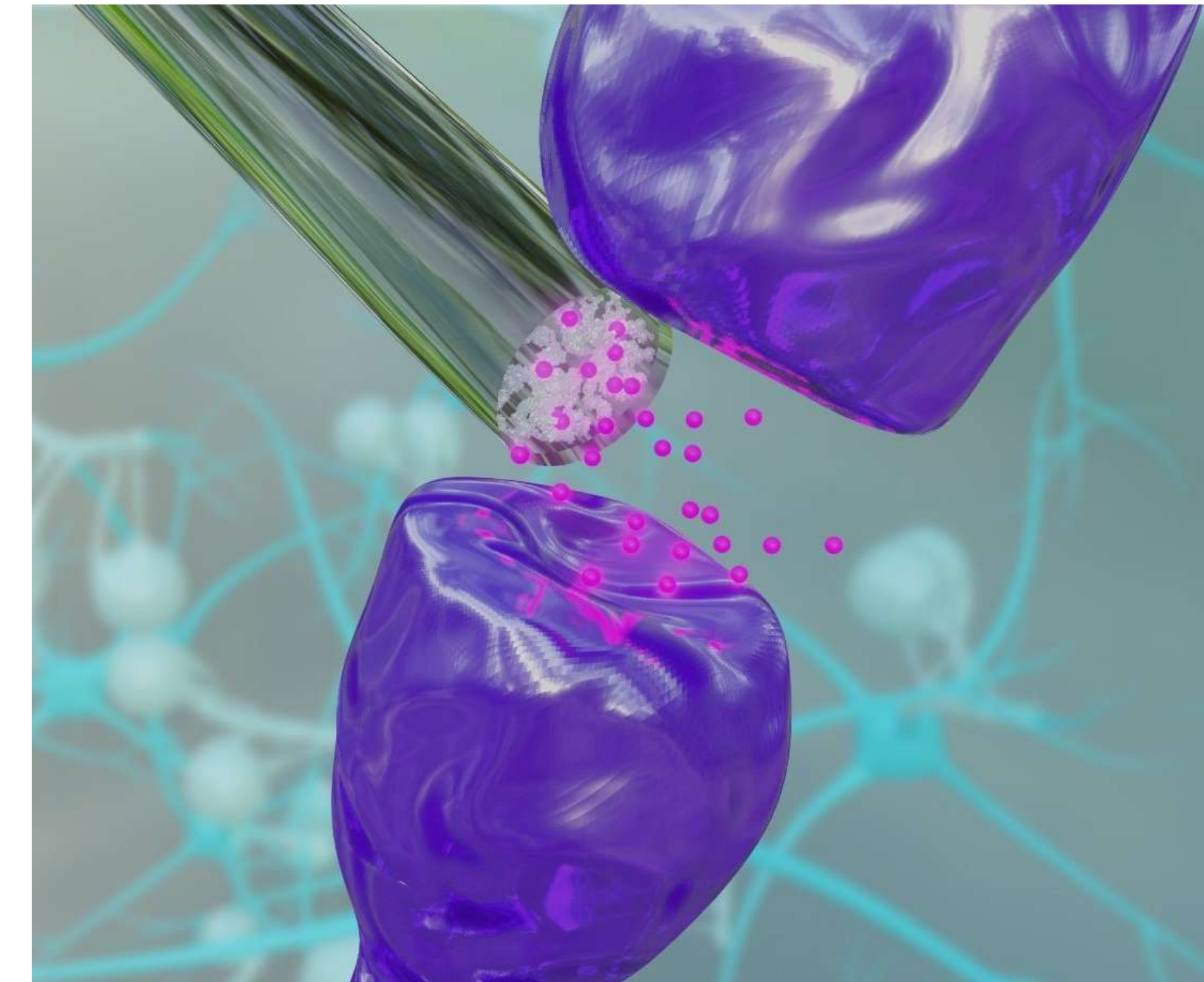
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Fundamentals of Biosensors



Challenges of Biosensing in Complex Environments

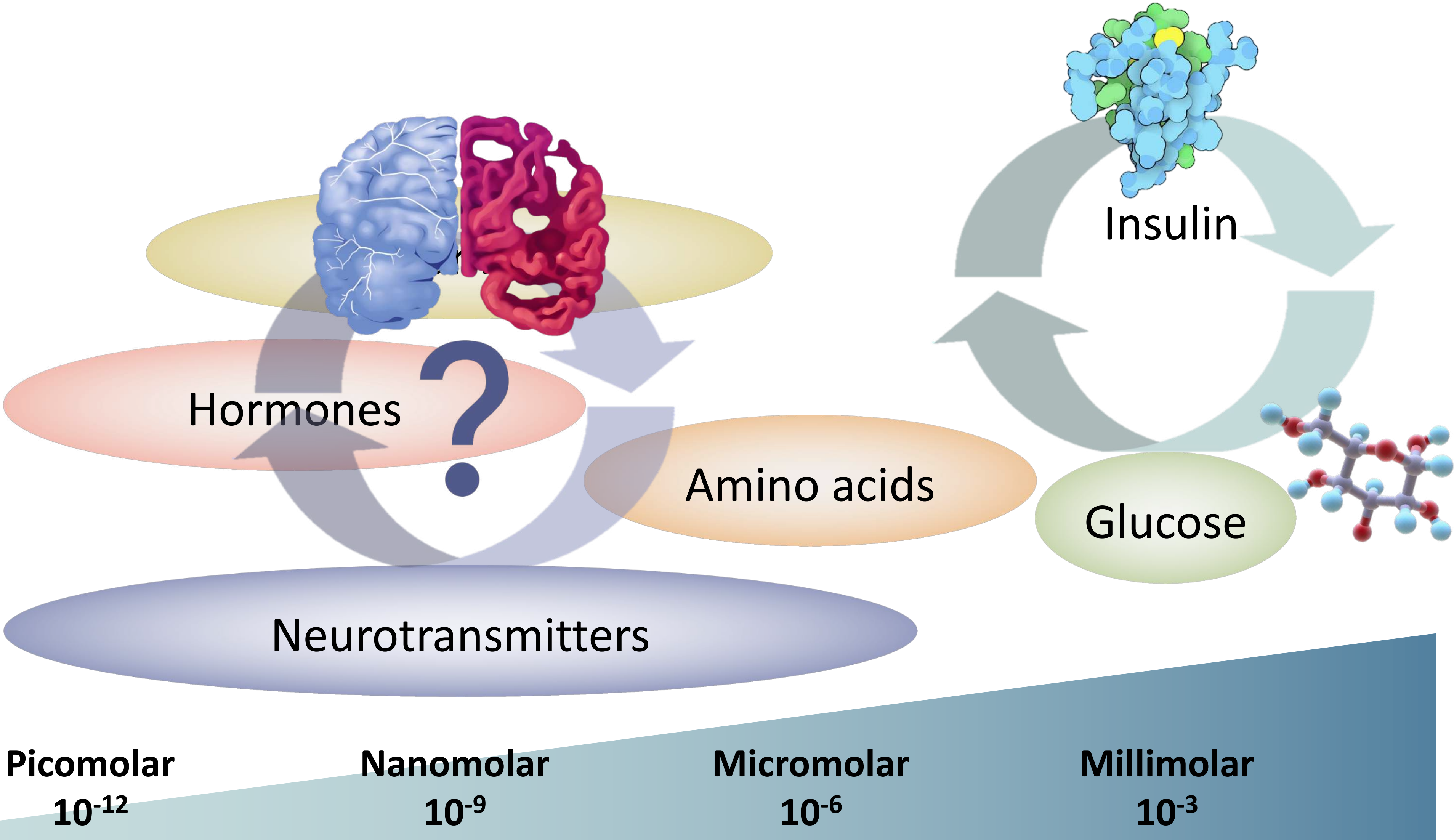


DNA-Based Biosensing that Tackle Challenges

Recall requirements for biosensors are application dependent

I now show you an example for **biosensing chemicals in the brain**

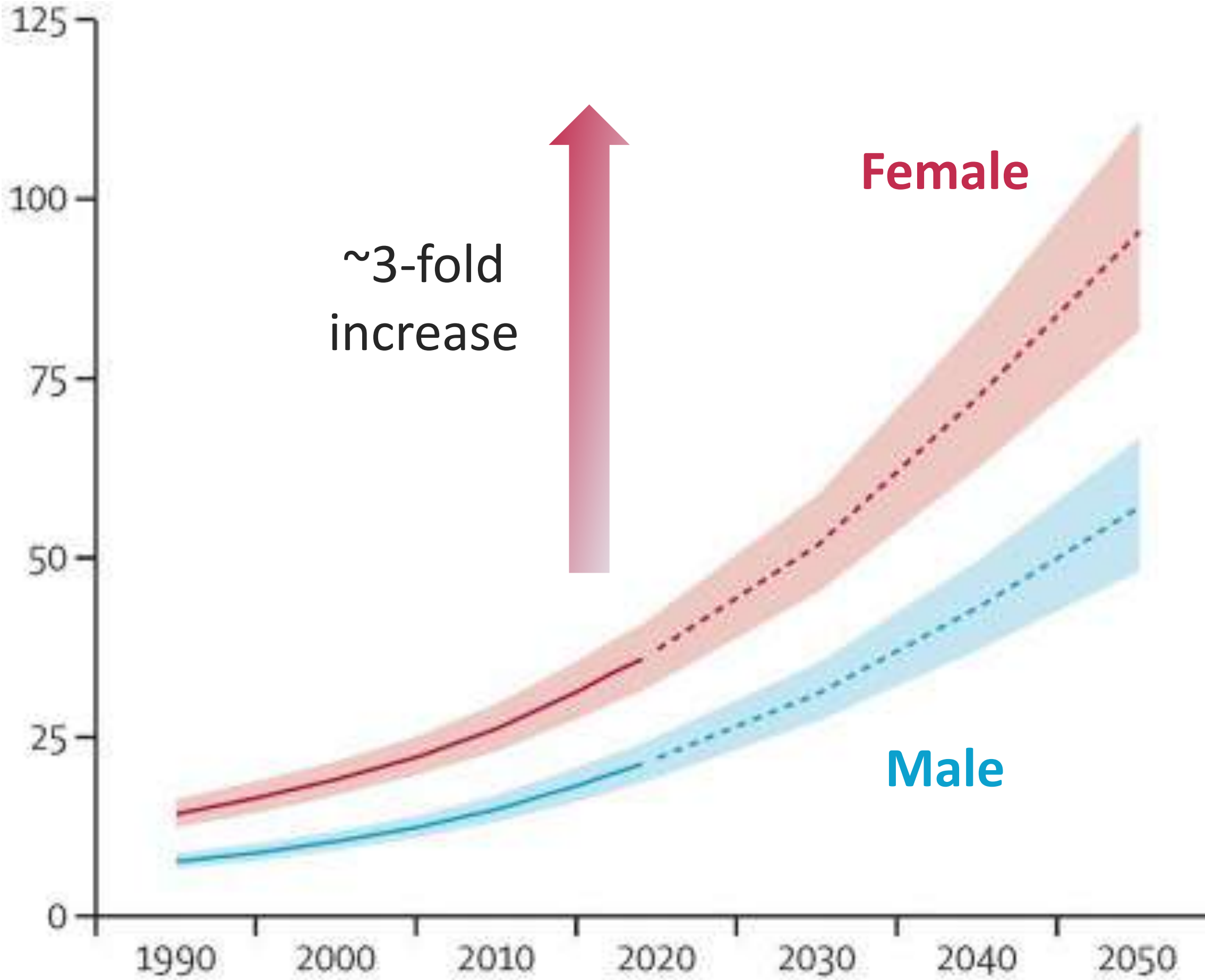
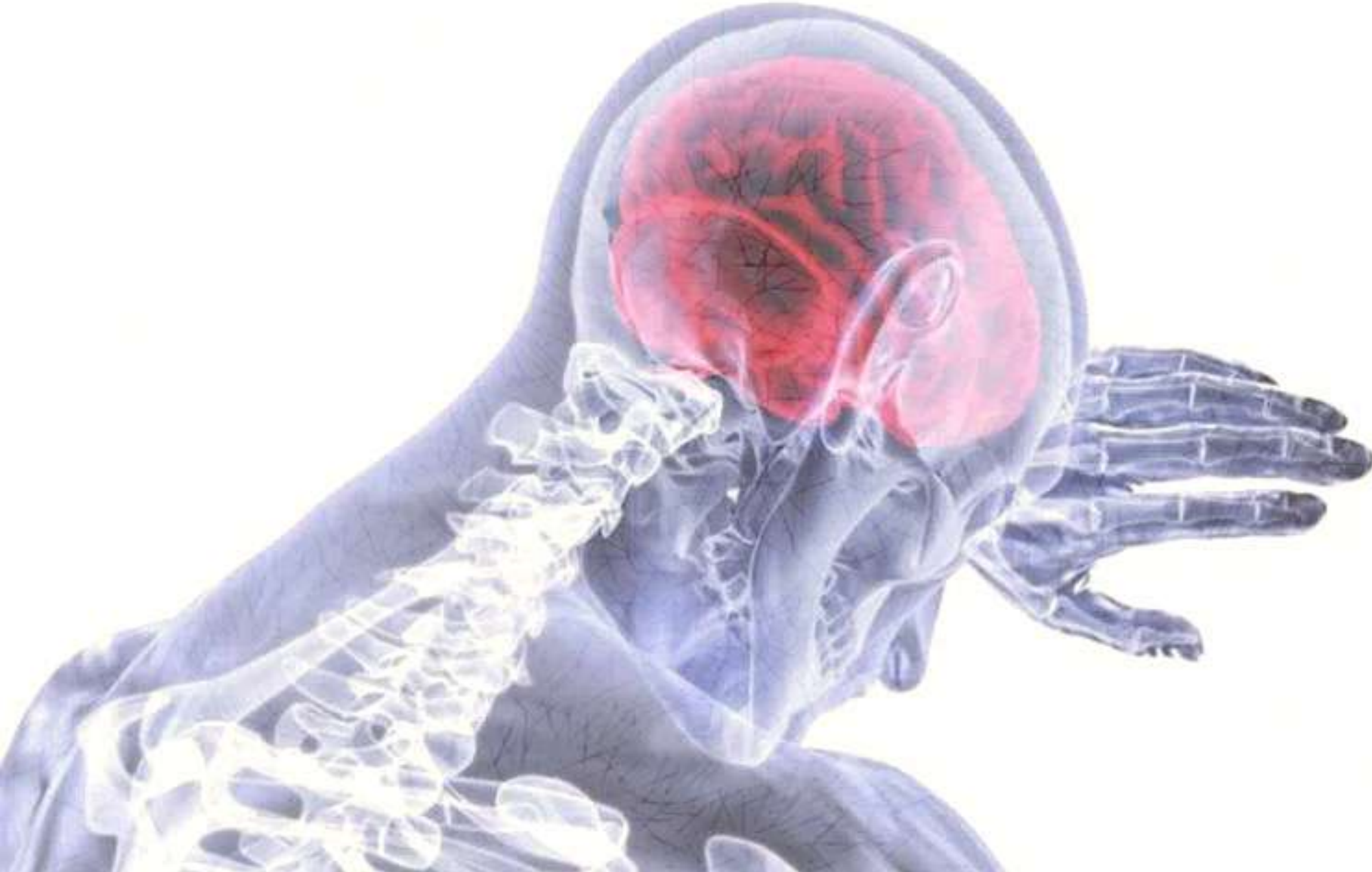
# Challenge of Detecting Neurotransmitters in the Brain



# Brain Disorders are a Global Health Crisis

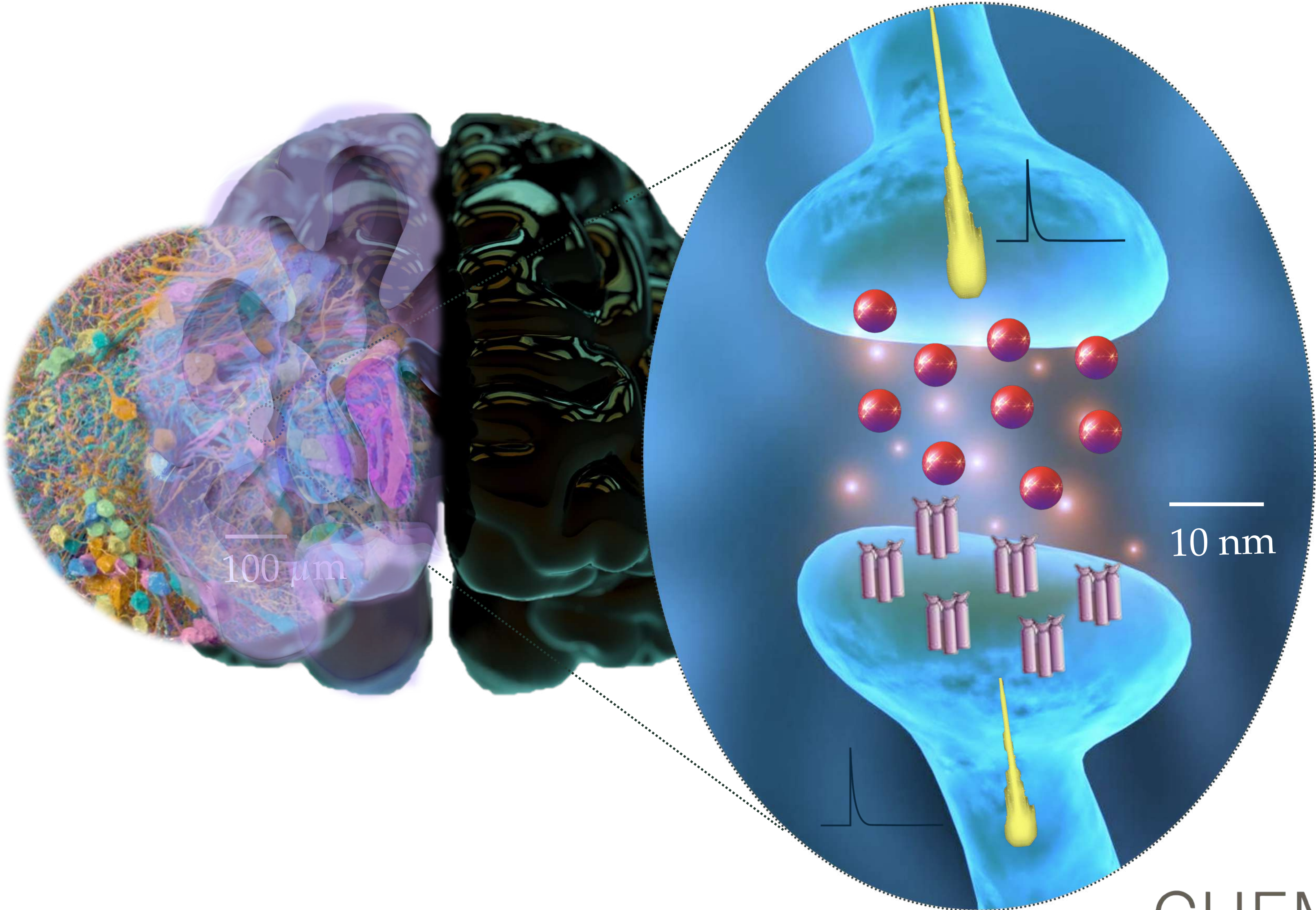
1 in 2 people globally will develop a mental health disorder in their life

McGrath et al. | *Lancet Psychiatry* | 2023

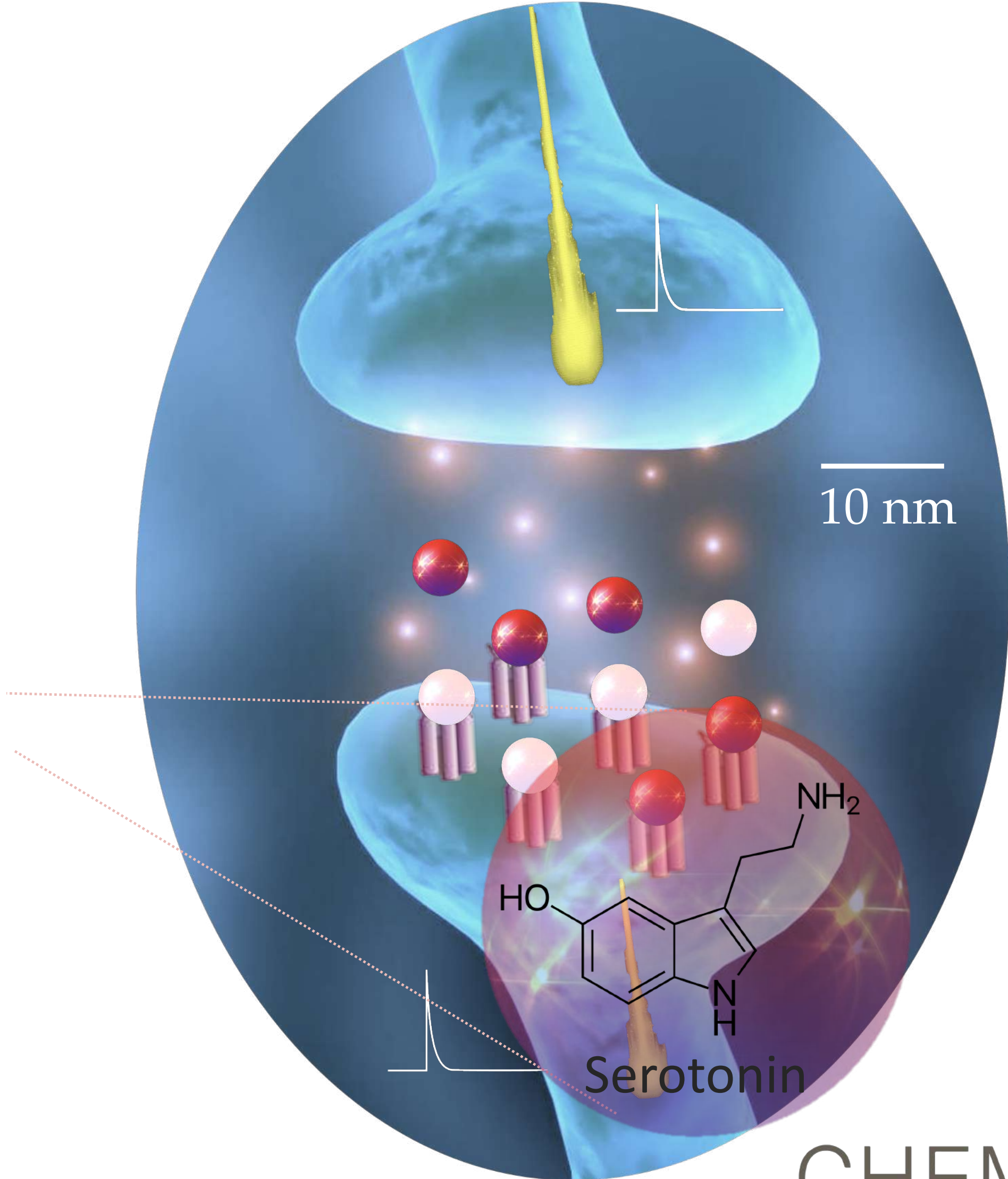
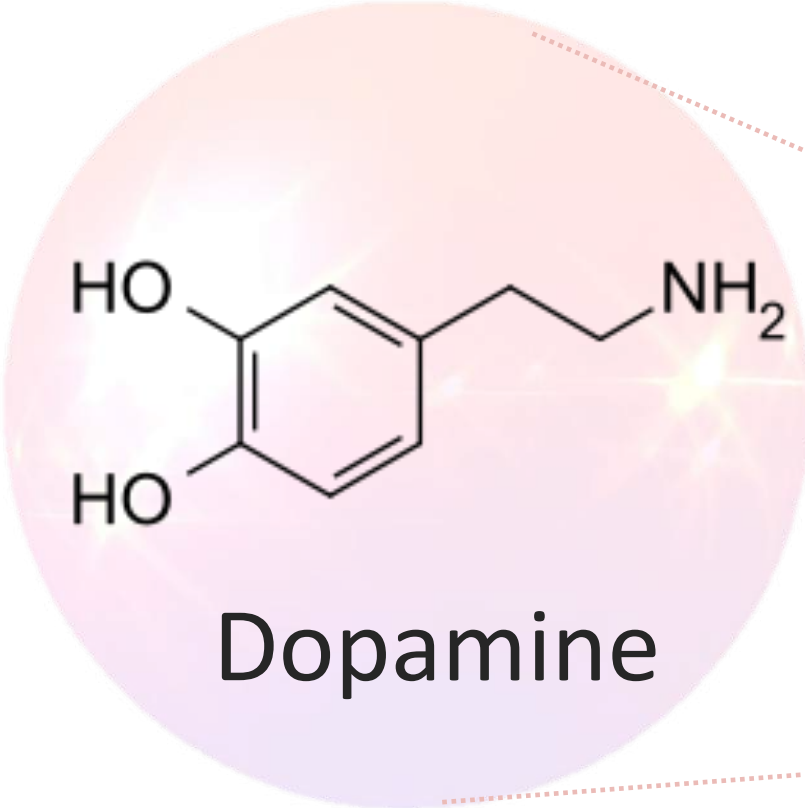


Nichols et al. | *The Lancet Public Health* | 2022

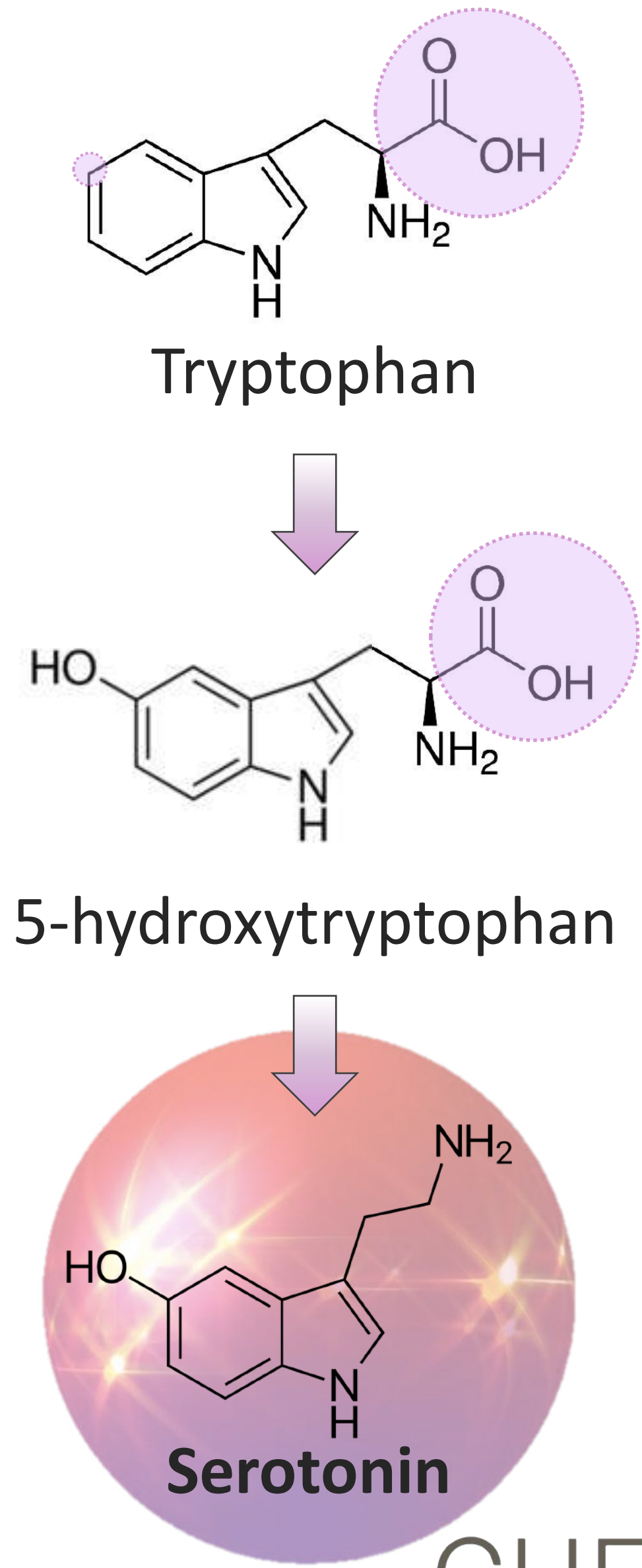
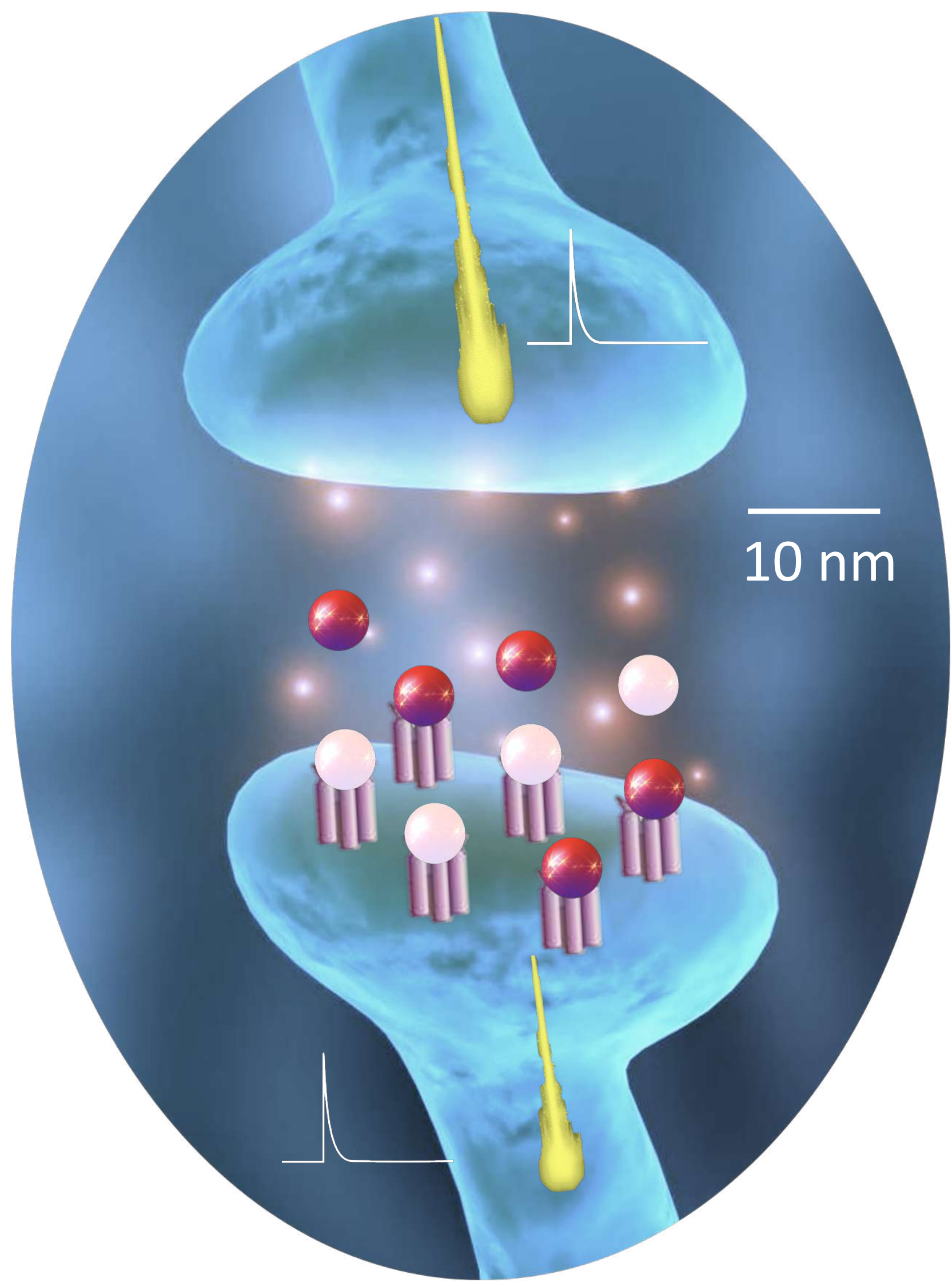
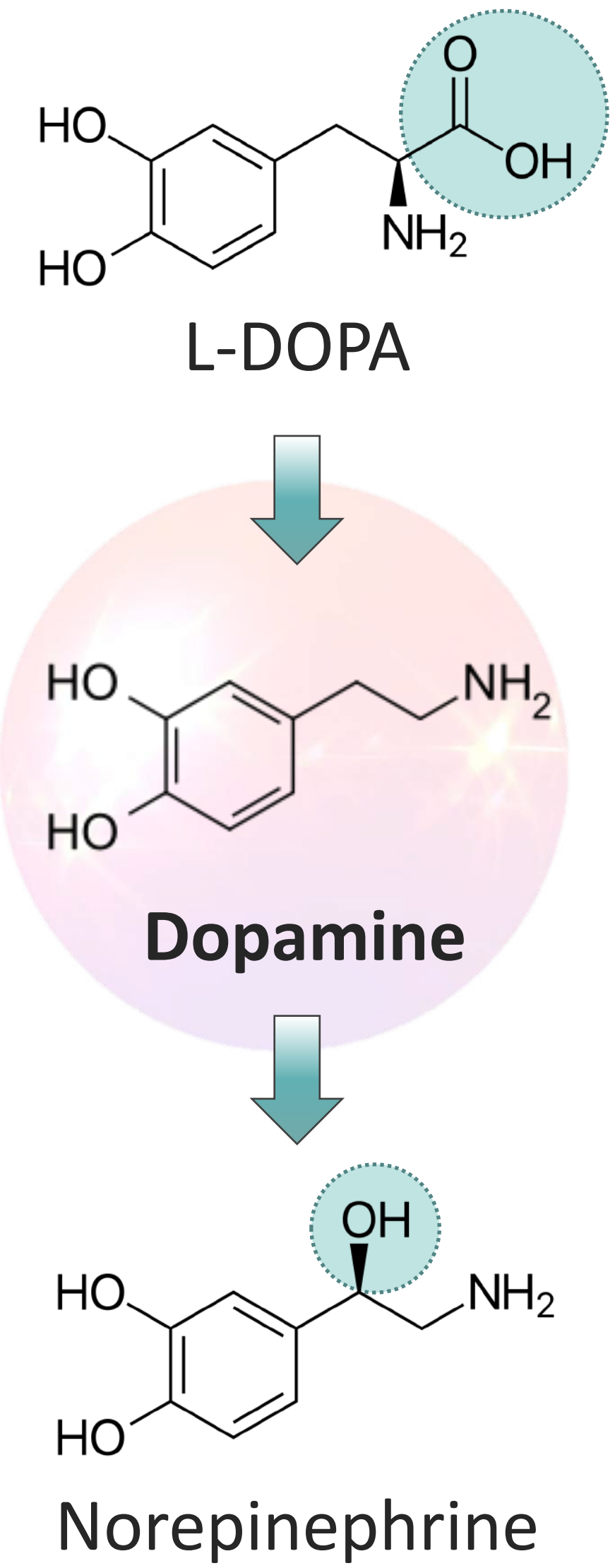
# Complexity of Human Brain – Spatial Scales



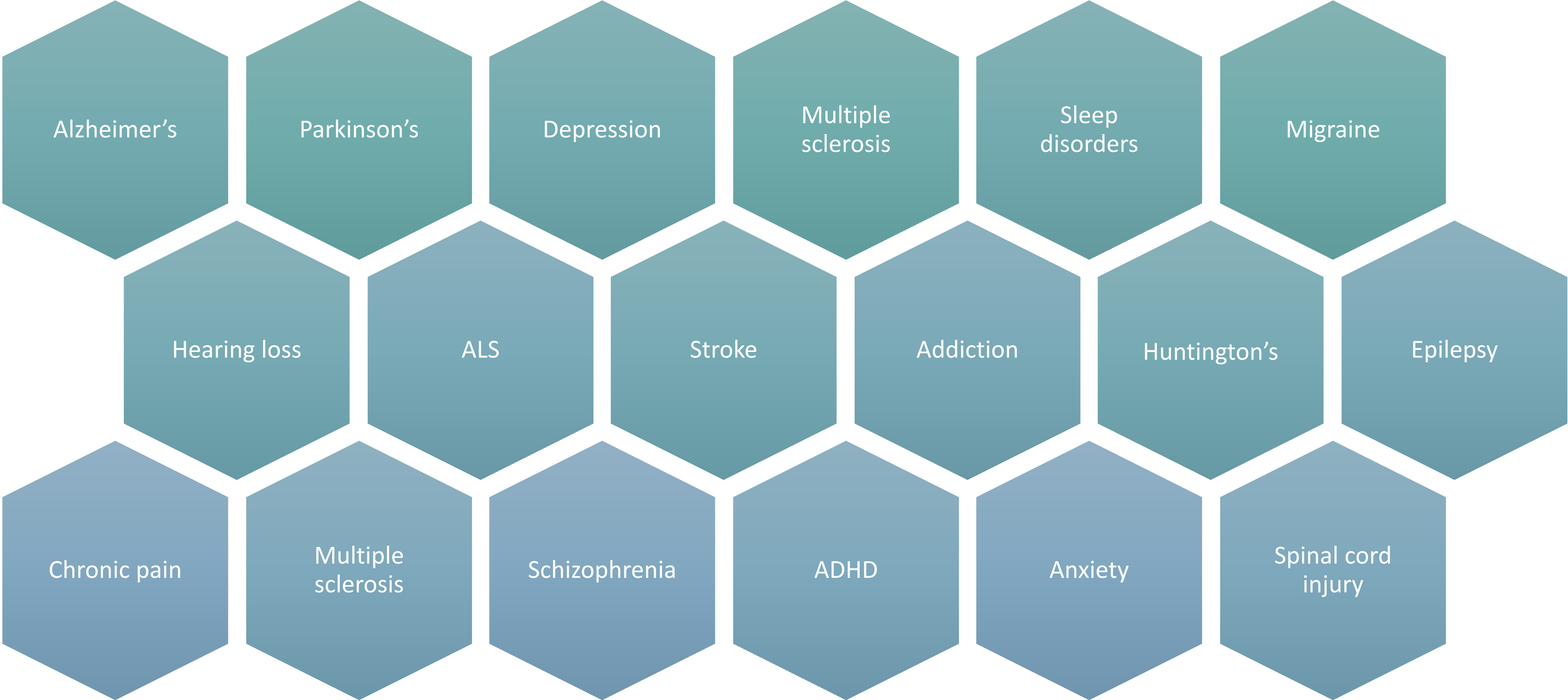
# The Brain Communicates Electrically and Chemically



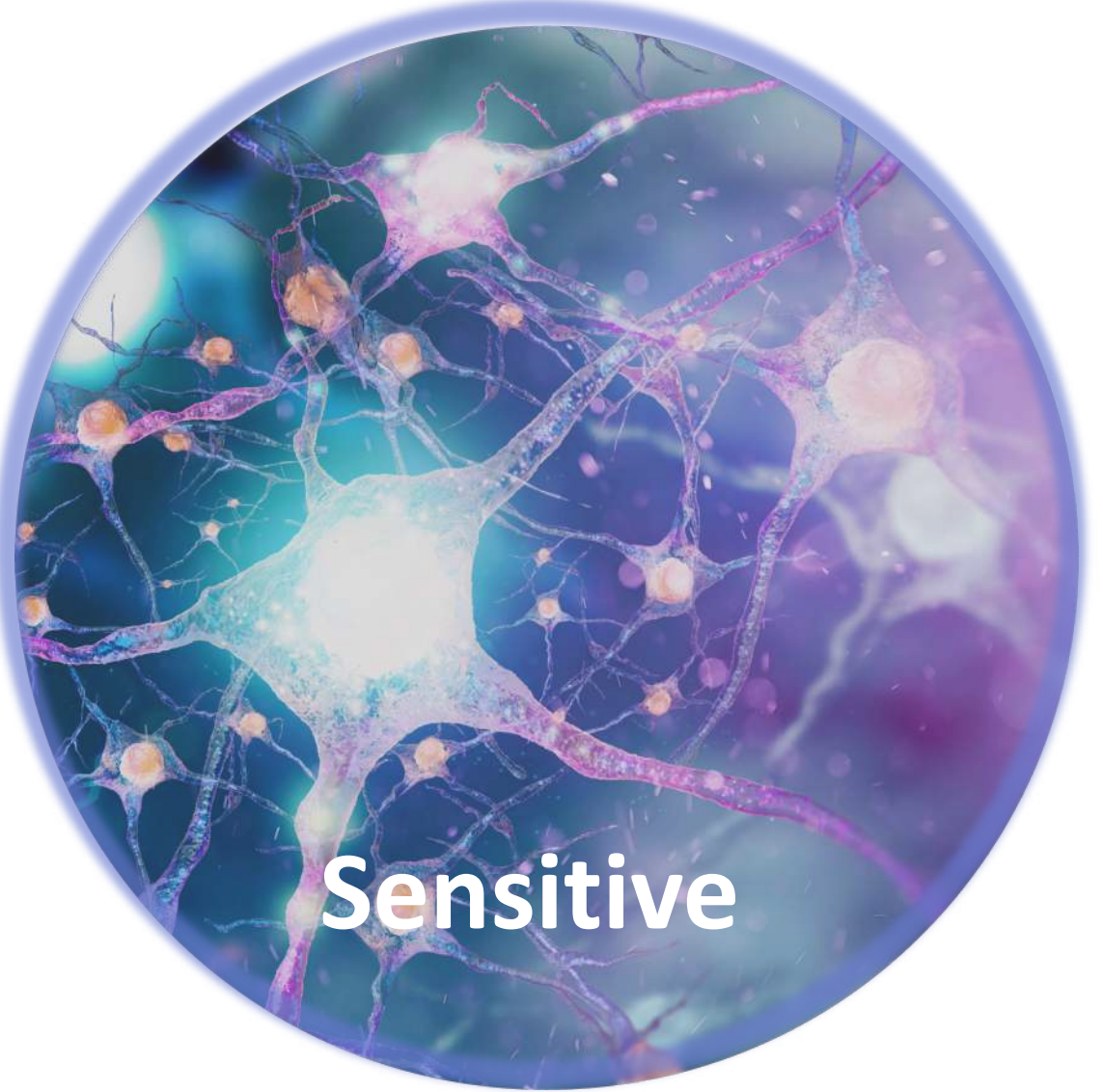
# Differentiating Structurally Similar Chemicals in the Brain



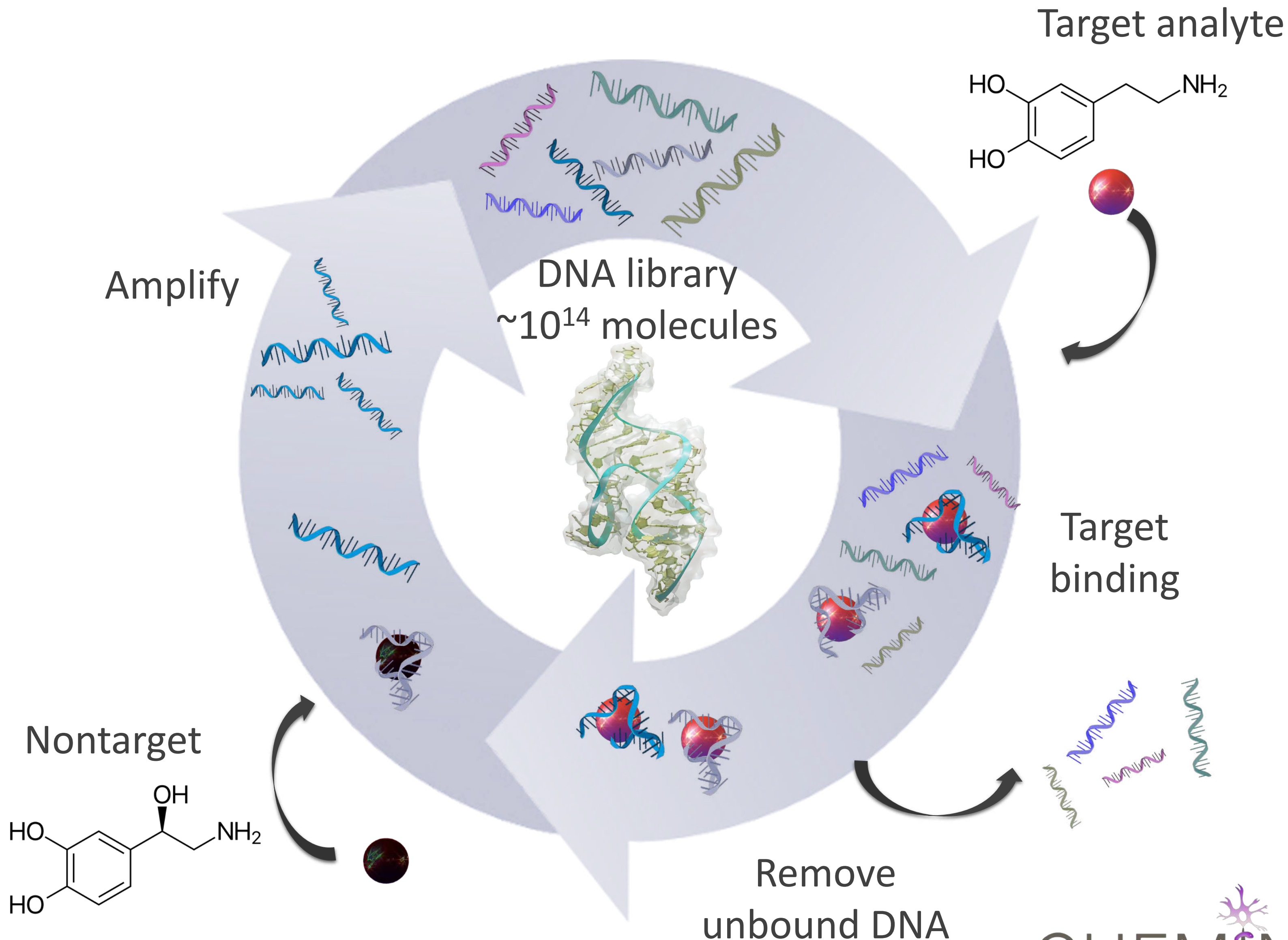
# Altered Levels of Neurotransmitters Linked to Brain Disorders



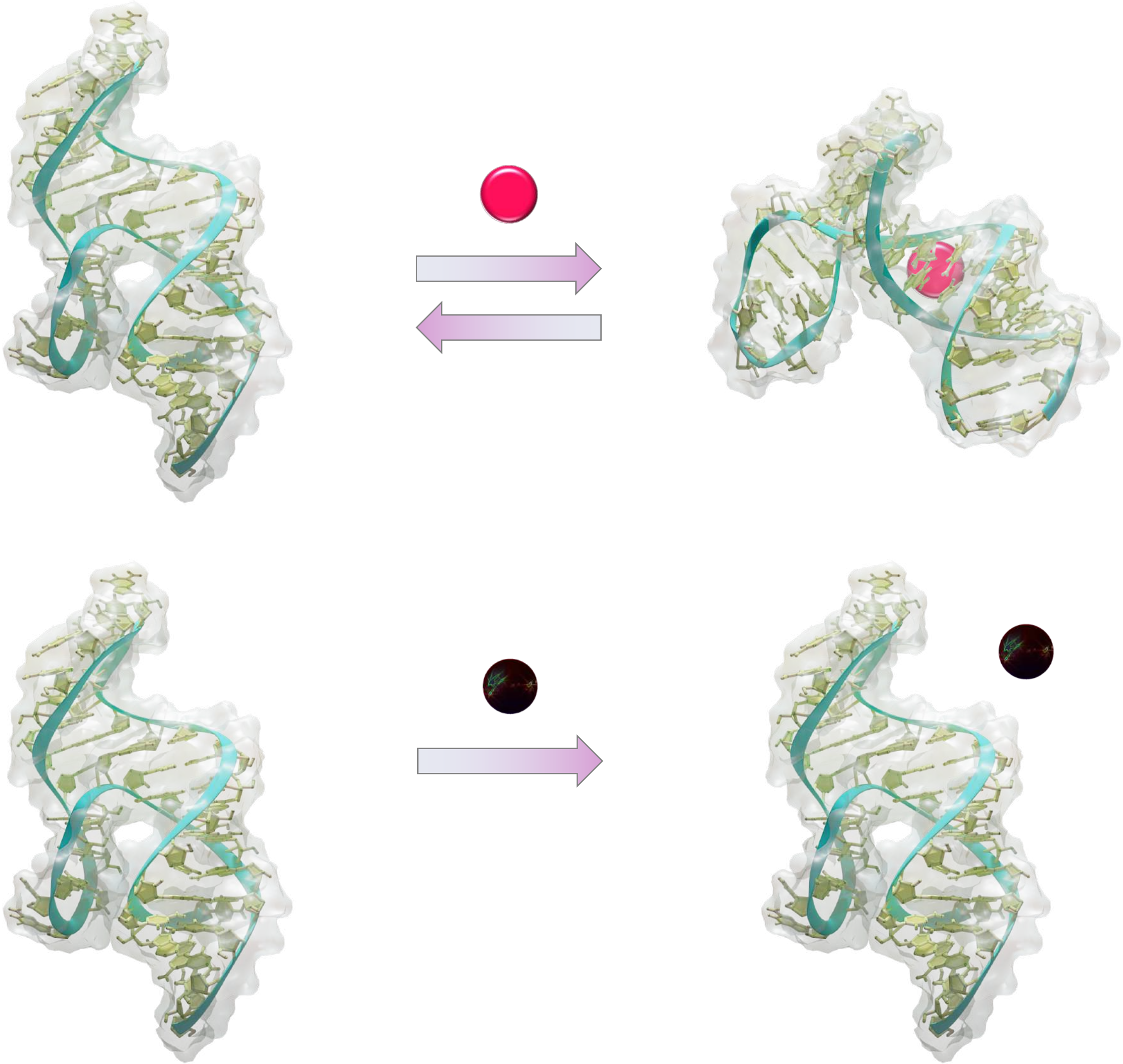
# Tackling the Gaps in Neurochemical Biosensing



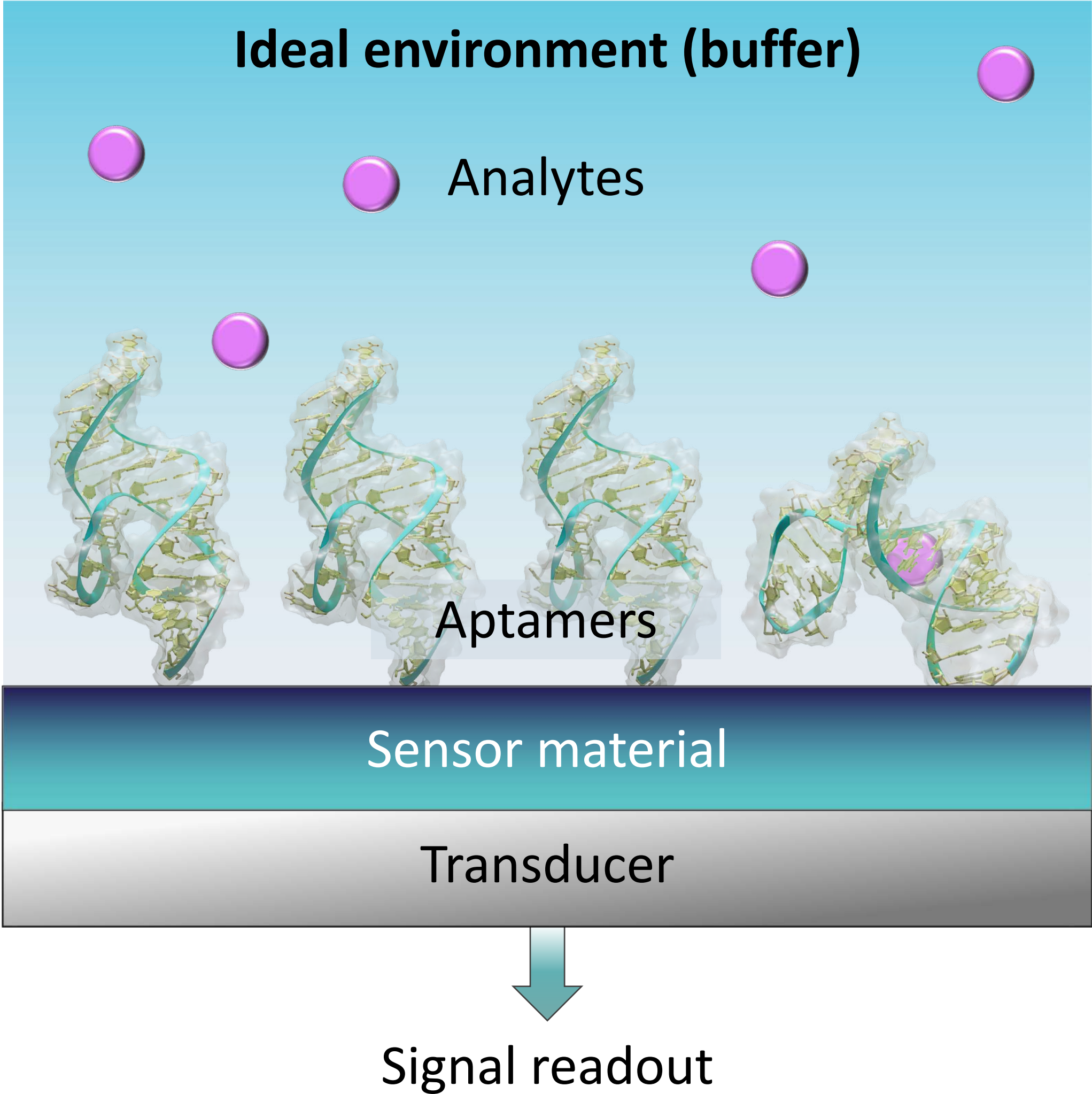
# DNA Aptamers as Selective Reversible Biological Receptors



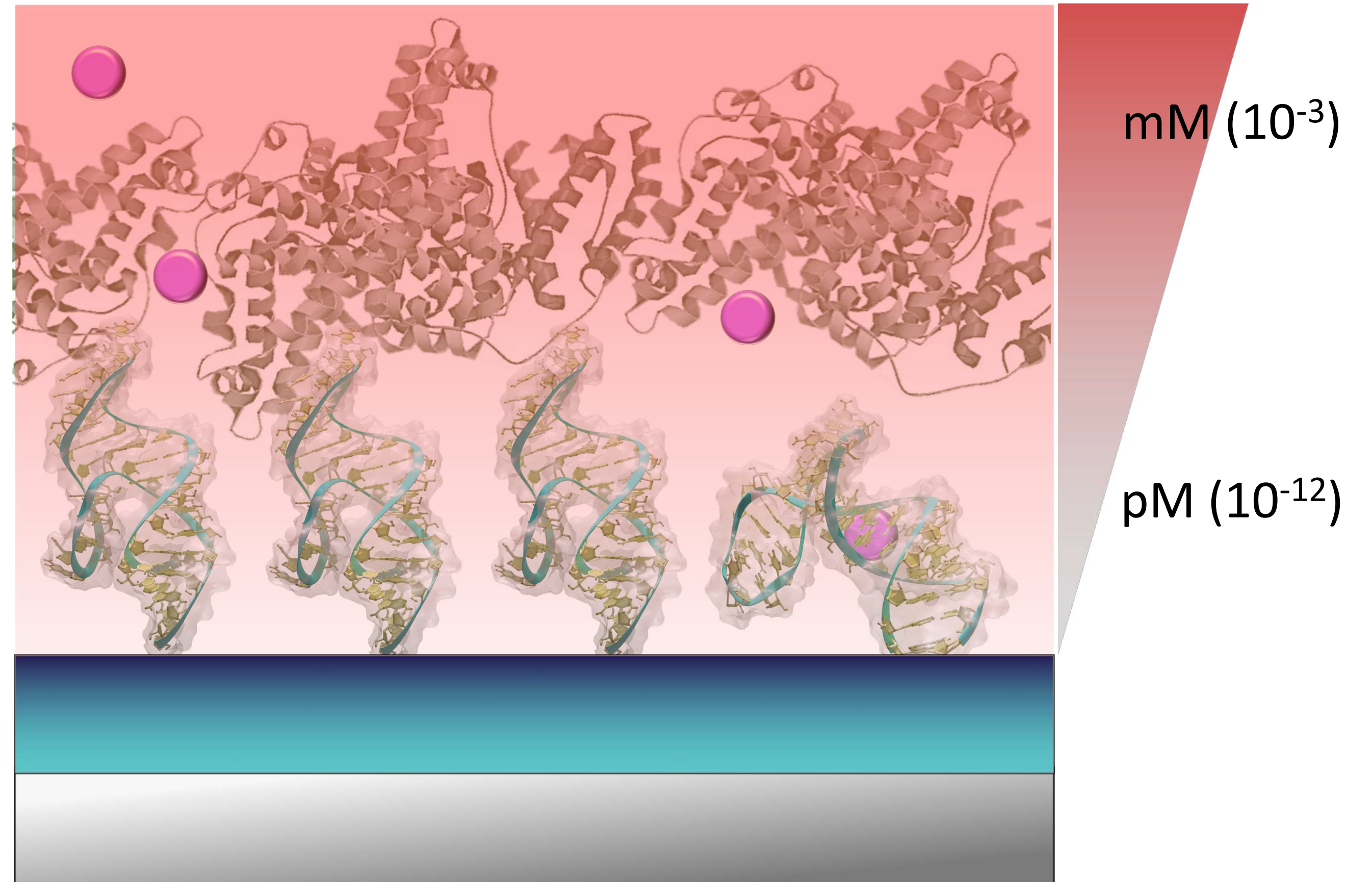
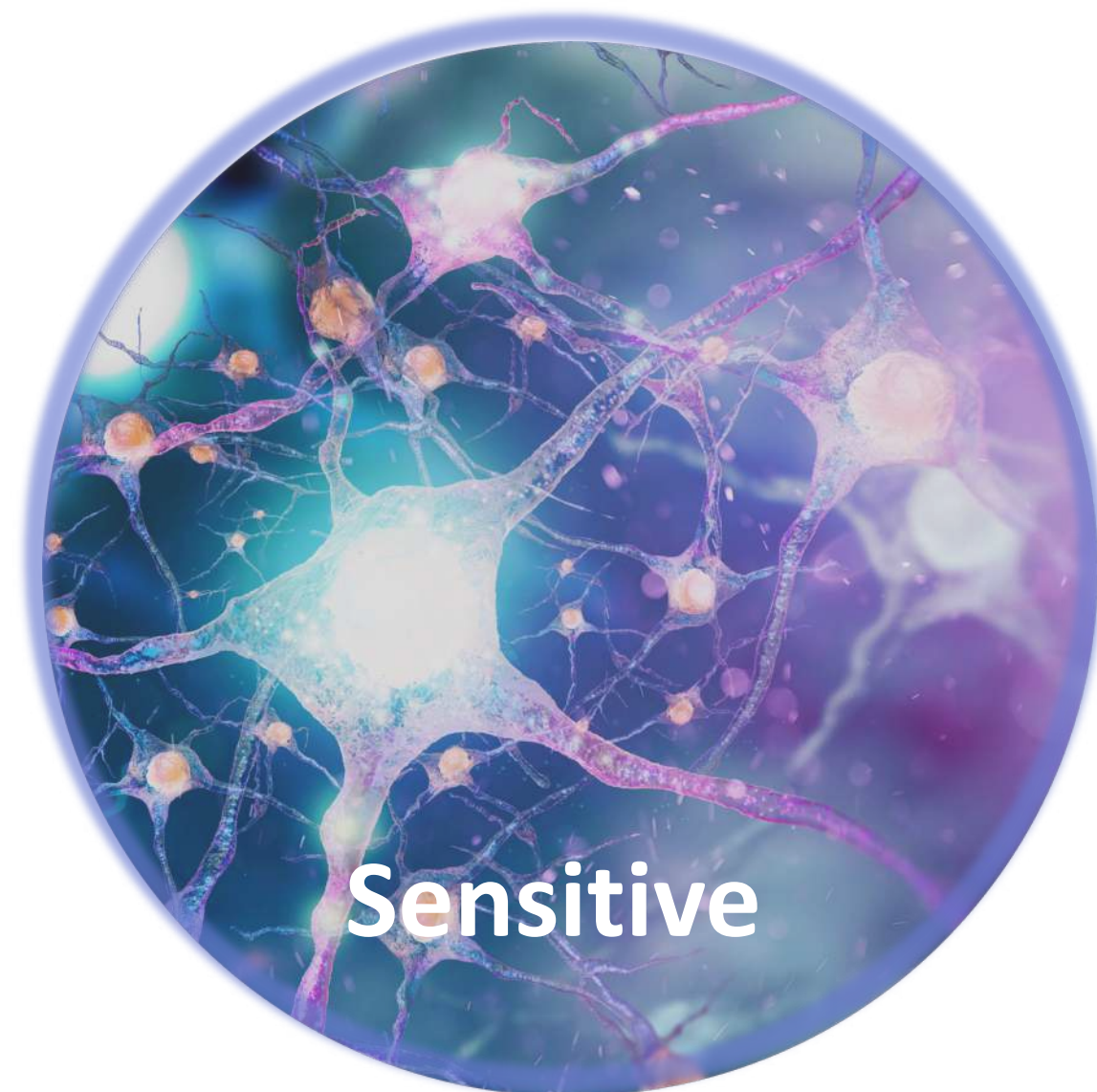
# DNA Aptamers as Selective Reversible Biological Receptors



# Affinity Biosensors as Label-Free Sensitive Platforms

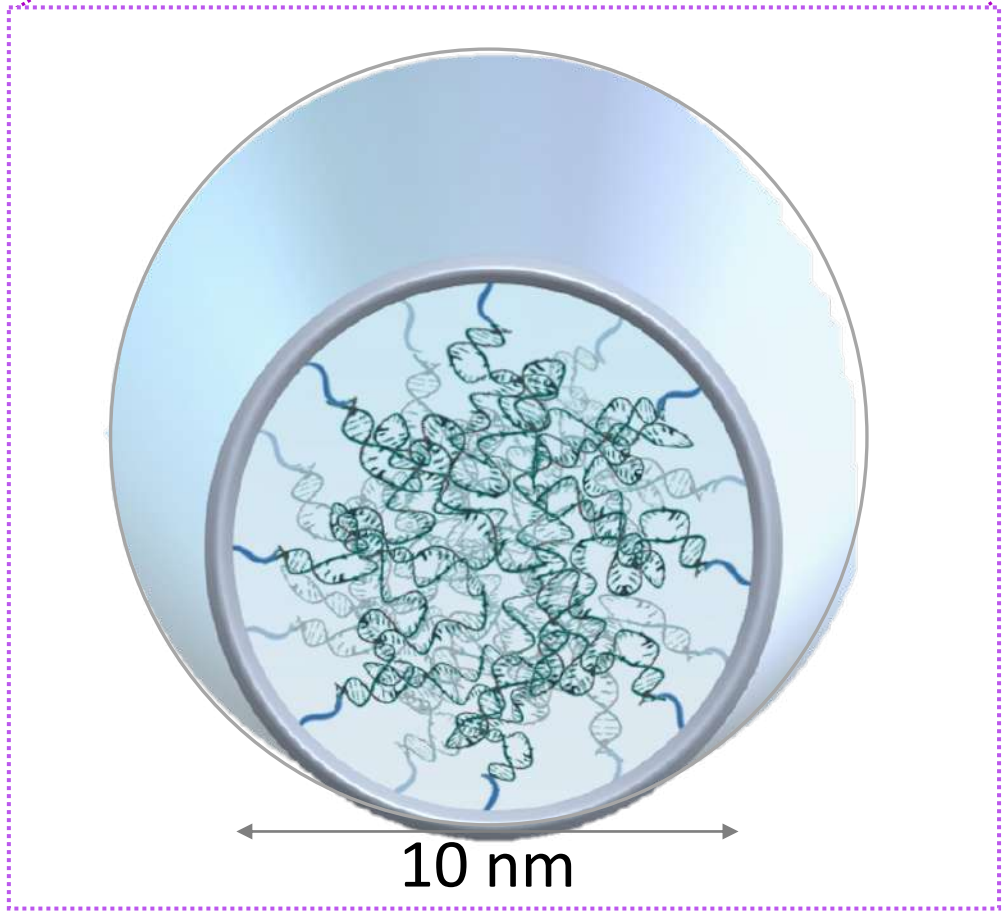
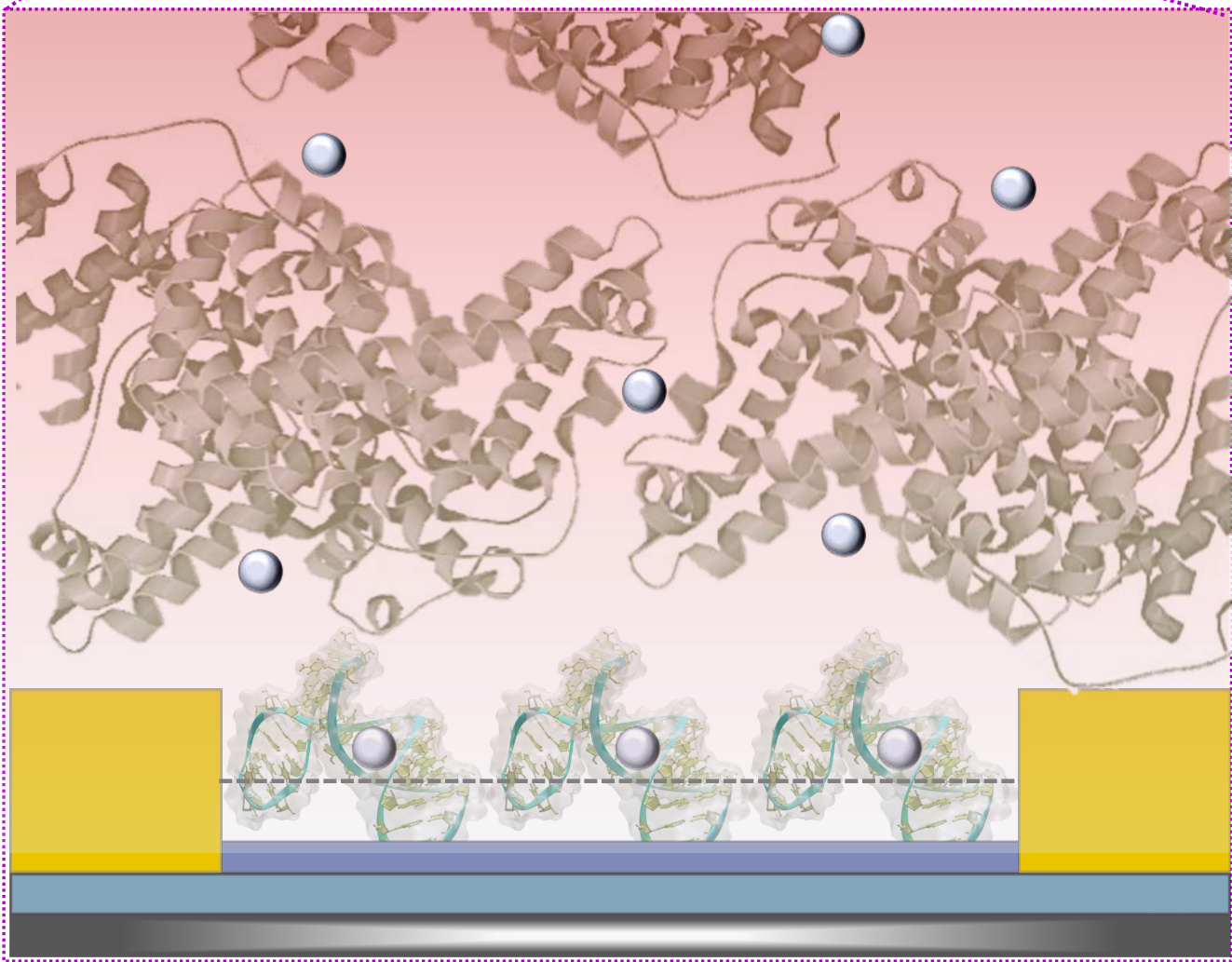
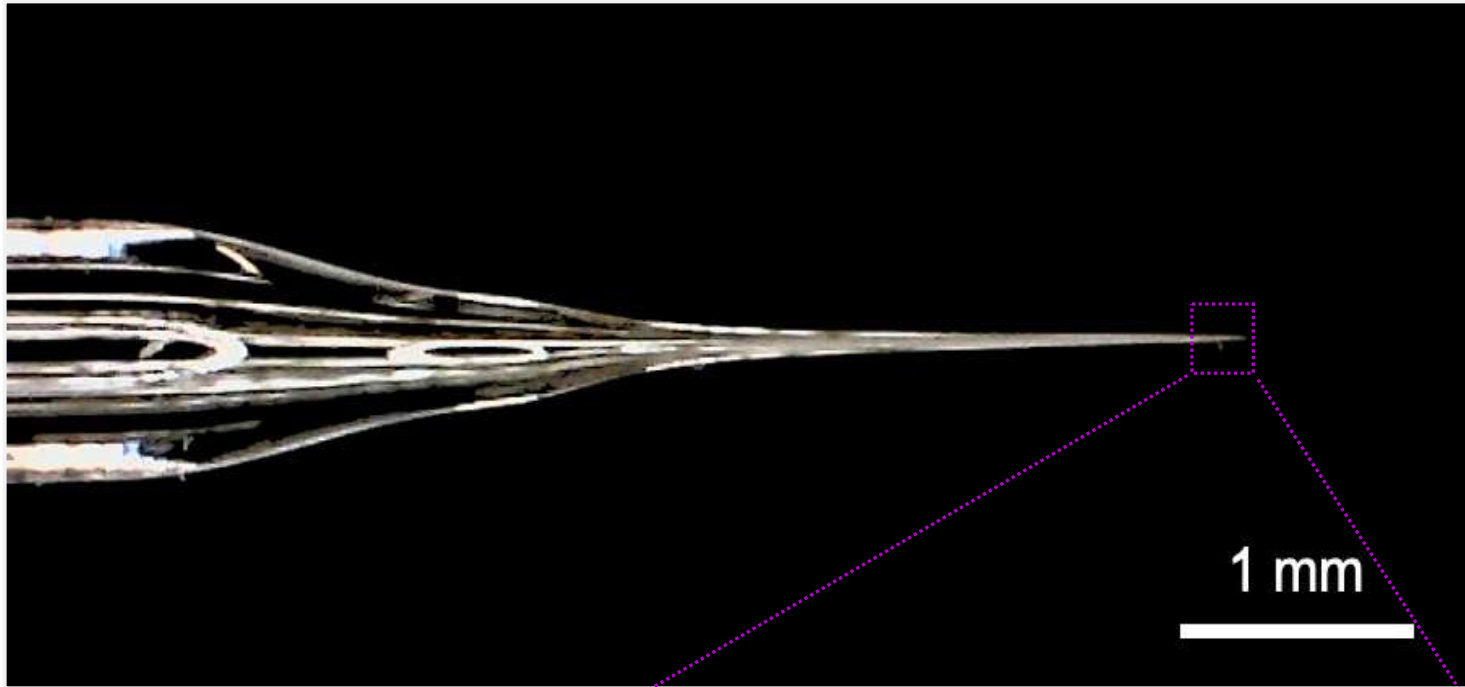
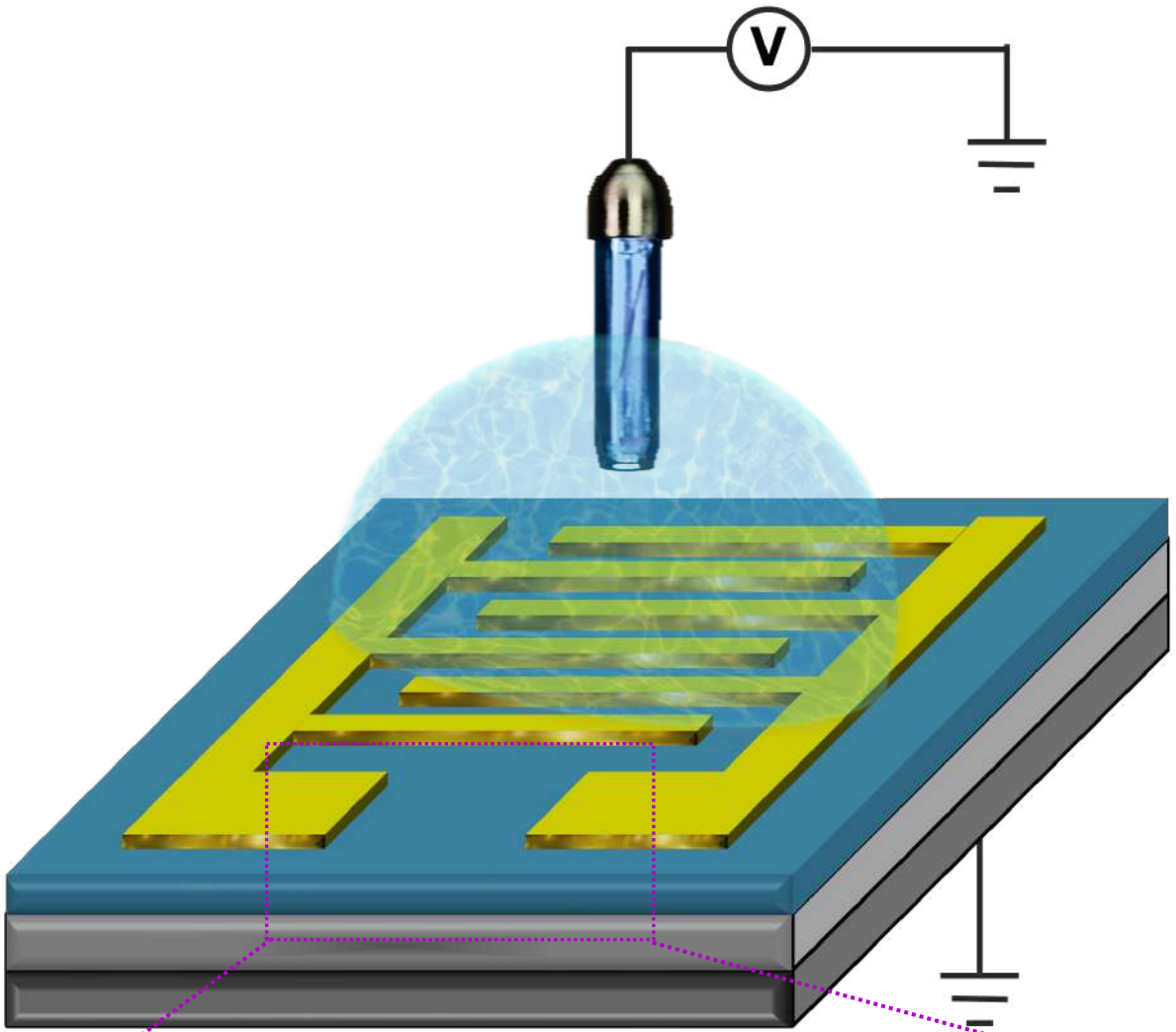


# Affinity Biosensors Suffer from Nonspecific Binding



**Critical bottleneck for biosensing:  
sensitivity to nonspecific binding**

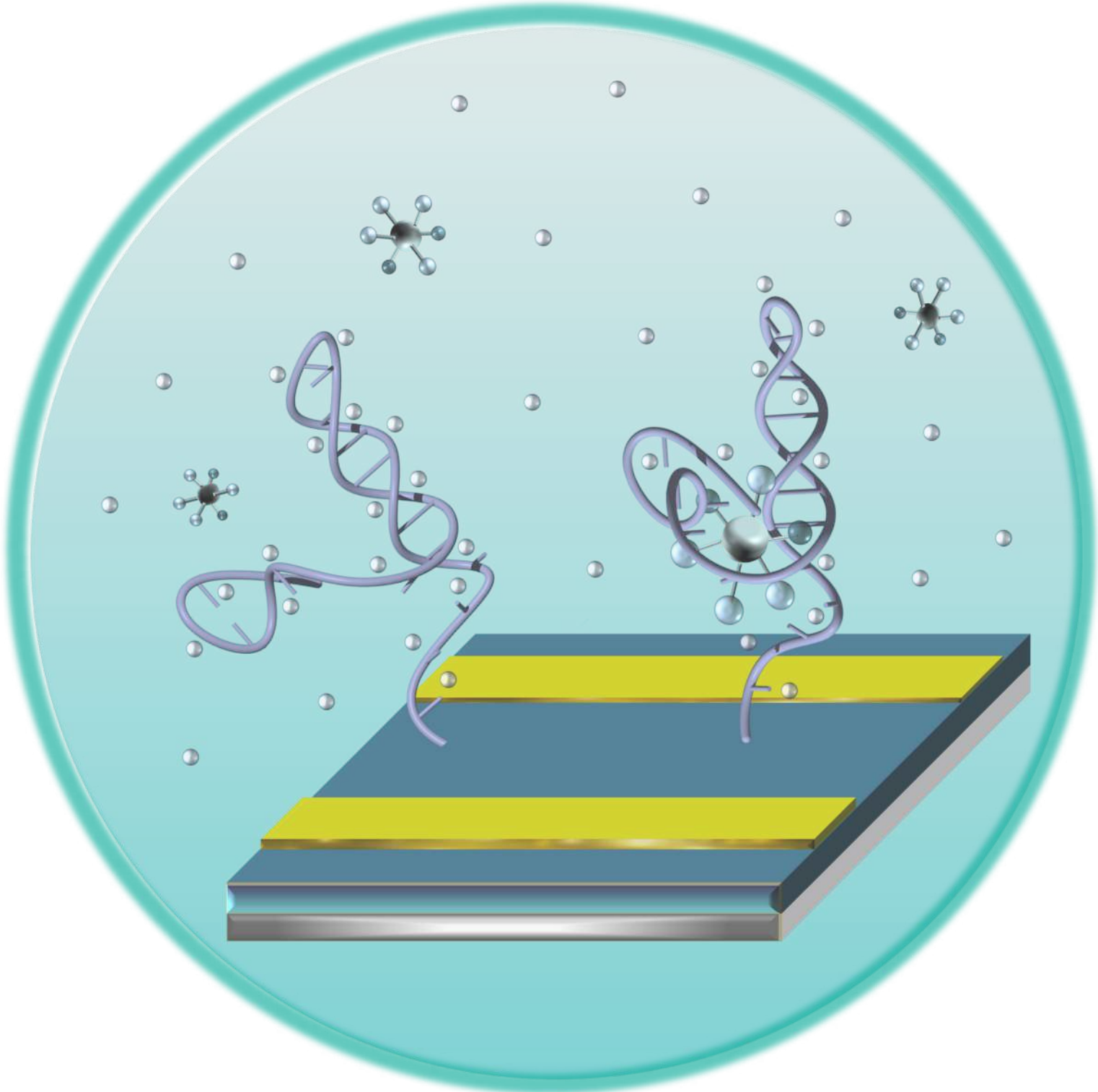
# Overcoming Nonspecific Binding from the Micro to Nanoscale



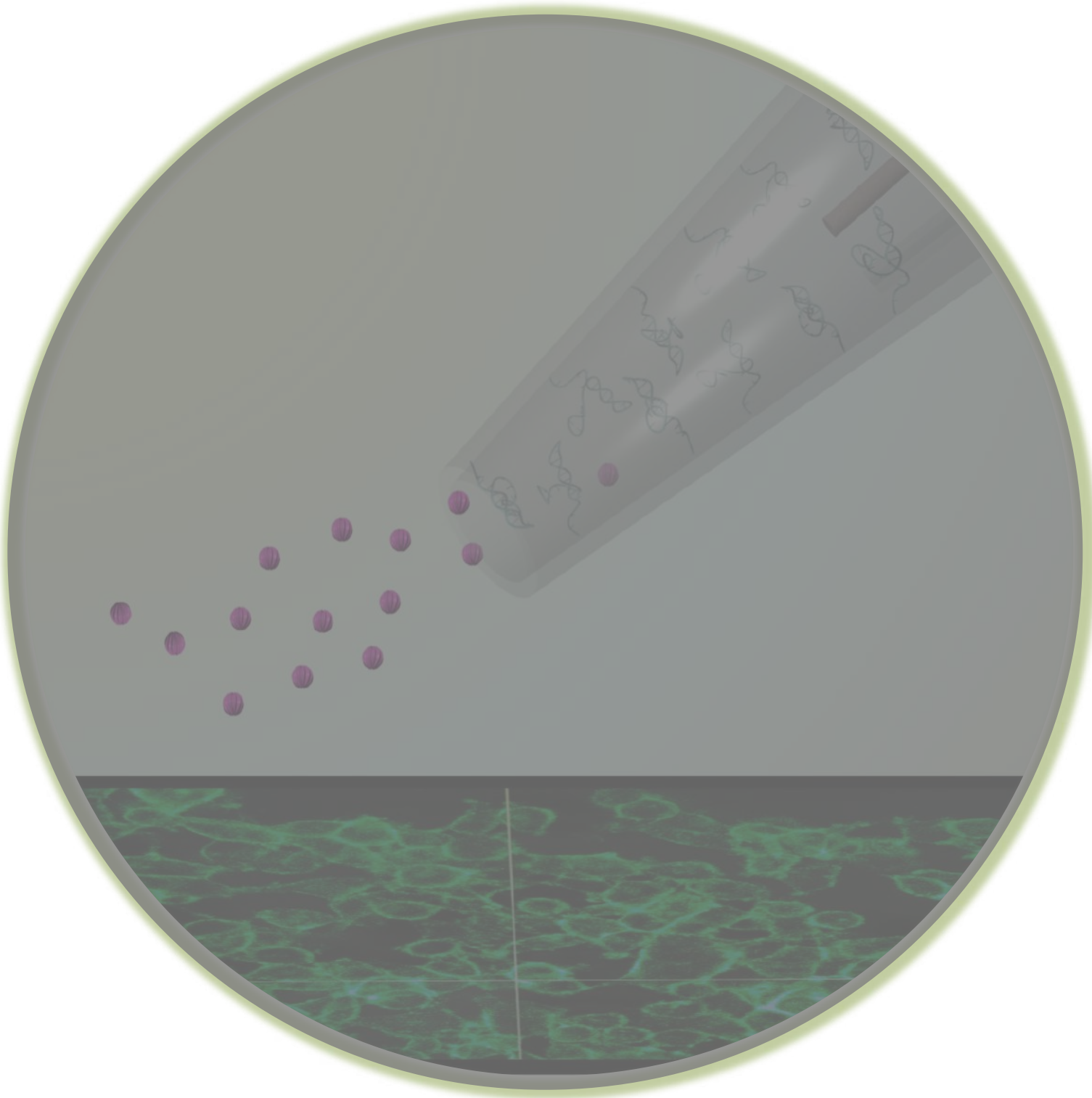
Microscale transistors

Nanoscale pipettes

# Chemical Nanotechnologies for Human Health

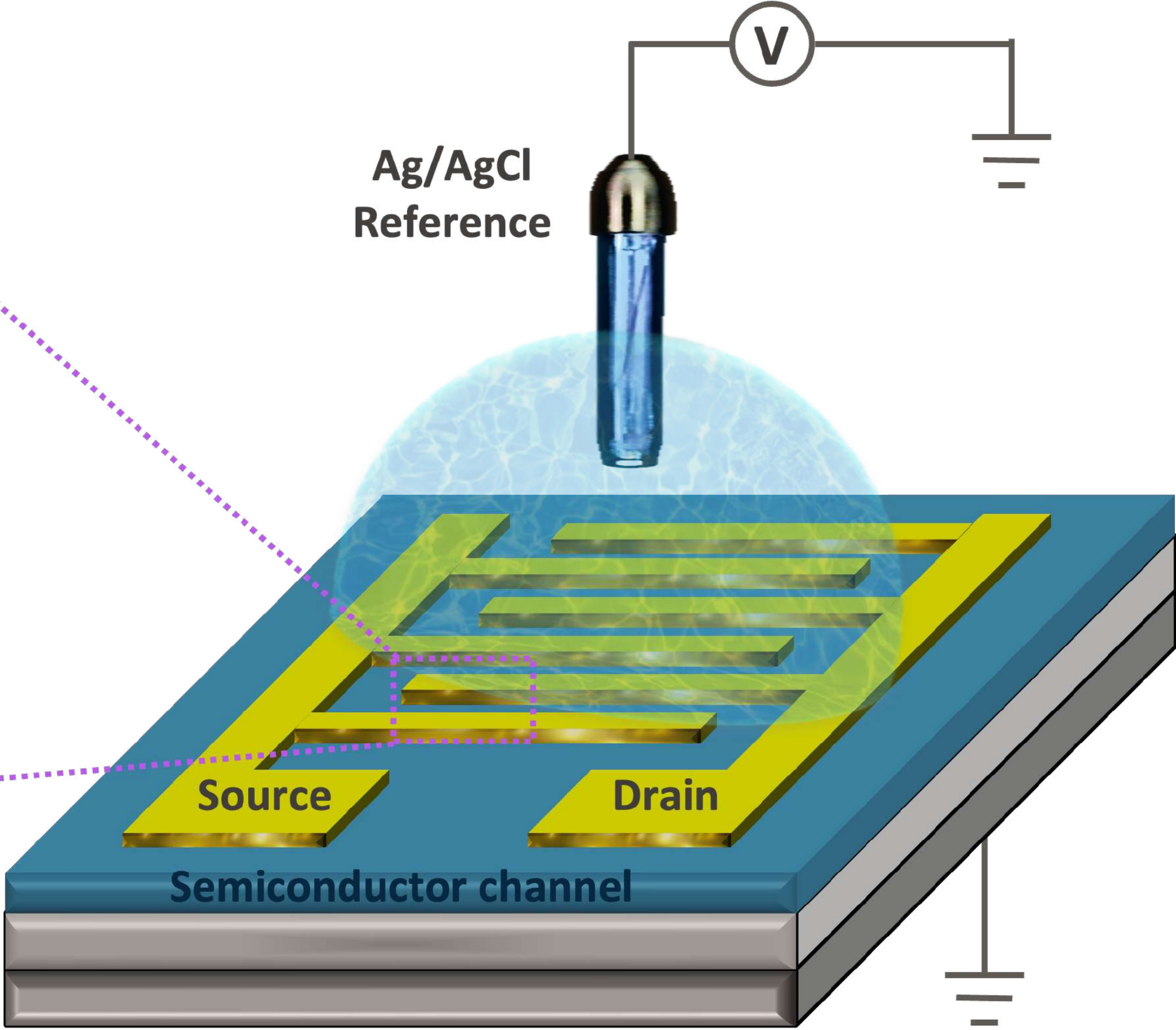
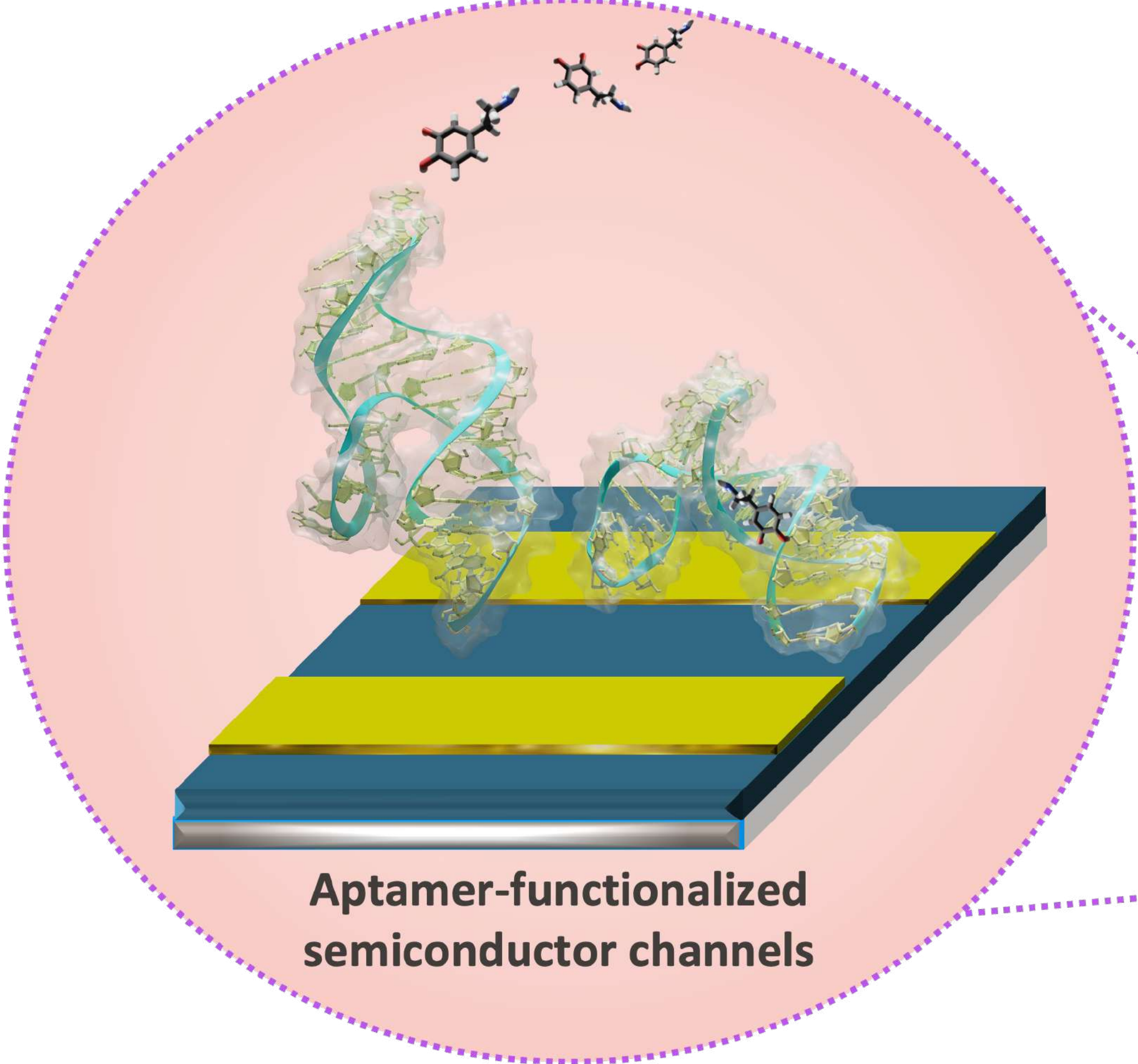


**Aptamer-modified  
field-effect transistors  
(microscale)**

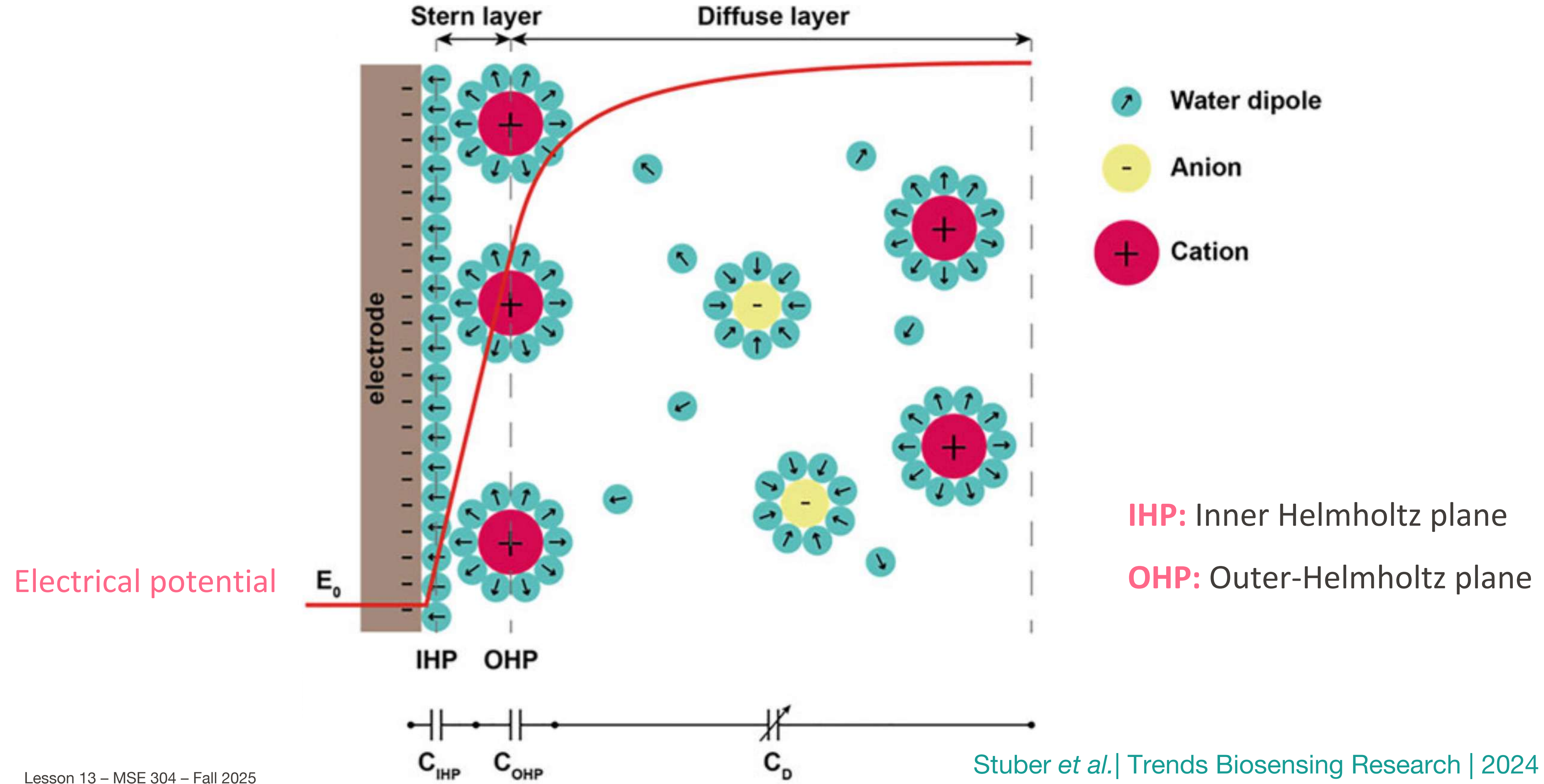


**Aptamer-modified  
nanopipettes  
(nanoscale)**

# Using DNA Aptamers for Biosensing on Semiconductors



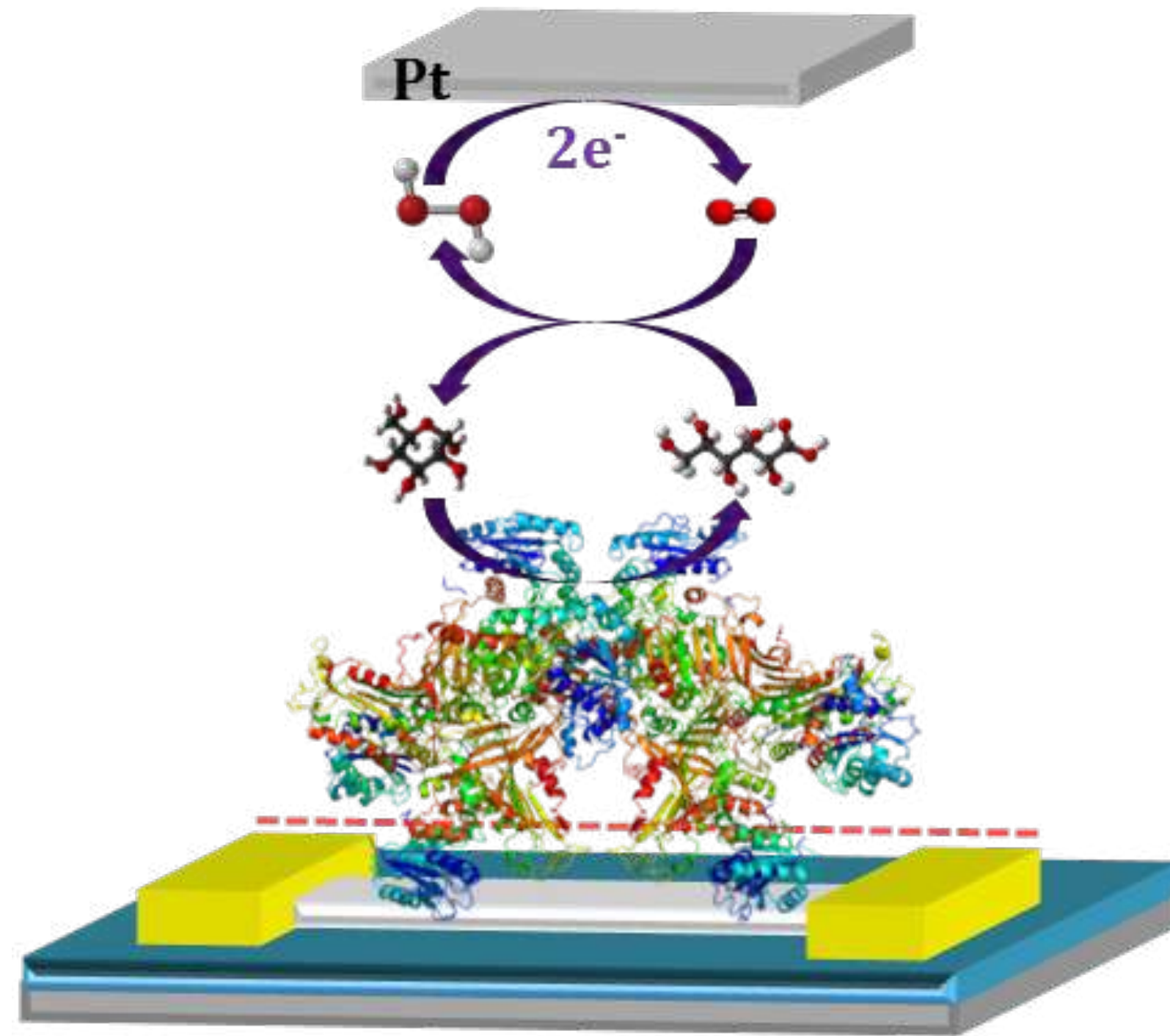
# Electrical Double Layer at Electrode-Liquid Interface



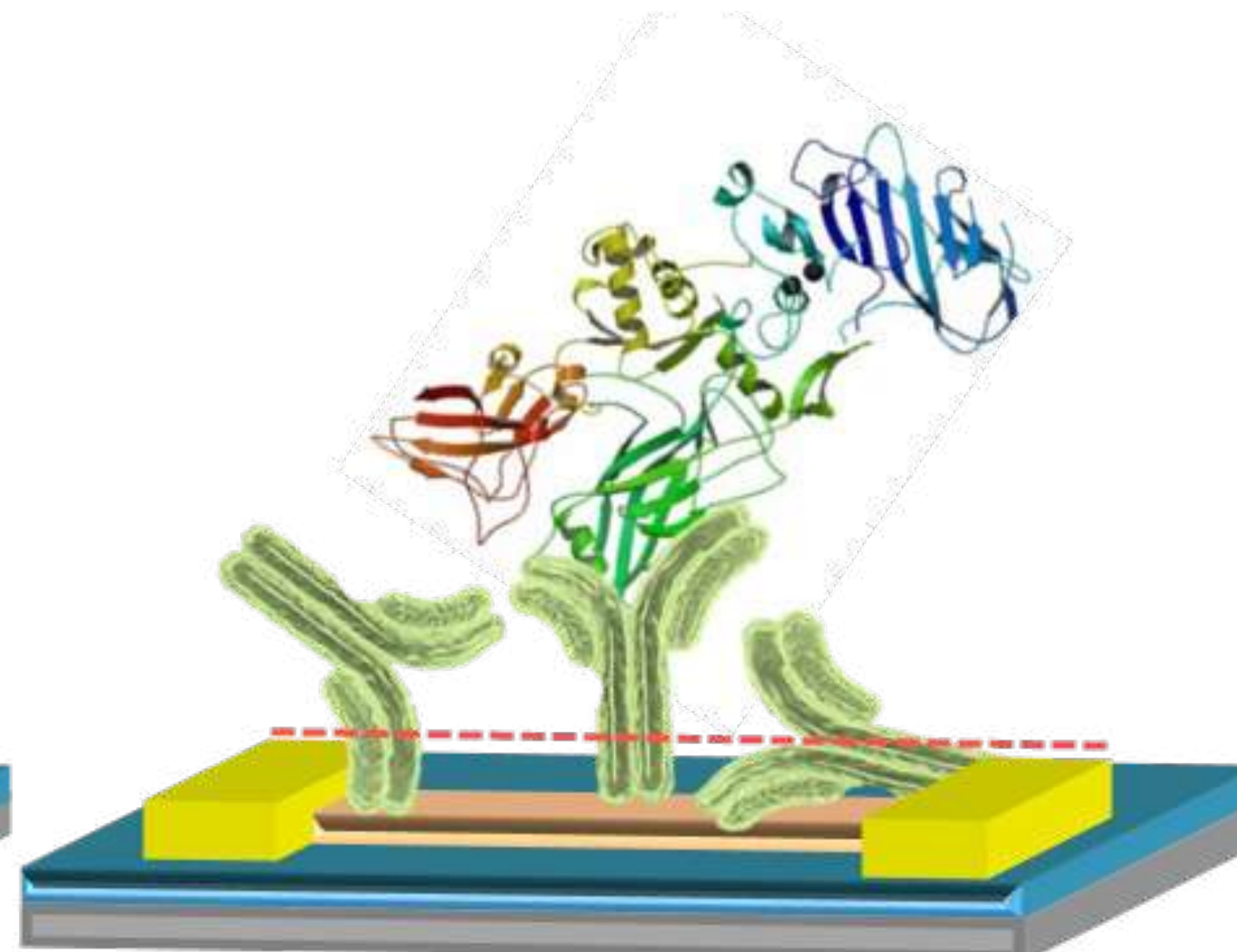
# The Debye Screening Length Complicates Sensitive Detection

$$\lambda_D = \sqrt{\frac{\epsilon_r \epsilon_0 k_B T}{2N_A e^2 I}}$$

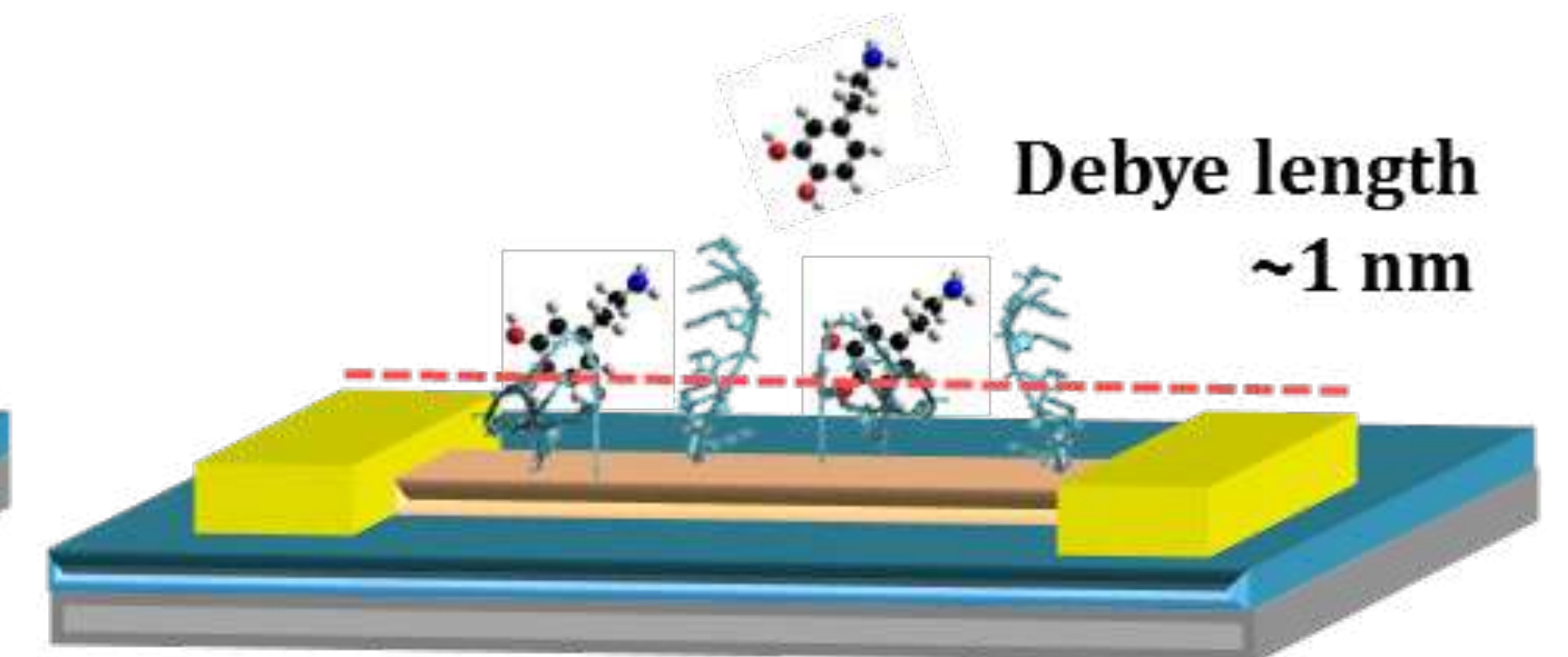
Buffer strength	Ionic strength ( $I$ )	Debye length ( $\lambda_D$ )
1.0 x	163 mM	0.75 nm
0.1 x	16.3 mM	2.38 nm
0.01 x	1.63 mM	7.53 nm



Enzyme transistors



Antibody transistors

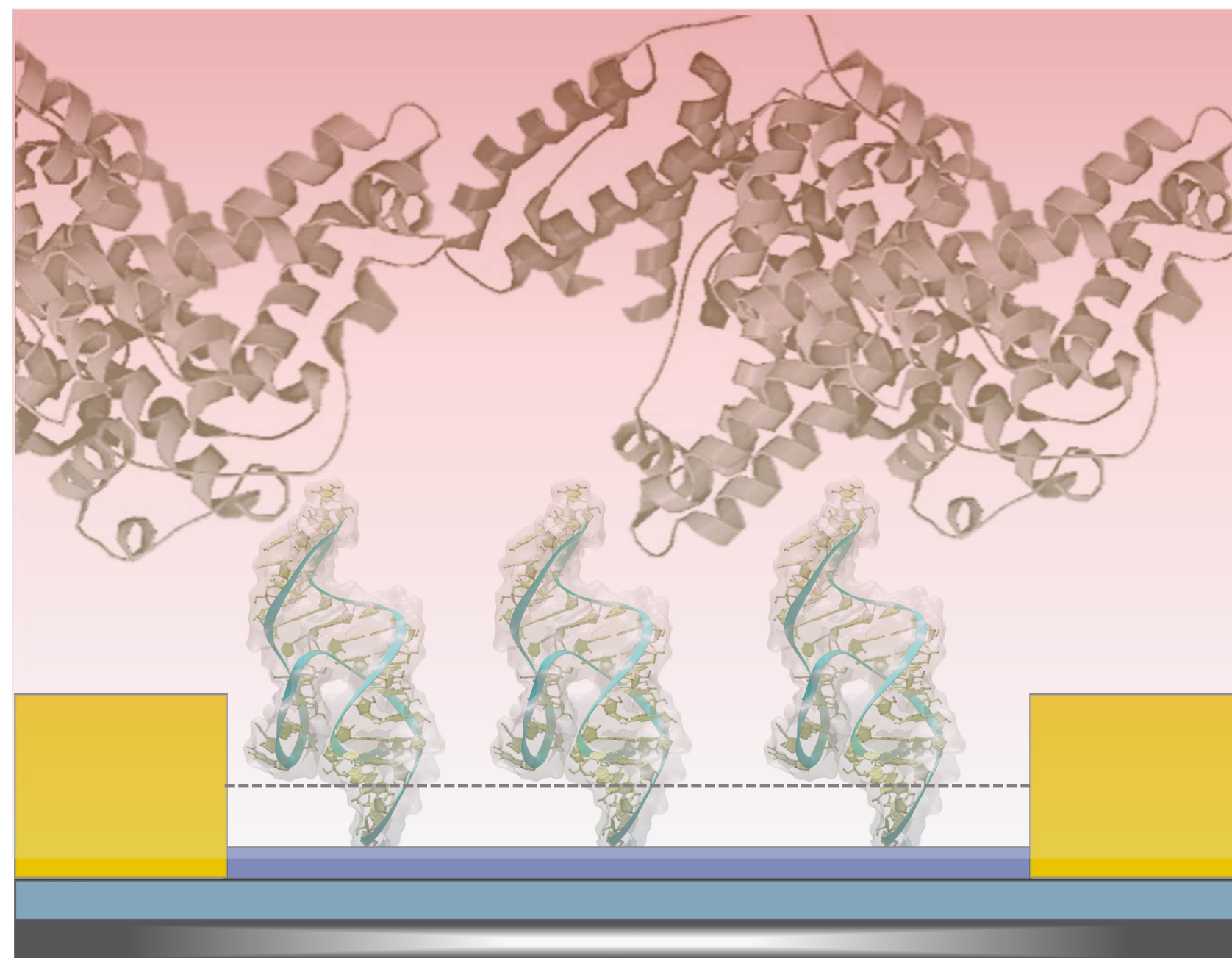


Aptamer transistors

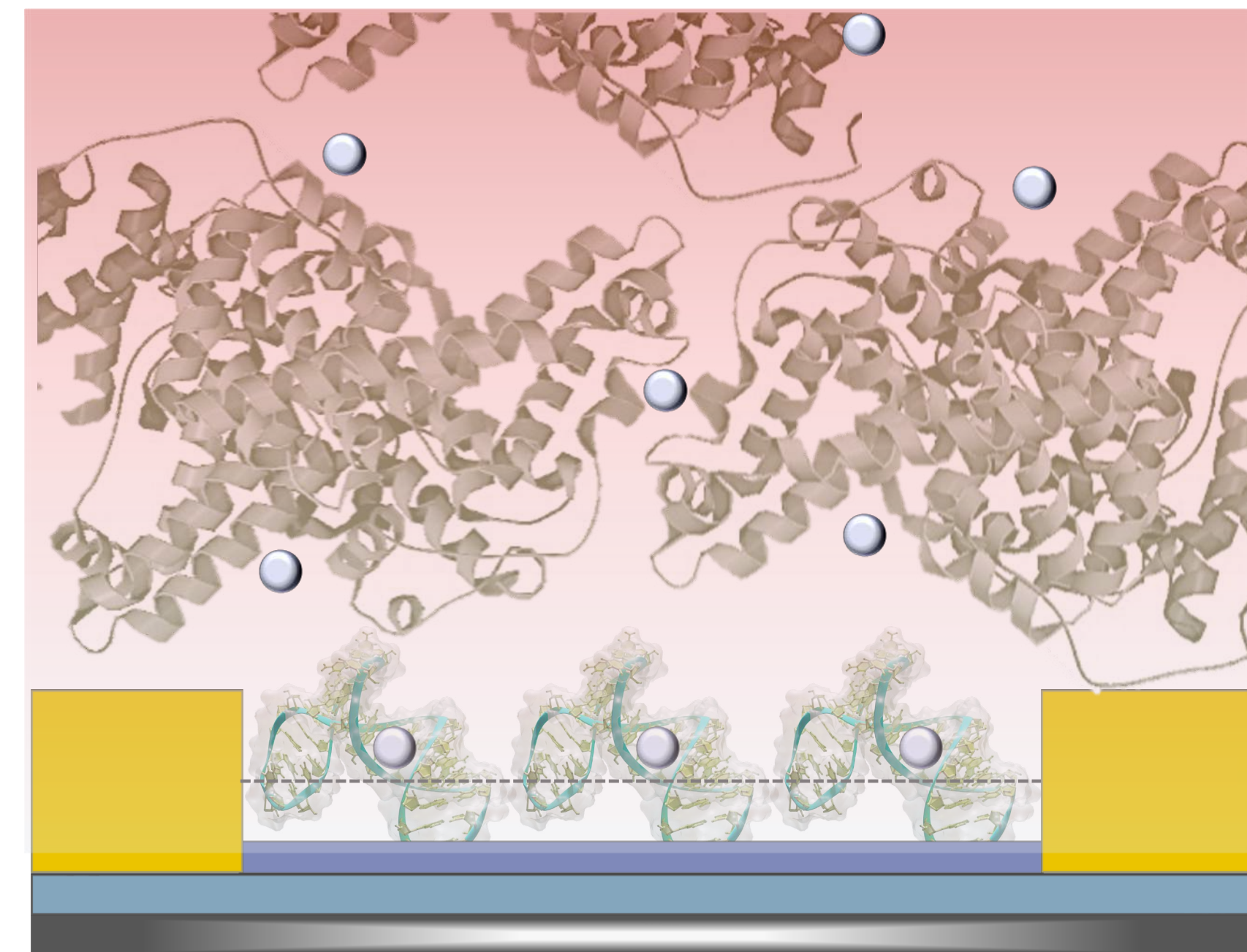
# The Debye Screening Length Complicates Sensitive Detection

$$\lambda_D = \sqrt{\frac{\epsilon_r \epsilon_0 k_B T}{2N_A e^2 I}}$$

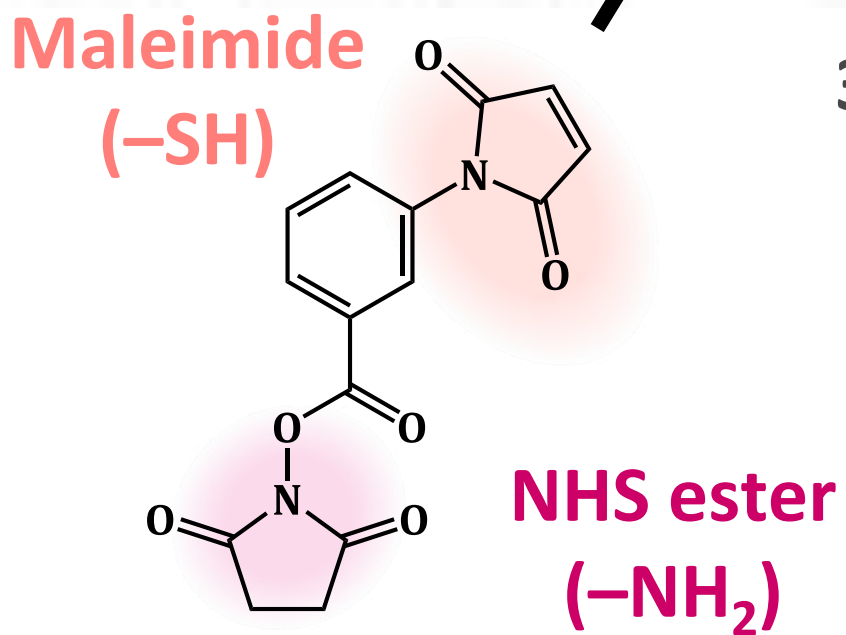
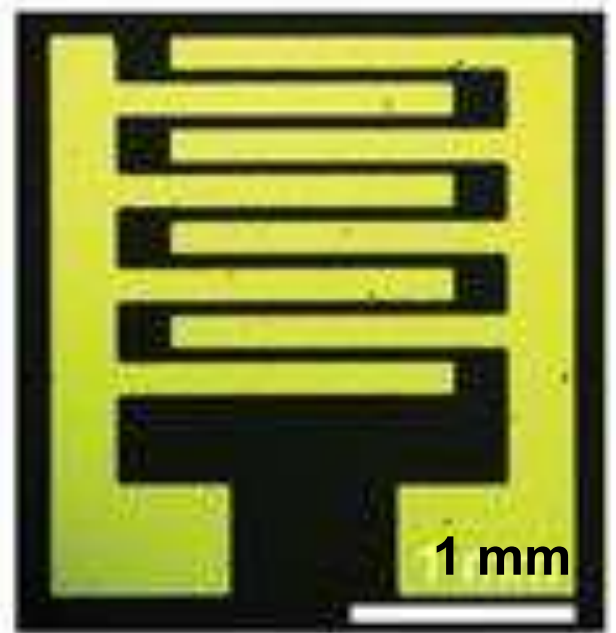
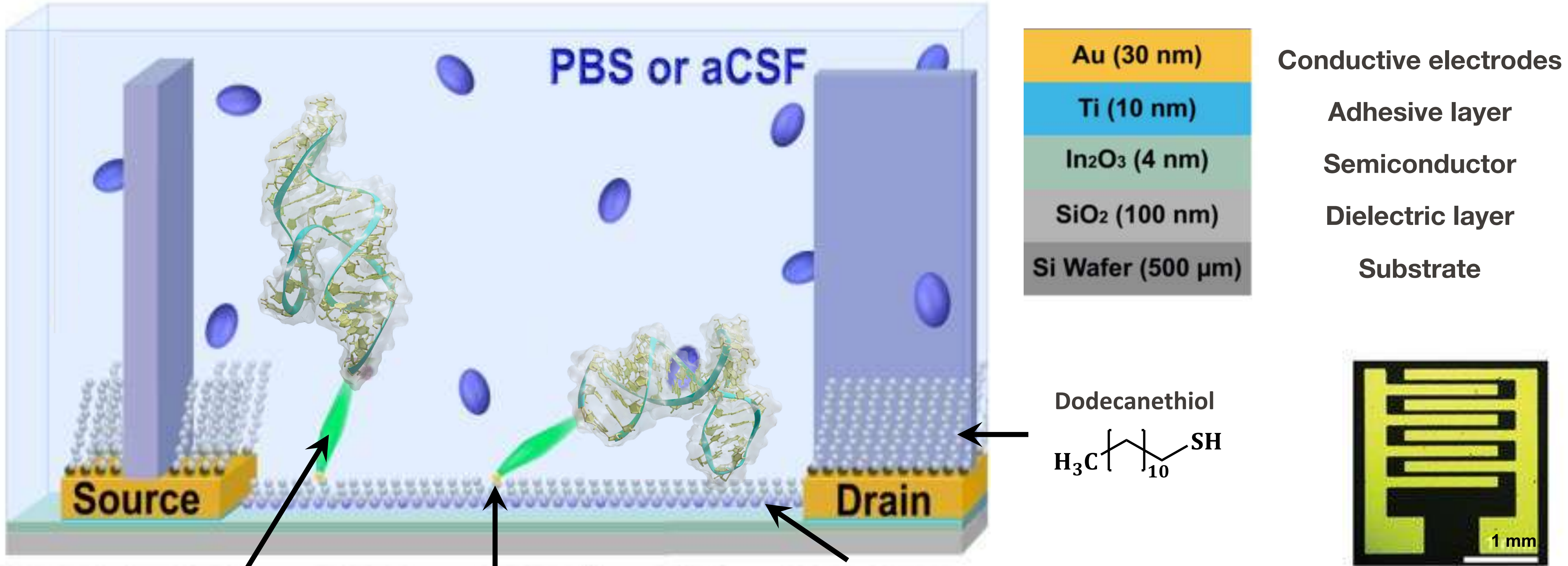
Buffer strength	Ionic strength ( $I$ )	Debye length ( $\lambda_D$ )
1.0 x	163 mM	0.75 nm
0.1 x	16.3 mM	2.38 nm
0.01 x	1.63 mM	7.53 nm



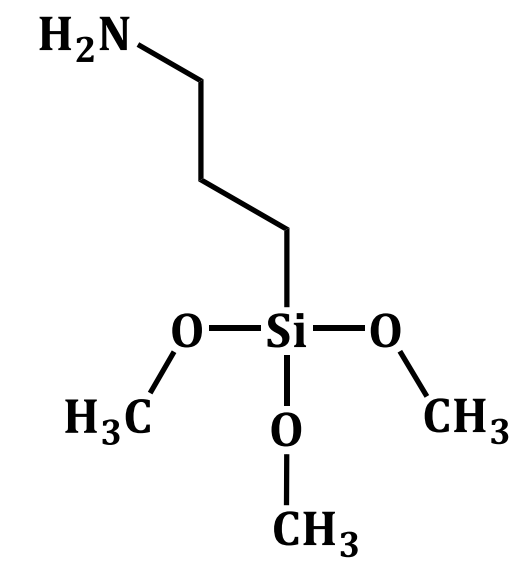
Analyte  
 $\lambda_D < 1 \text{ nm}$



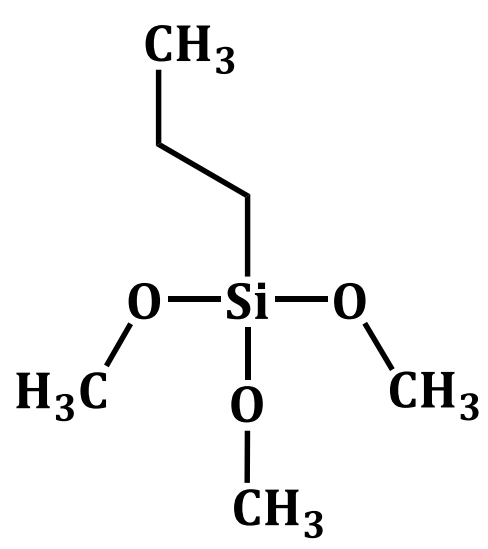
# Various Surface Chemistries Enable Biosensor Configuration



**3-Aminopropyltrimethoxysilane**



**Propyltrimethoxysilane**



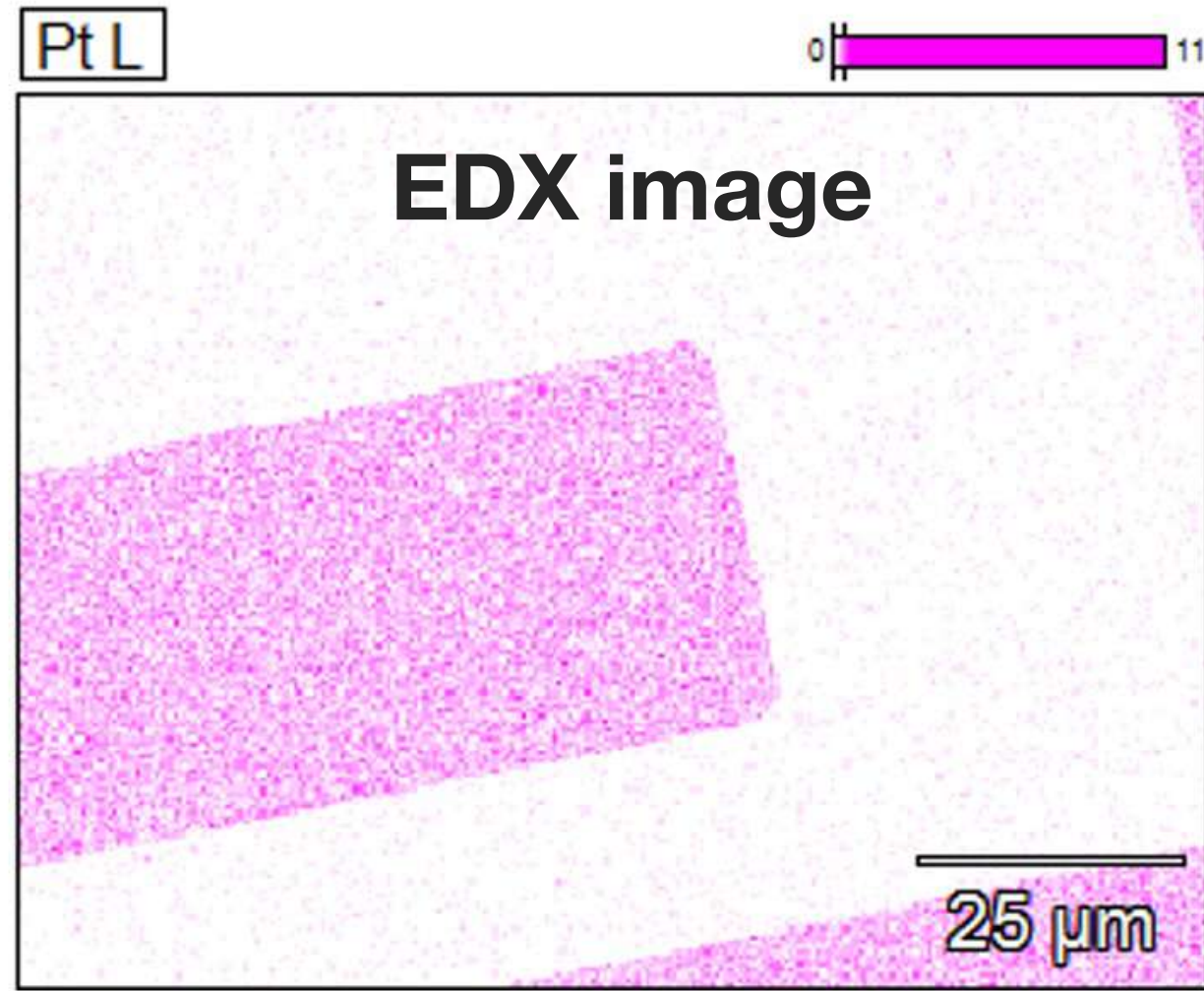
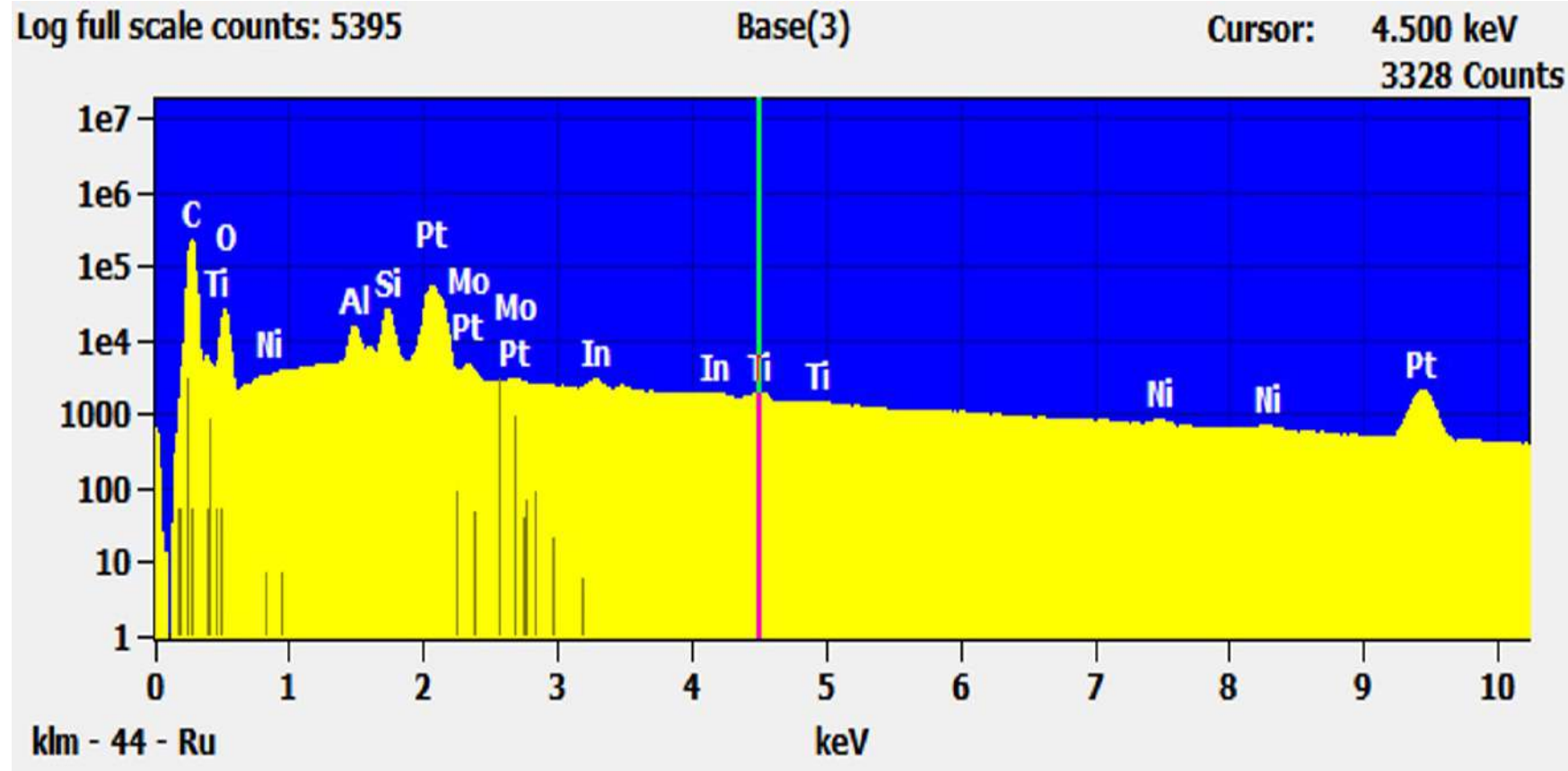
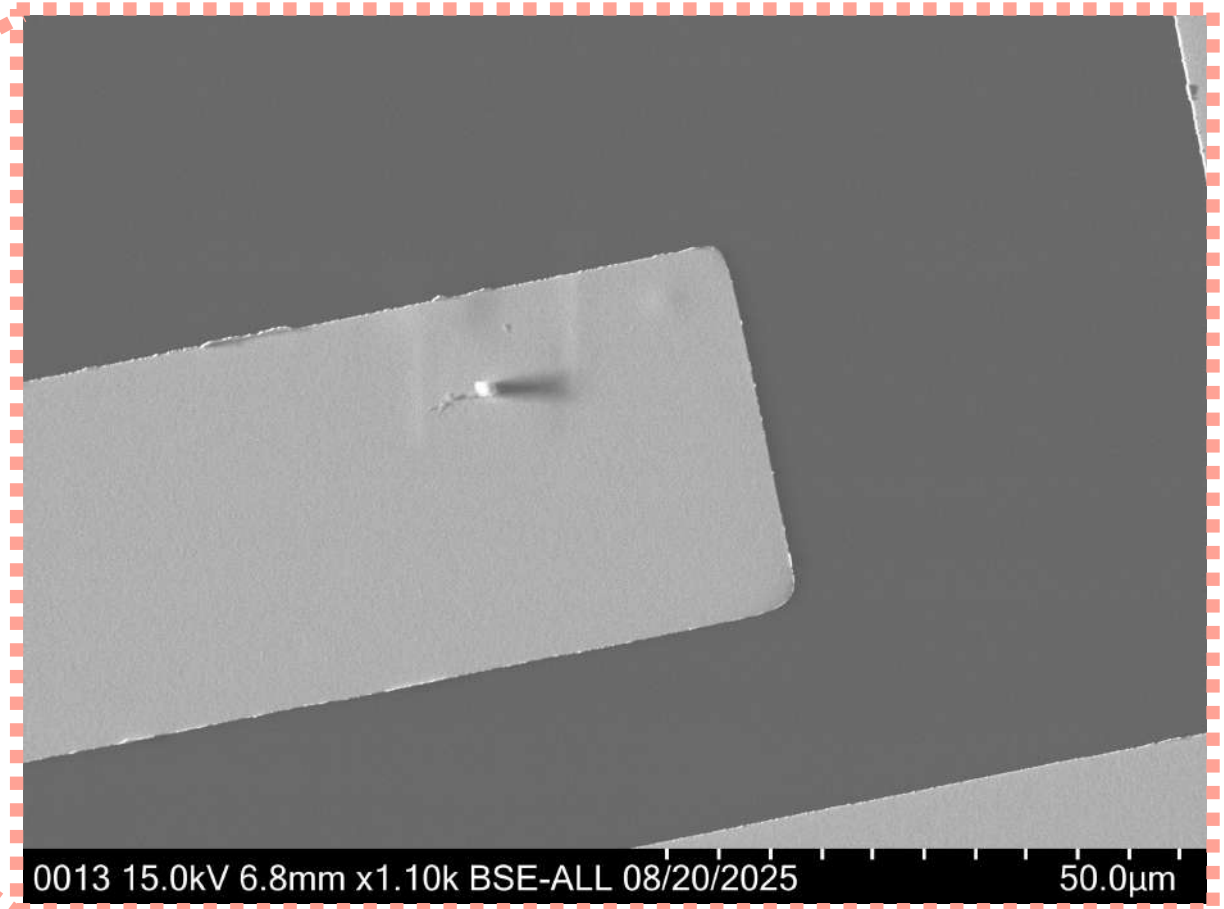
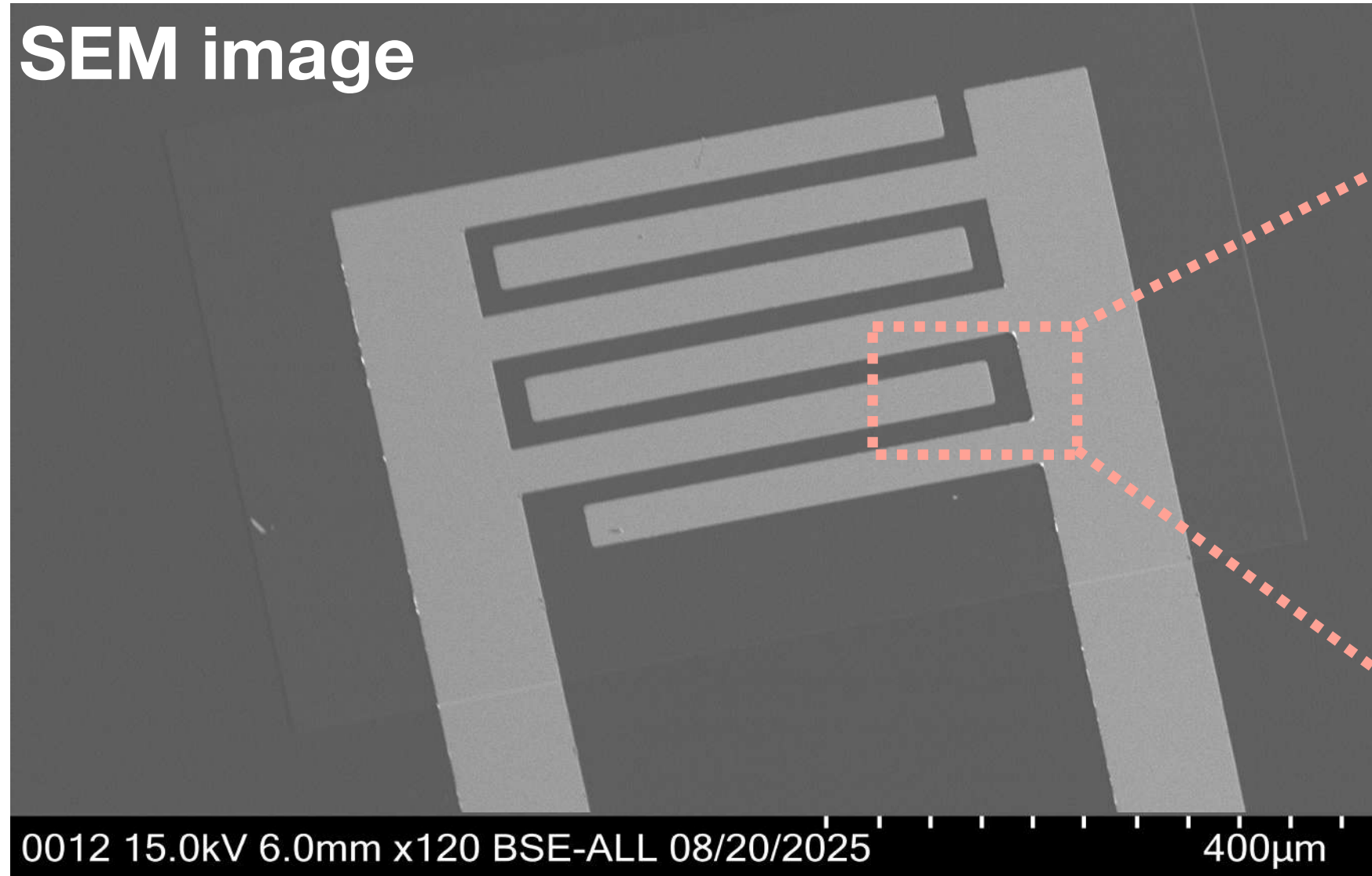
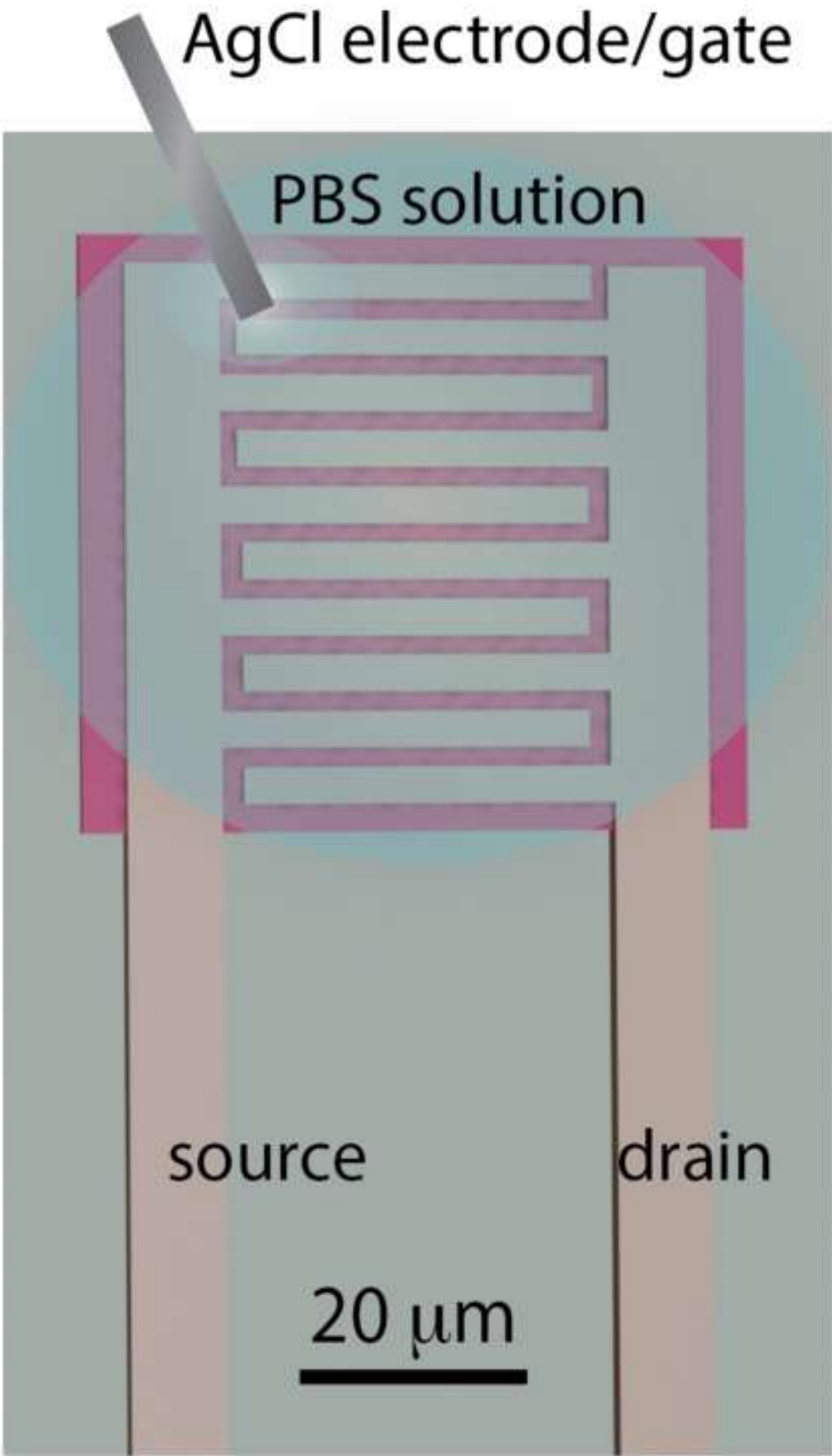
Nakatsuka et al. | Science | 2018



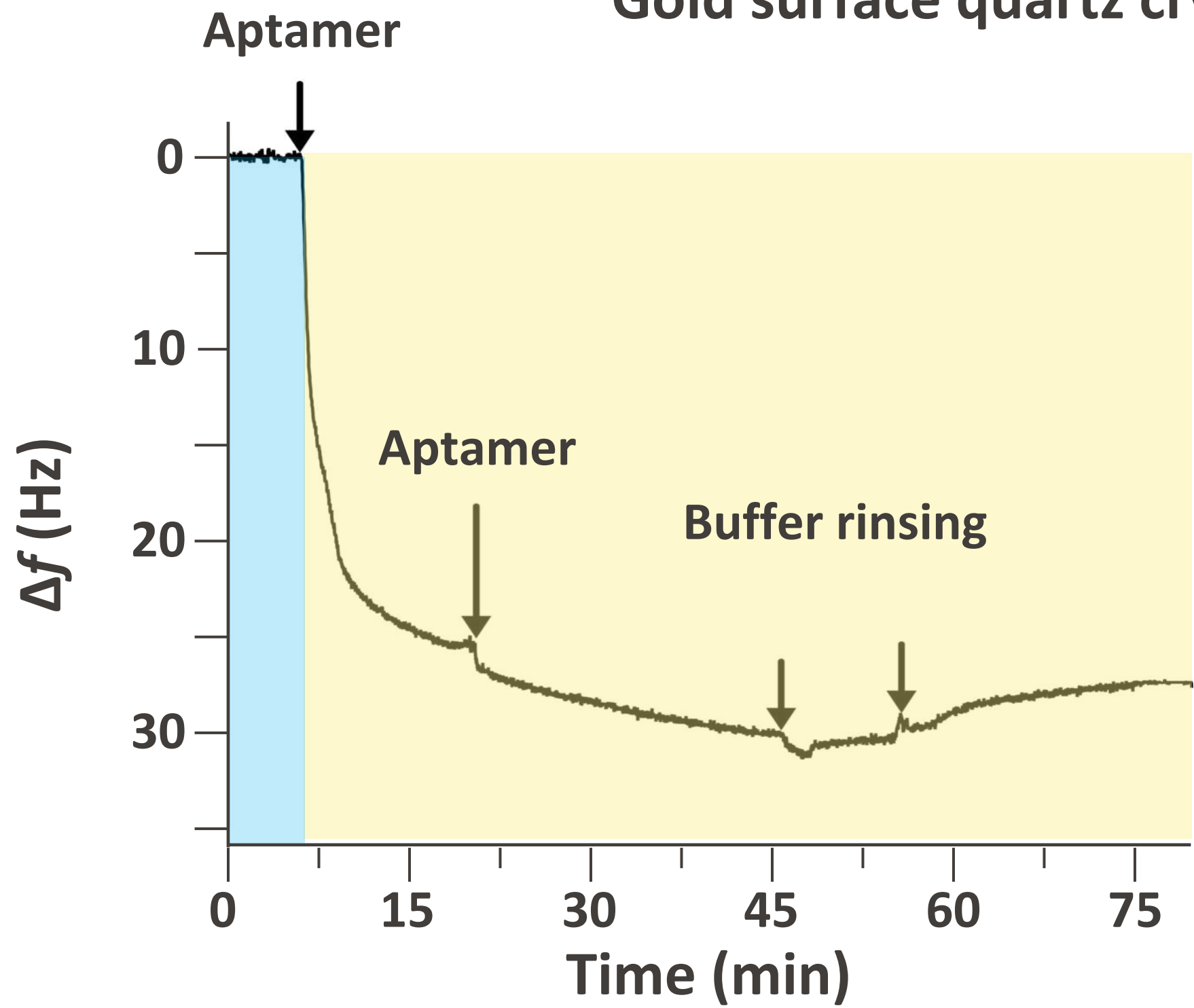
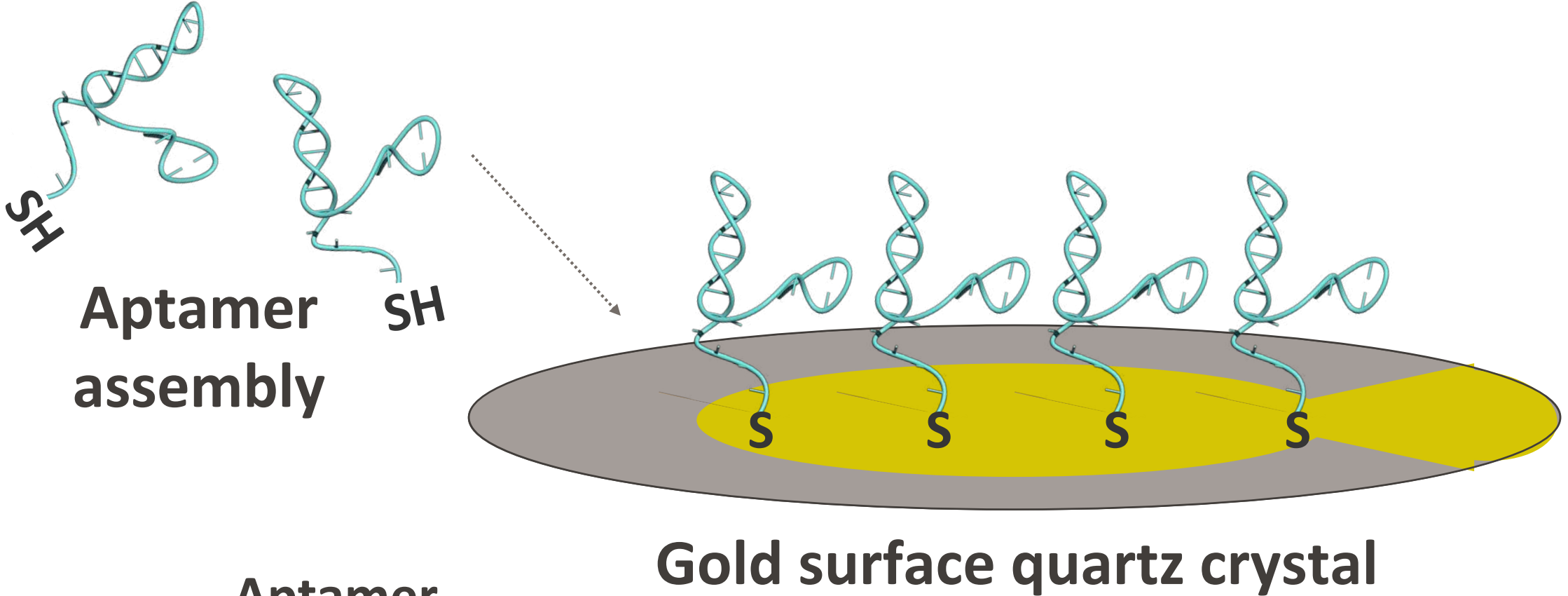
# Transistor Characterization Using SEM + EDX



Sandra Hernandez Escobar

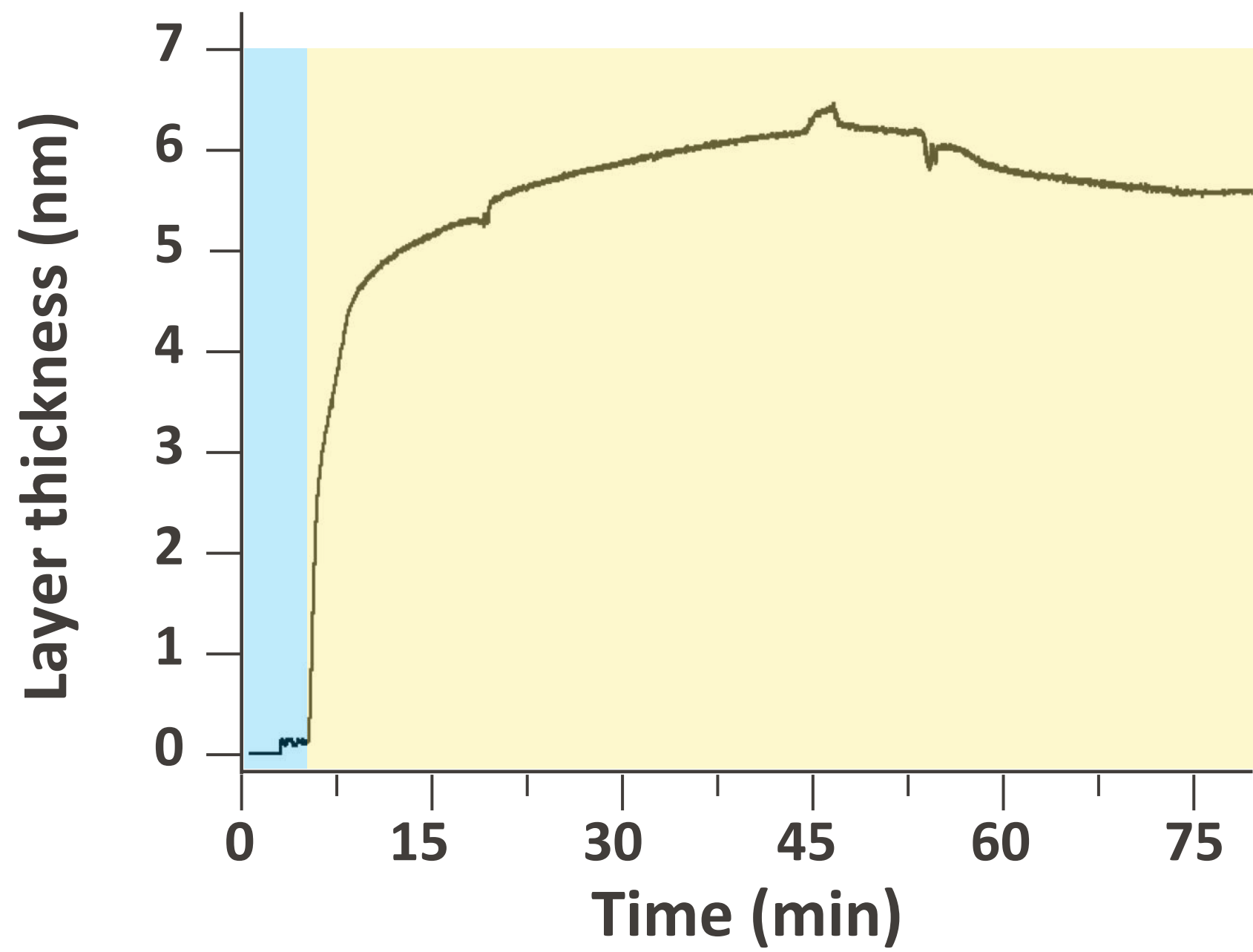


# Monitoring the Assembly of Aptamers on Surfaces

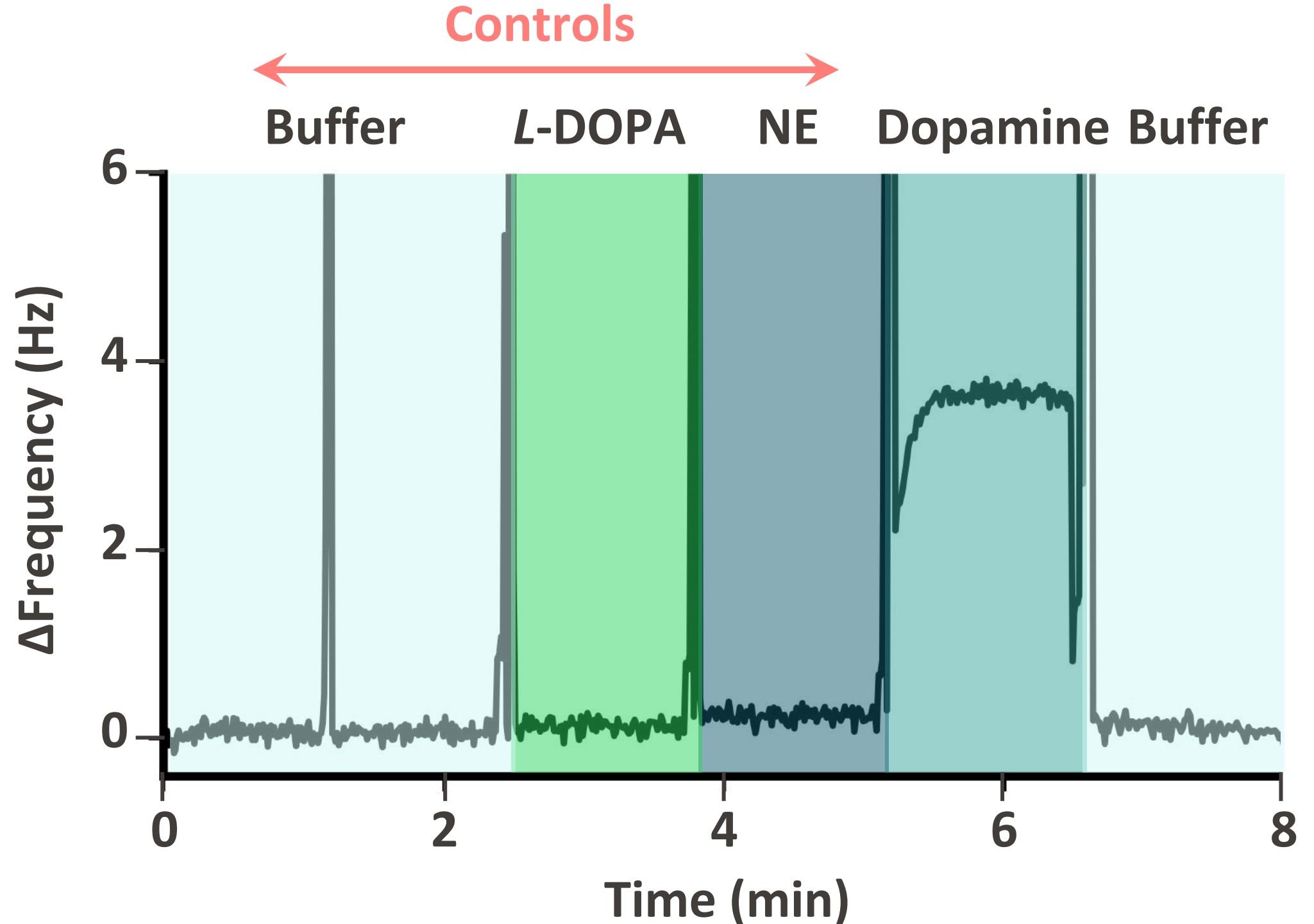
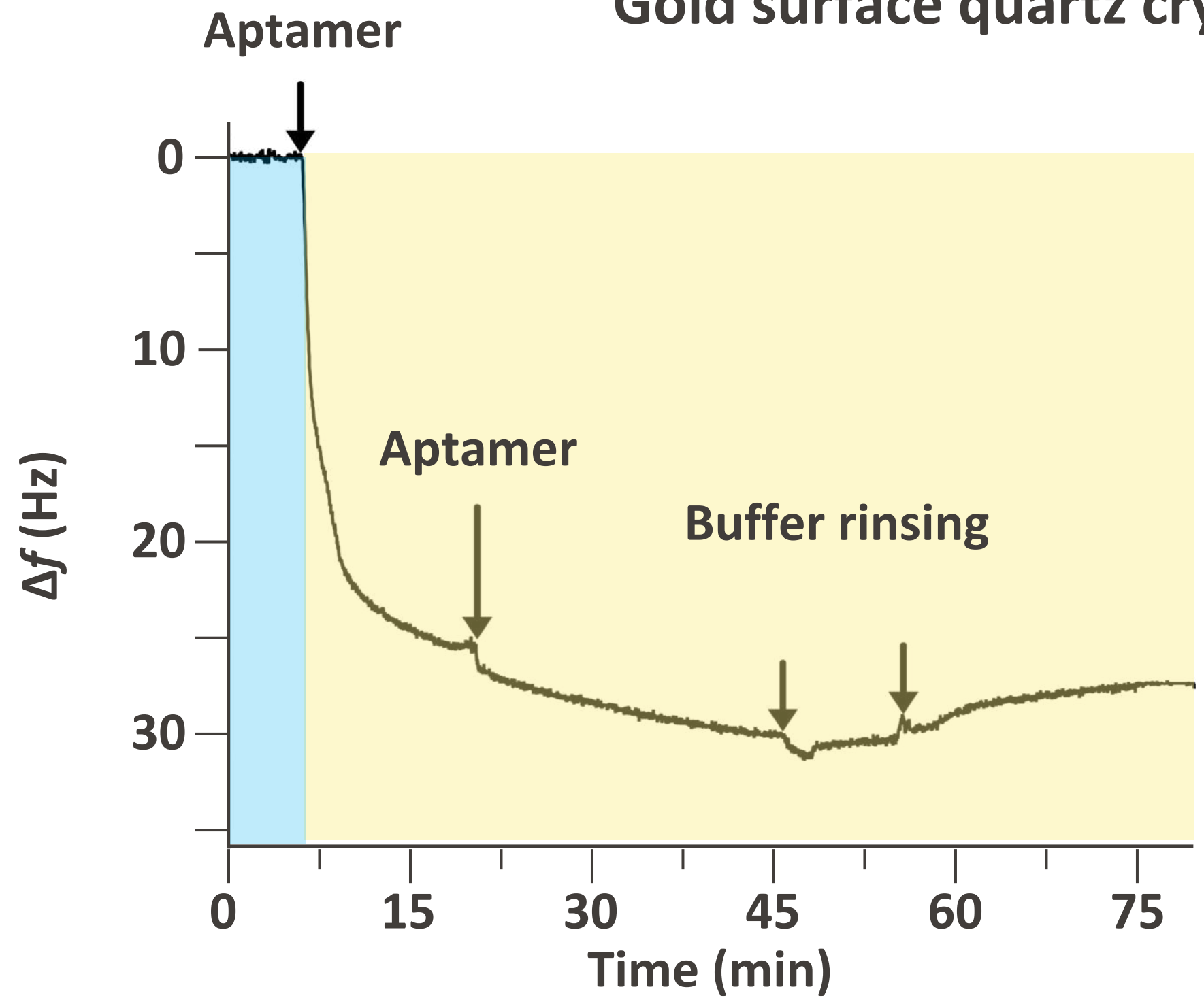
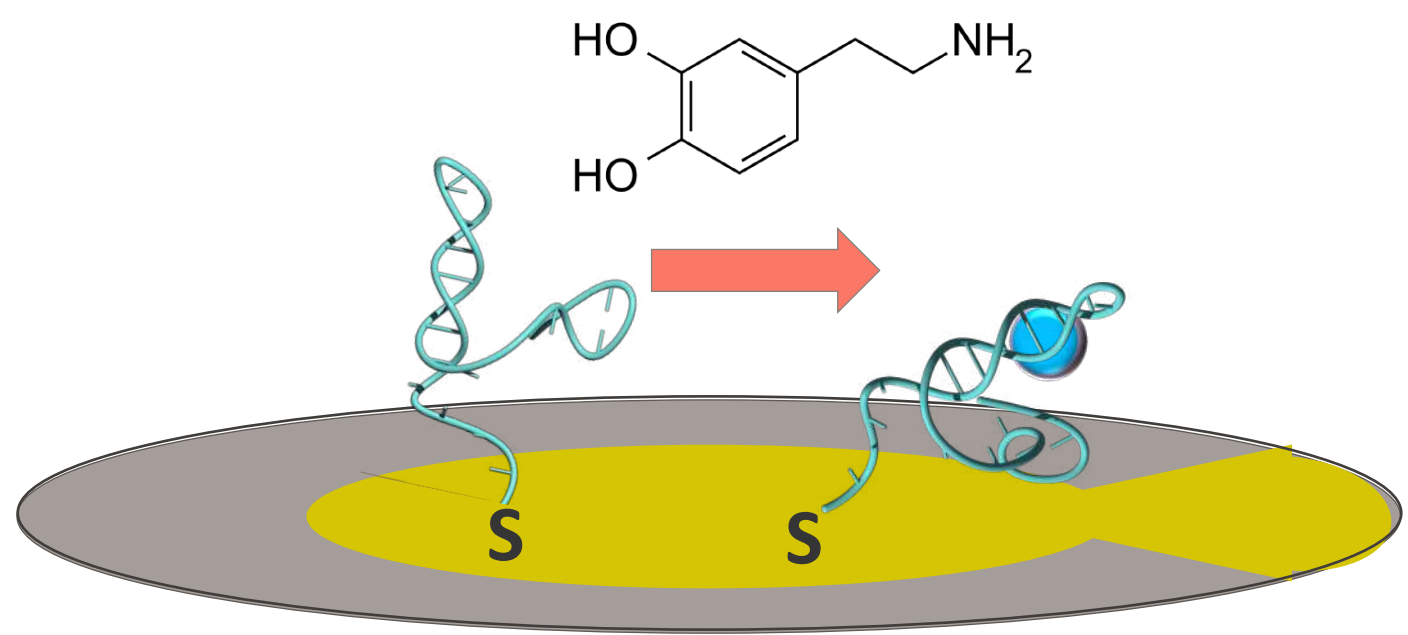
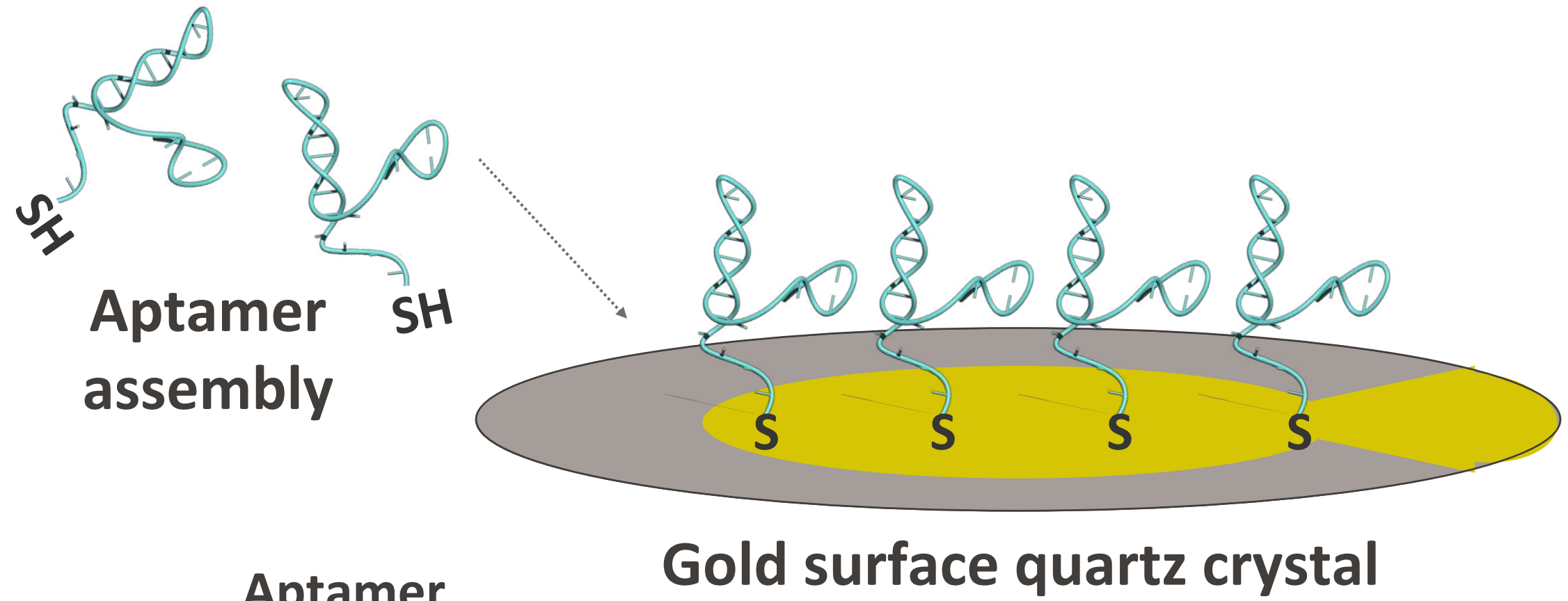


$$\Delta m = -C \cdot \frac{\Delta f}{n}$$

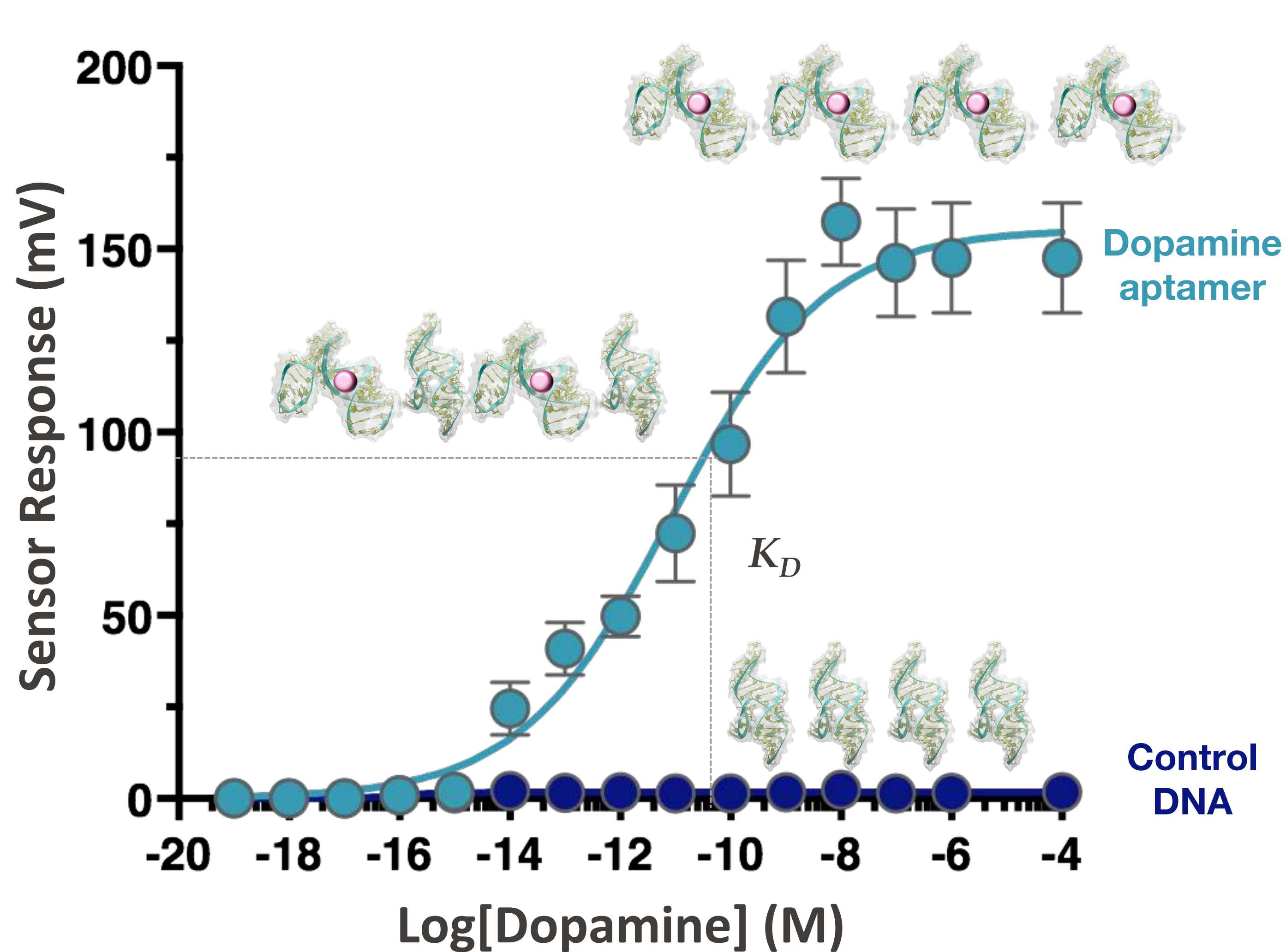
Mass sensitivity constant



# DNA Aptamer SAMs for Biosensing Applications

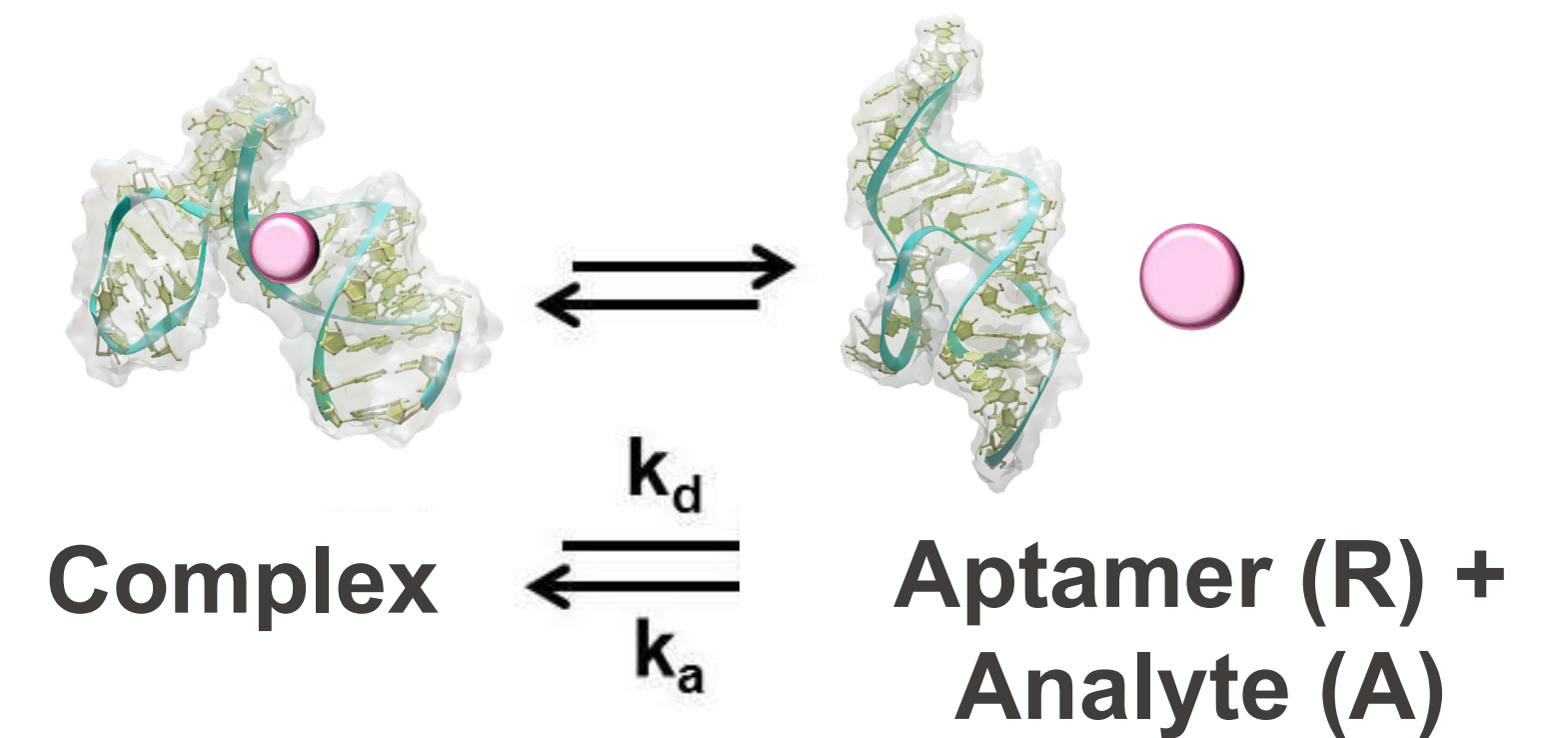


# Biosensor Response Follows a Langmuir Isotherm



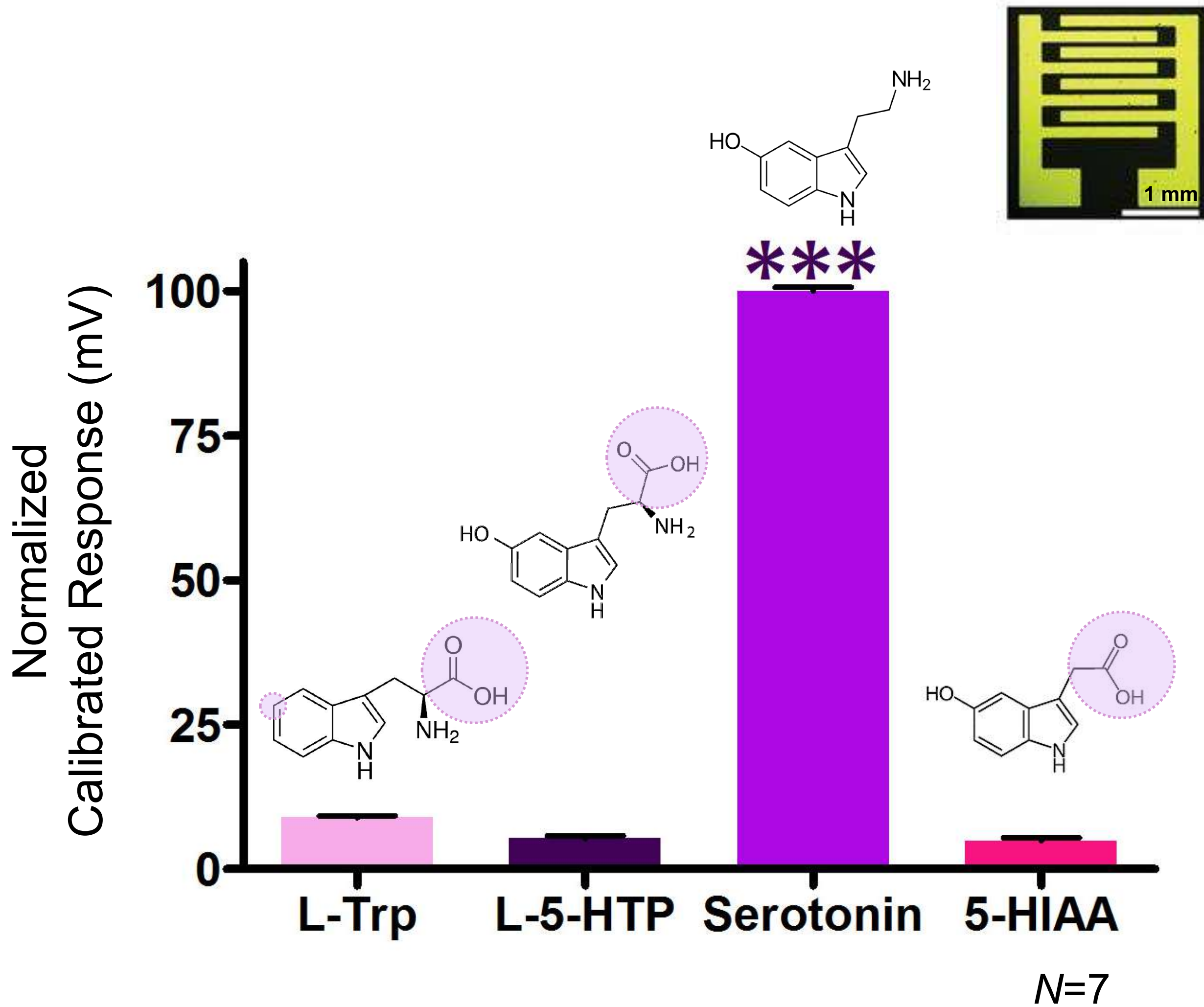
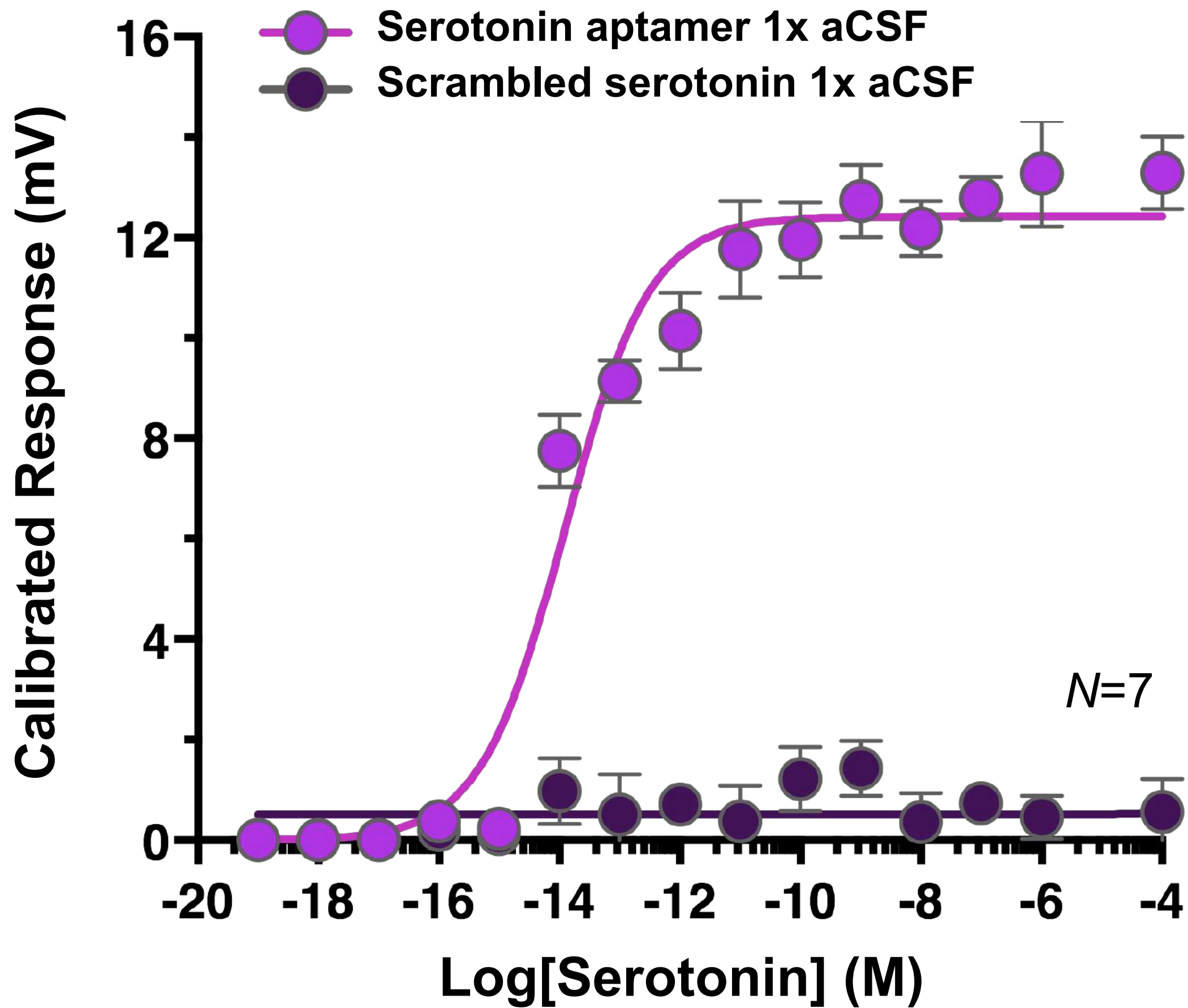
$$\theta = \frac{[A]K}{1 + [A]K}$$

Fractional occupation



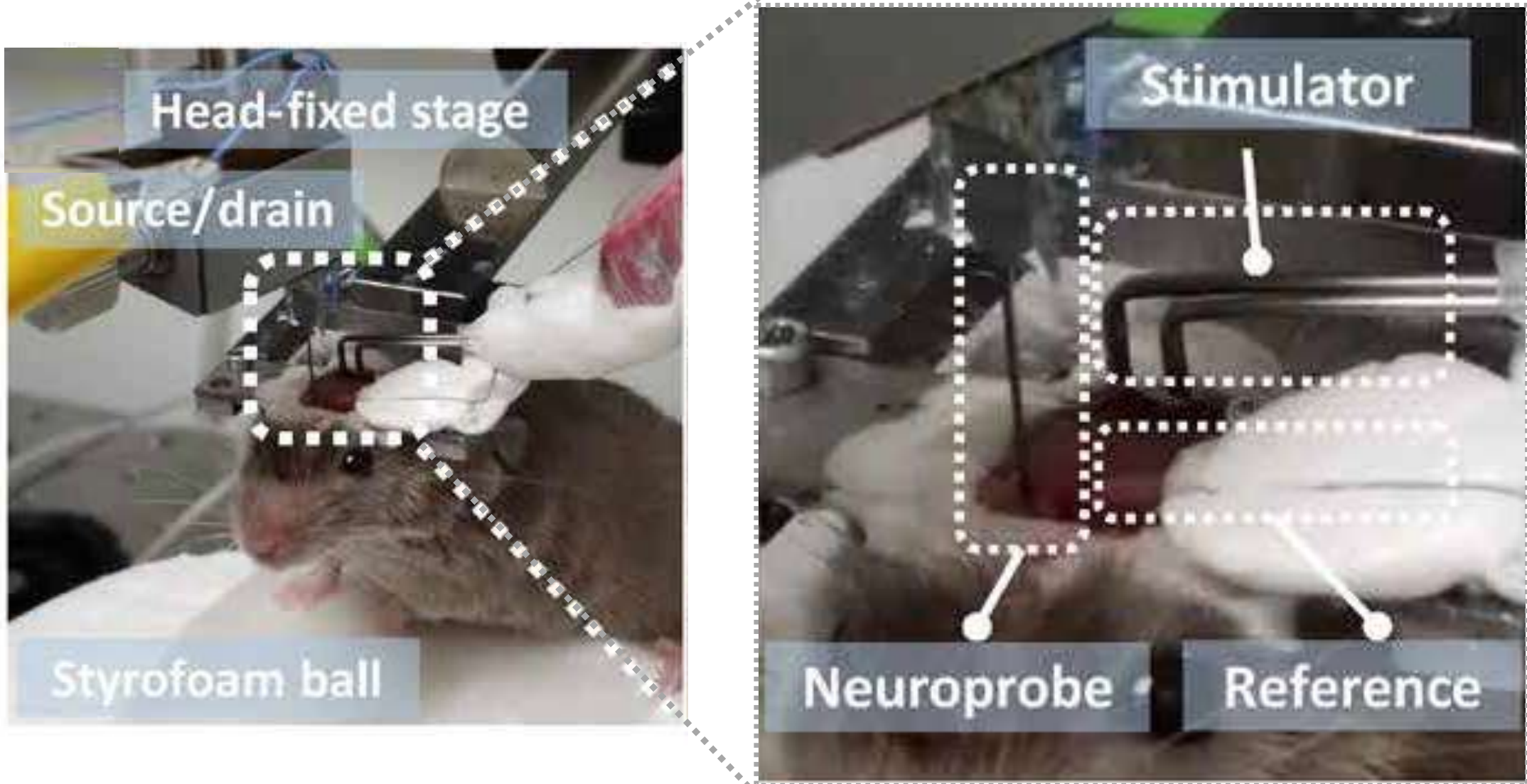
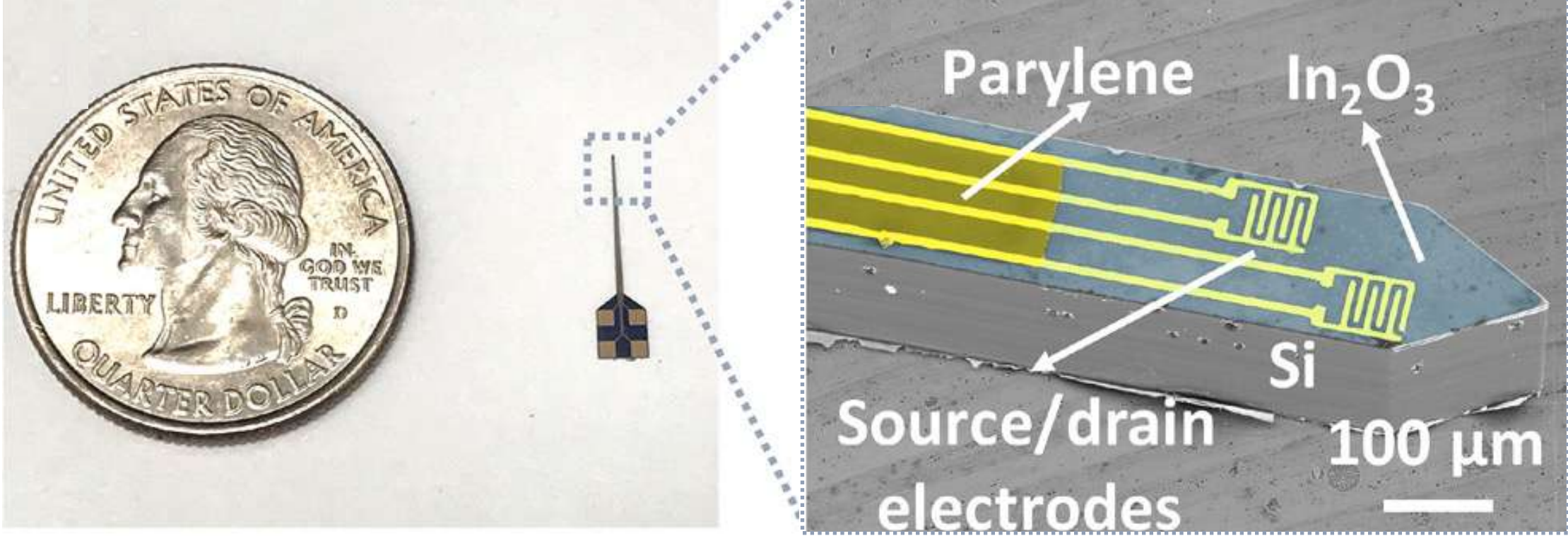
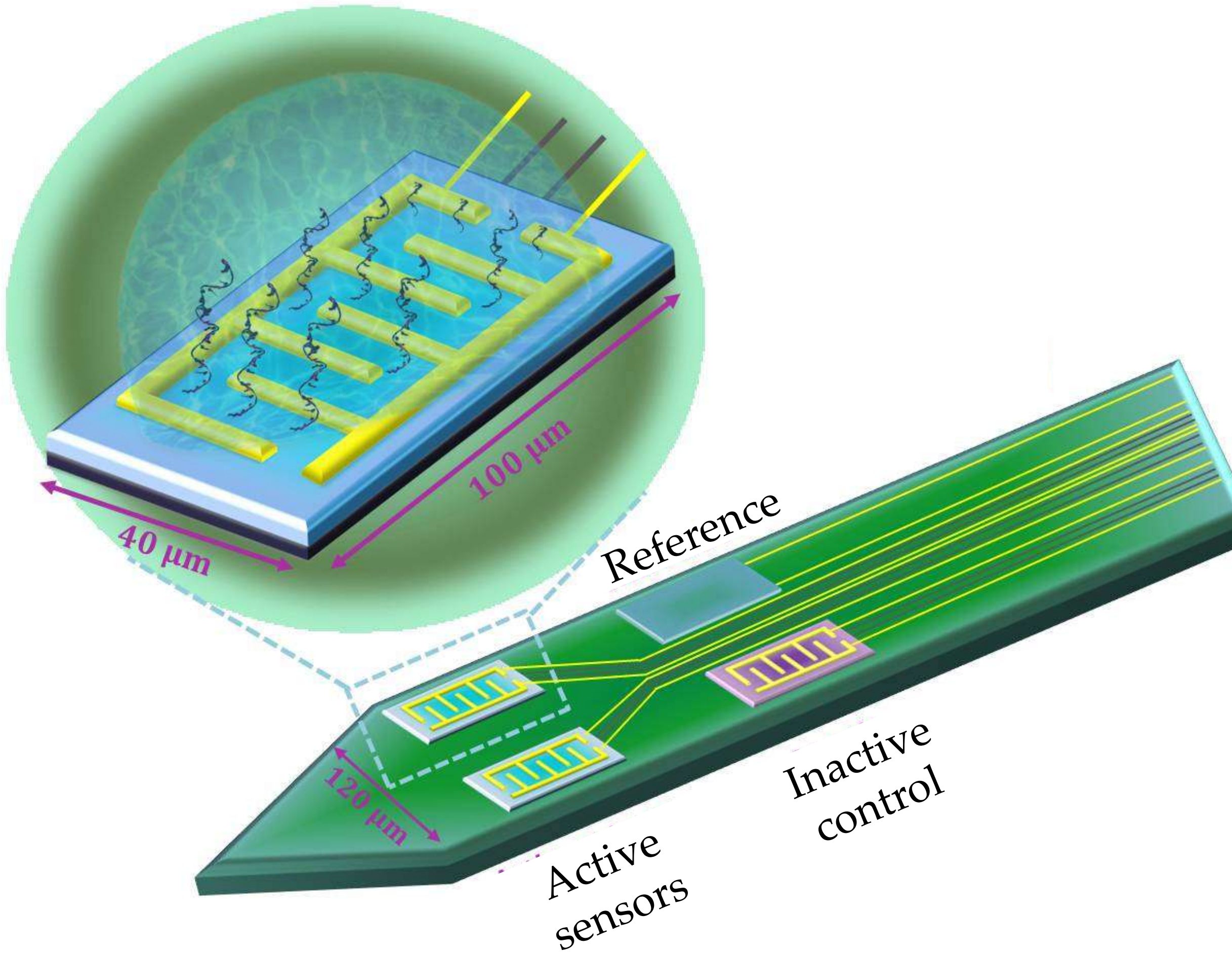
$$K_d = \frac{[R][A]}{[RA]} = \frac{k_d}{k_a} = \frac{1}{K_a}$$

# Specific and Selective Serotonin Aptamer Biosensors



aCSF = Artificial cerebrospinal fluid

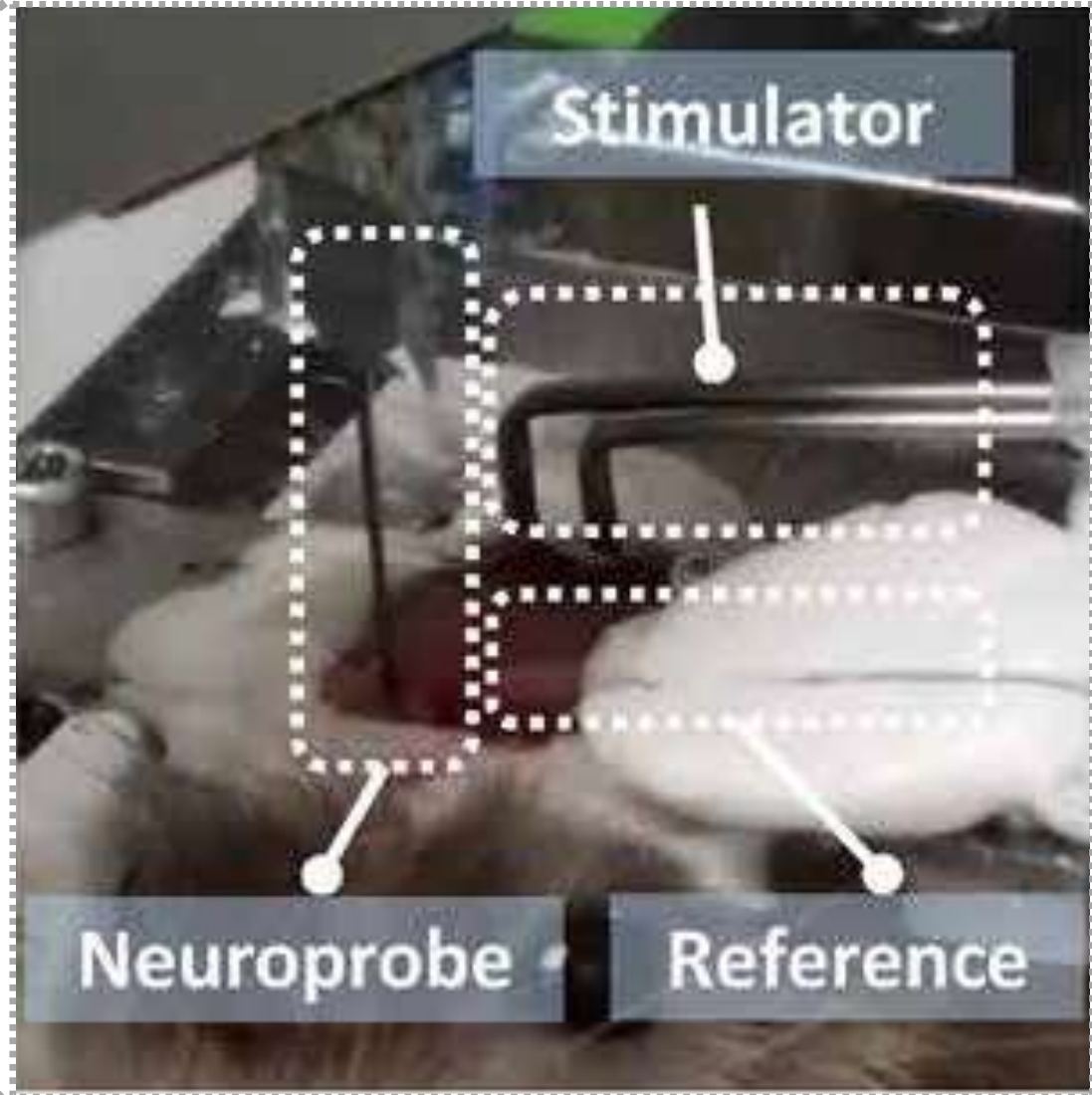
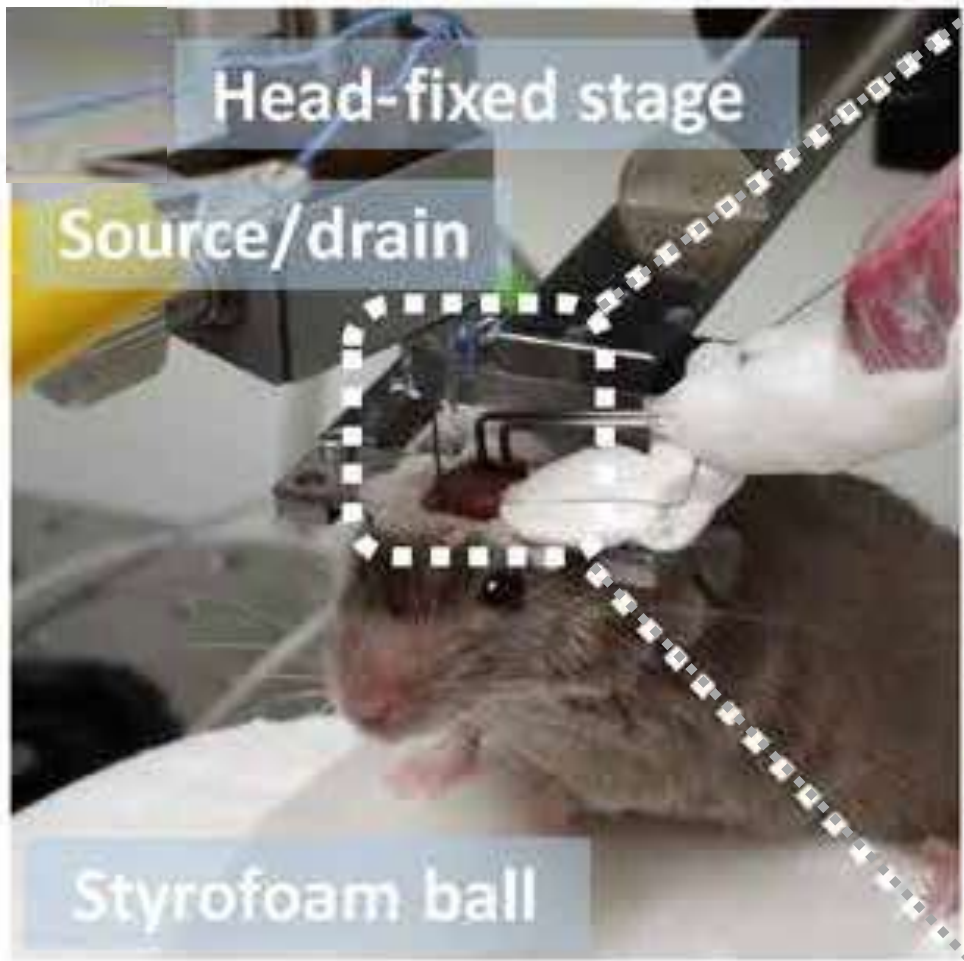
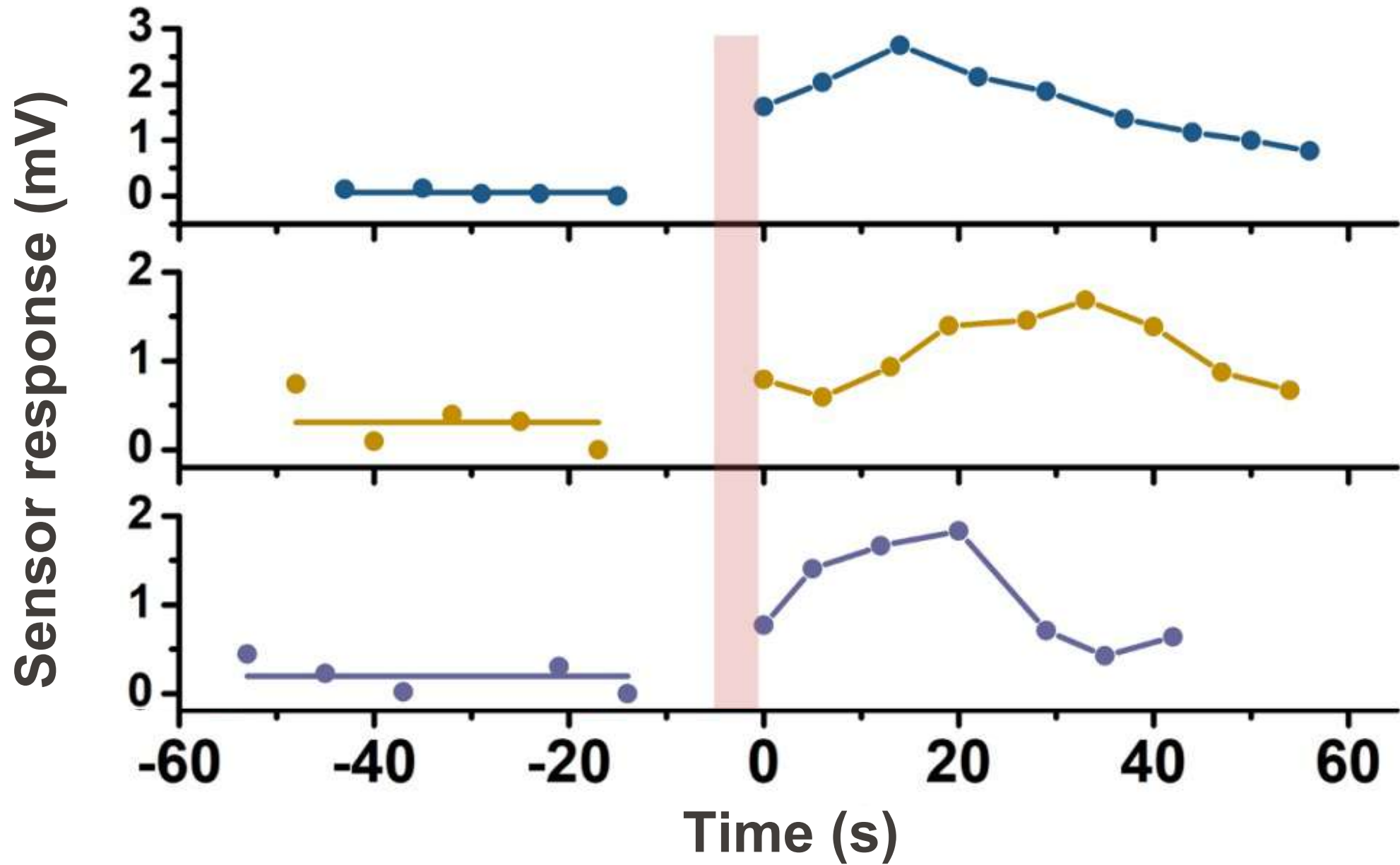
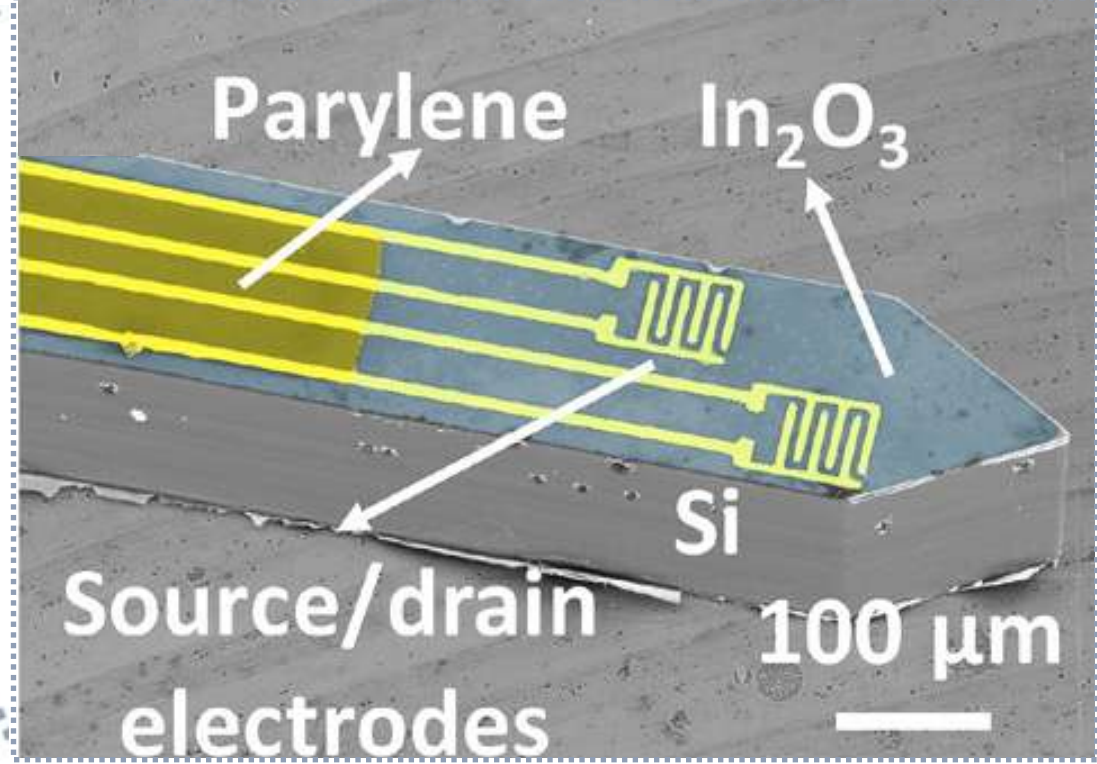
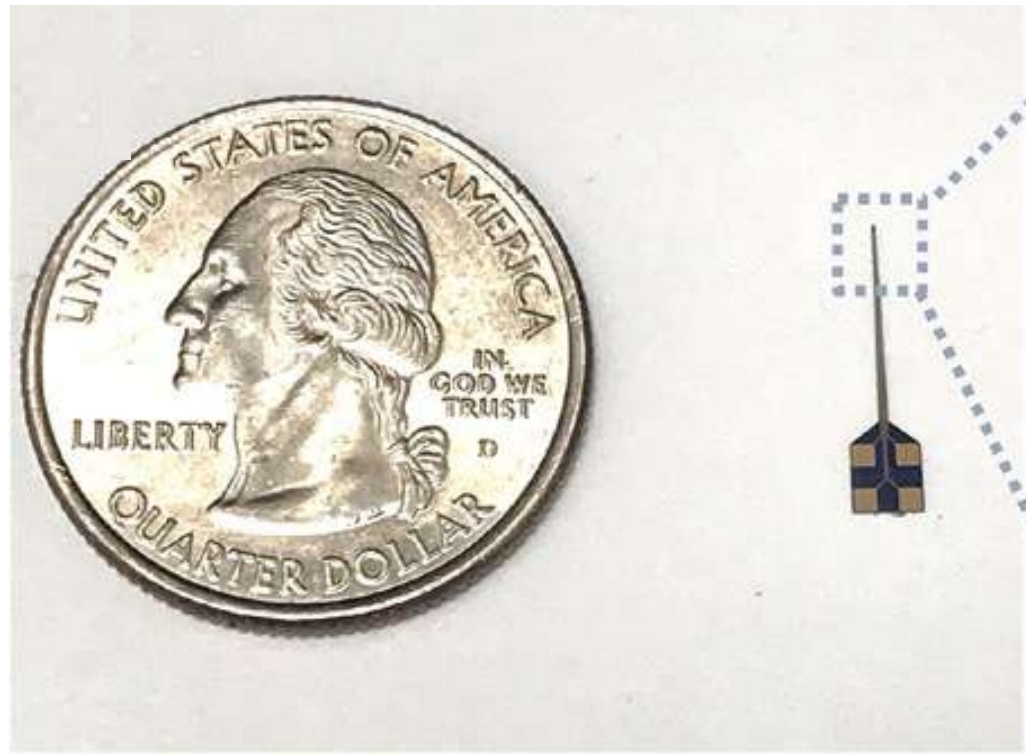
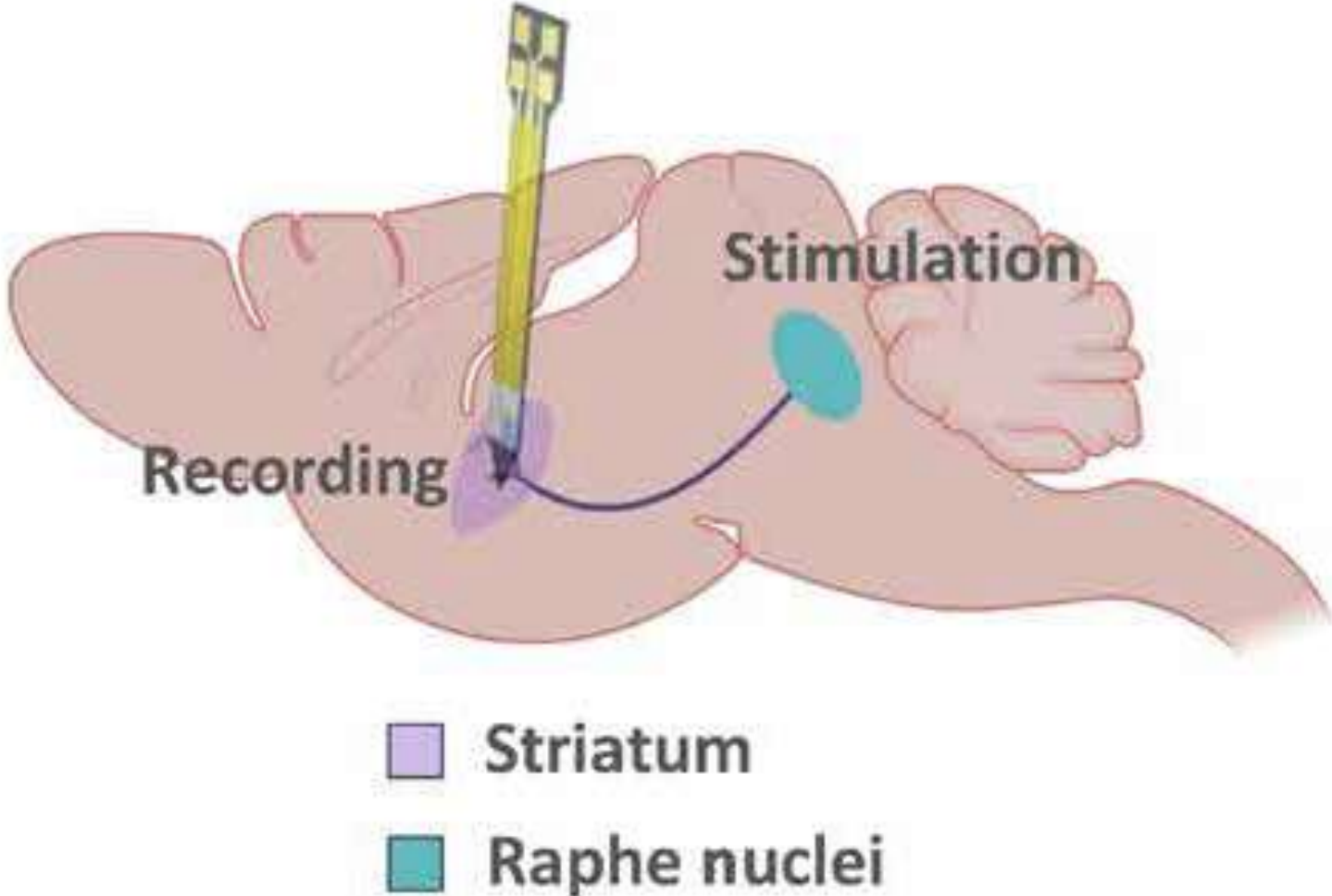
# Miniaturization of Biosensors for Detection in the Brain



Nakatsuka & Andrews | *Neuropsychopharmacology* | 2016

Zhao et al. | *Sci. Adv.* | 2021

# Miniaturization of Biosensors for Detection in the Brain

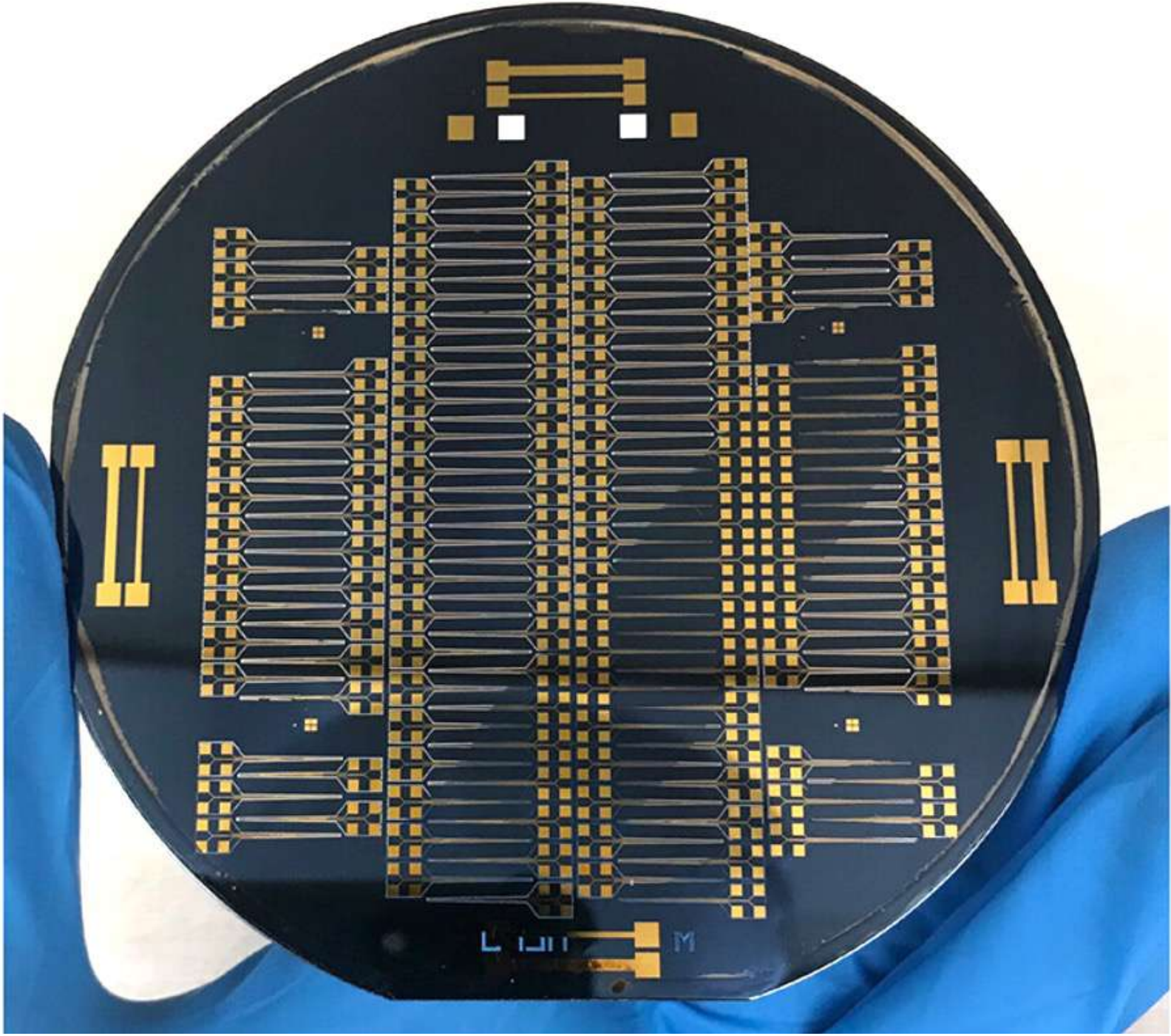


Zhao et al. | *Sci. Adv.* | 2021

# Pros and Cons of Silicon Neural Probes

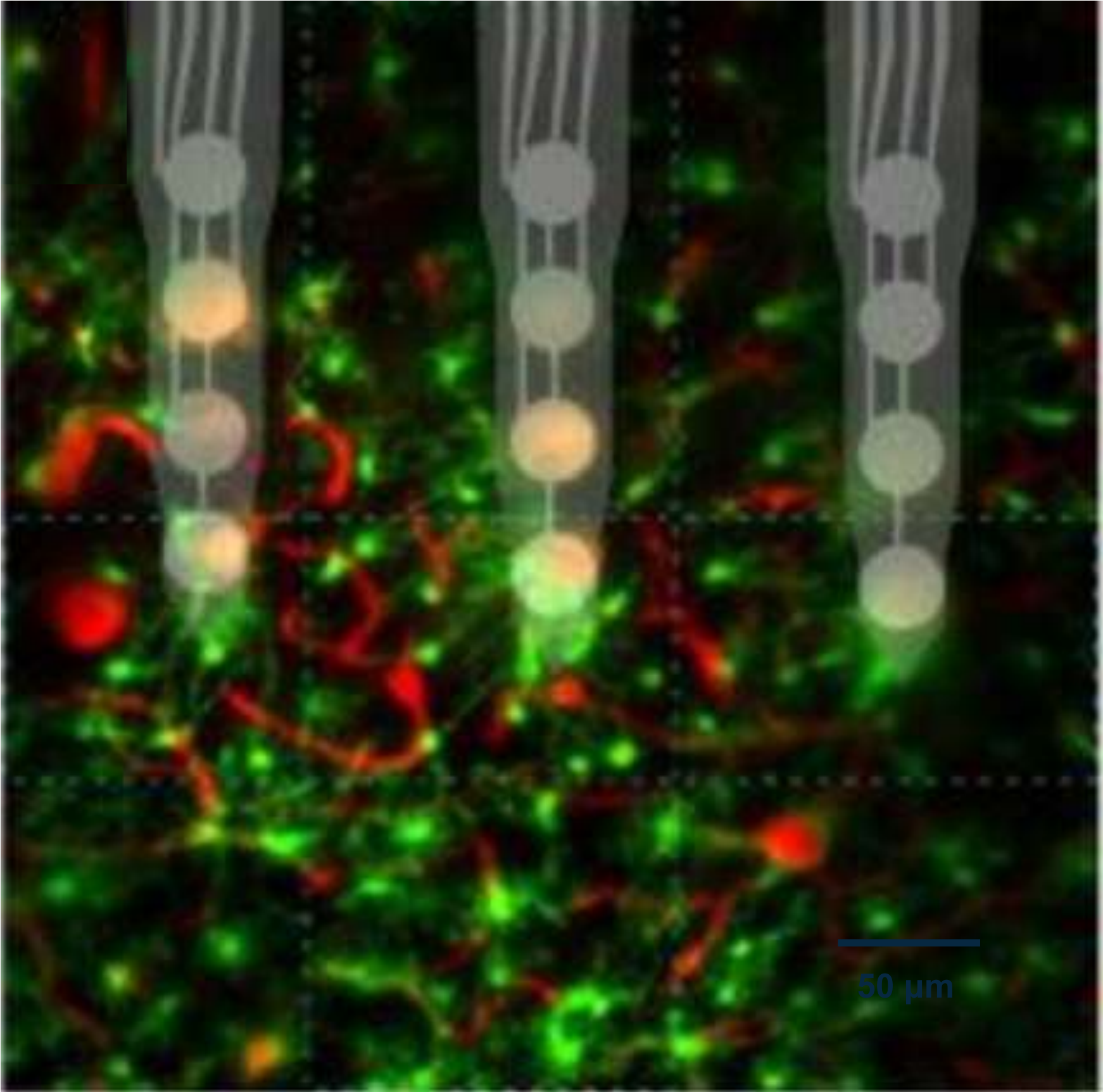
## Wafer-scale microfabrication process

150 probes per wafer



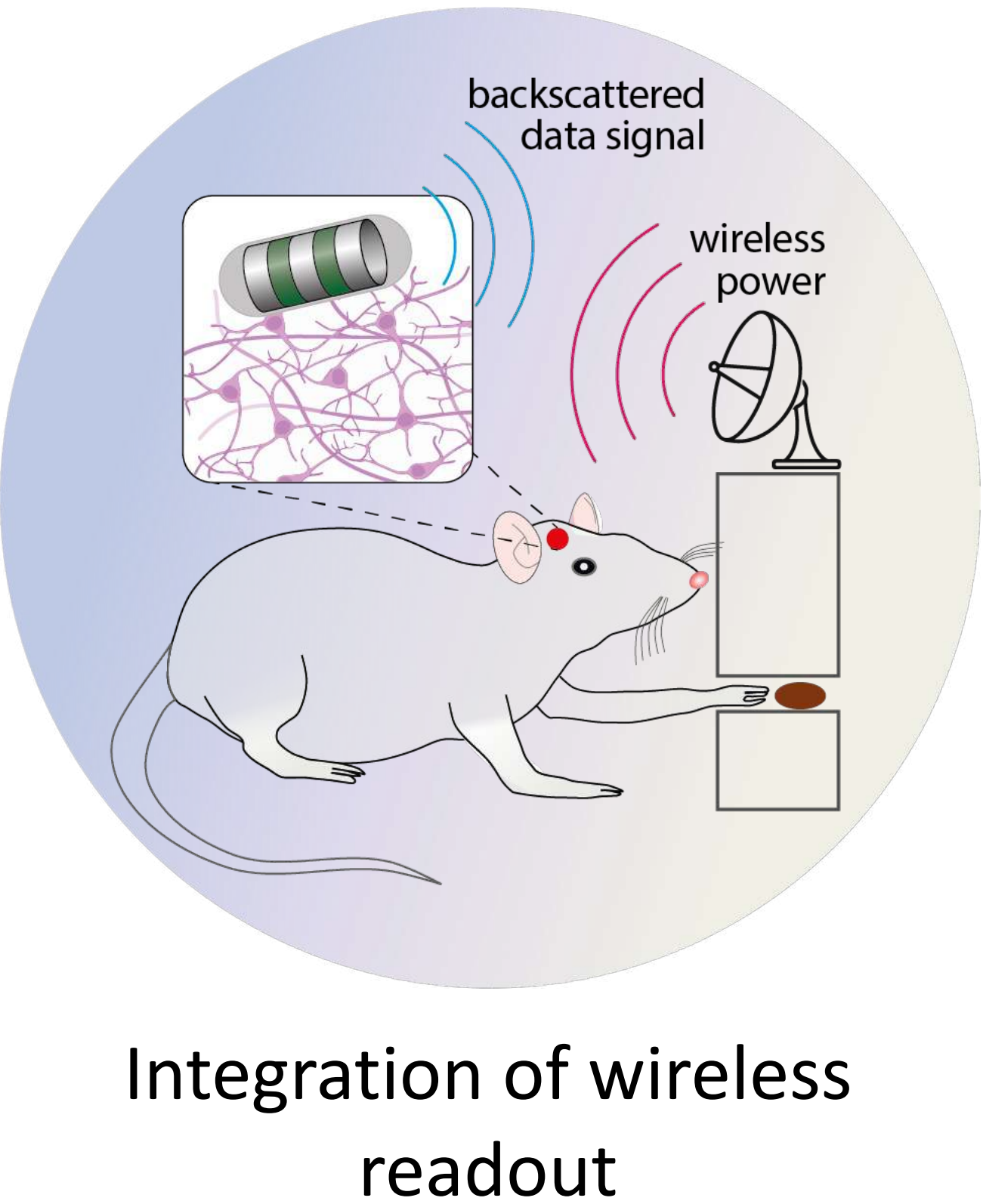
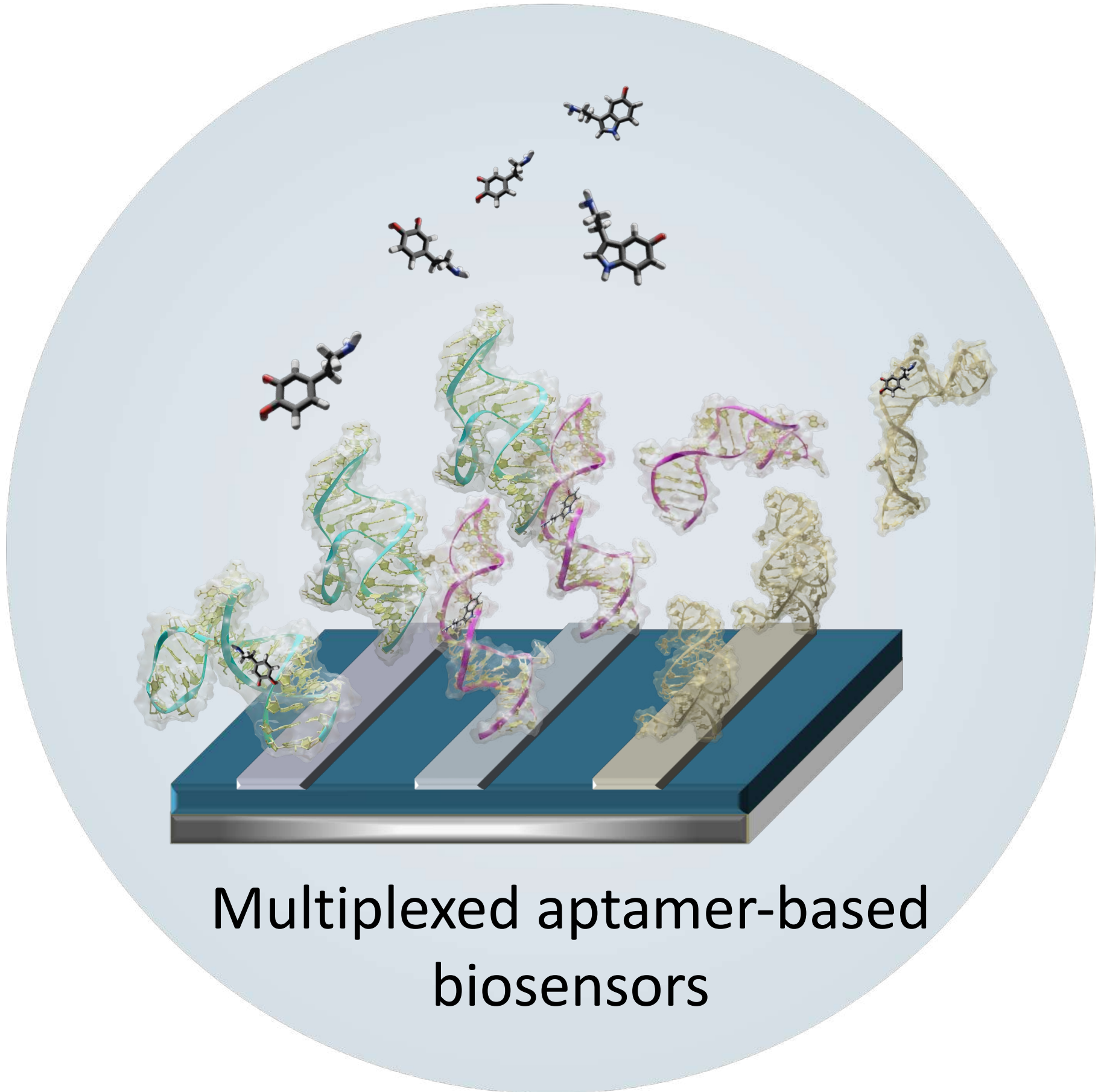
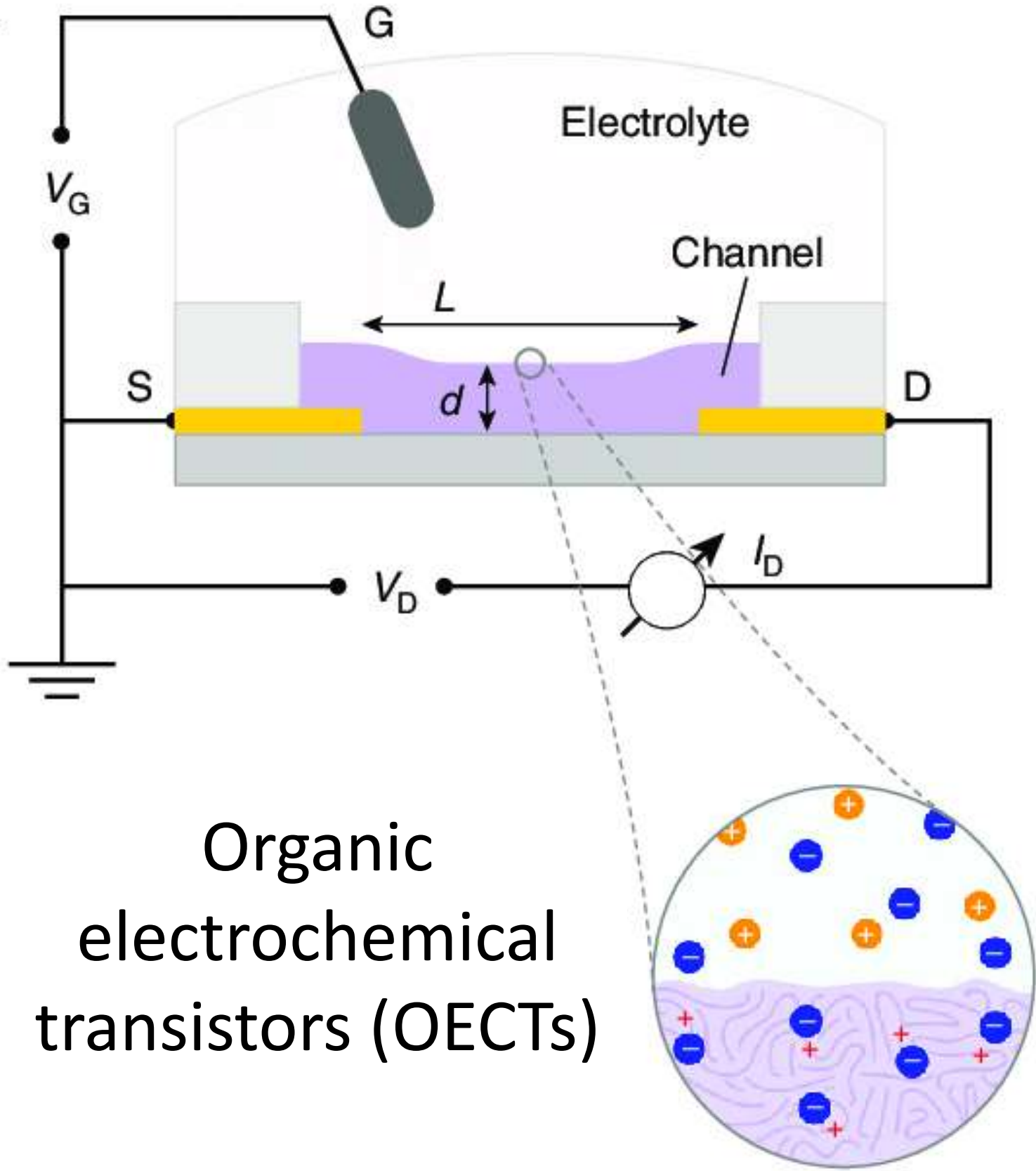
Zhao *et al.* | *Sci. Adv.* | 2021

## Silicon-based materials cause damage to soft brain tissue



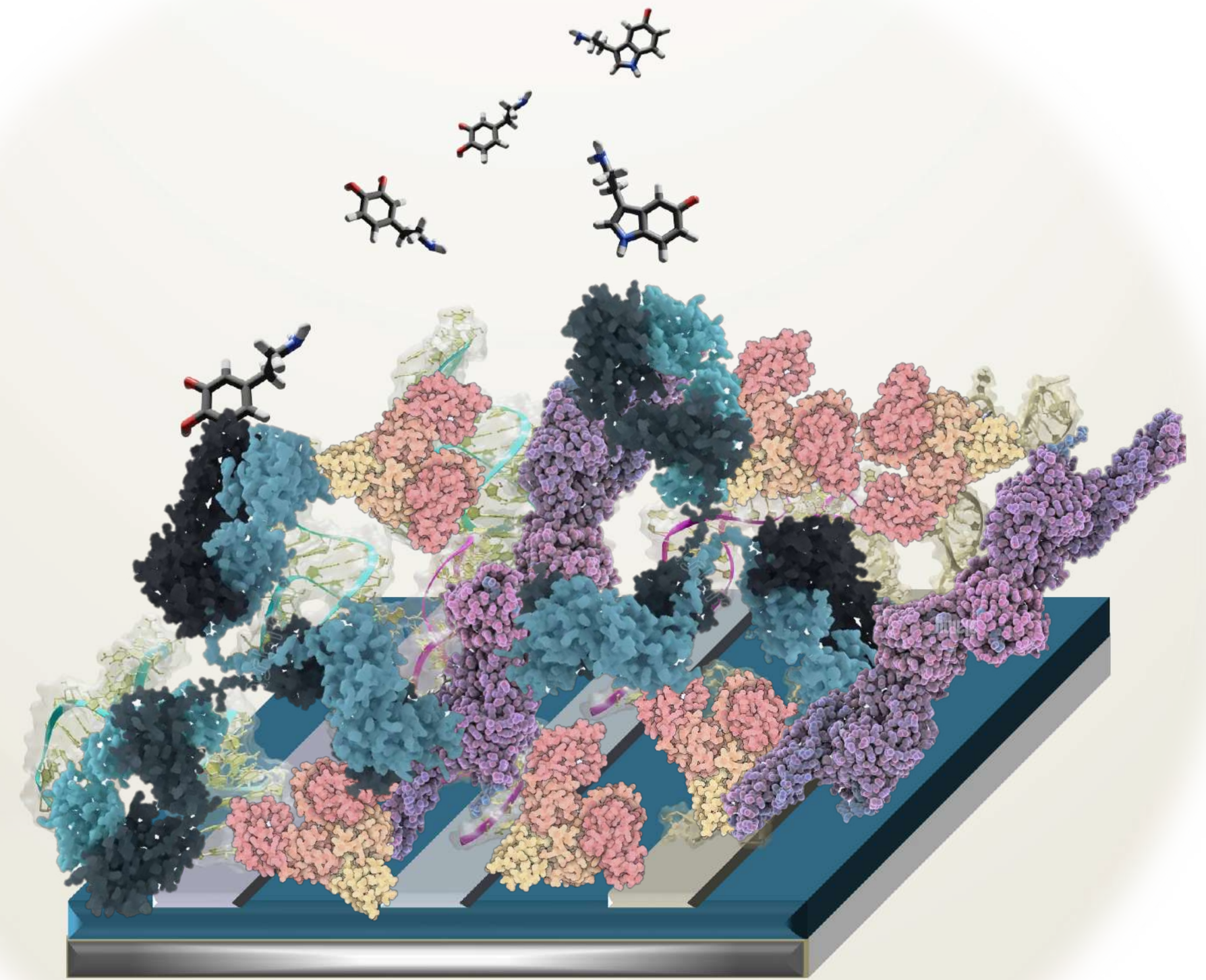
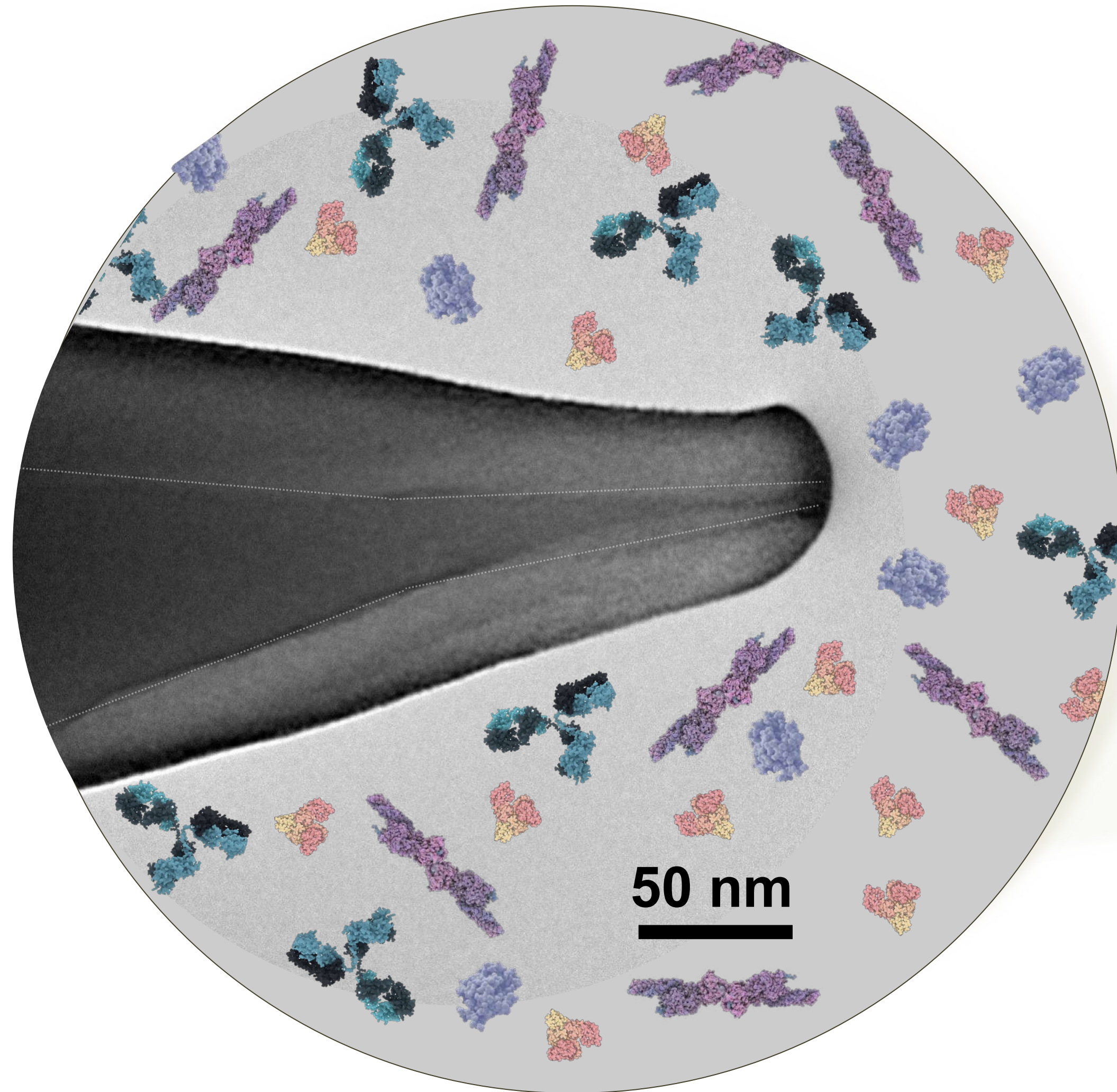
Kozai *et al.* | *ACS Chemical Neuroscience* | 2015

# Polymer-Based Materials for Improved Mechanical Compatibility



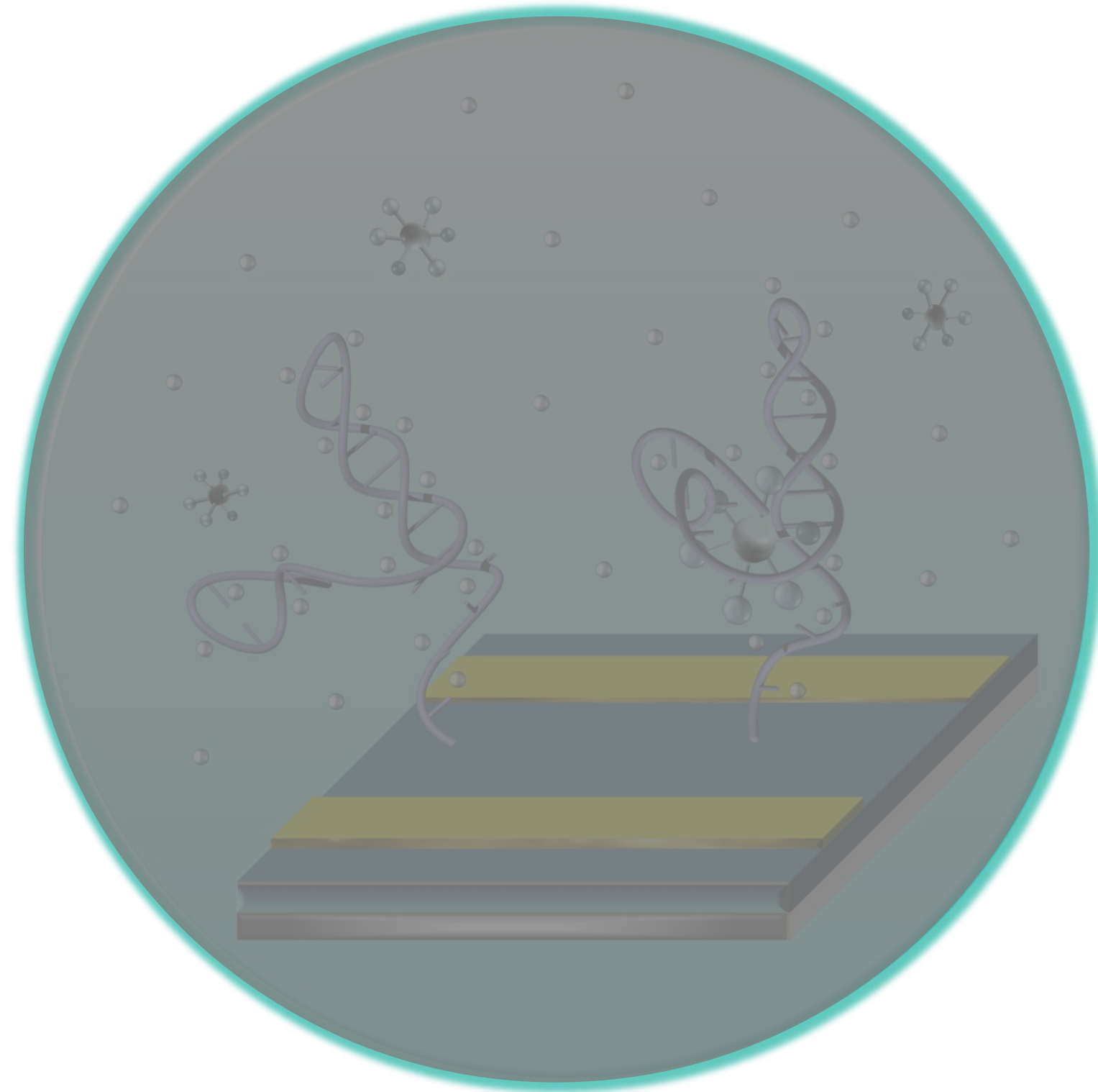
Inal *et al.* | Nature Communications / 2017

# Challenge of Long-Term Monitoring in Complex Biological Systems

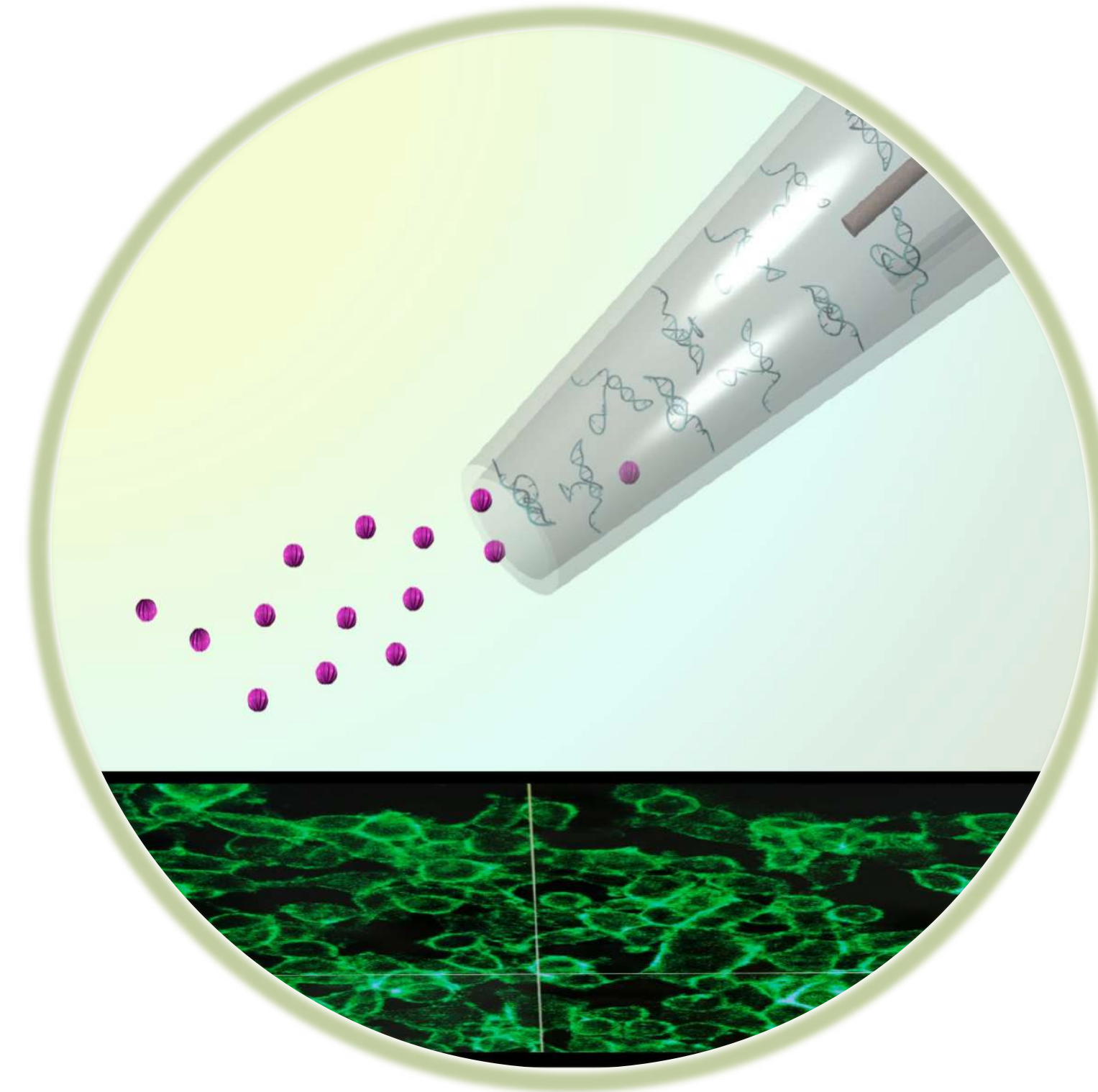


# Chemical Nanotechnologies for Human Health

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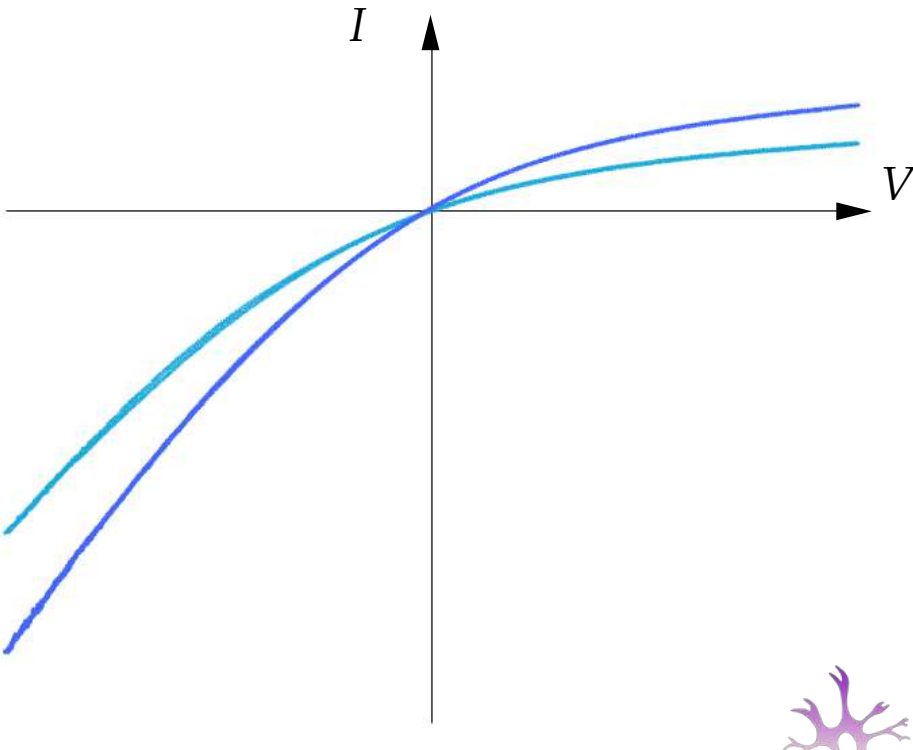
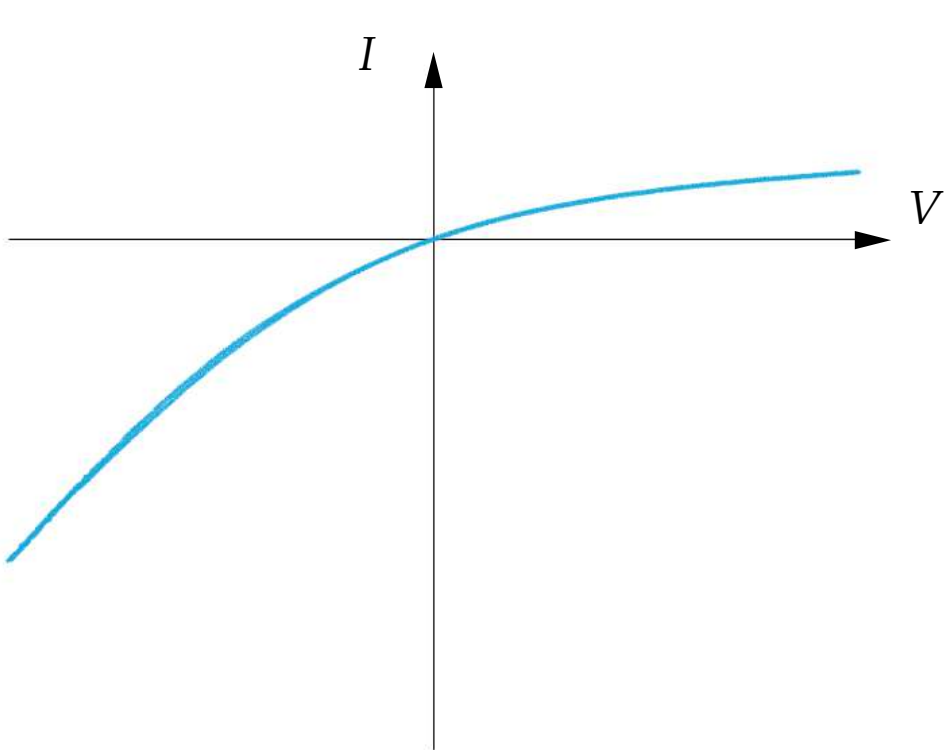
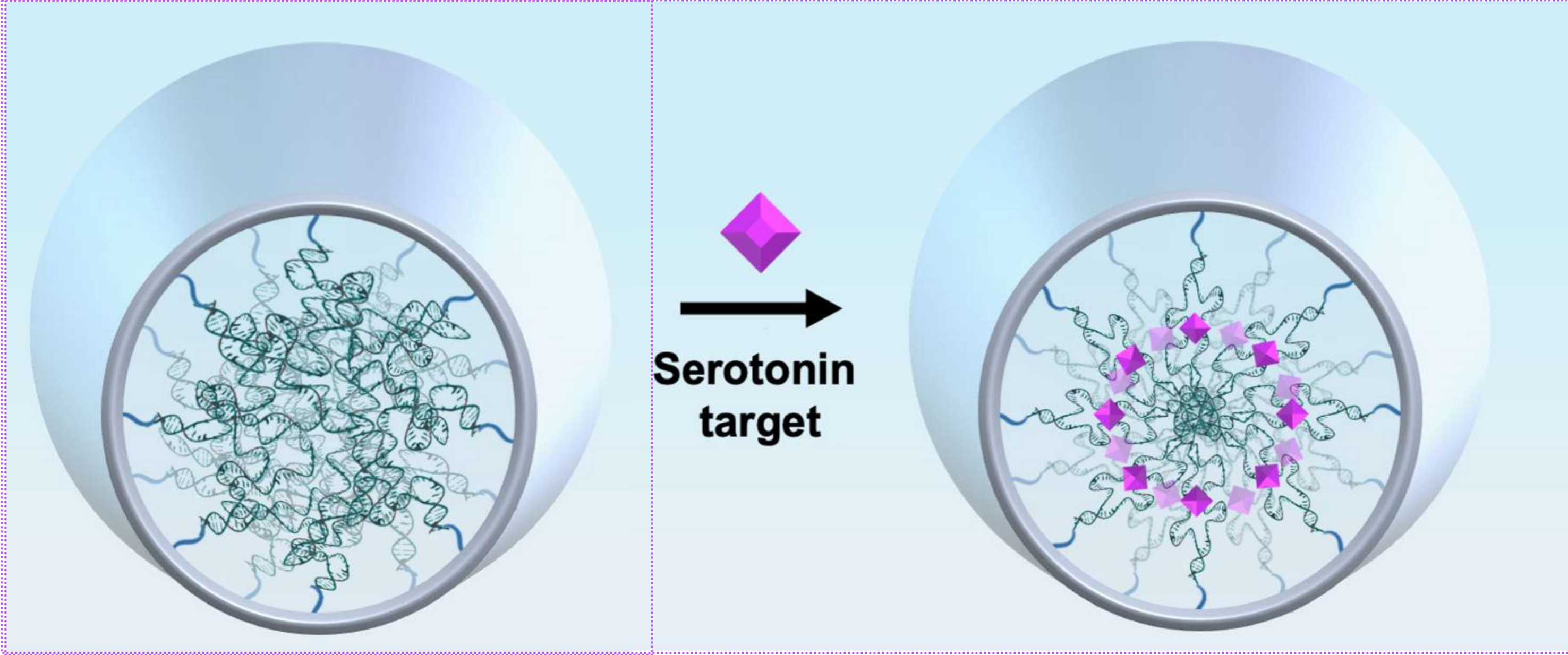
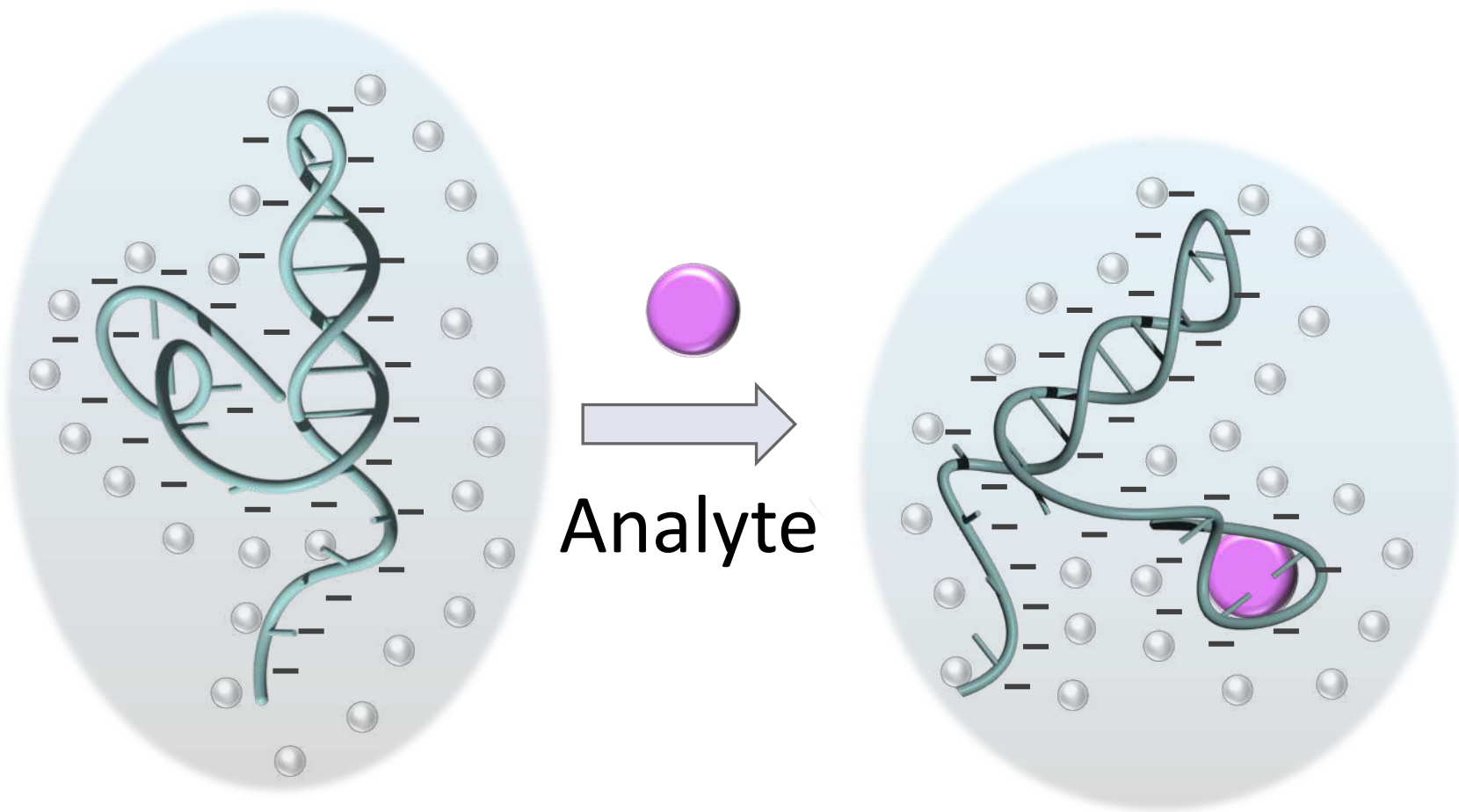


**Aptamer-modified  
field-effect transistors**  
(microscale)

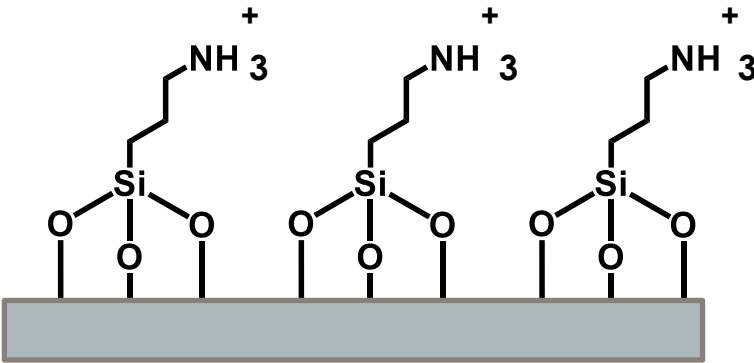
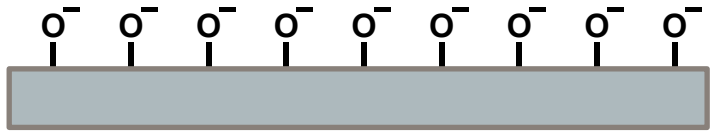
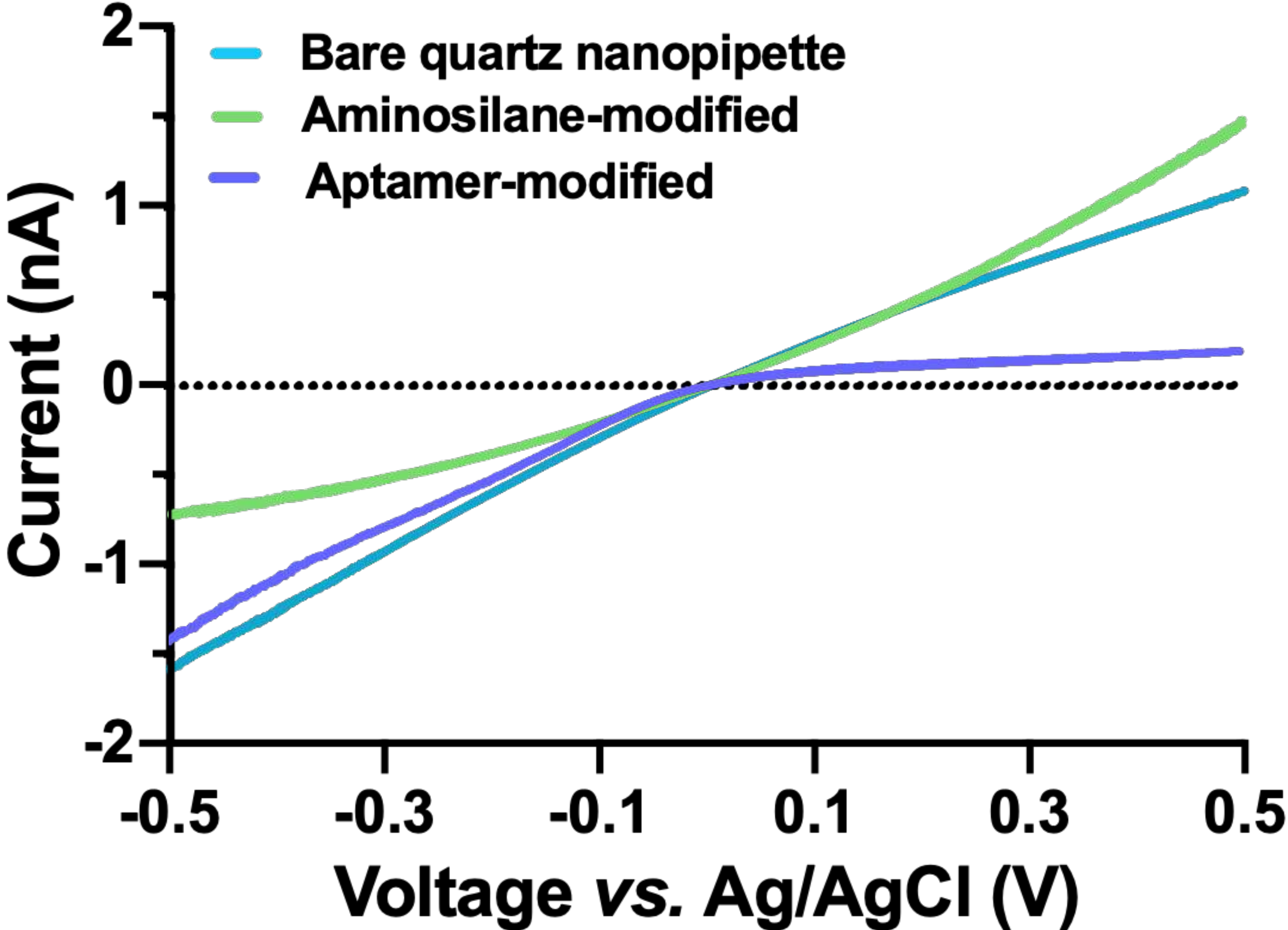


**Aptamer-modified  
nanopipettes**  
(nanoscale)

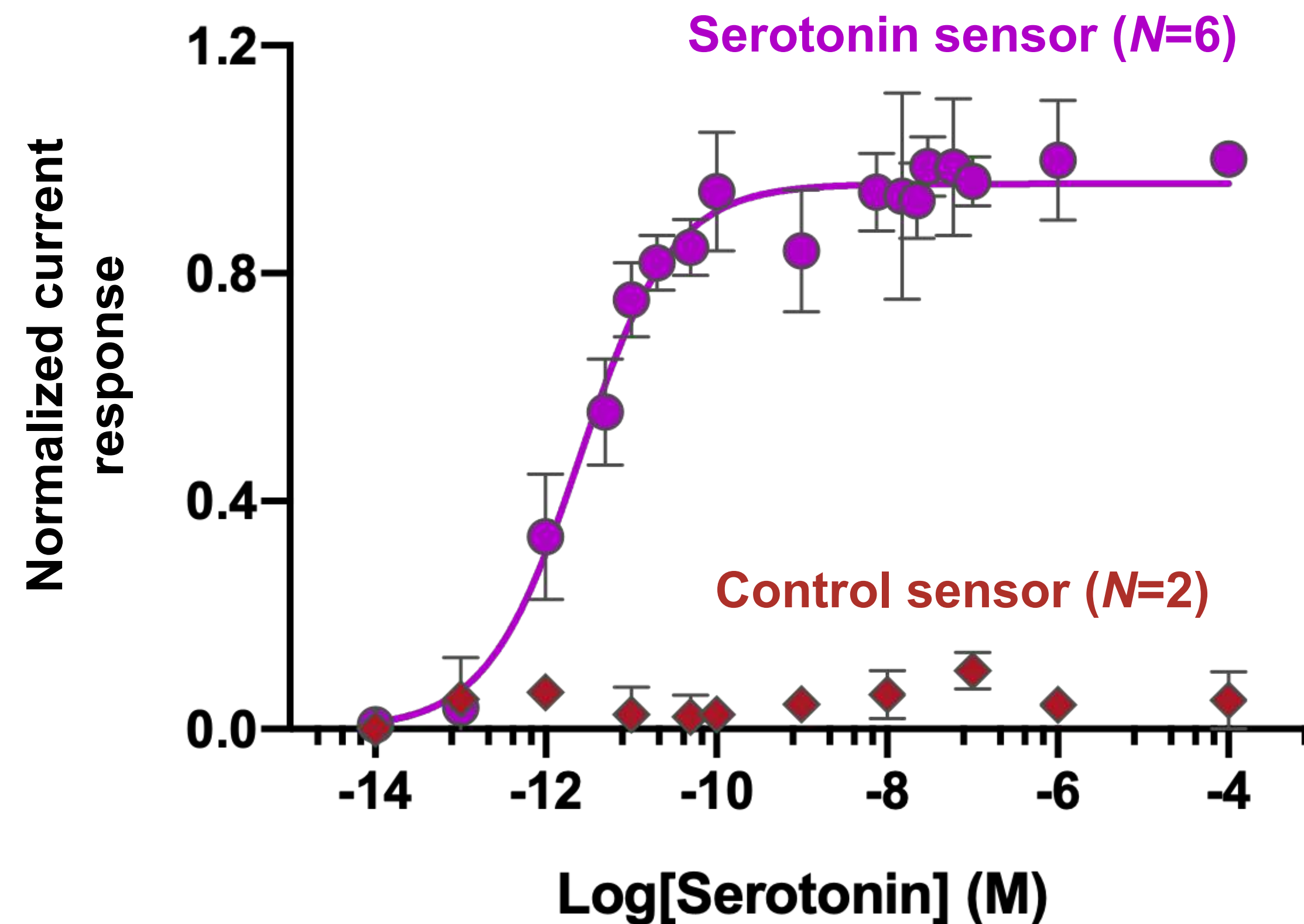
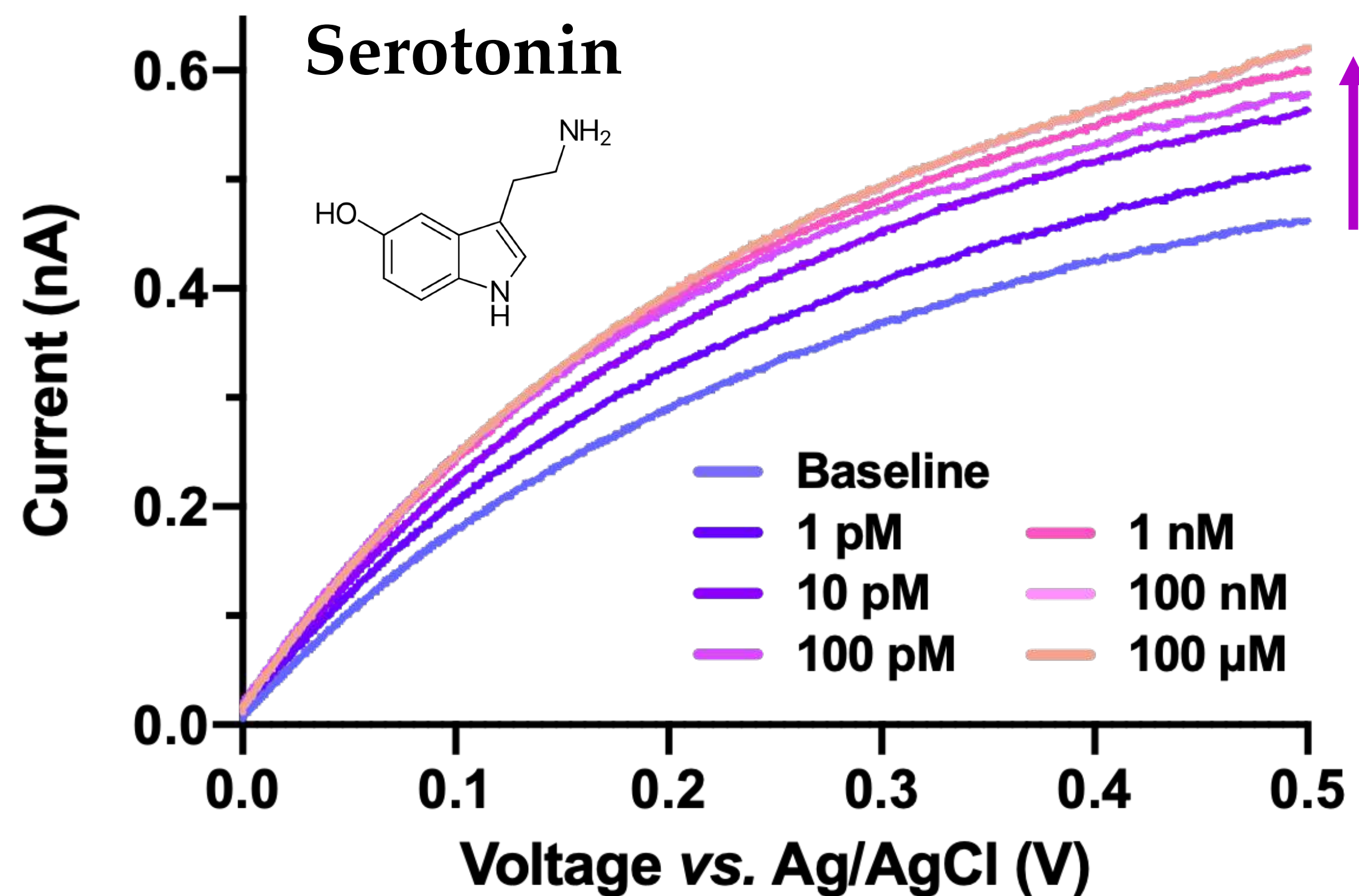
# Structure-Switching Aptamers Modulate Ionic Flux in Nanopores



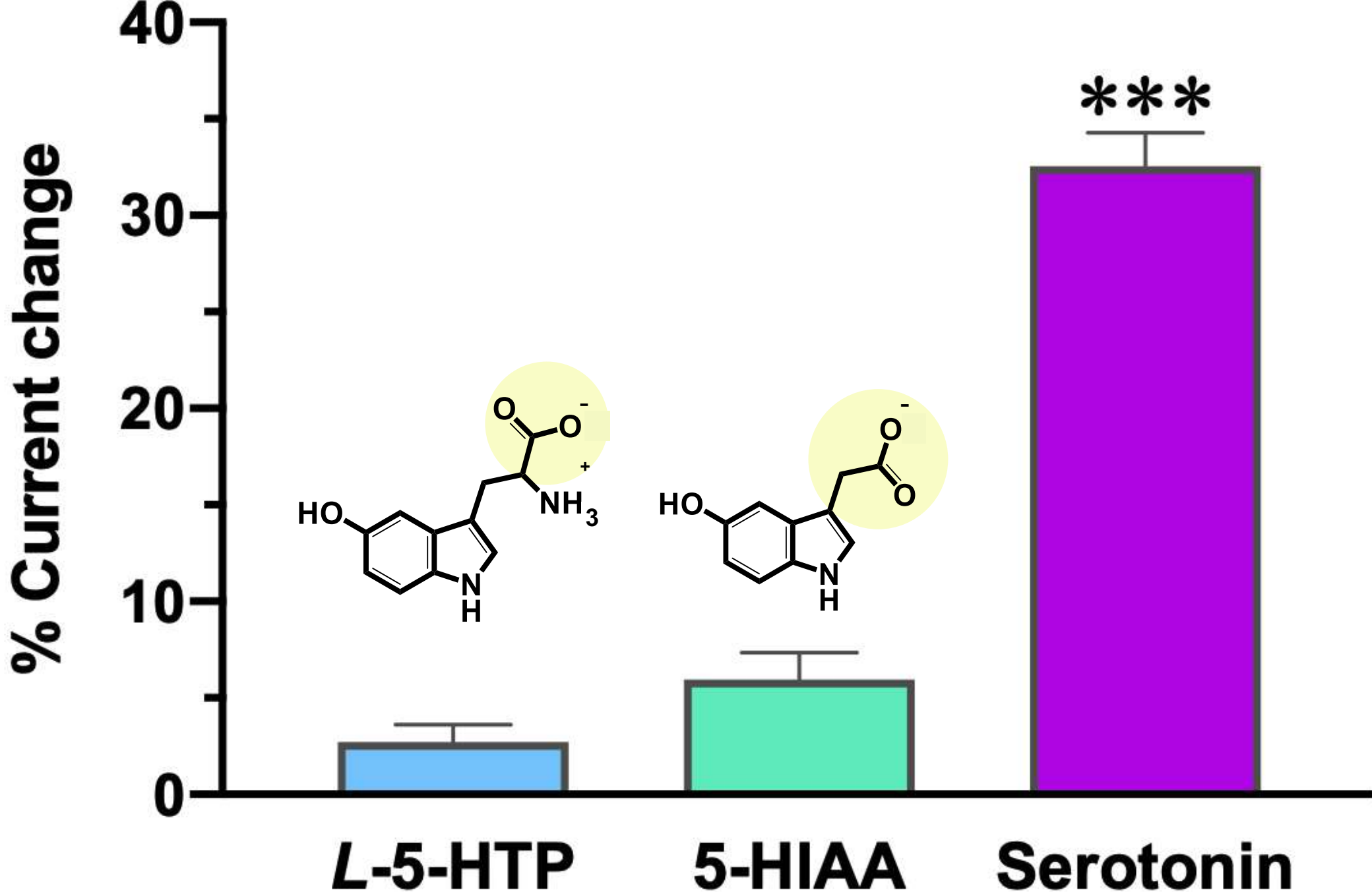
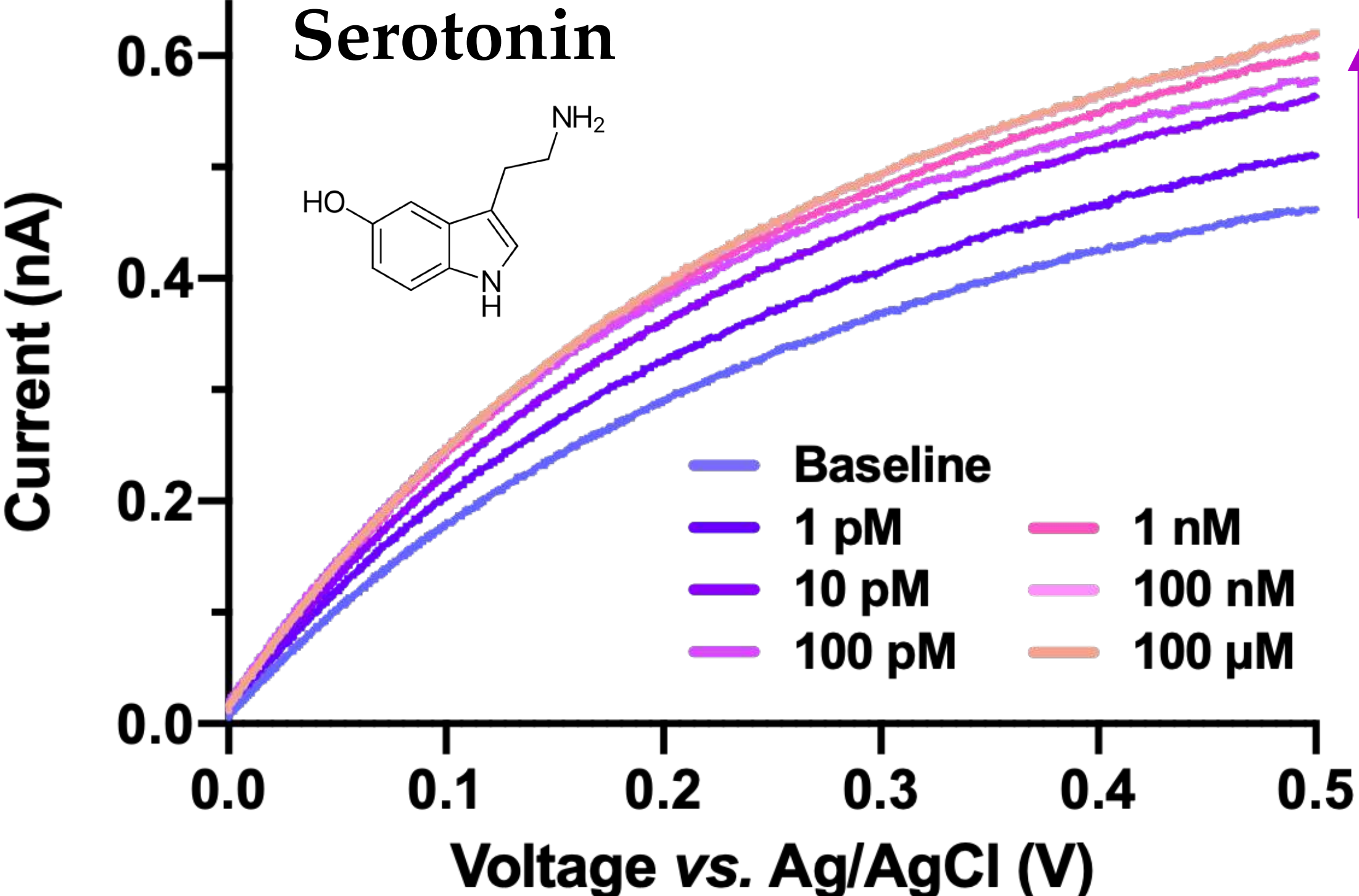
# Structure-Switching Aptamers Modulate Ionic Flux in Nanopores



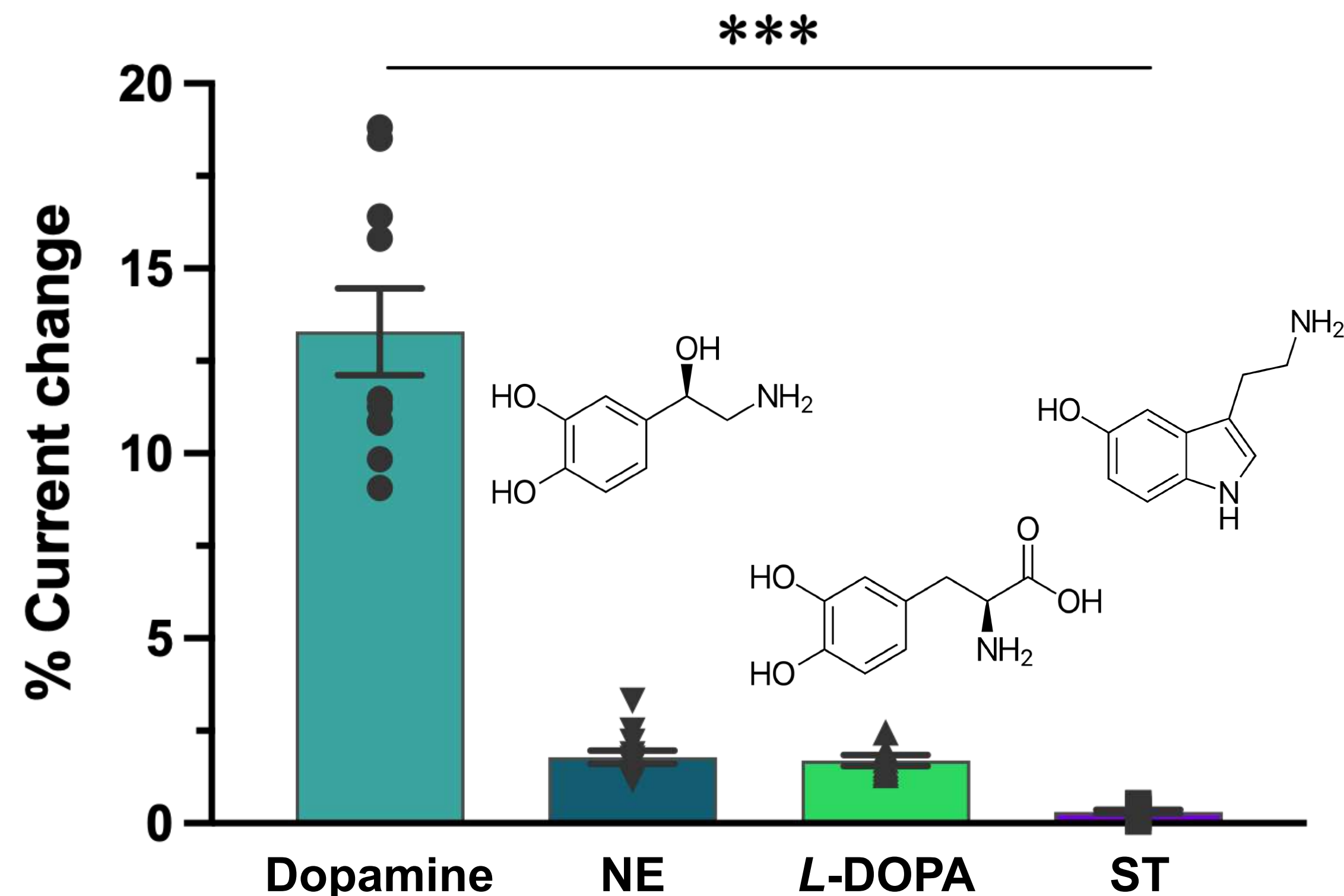
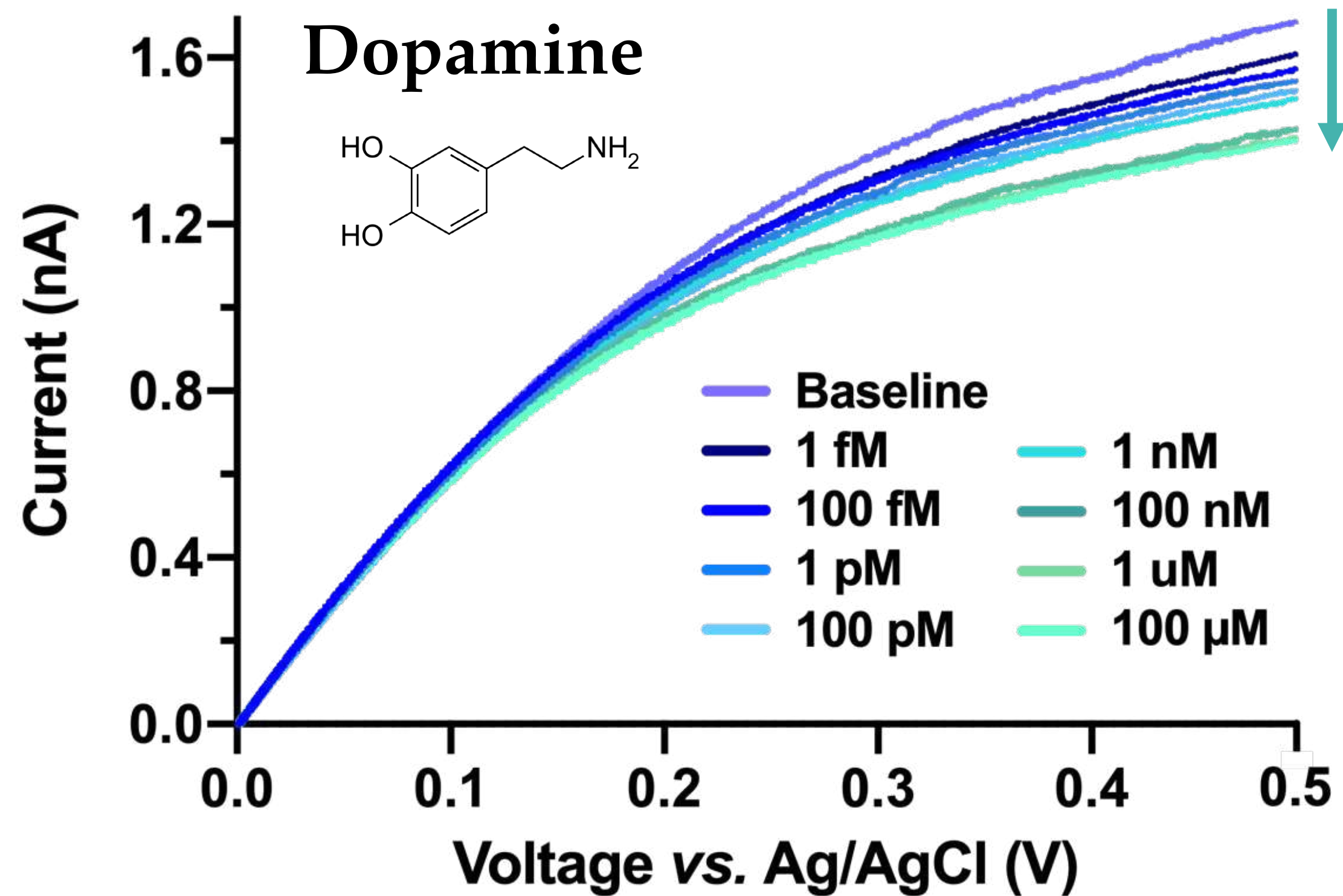
# Serotonin Sensing with Aptamer-Modified Nanopipettes



# Serotonin Sensing with Aptamer-Modified Nanopipettes

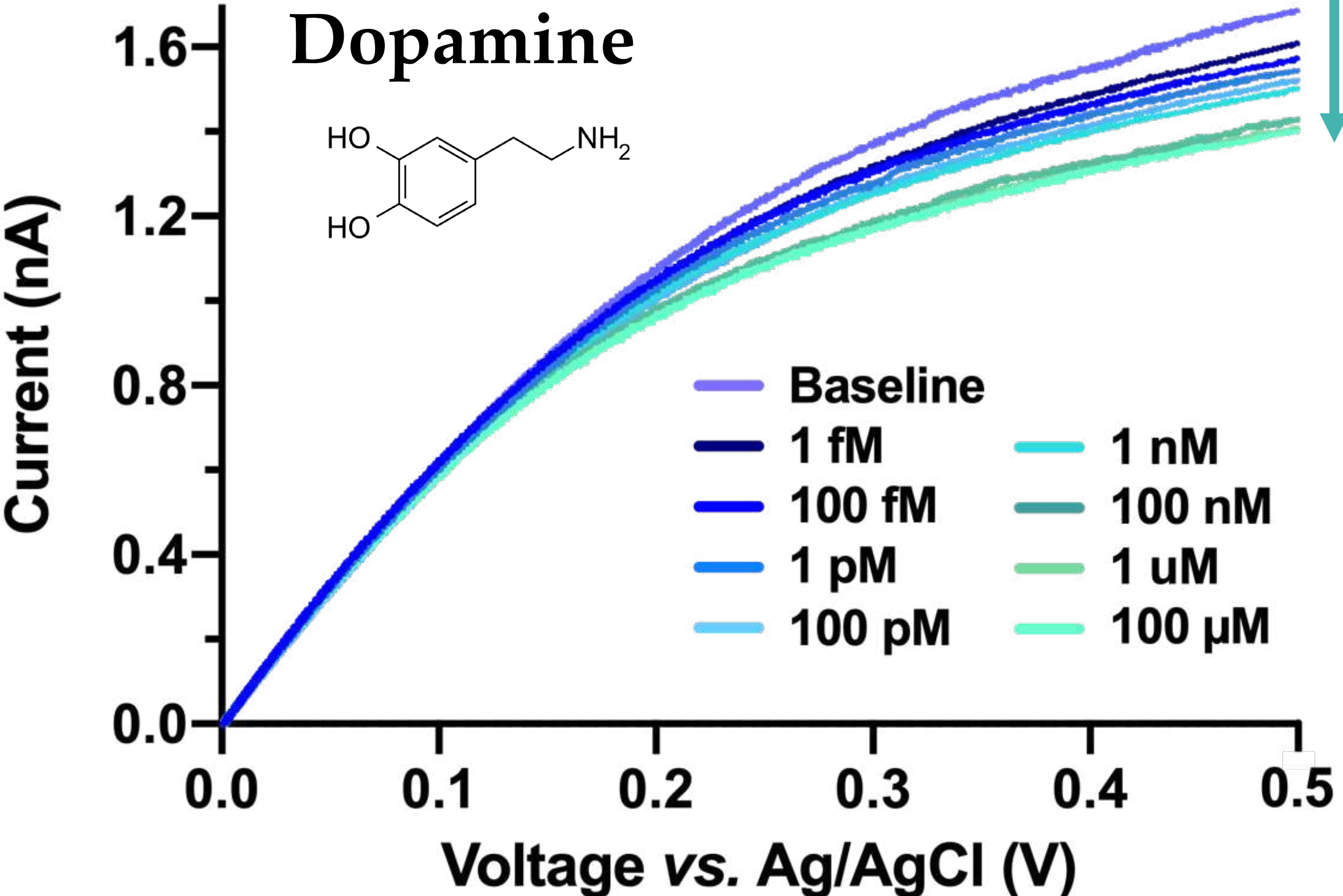


# Dopamine Sensing with Aptamer-Modified Nanopipettes

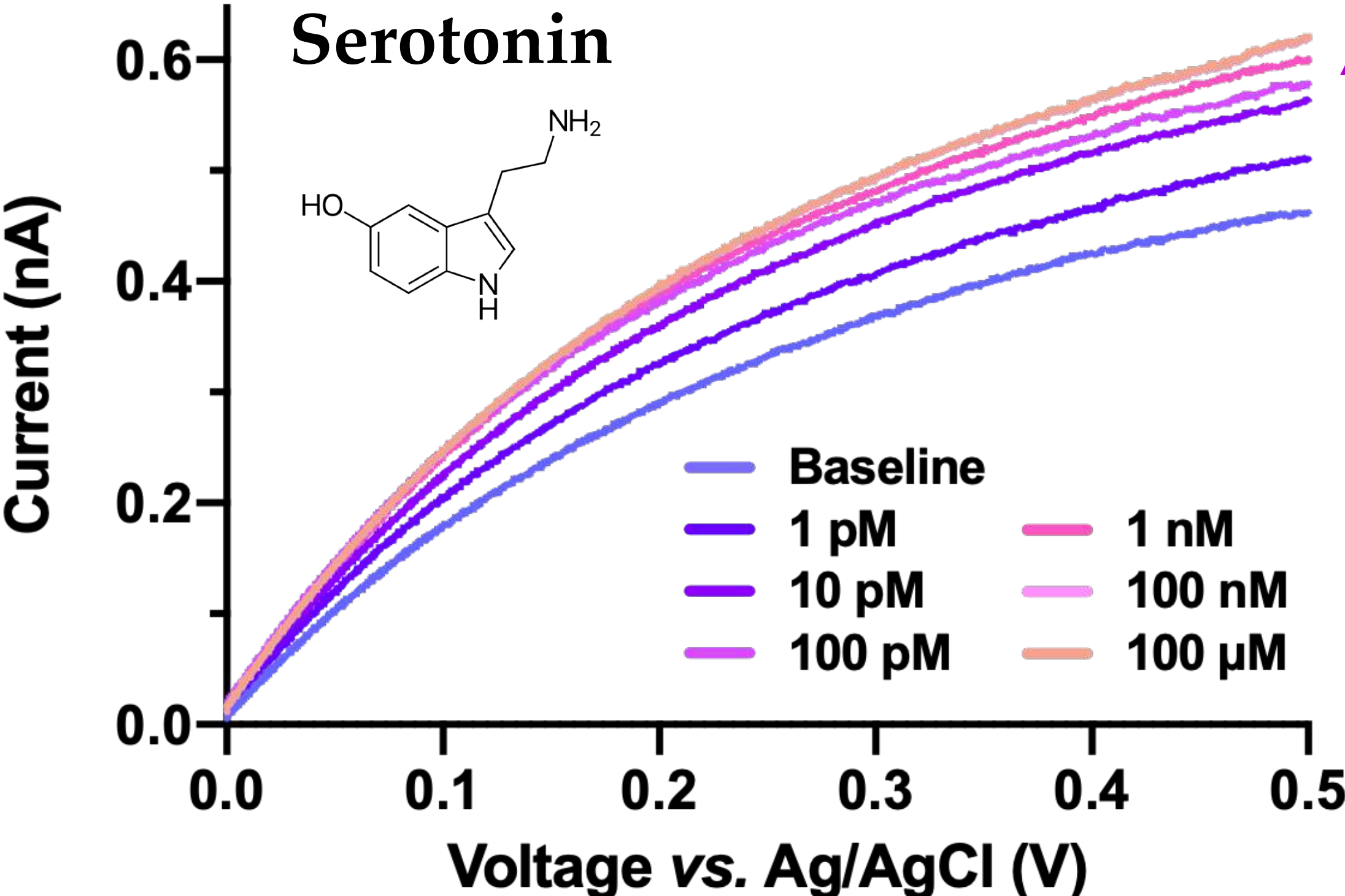


NE = norepinephrine  
ST = serotonin

# Understanding the Unexpected Behavior of Aptamer Biosensors

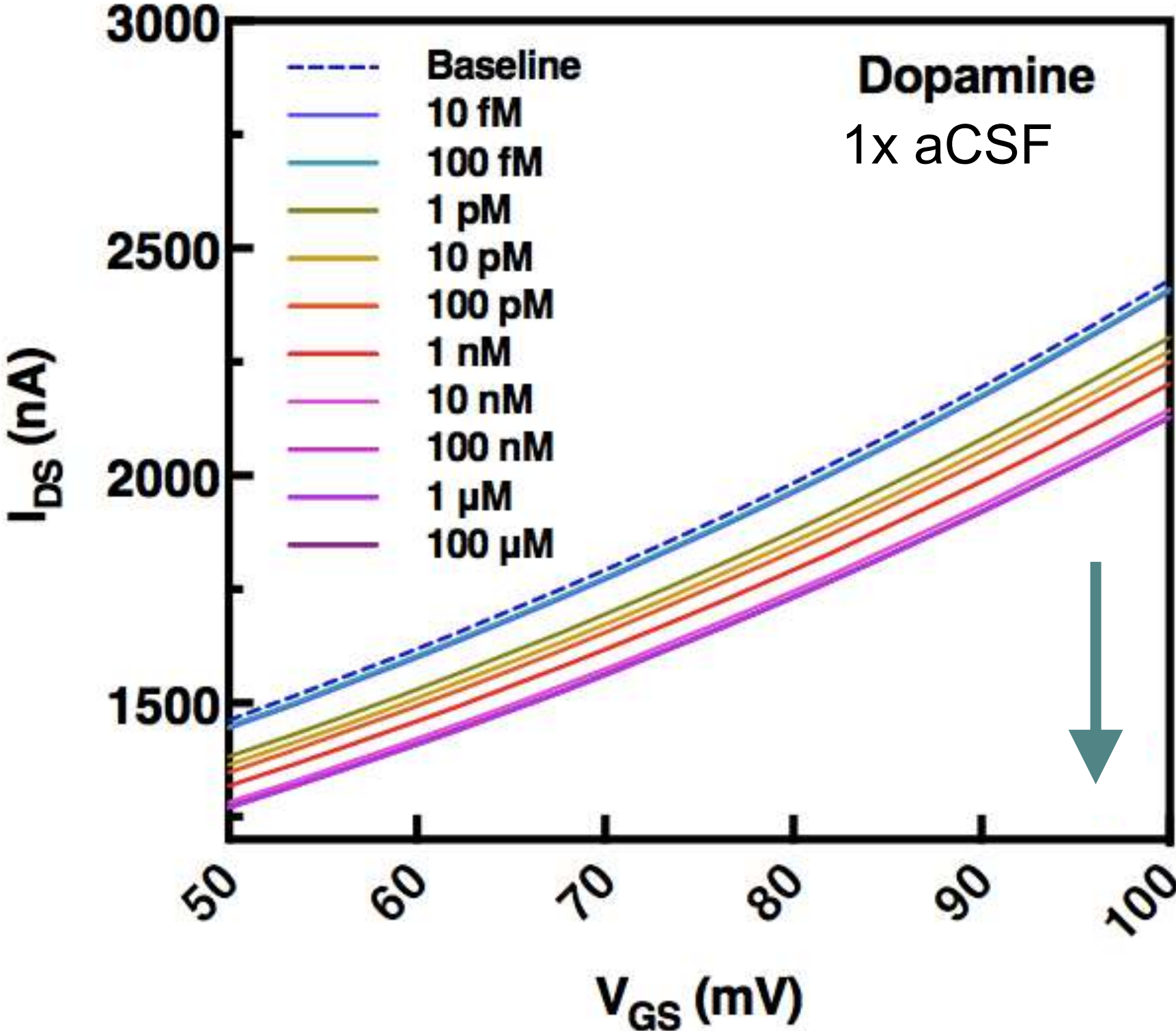
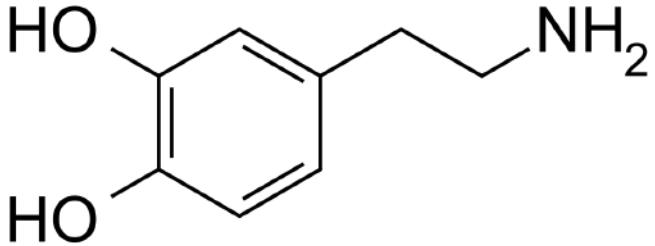
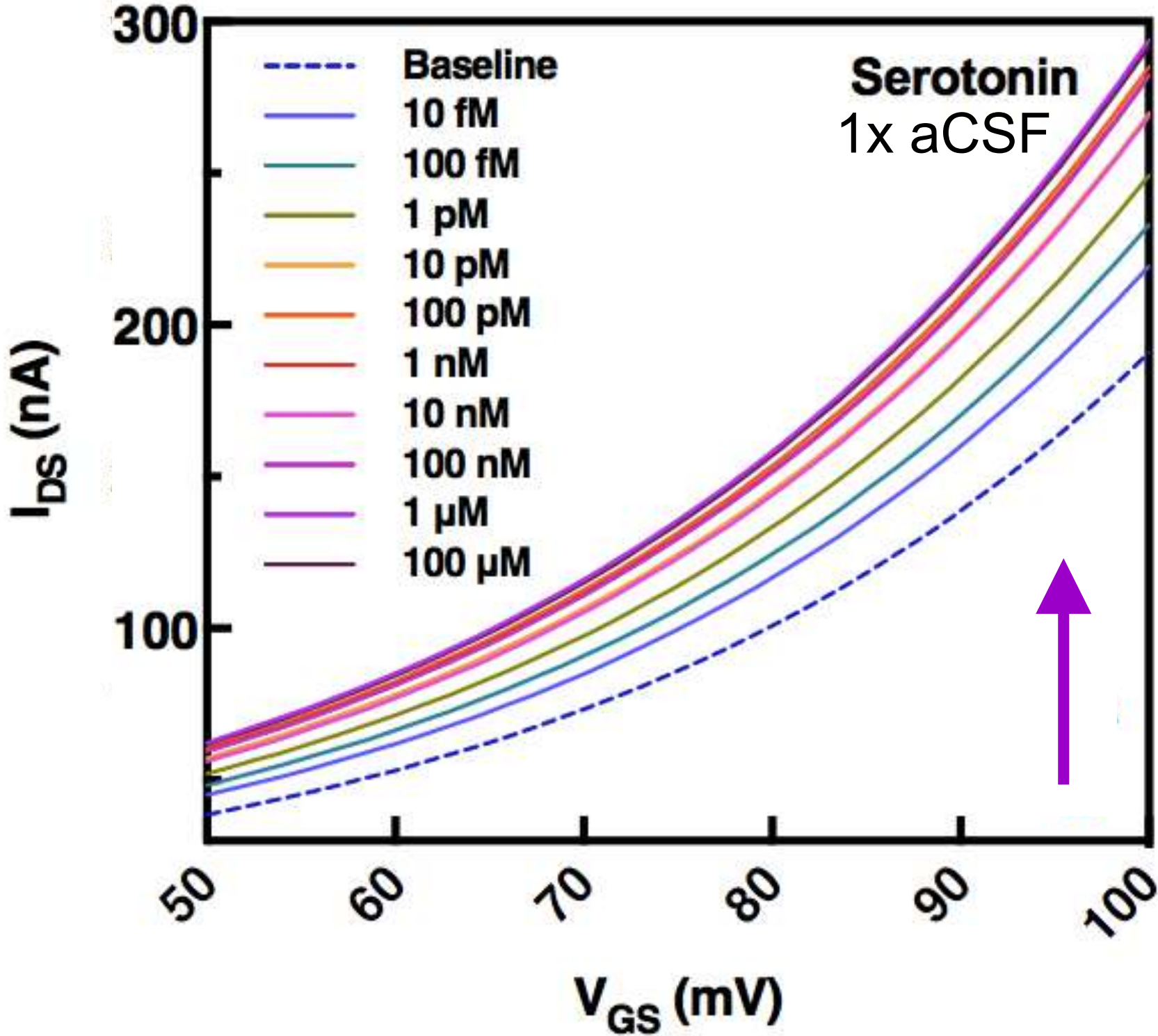
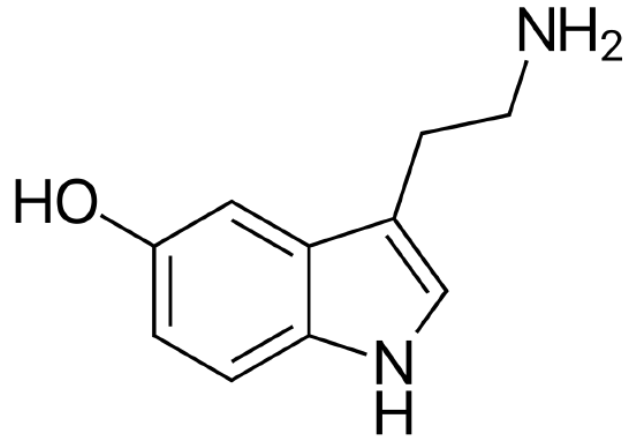


Stuber & Douaki *et al.* | *ACS Nano* | 2023



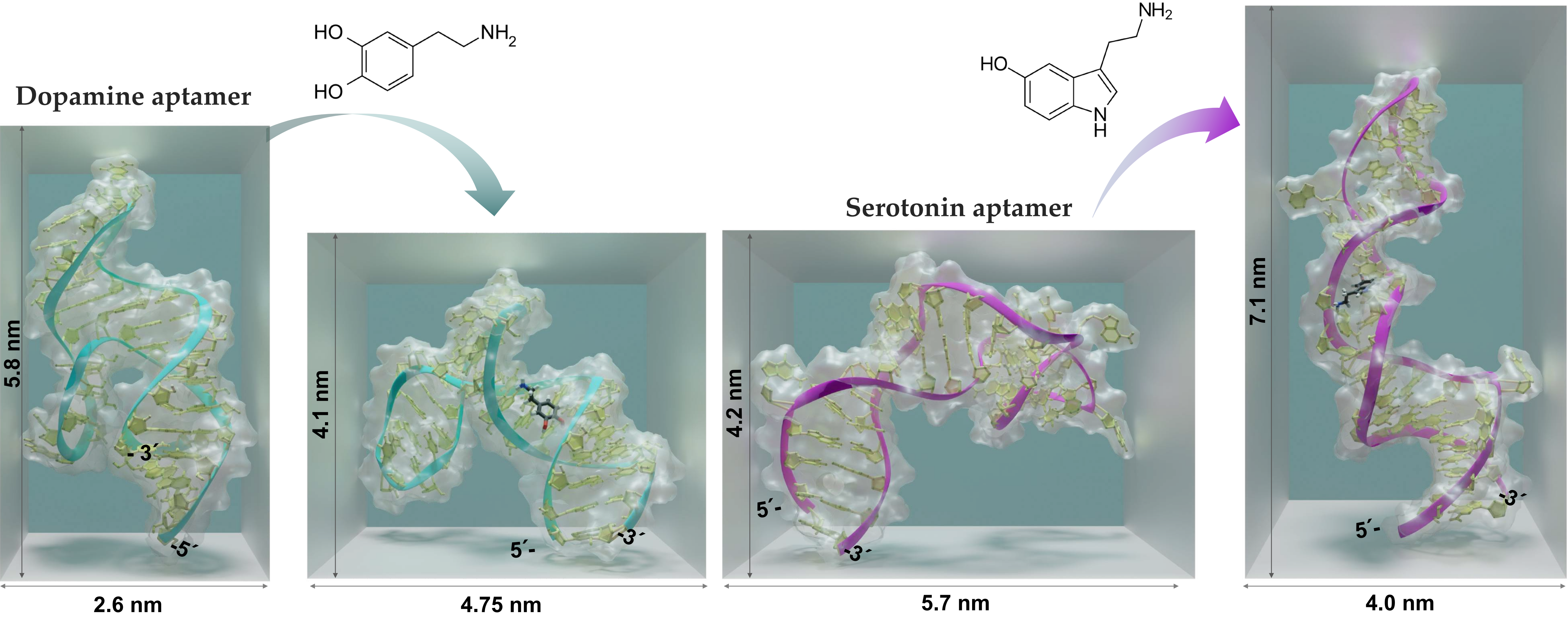
Nakatsuka *et al.* | *Analytical Chemistry* | 2021

# Divergent Sensing Behavior Conserved on Transistors

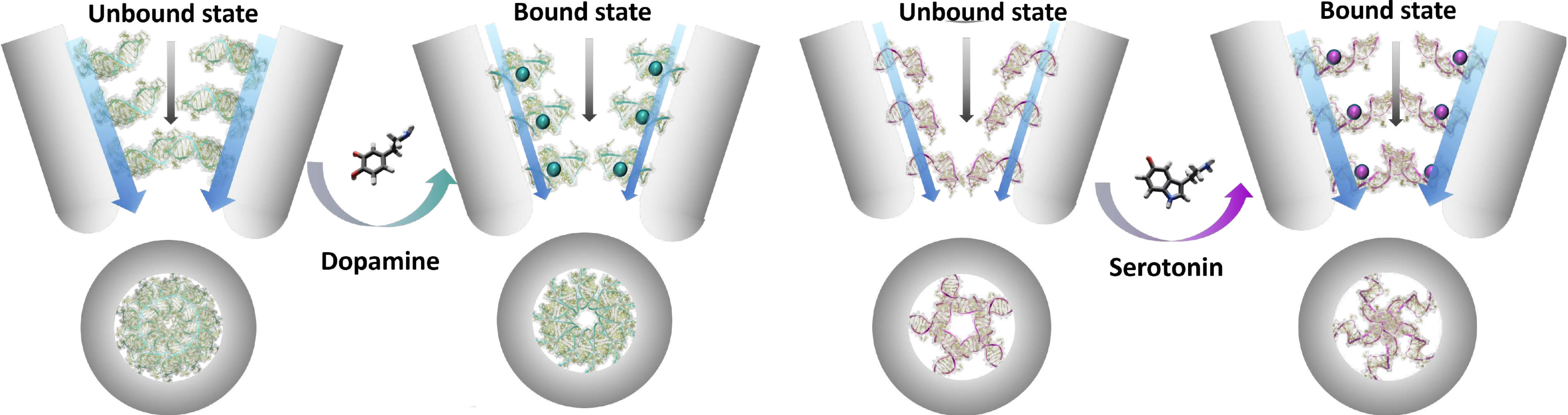


aCSF = Artificial cerebrospinal fluid

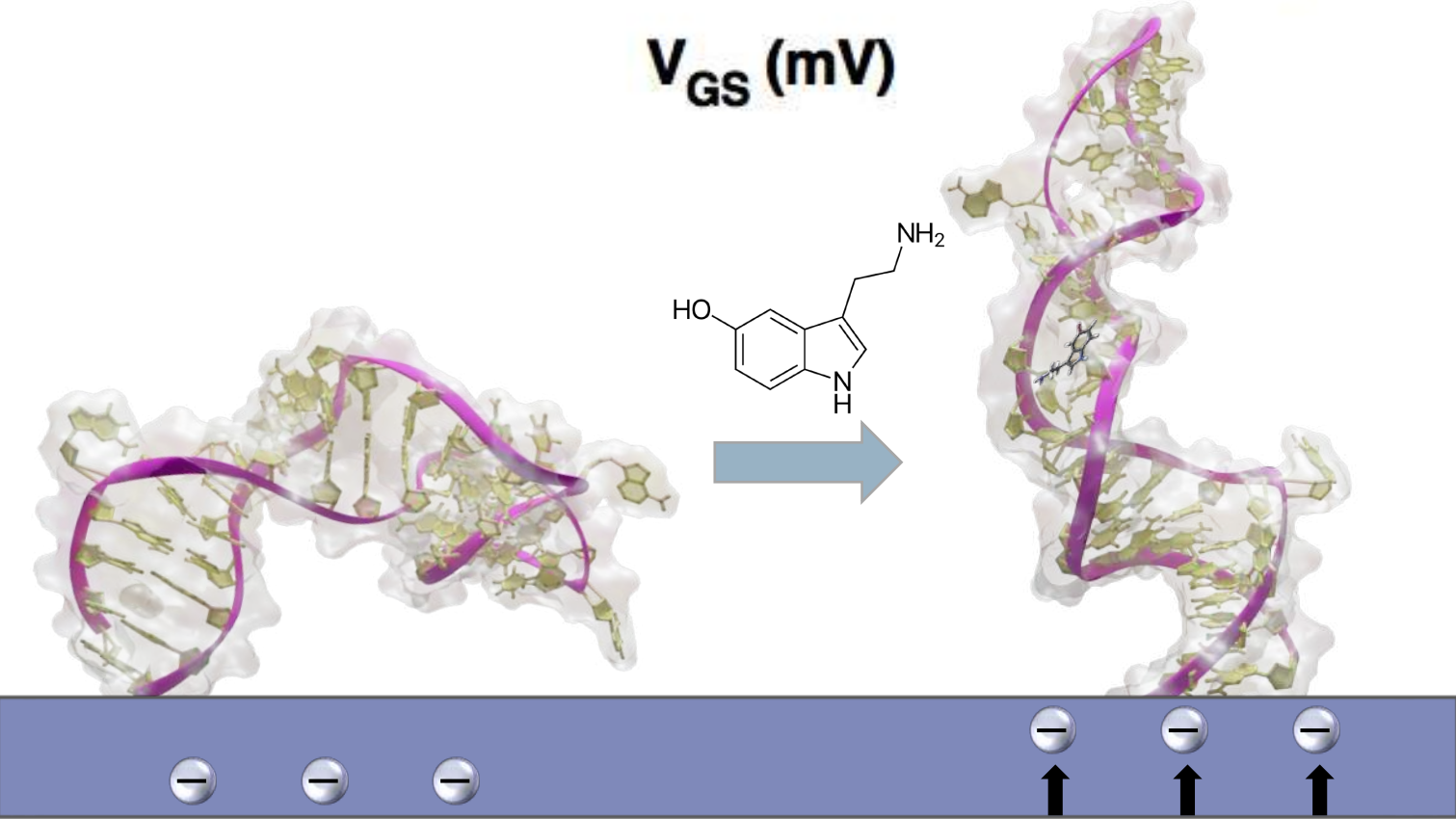
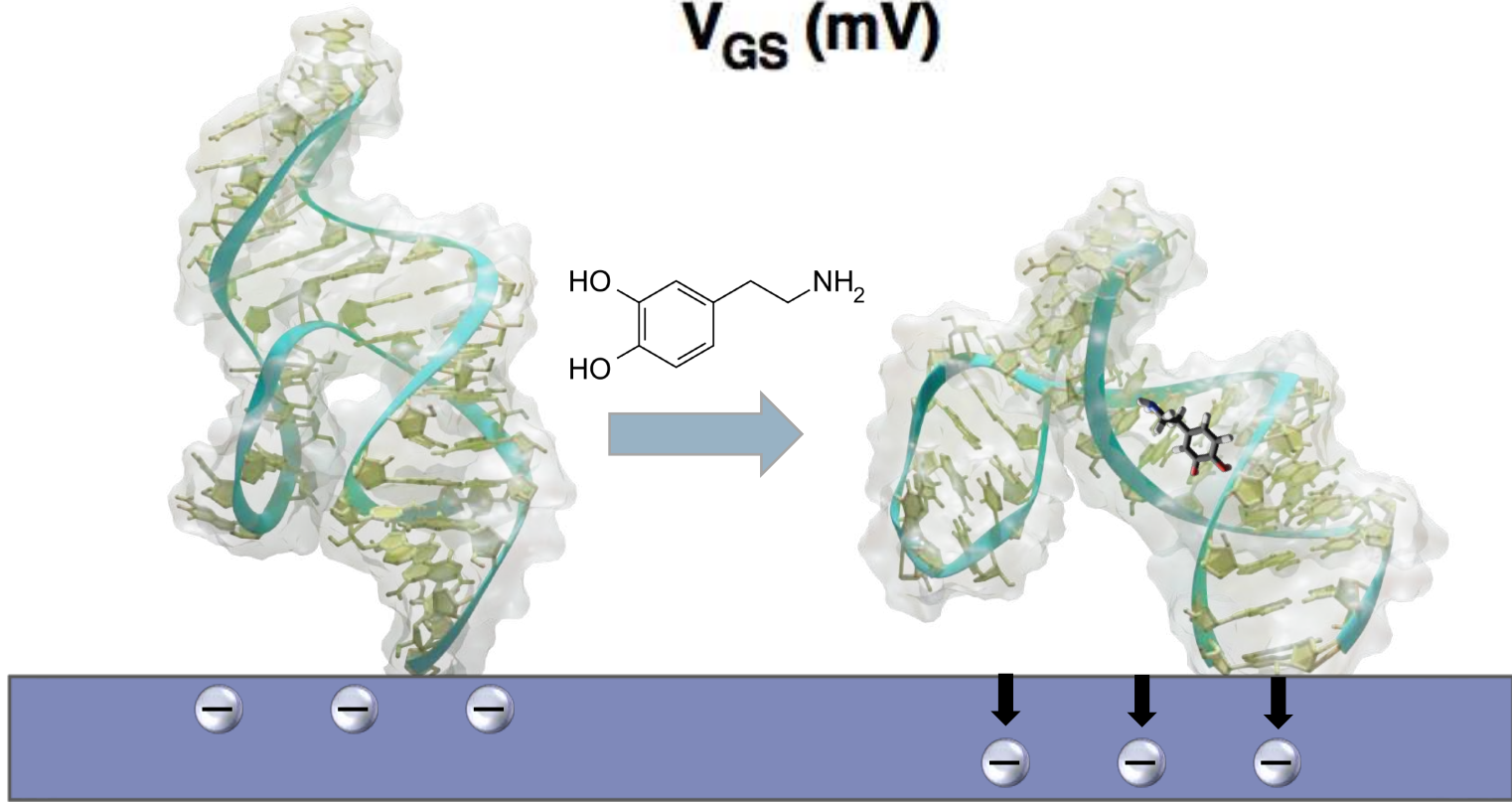
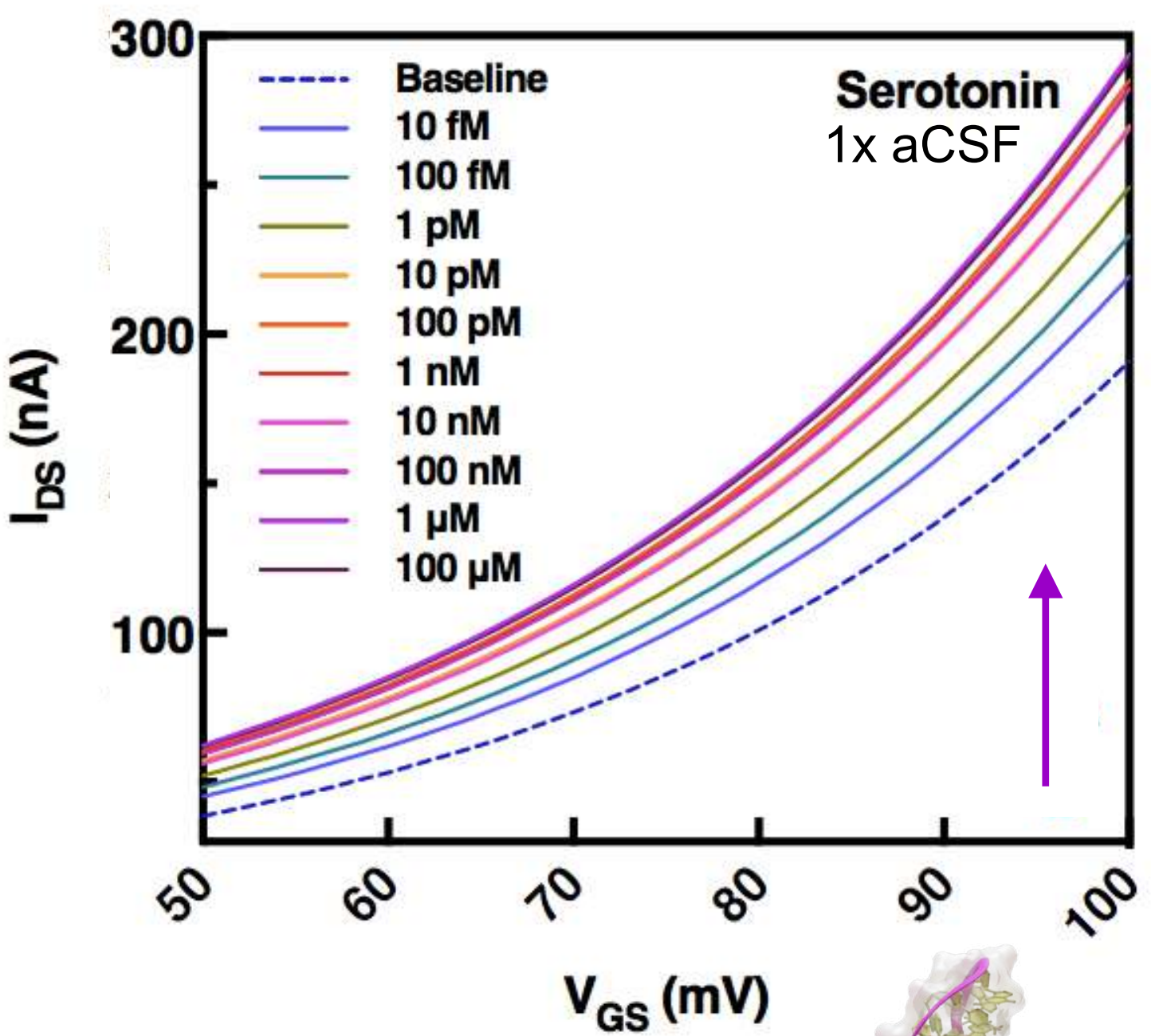
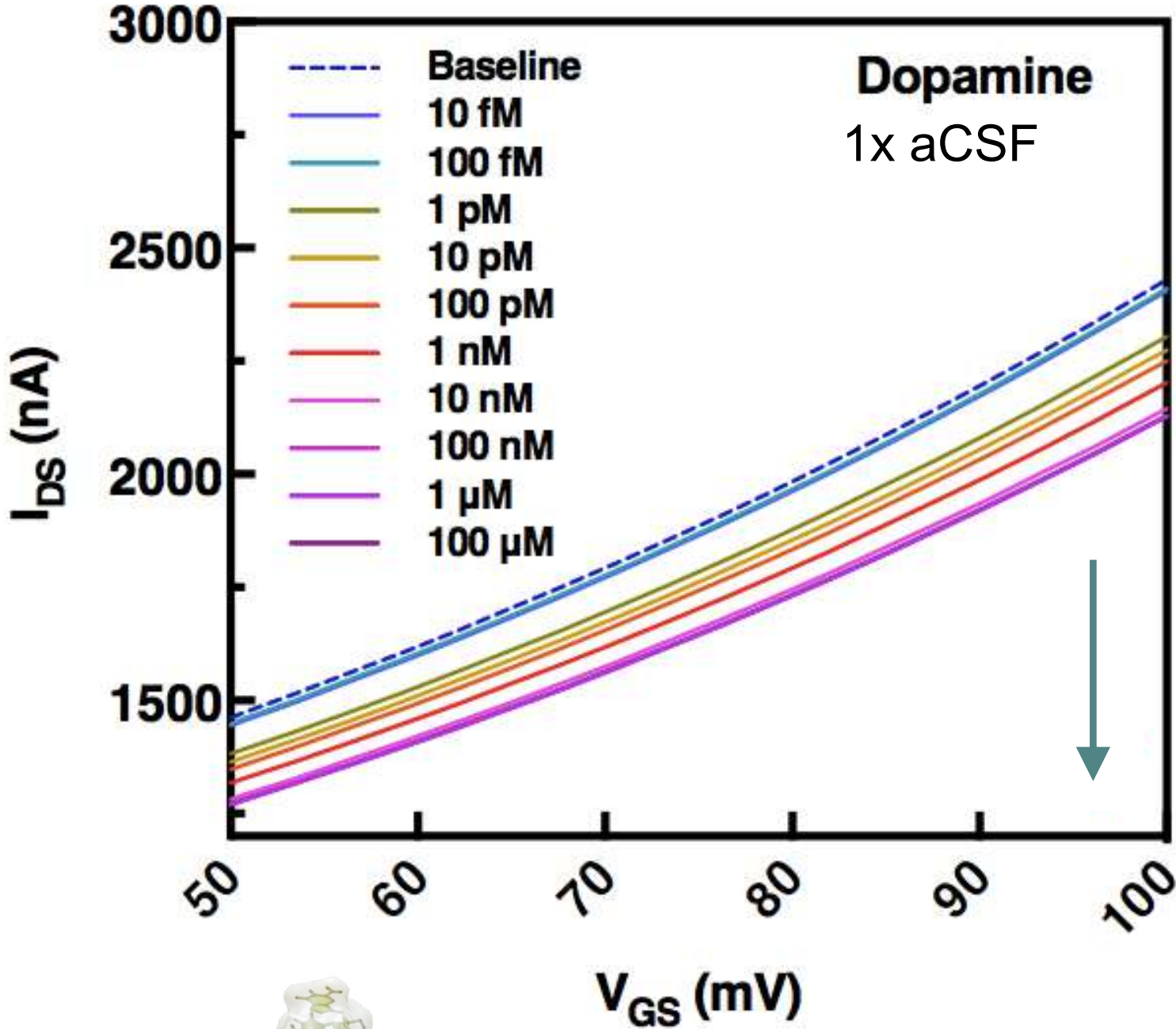
# Characterizing Aptamer-Target Binding Through Various Methods



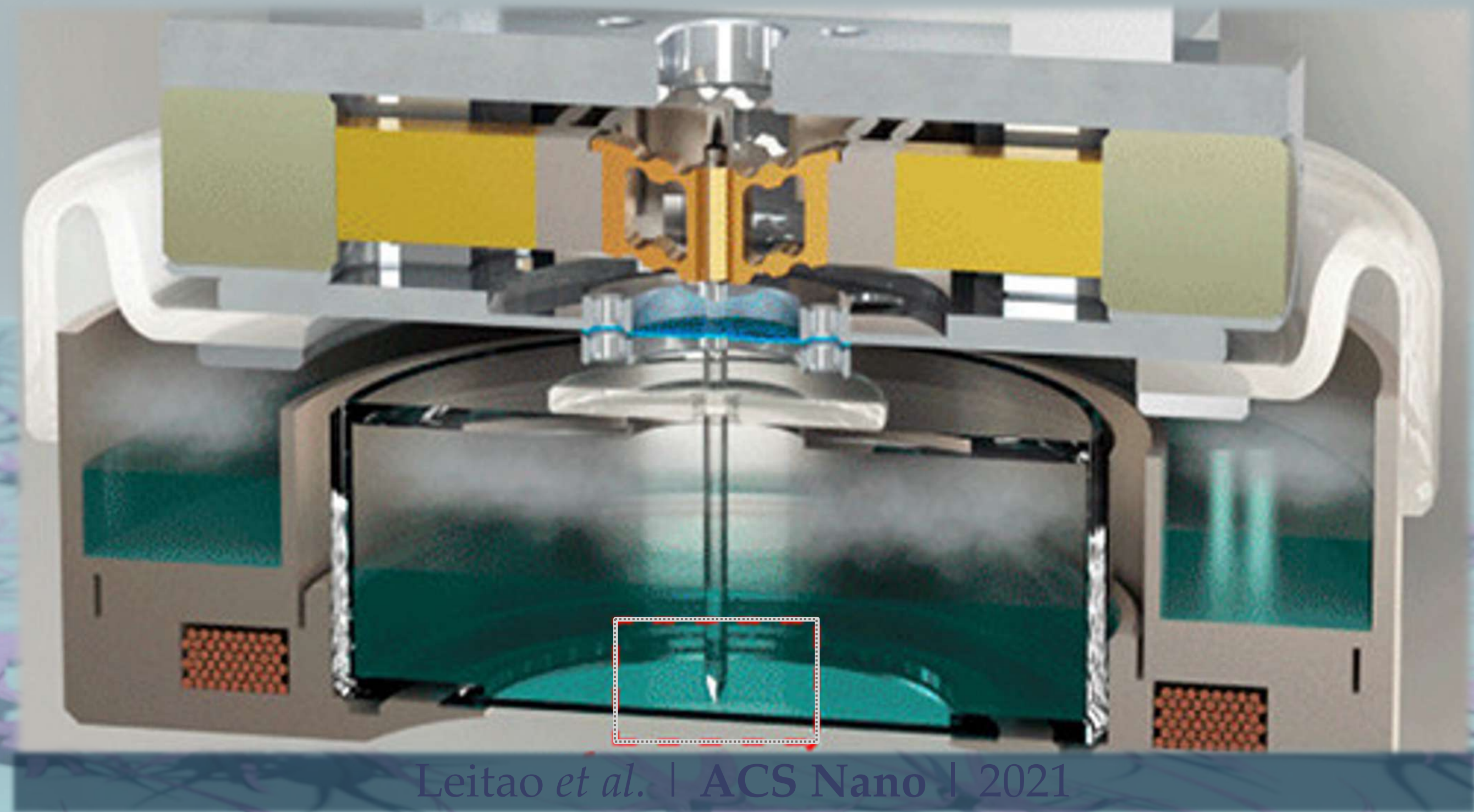
# Structure Switching of Aptamers Drives Nanopore Responses



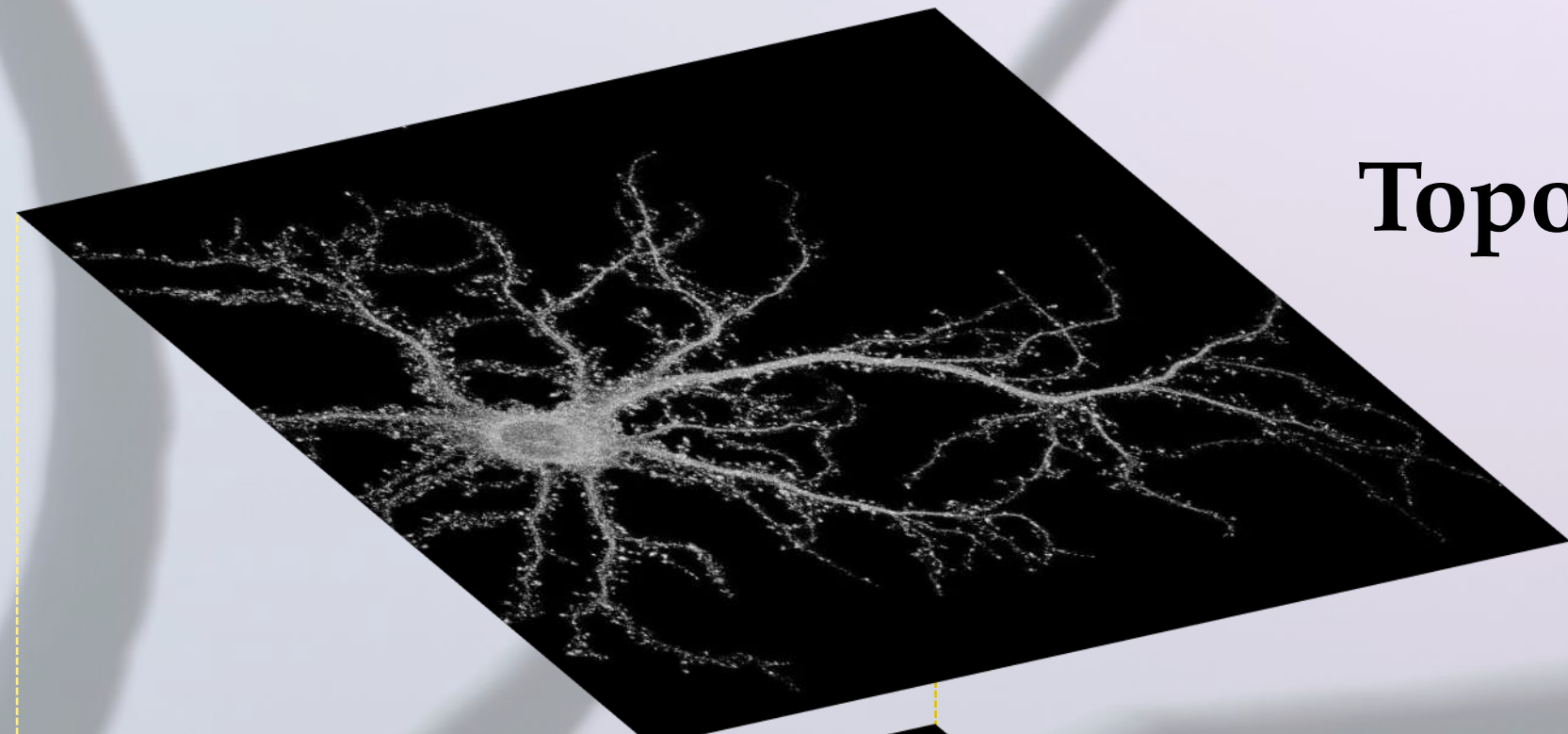
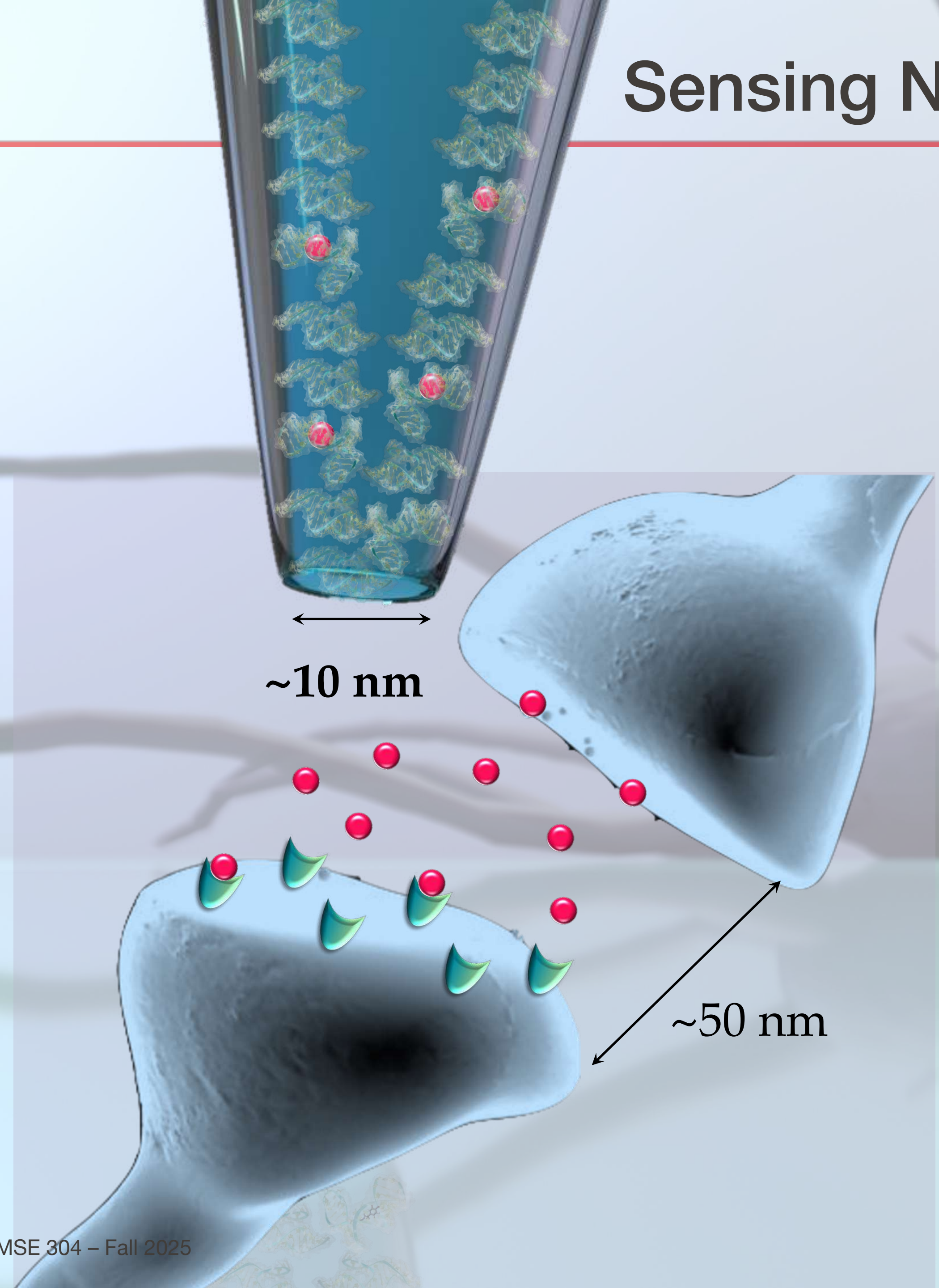
# Structure Switching of Aptamers Drives Transistor Responses



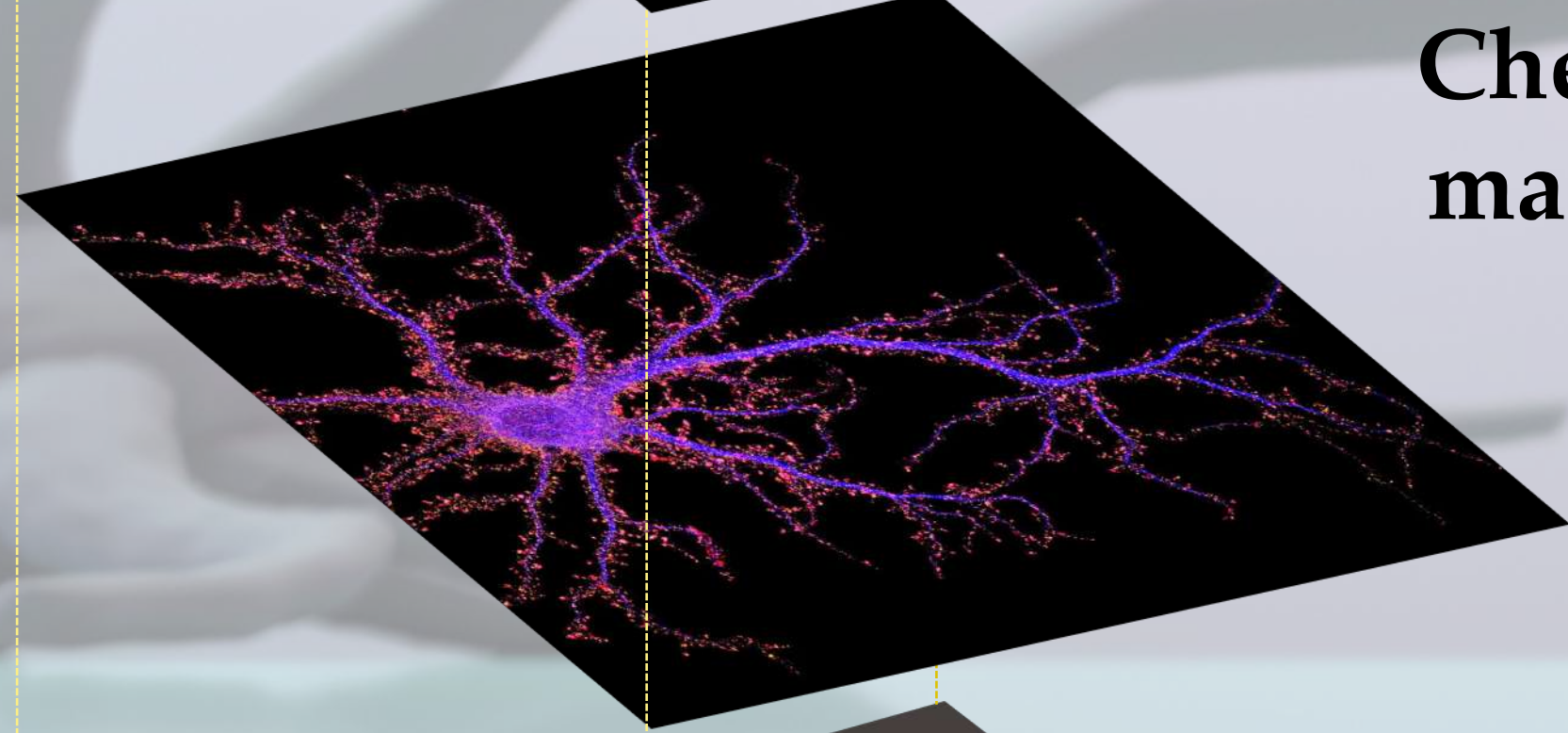
# Interfacing with Biology: Scanning Ion Conductance Microscopy



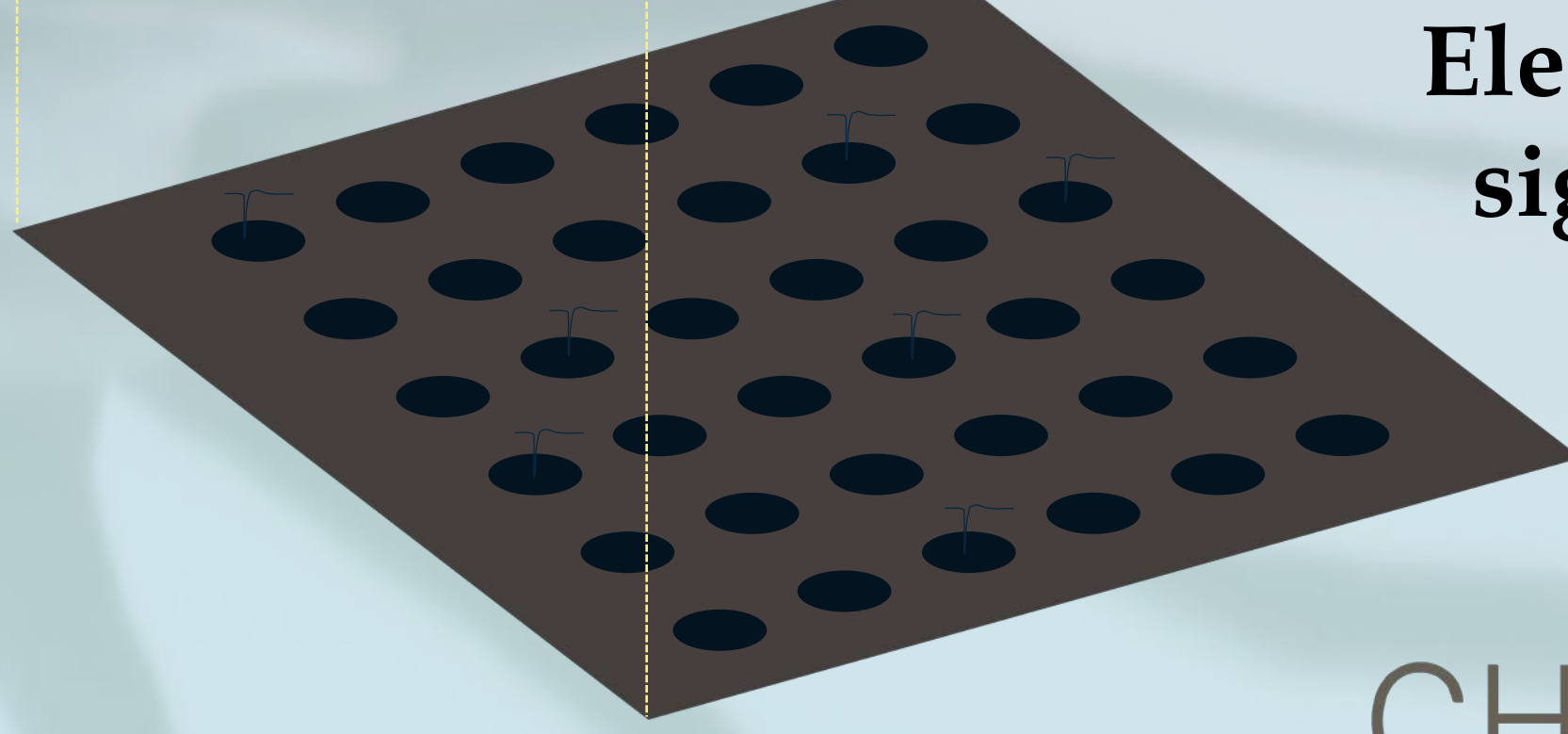
# Sensing Neurotransmitters at the Nanoscale



Topography



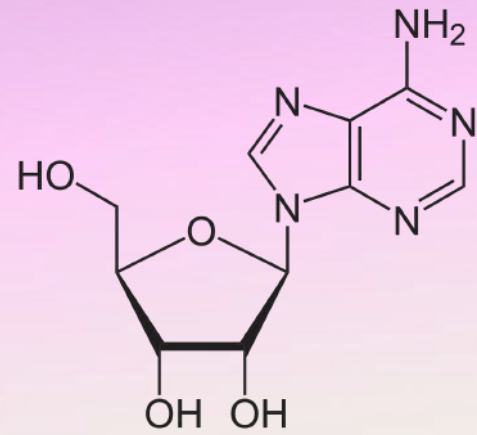
Chemical mapping



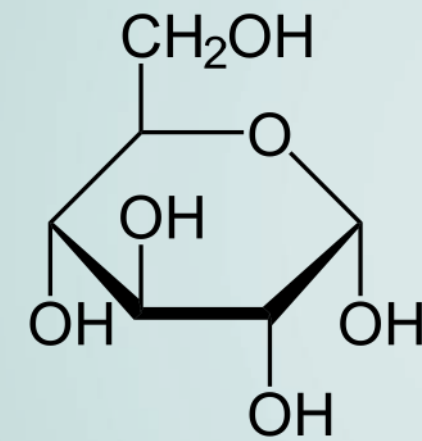
Electrical signals

# Diversity of Aptamers for Small-Molecule Targets

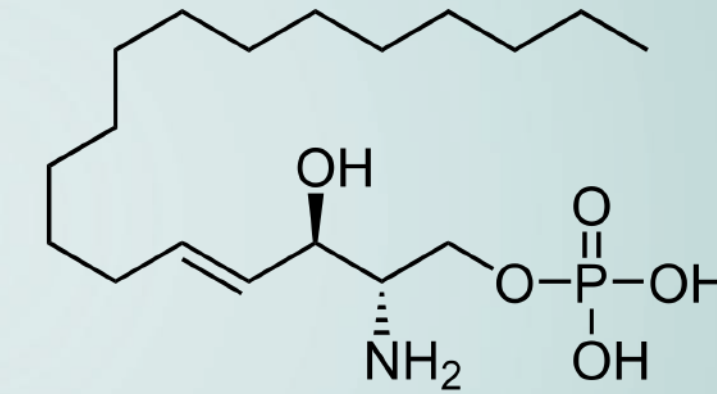
Adenosine



Sugar

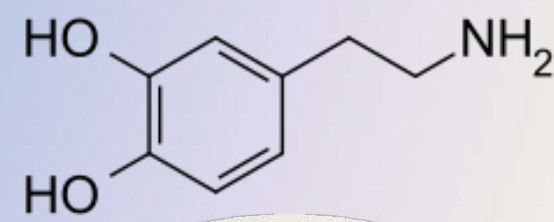


Lipid

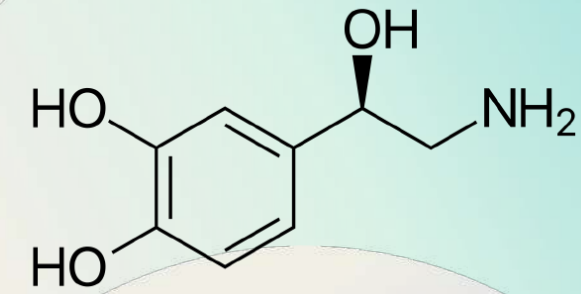


*Nakatsuka et al. | Science | 2018*

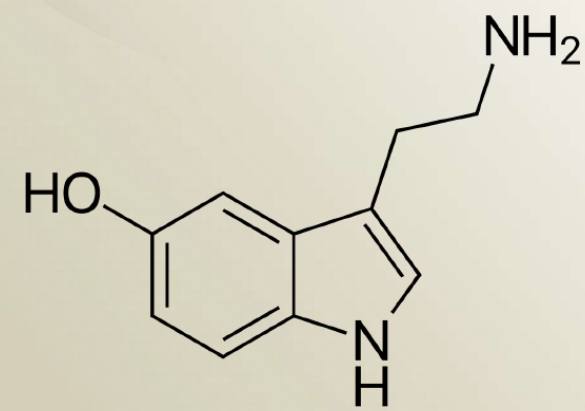
Dopamine



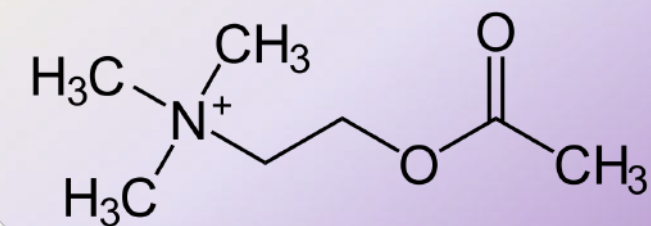
Norepinephrine



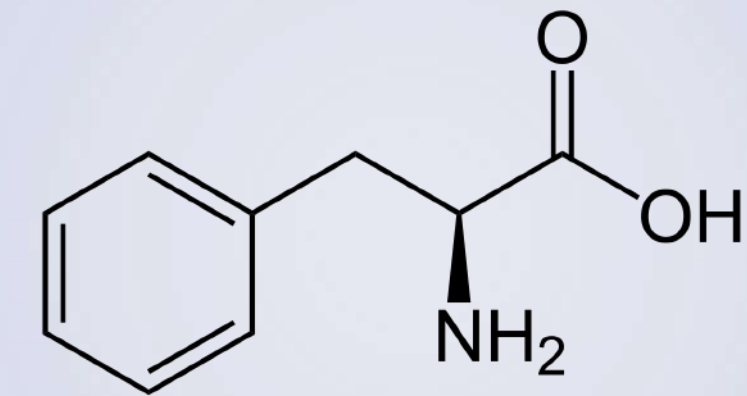
Serotonin



Acetylcholine

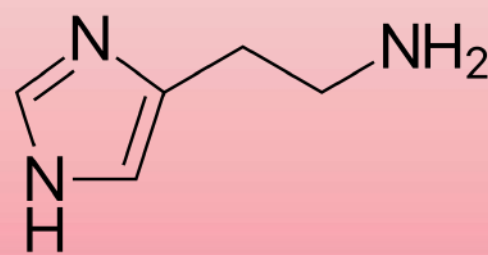


Amino acid

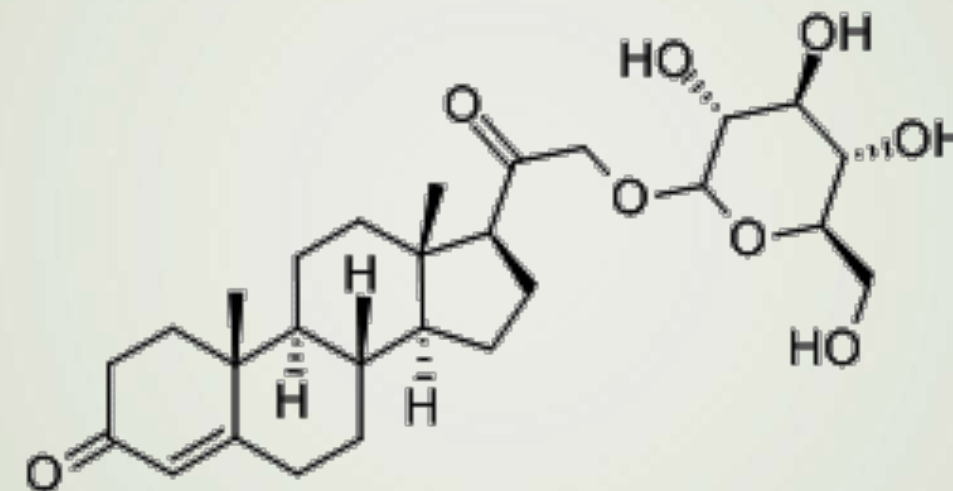


*Schlotter et al. | ACS Nano | 2024*

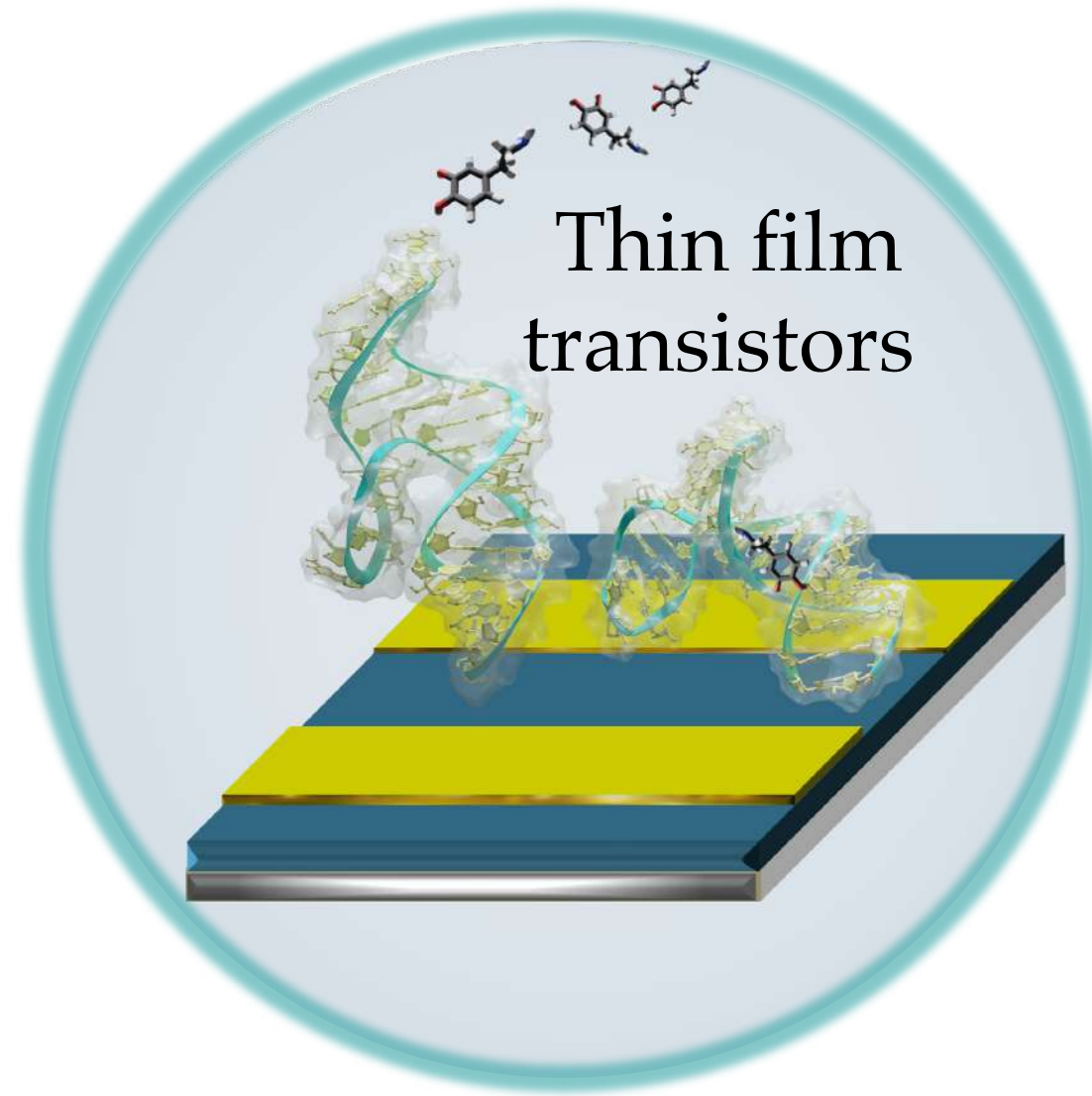
Histamine



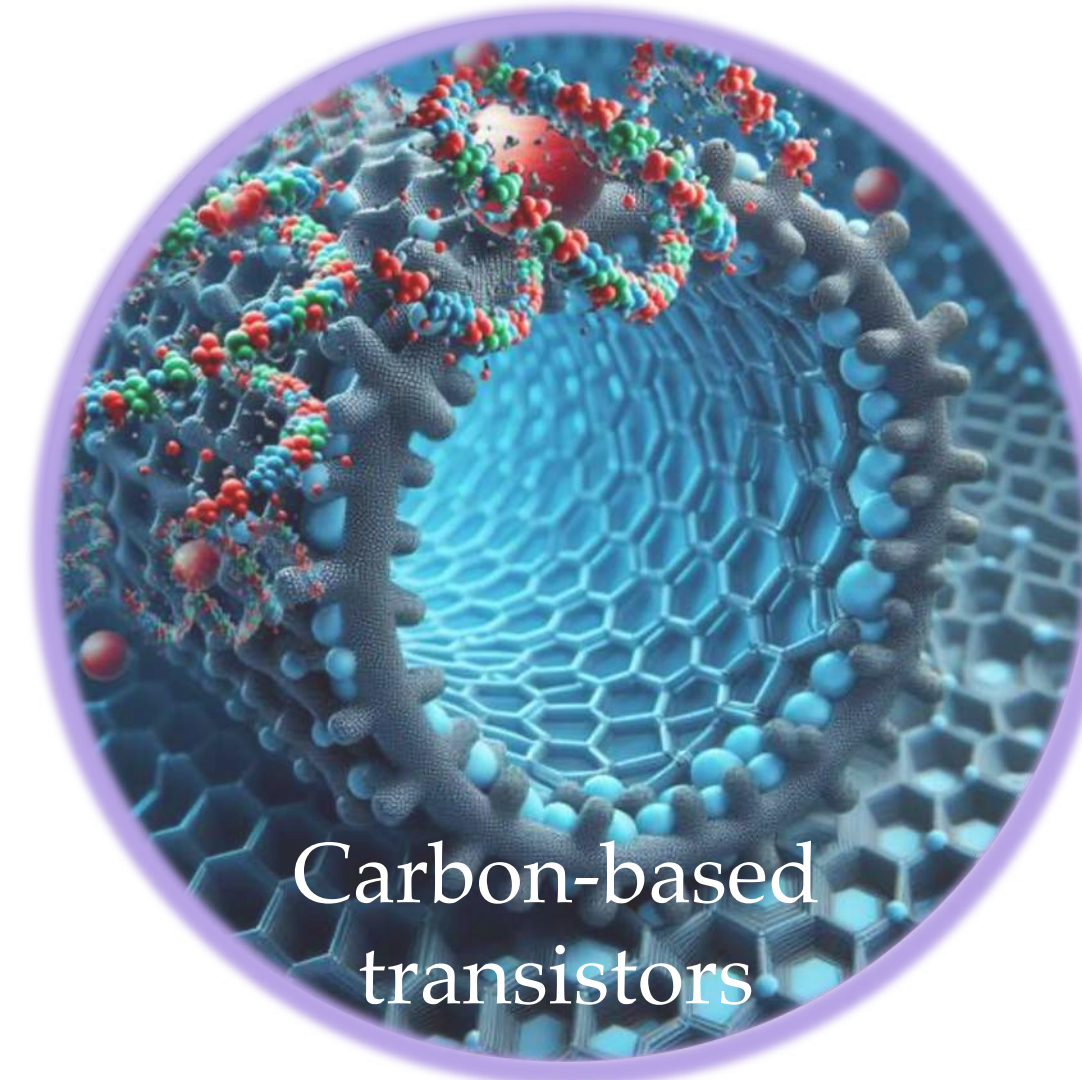
Steroid



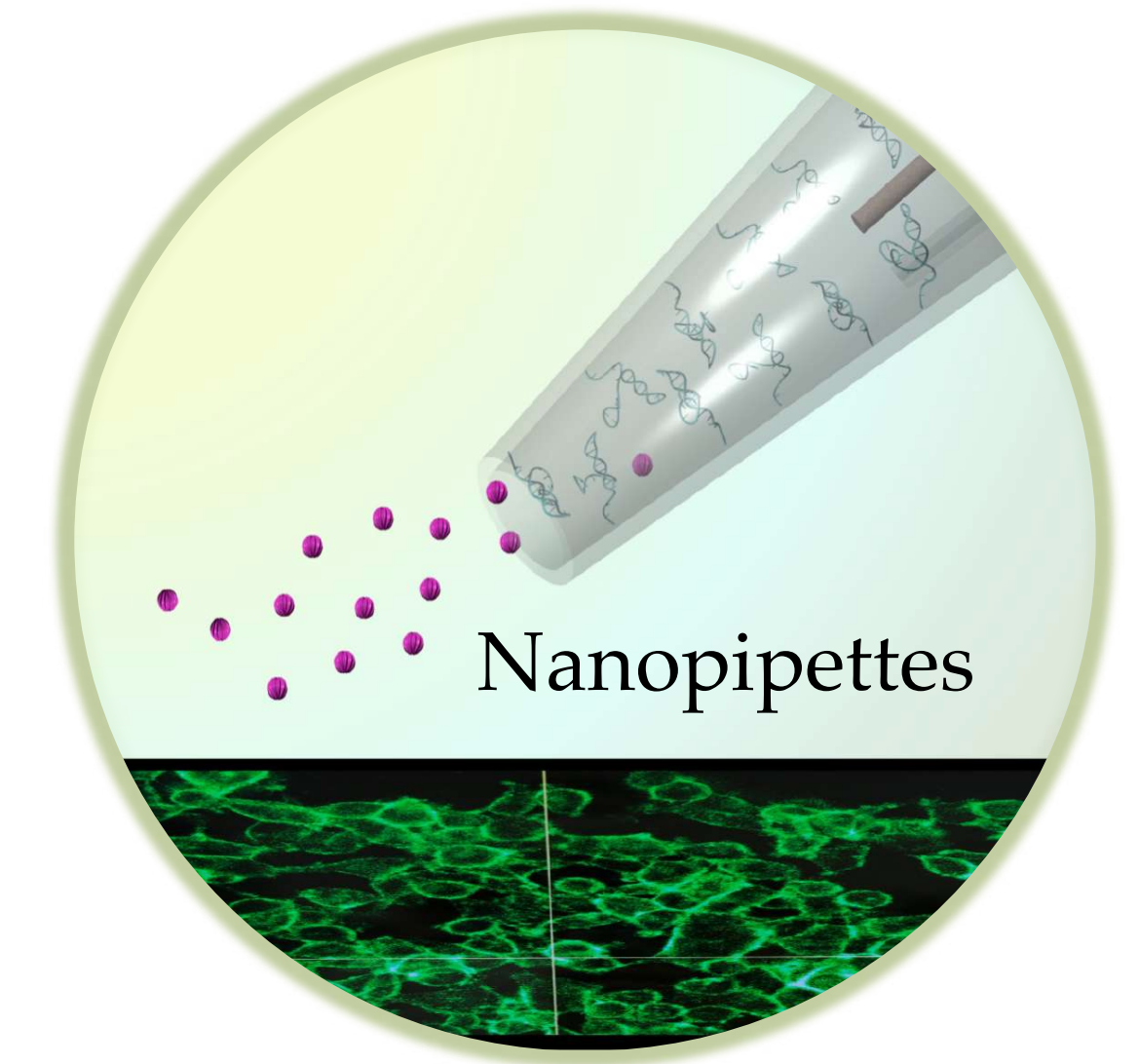
# Diversity of Technological Platforms for Biosensing



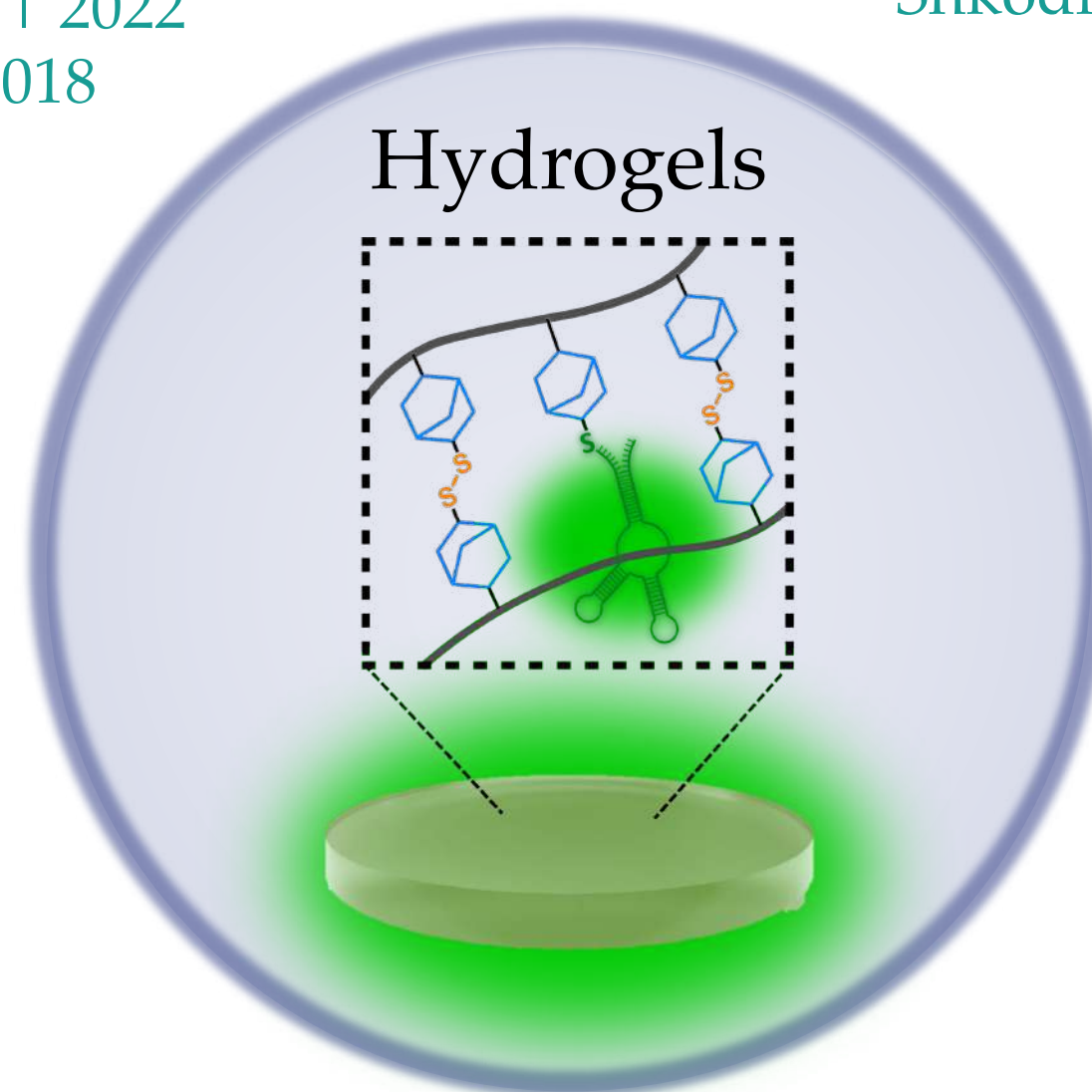
Nakatsuka | *Methods Mol. Biol.* | 2022  
Nakatsuka et al. | *Science* | 2018



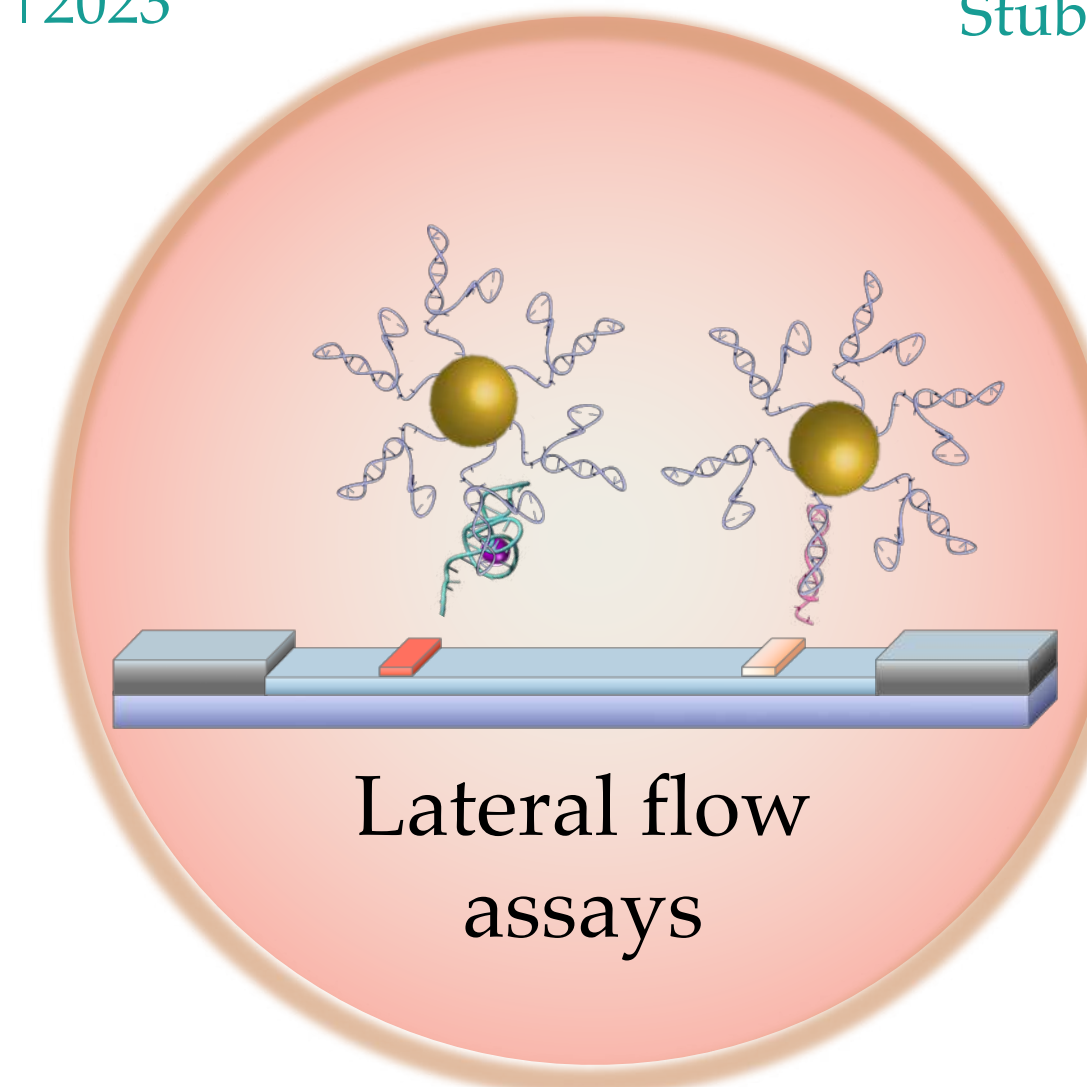
Shkodra, et al. | *Faraday Discussions* | 2024  
Broesel et al. | *Small* | 2023



Nakatsuka, et al. | *Molecular Psychiatry* | 2021  
Stuber, et al. | *ACS Nano* | 2023

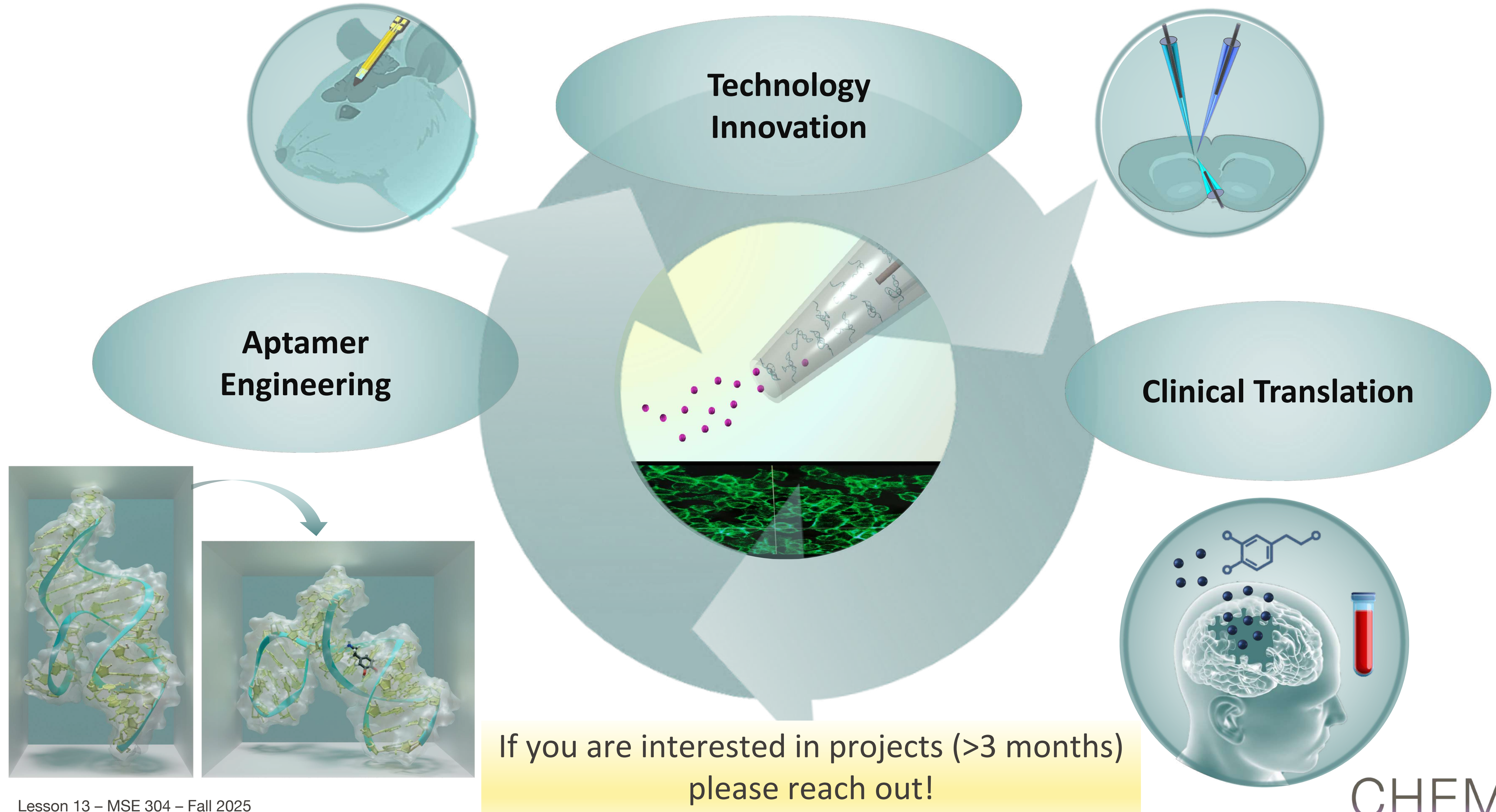


Roost, Stuber, et al.  
*Advanced Materials Interfaces* | 2025

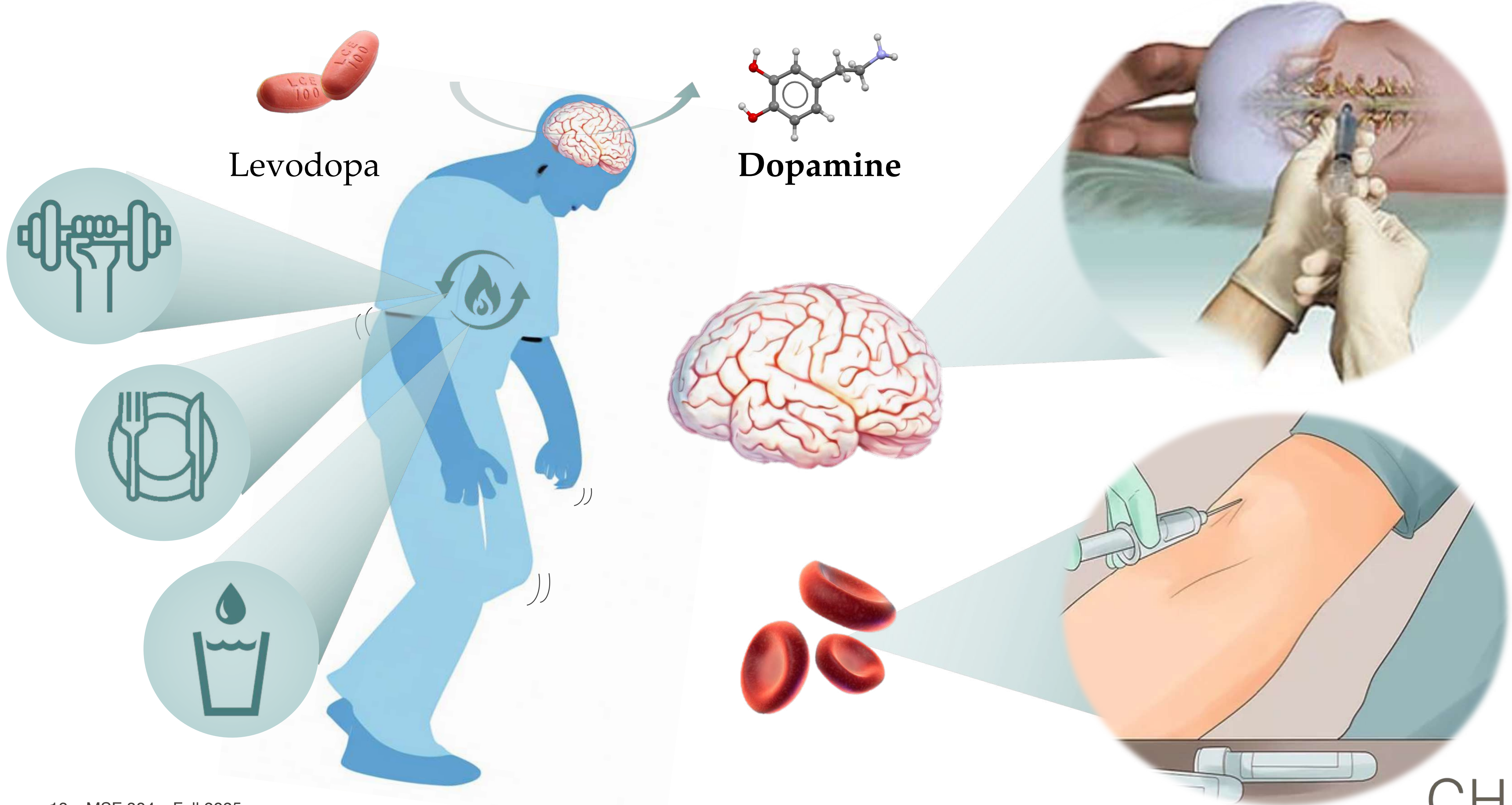


Stuber, Yang, et al. | *in review*

# CHEMINA Lab: Chemical Nanotechnologies for Human Health



# Clinical Translation: Dopamine Sensing for Parkinson's Disease



# Future of Biosensing for Human Health – Beyond Glucose Sensing



Picomolar  
 $10^{-12}$

Nanomolar  
 $10^{-9}$

Micromolar  
 $10^{-6}$

Millimolar  
 $10^{-3}$

# Summary of Today's Class

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- Different requirements for biosensors that function in biological environments
- The final application drives the different parameters
- Challenges of biosensing neurotransmitters in brain research
- Aptamer-based biosensors – transistors and nanopores
- Diversity of Molecules and Biosensing Platforms
- Come and do a project in our lab in the future if these topics interest you 😊

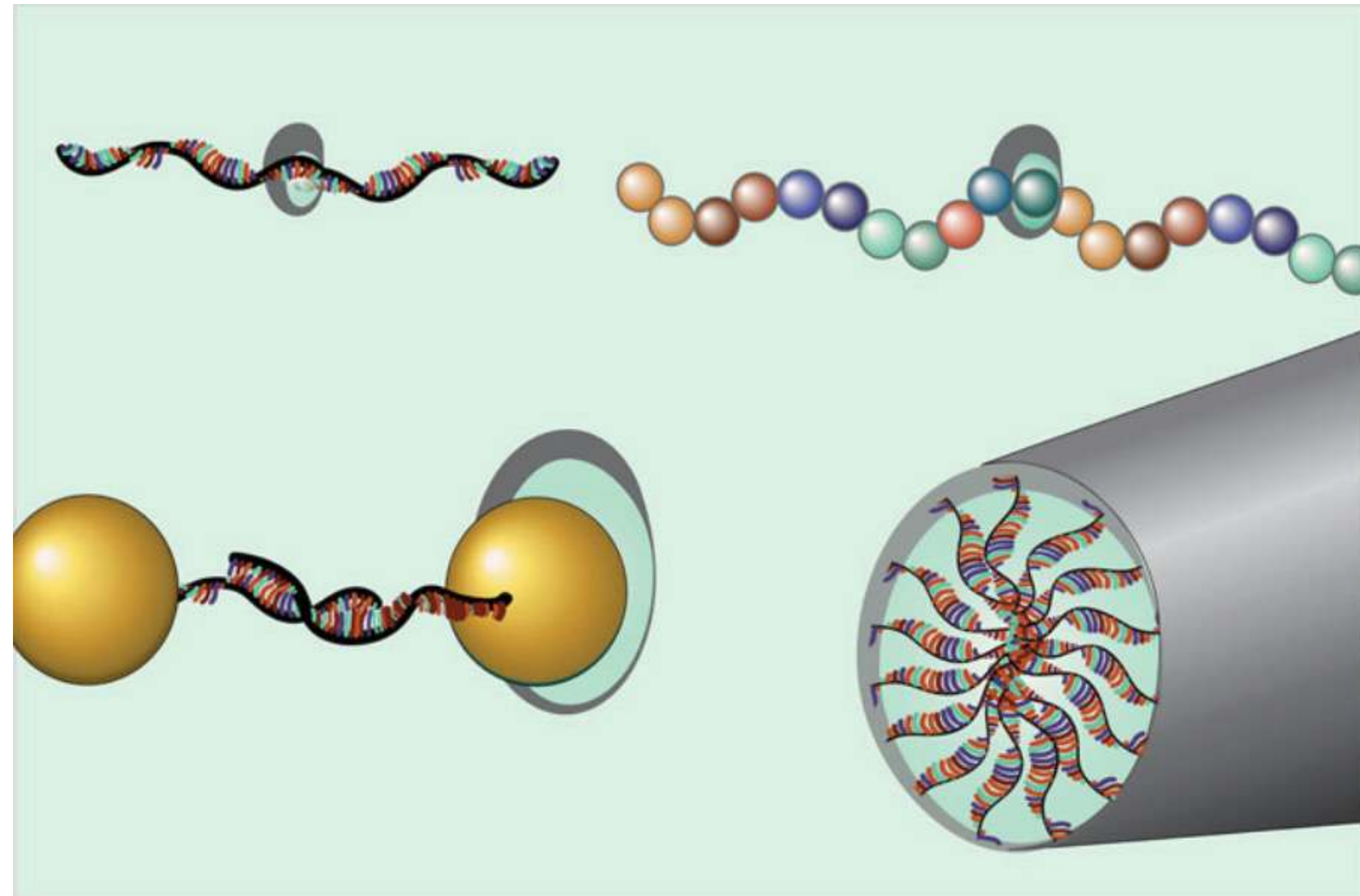
# Biosensing Textbook (Resource on Moodle)



## Solid-State Nanopores for Biomolecular Analysis and Detection



**Annina Stuber, Tilman Schlotter, Julian Hengsteler, and Nako Nakatsuka**



# Laboratory of Chemical Nanotechnology

Driving Innovation with a Multidisciplinary International Team



Nako  
Nakatsuka



Jessica  
Empain



Emily  
Schafer



Annina  
Stuber



Lianxin  
Xu



Ali  
Elmorsy



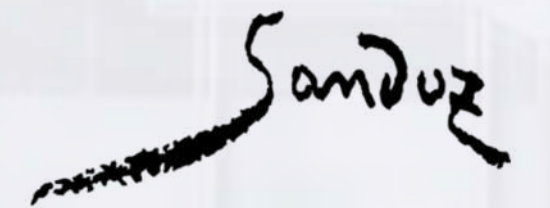
Sandra Hernandez  
Escobar



Alexandra  
Banbanaste



Maxime  
Henrion



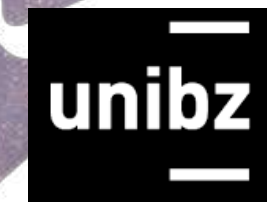
FONDATION  
PHILANTHROPIQUE  
FAMILLE SANDOZ



"la Caixa"



# Global Collaborations Enable Impactful Research



**Thank you for a wonderful semester!  
See you in January for the oral exams!  
Happy Holidays!**

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