Novel Chemical Sensors Based on Boronic Acids for Glucose Detection

Danielle Bruen, **Colm Delaney, Larisa Florea* and Dermot Diamond**

Insight Centre for Data Analytics, National Centre for Sensor Research (NCSR), School of Chemical Sciences, Dublin City University, Ireland.

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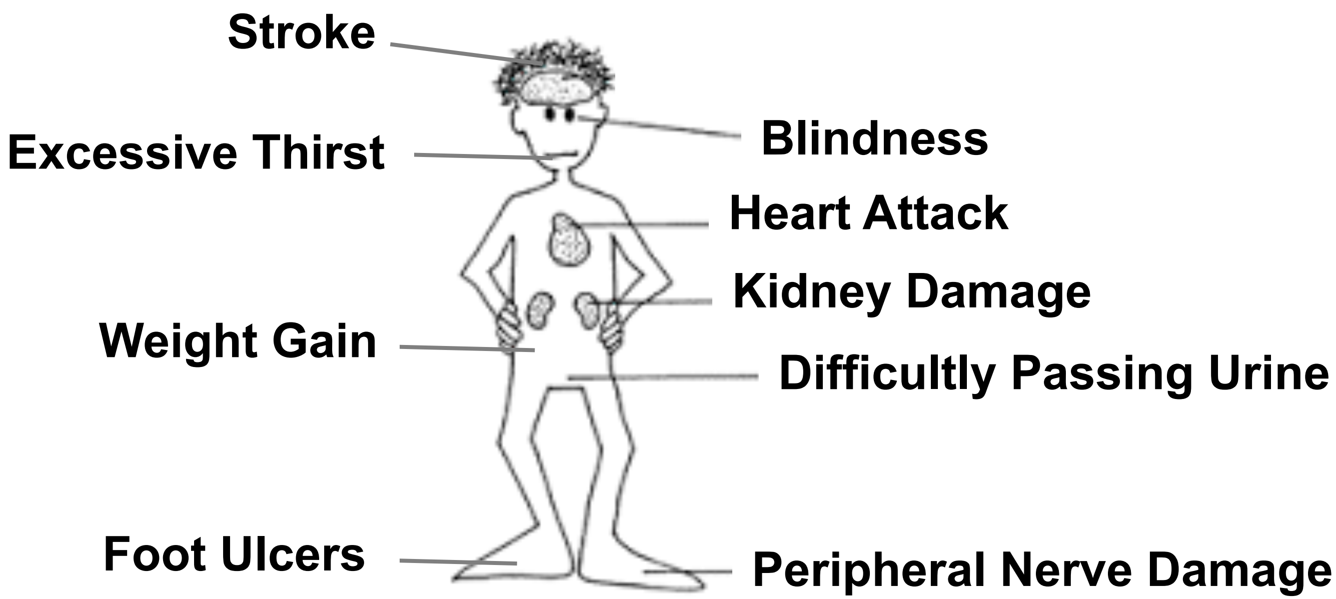
Overview

- Background
- Project Aim
- Boronic Acids (BAs) for Sugar Recognition
- Direct Sensing in Solution
- Indirect Sensing
  - In Solution
  - In Ionogels
- Conclusions
- Future Work

http://www.myomnipod.com/

Importance of Saccharide Sensing

- **Disease: Diabetes and the consequential side effects**



- **Monitoring glucose levels to prolong life expectancy**
- **Currently no non-invasive, continuous monitoring systems available**
- **Demonstrates a need for real-time, non-invasive monitoring**

http://mevsdiabetes-bloglapedia.blogspot.ie/2014/09/fda-approves-once-weekly-dulaglutide.html

Current Monitoring Methods

Implanted Wearable Devices

Roche

ACCU-CHEK®

Advantages:

- Real-time monitoring
- Continuous
- Coupled to insulin pump
- Elimates injections *via* syringe

Disadvantages:

- Invasive

Finger Pricking Method

Advantages:

- Minimally Invasive

Disadvantages

- Not continuous
- Insulin injections required
- Miss episodes of hyper- and hypoglycaemia

https://www.accu-chek.co.uk/gb/products/

Contact Lenses – The Answer!

Electrochemical sensor in a wearable platform

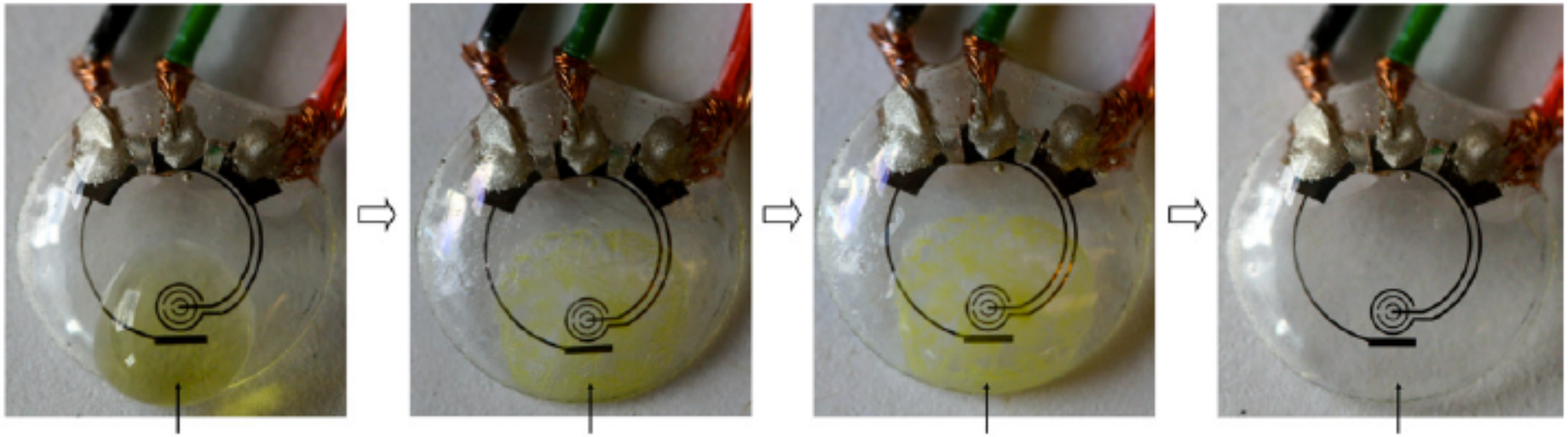
Battery Powered

Interference from Electroactive Species in Ocular fluid

Use of Enzymes

H. Yao, et al, *Biosensors and Bioelectronics*, **2011**, *26*, 3290-3296
B.E. Watt, et al, *Toxicol. Rev.*, **2004**, *23(1)*, 51-57

Realistically....Not a Real Working Device

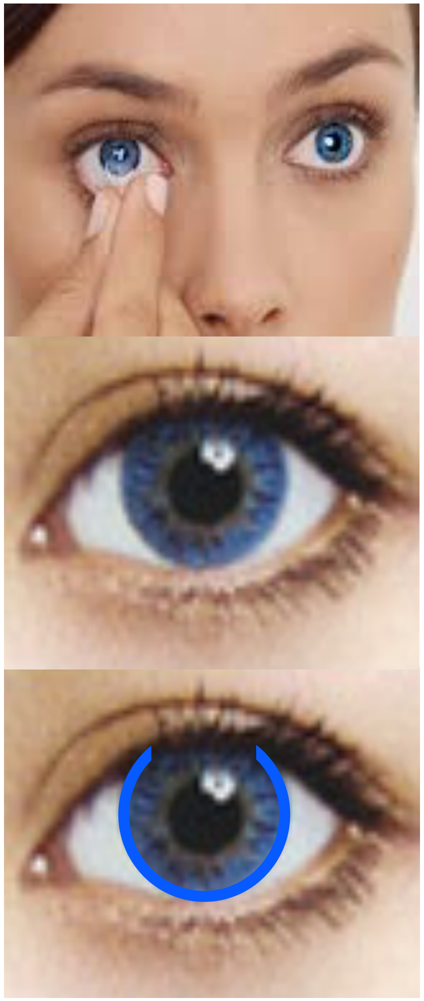


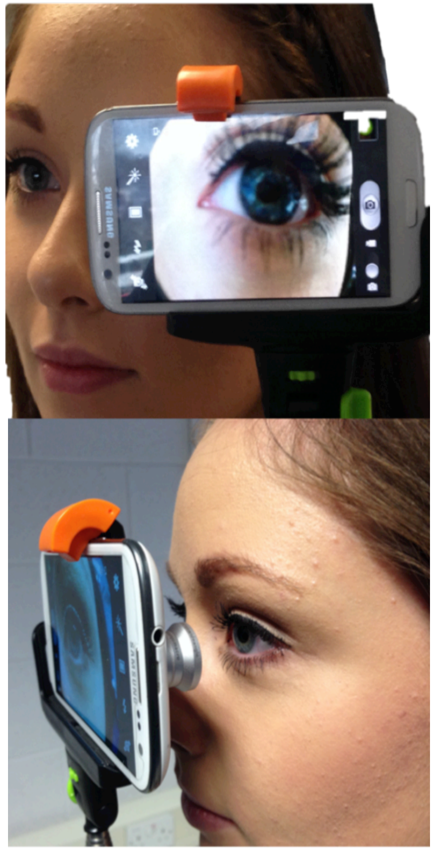
A 30 μL solution of glucose oxidase | A layer of GOD/titania sol-gel membrane | A spread of 30 μL Nafion® on sol-gel membrane | A transparent sensing area after rinsing with DI water

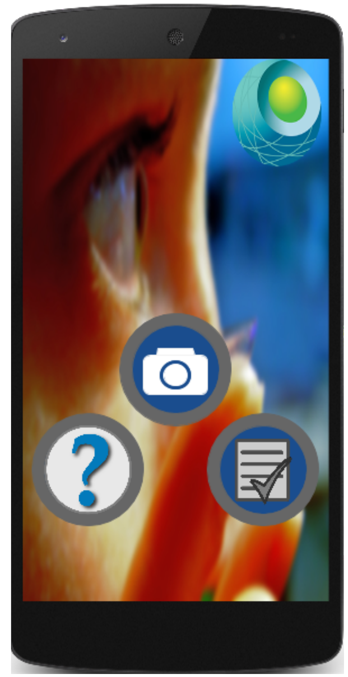
- **Attached to a BASi Epsilon- EC Potentiostat +400 mV**
- **Sensing platform proposes glucose monitoring between 0.5-50 mM**
- **Ocular glucose range is 0.05-0.5 mM and up to 5 mM in diabetics**
- **Major shortcomings to meet immediate expectations**

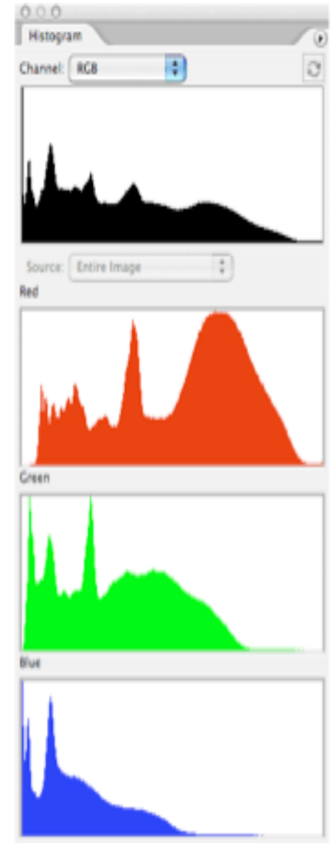
H. Yao, et al, *Biosensors and Bioelectronics*, **2011**, *26*, 3290-3296

Project Aim

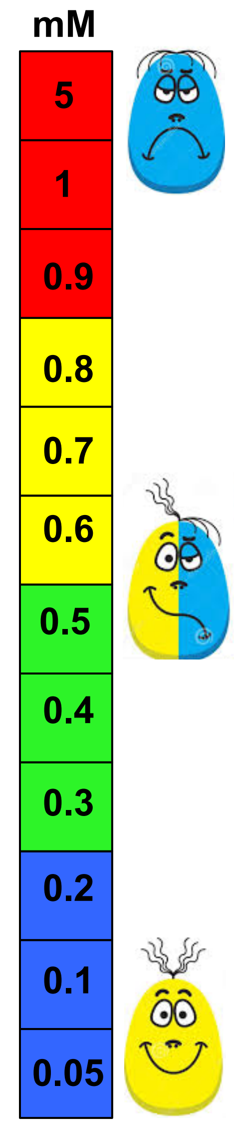






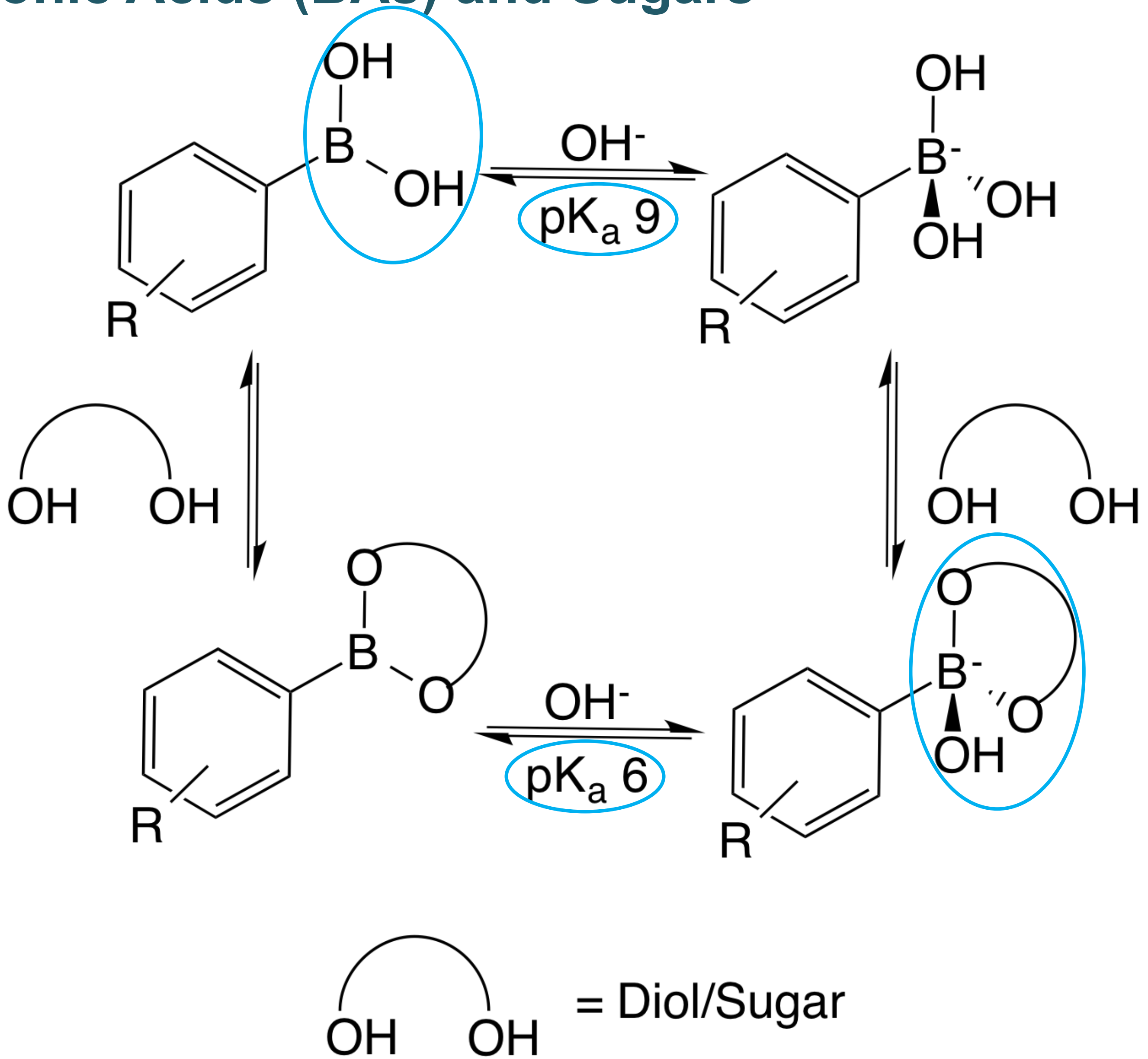


Histogram
Channel: RGB
Source: Entire Image
Red
Green
Blue



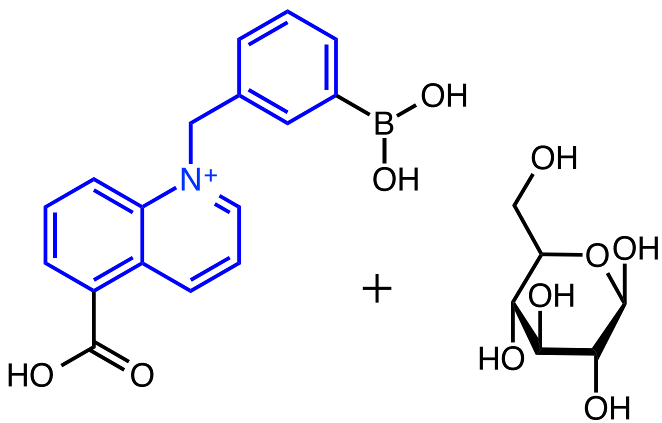
mM
5
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.05

Boronic Acids (BAs) and Sugars



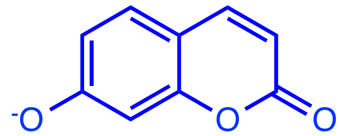
Direct vs. Indirect Sensing

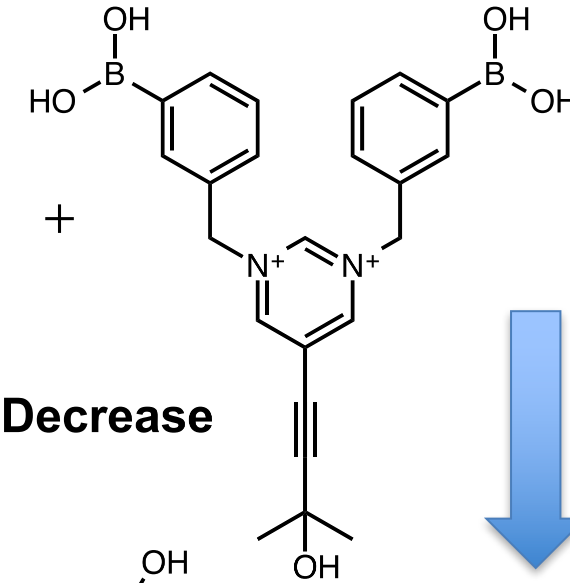
Direct Sensing



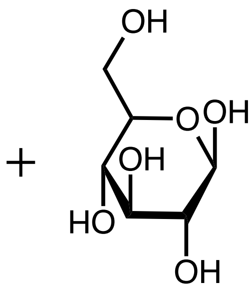
Fluorescence Decrease

Indirect Sensing





Fluorescence Decrease

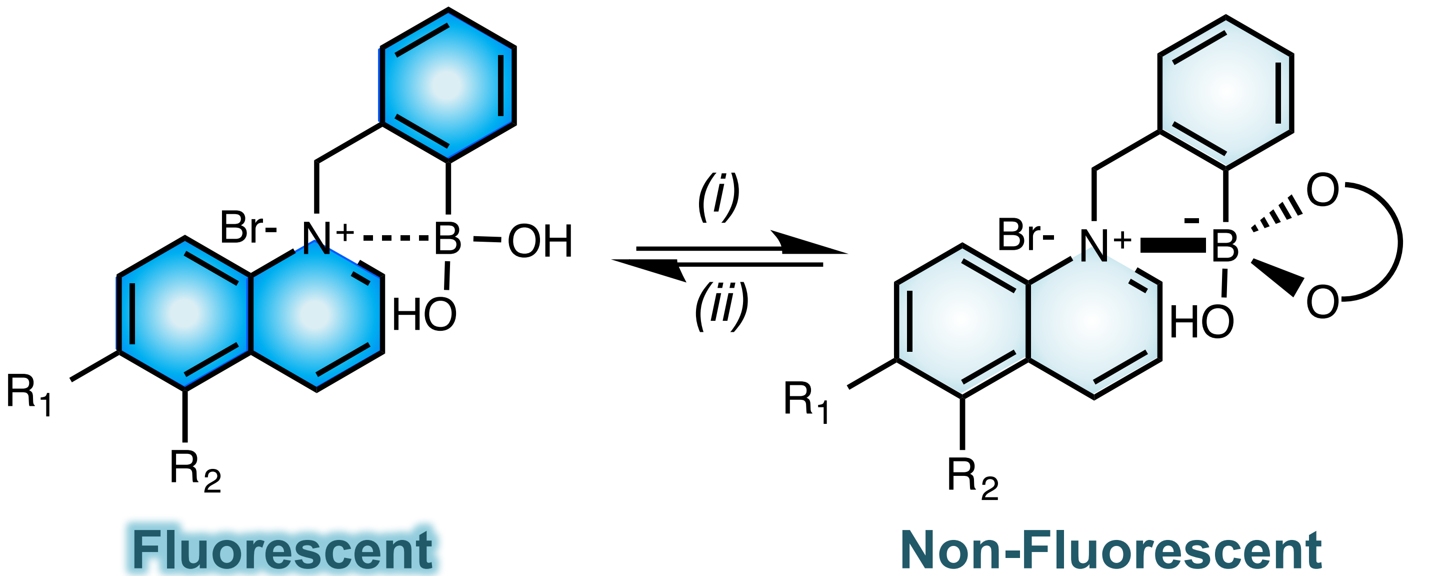


Fluorescence Increase

Fluorophore

Direct Sensing

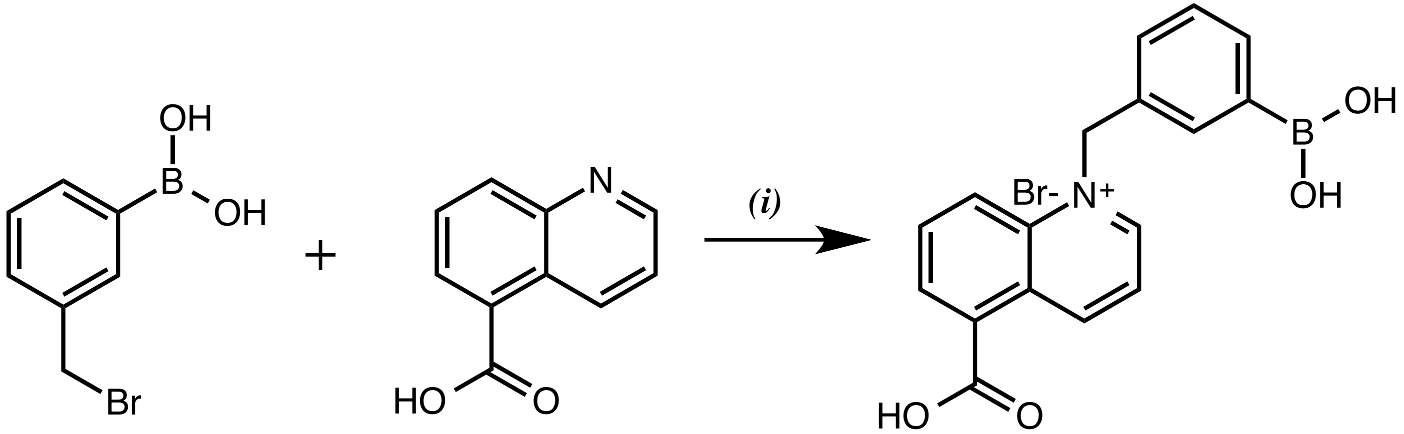
Direct Sensing



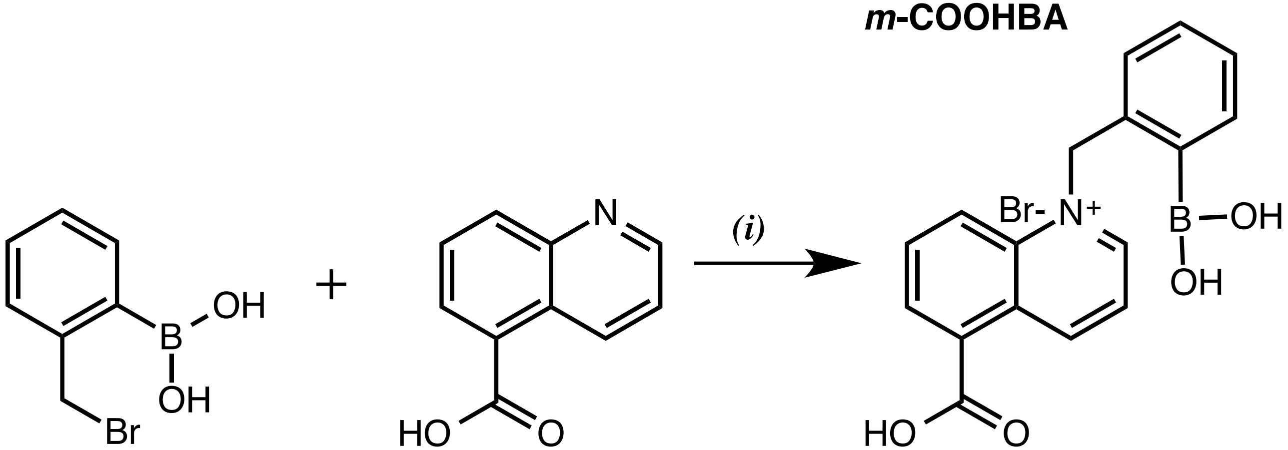
(i) Addition of OH^- ions/glucose

(ii) Addition of water/removal of glucose

Synthesis of COOHBA Sensors



***m*-COOHBA**

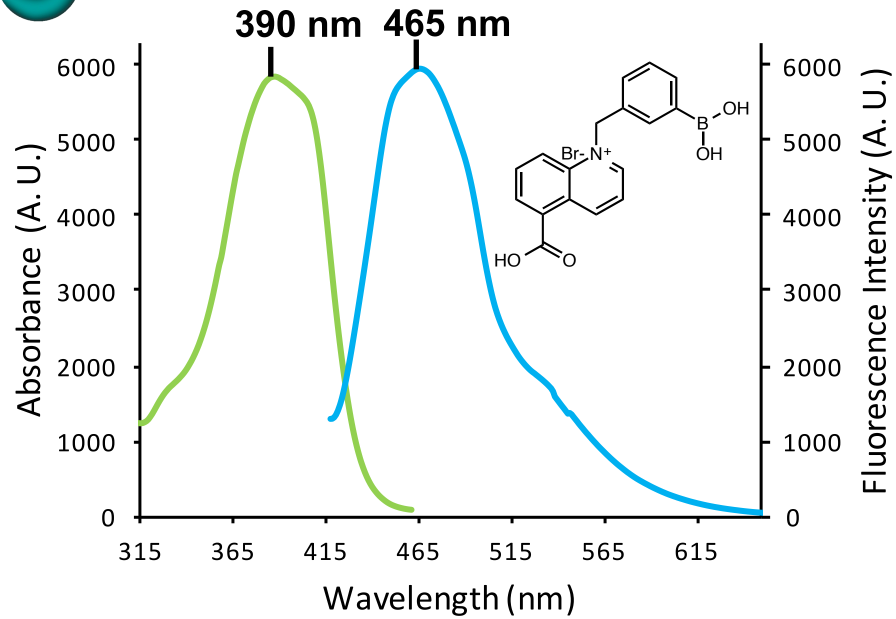


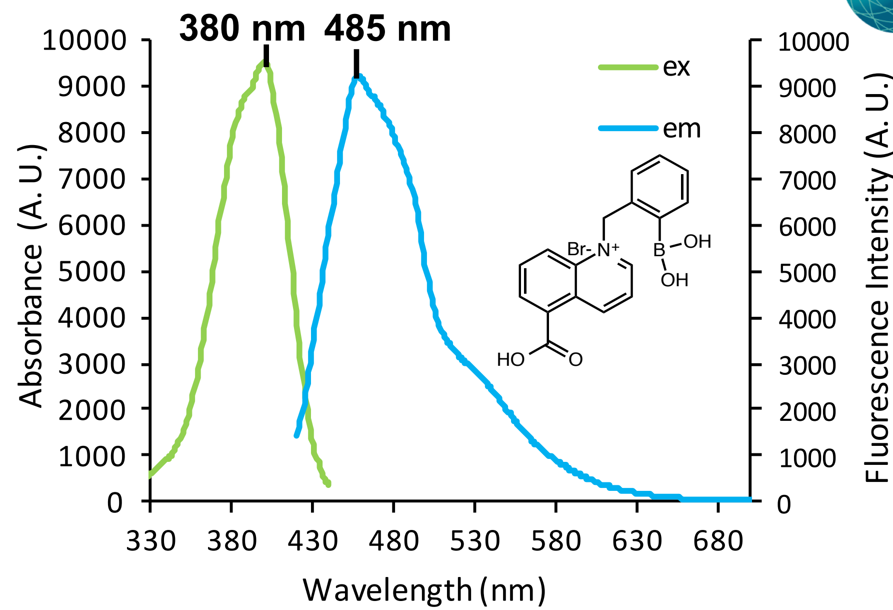
***o*-COOHBA**

(i) Anhydrous dimethylformamide, N_2, 80 ^{0}C for 48h.

Successful synthesis of novel BA sensors were confirmed by NMR.

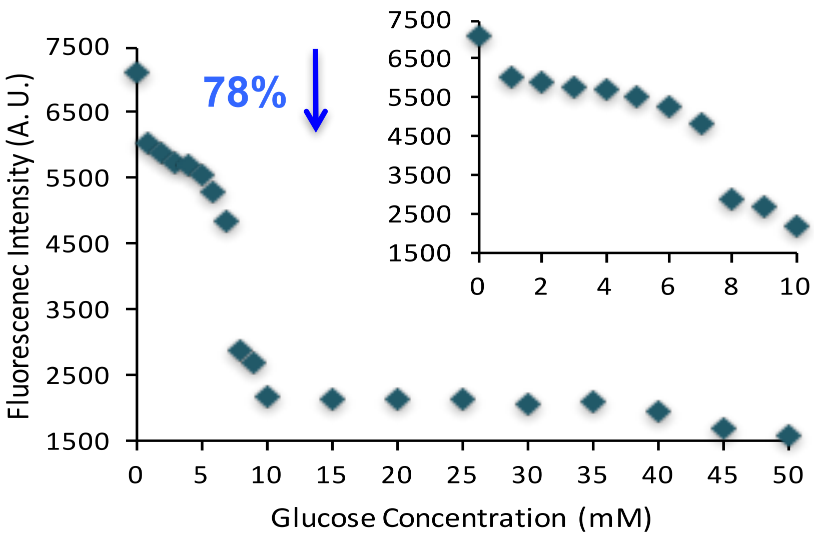
Fluorescence Results

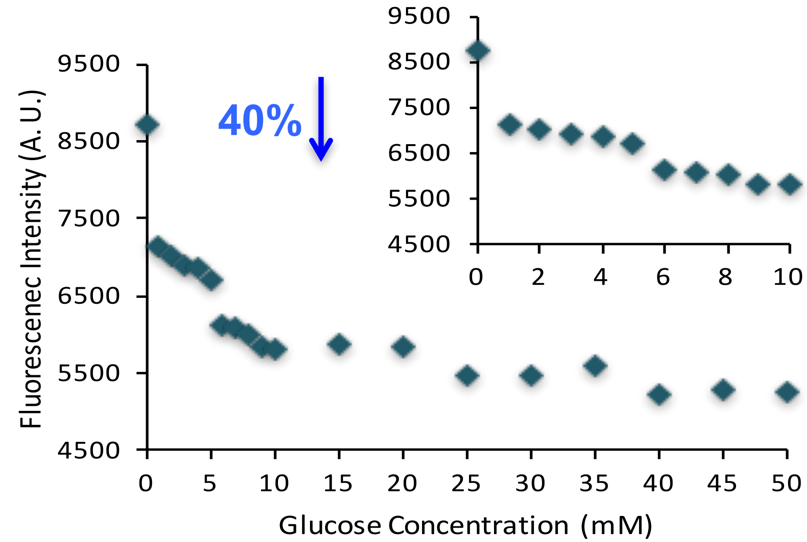




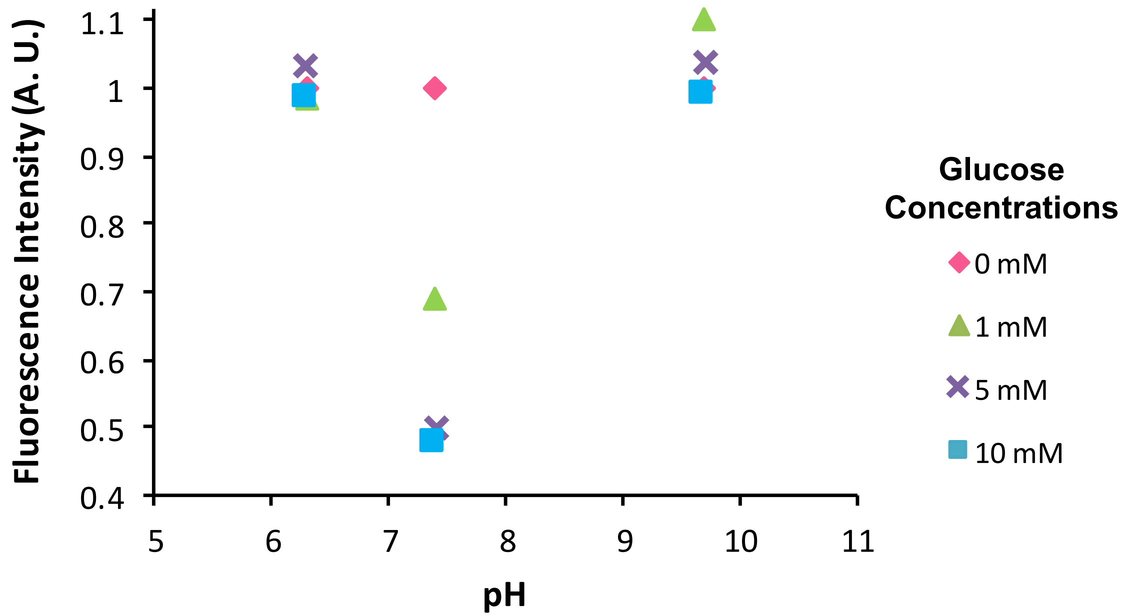
Excitation and emission spectrum of m-COOHBA 0.5 mM in pH 7.4 phosphate buffer.

Excitation and emission spectrum of o-COOHBA 0.5 mM in pH 7.4 phosphate buffer.

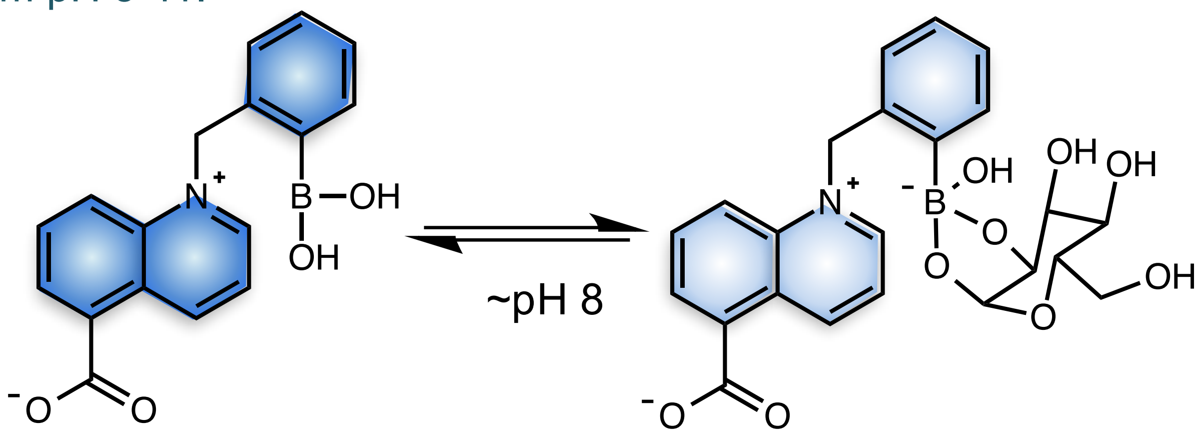




pK_a Investigation – Glucose Sensing pH Range



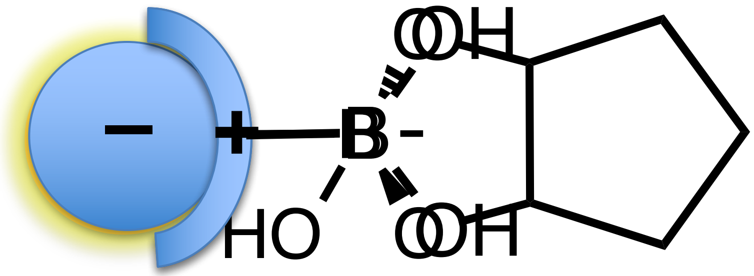
Glucose response for m-COOHBA and o-COOHBA (0.5 mM) in different pH buffer solutions ranging from pH 5-11.



α-D-Glucose binding to the BA derivatives forming 1,2-*cis*-boronate esters

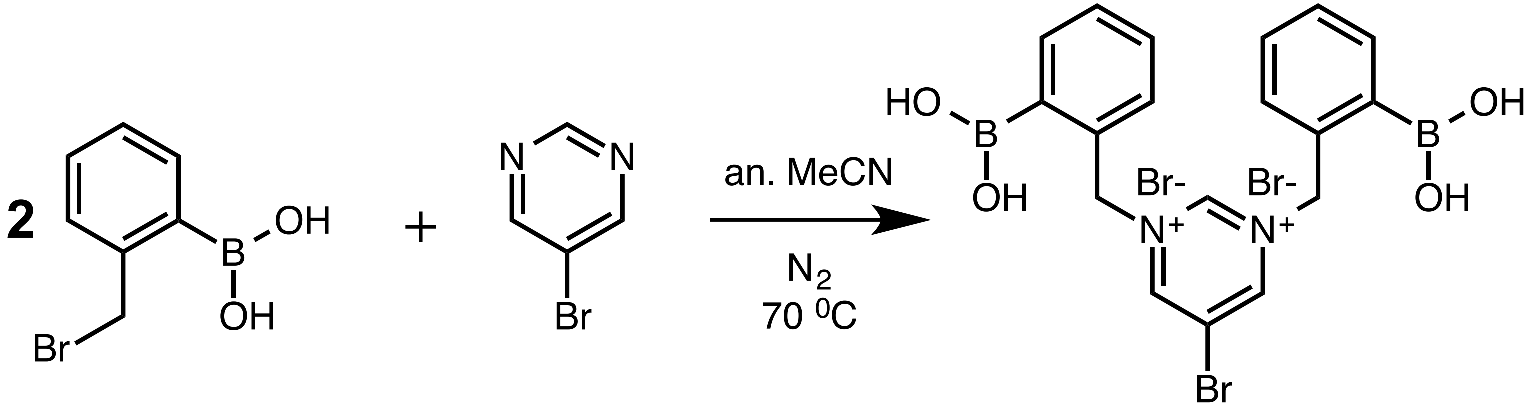
Indirect Sensing

Two-Component Sensing

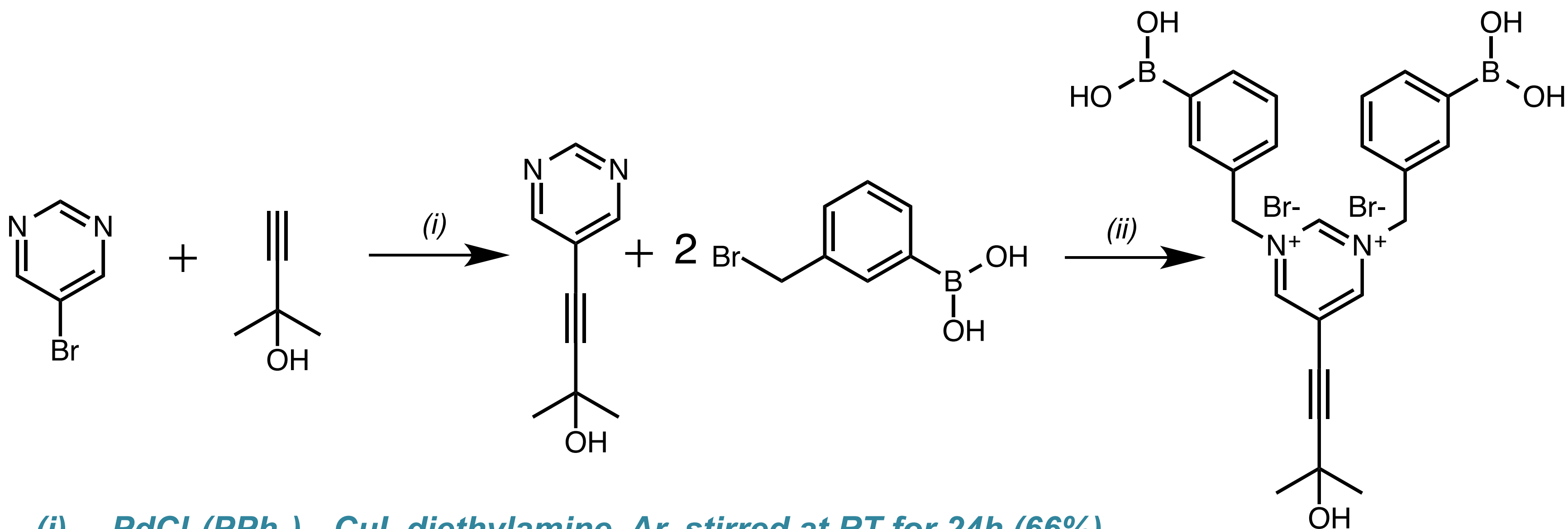


Indirect Sensing in Solution

Indirect Sensing in Solution – Sensor Synthesis



DBA1

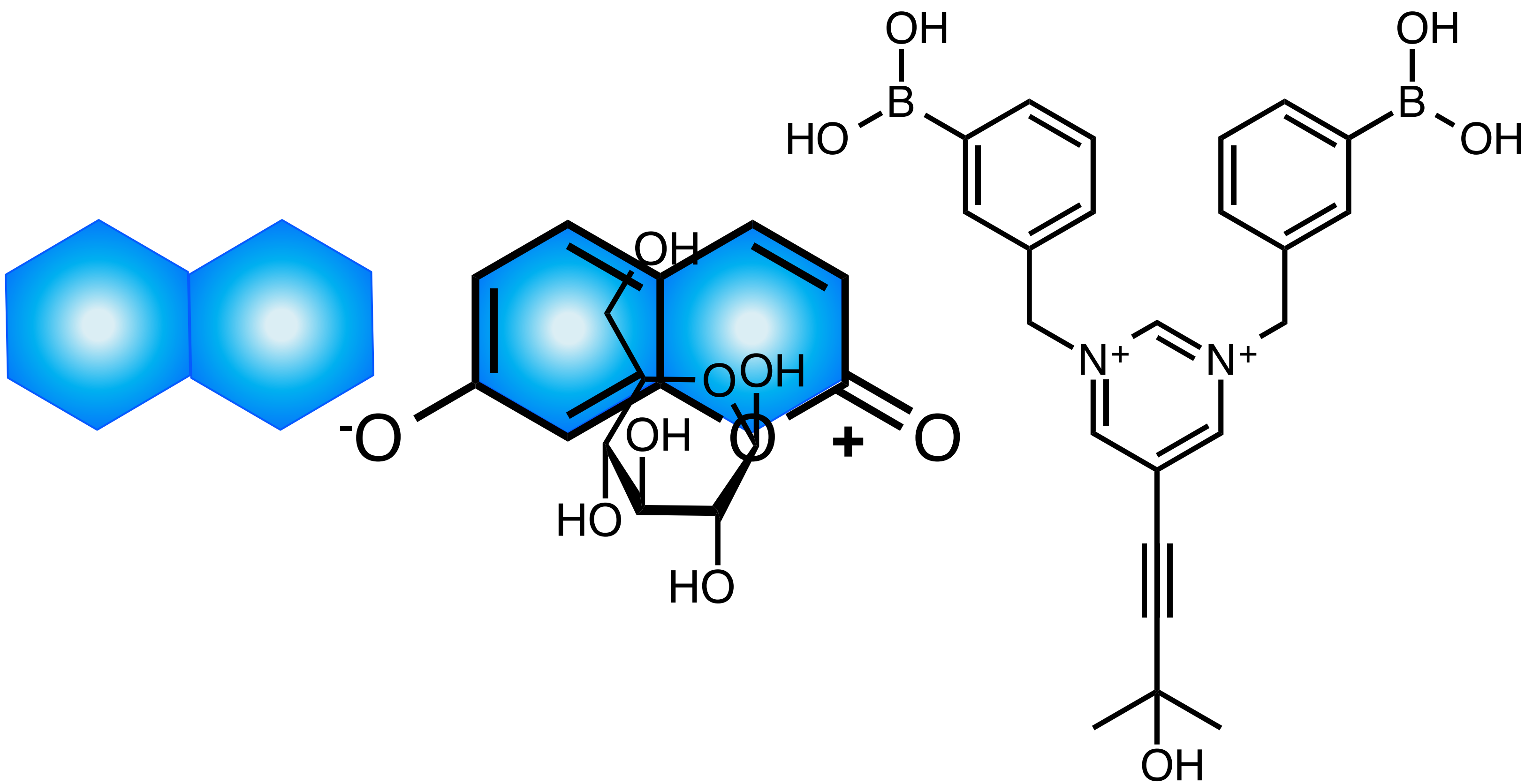


DBA2

(i) $PdCl_2(PPh_3)_2$, CuI, diethylamine, Ar, stirred at RT for 24h (66%).
(ii) anhydrous tetrahydrofuran, N_2, reflux at 80 ^{0}C for 48h (21%).

Successful product formation confirmed by NMR.

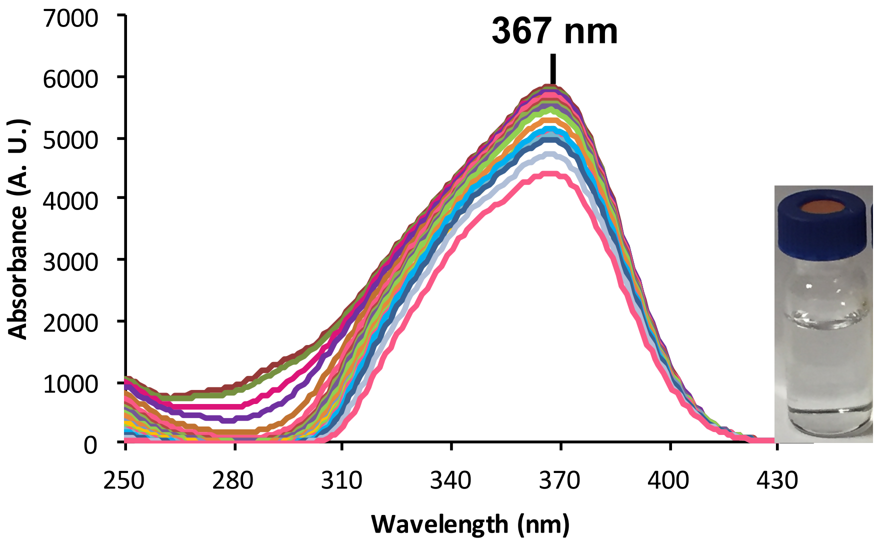
Two-Component Sensing

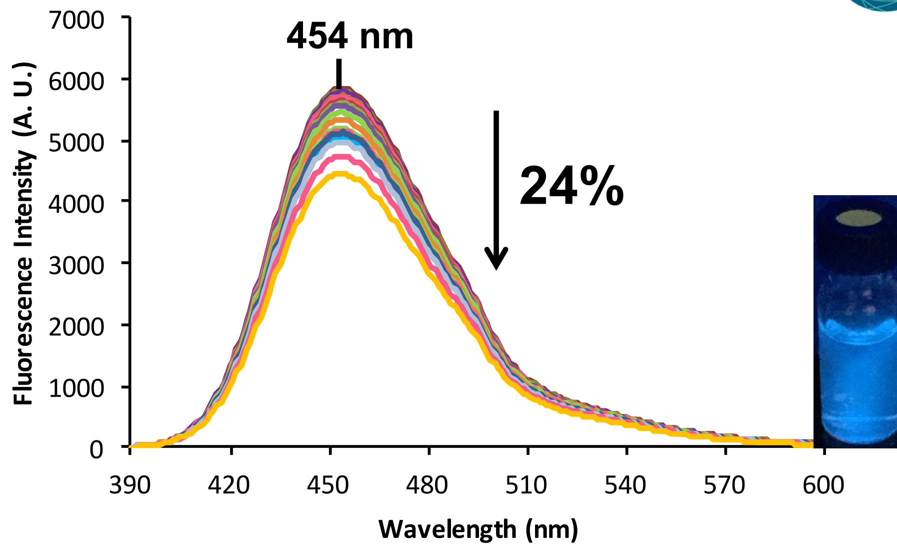


Non Fluorescent

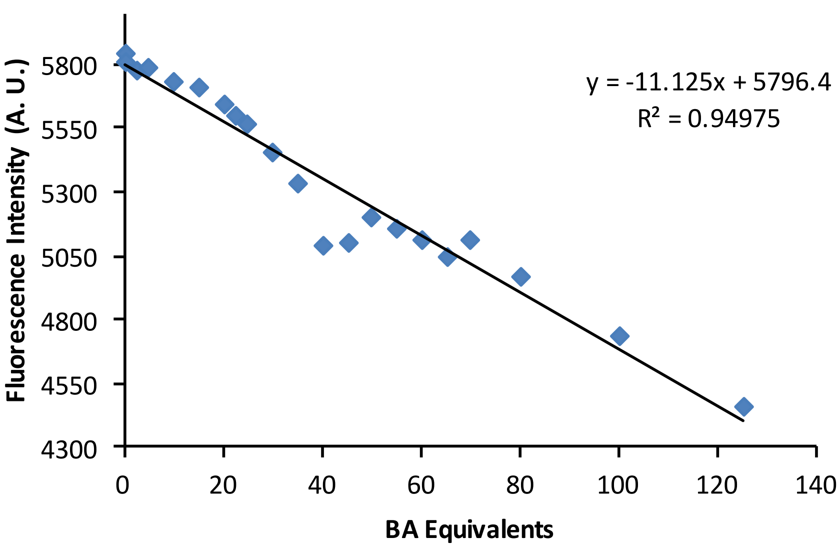
Fluorescent

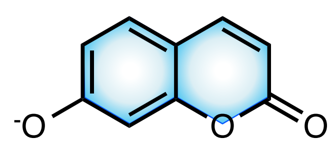
Two-Component Sensing in Solution – Fluorescence Quenching





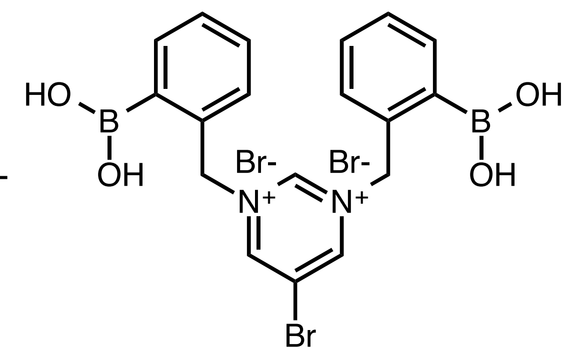
Excitation and emission spectra of 4 µM 7HC in pH 8.12 buffer solution with increasing DBA1 concentrations up to 0.5 mM (125 eq.); Medium sensitivity; 2.5 nm bandwidth





7HC

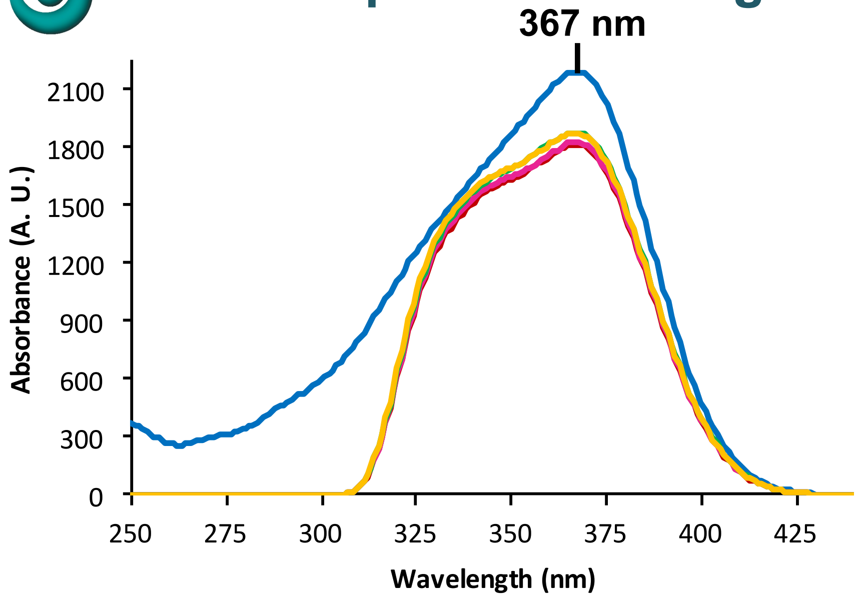
+

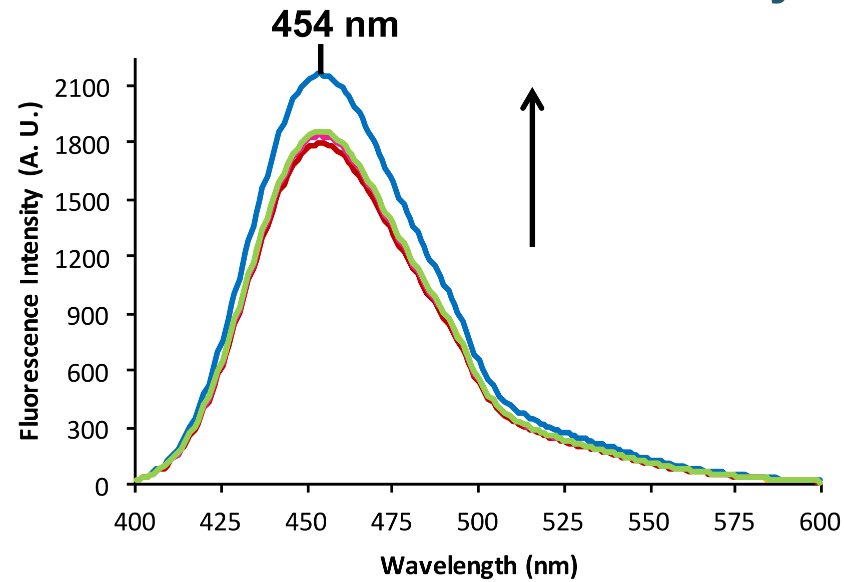


Fluorescence OFF

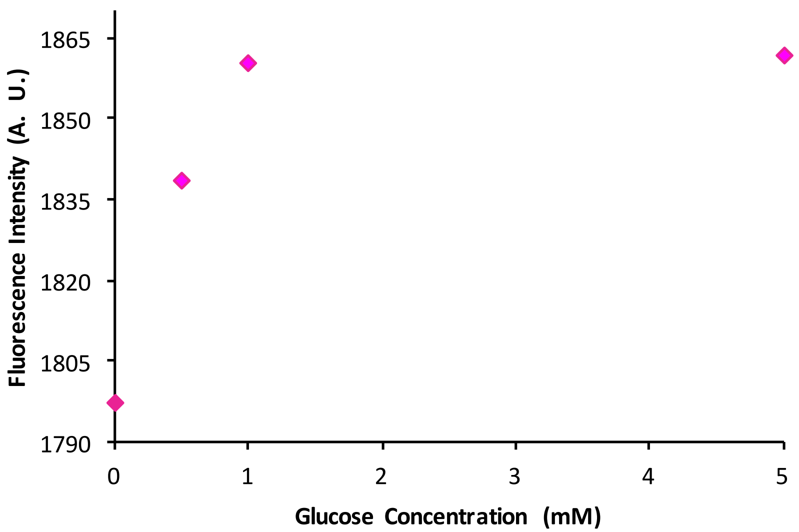
DBA1

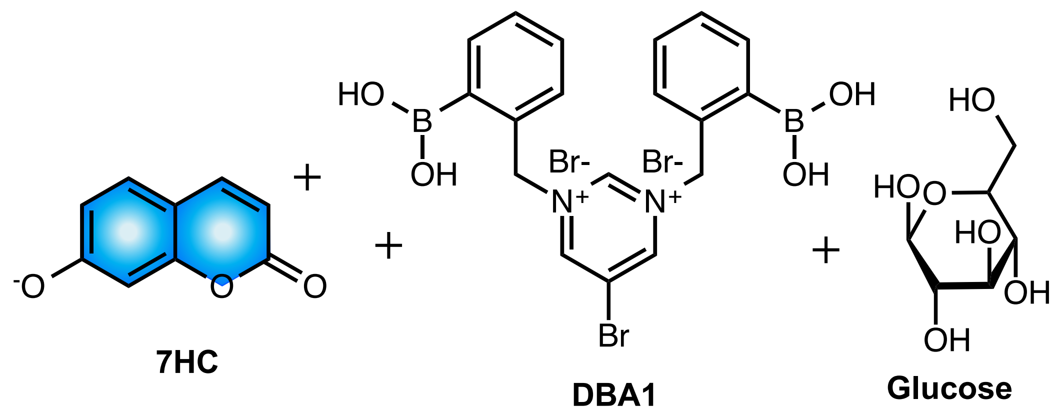
Two-Component Sensing in Solution – Fluorescence Recovery





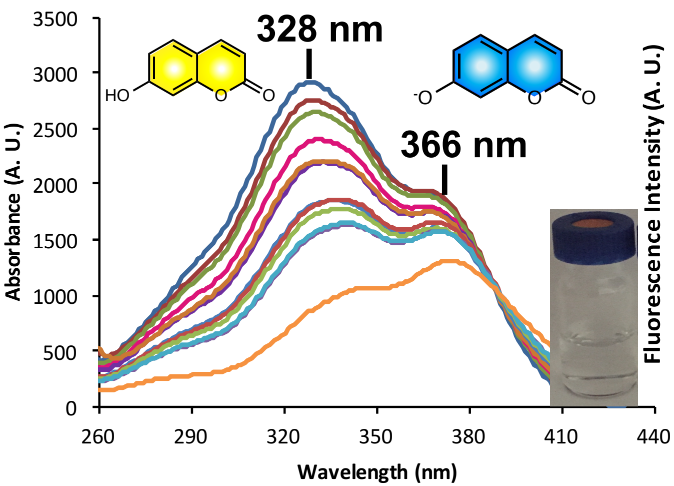
Excitation and emission spectra of 7HC (4 µM) and DBA1 (700 µM) (1:175 eq.) in pH 8.12 buffer solution with increasing concentrations of glucose up to 5 mM; Medium sensitivity; 2.5 nm bandwidth

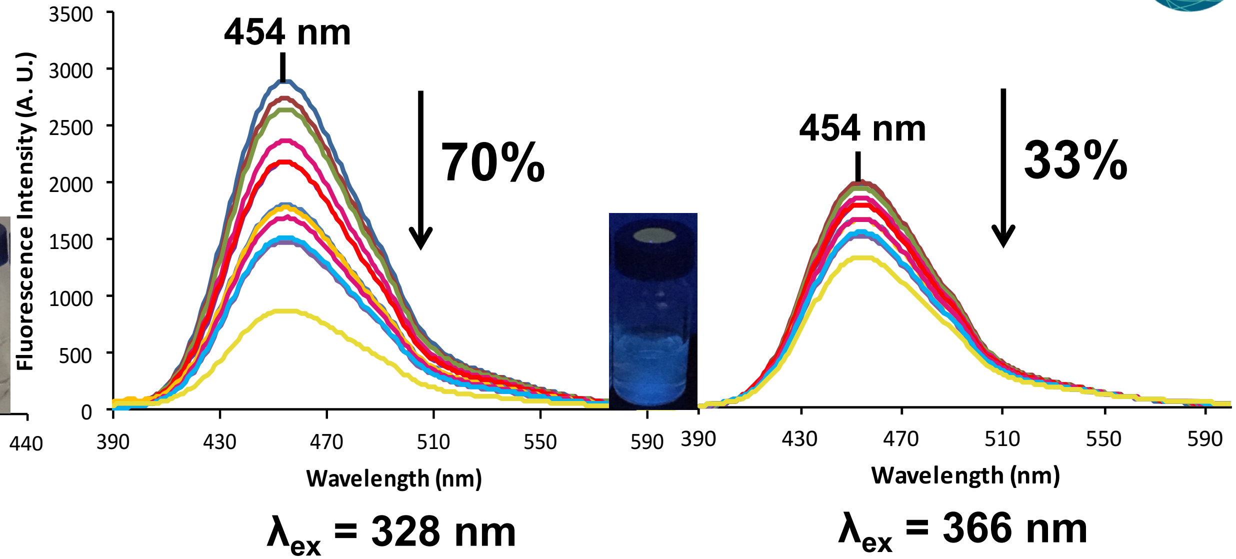




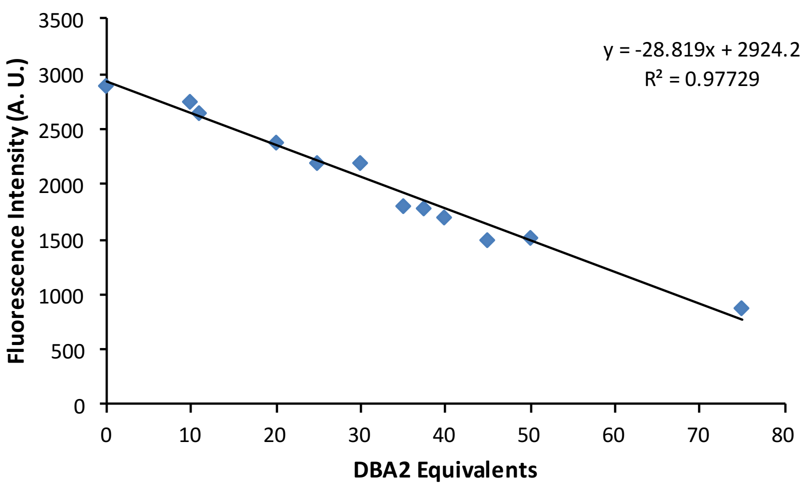
Fluorescence ON

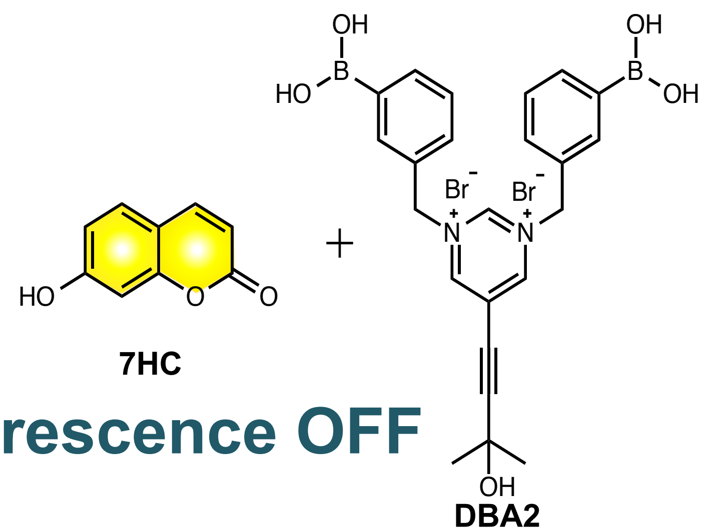
Two-Component Sensing in Solution – Fluorescence Quenching





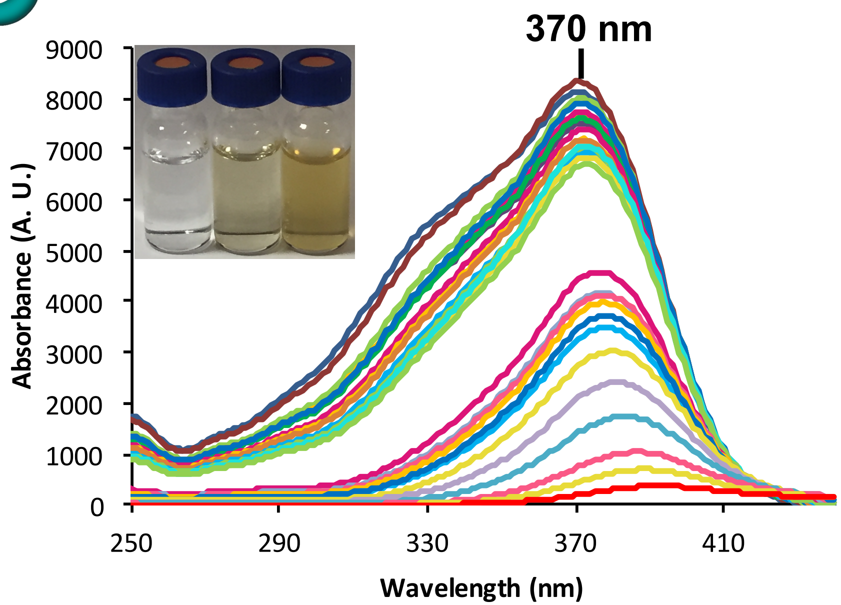
Excitation and emission spectra of 4 µM 7HC in pH 7.4 with minimal MeOH (40 µL) with increasing DBA2 concentrations up to 0.3 mM (75 eq.); Medium sensitivity; 2.5 nm bandwidth

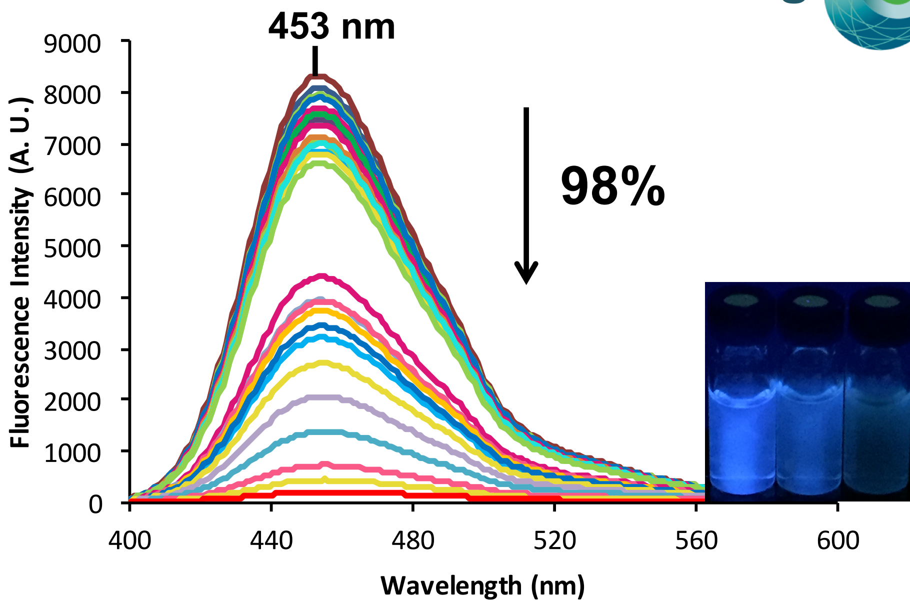




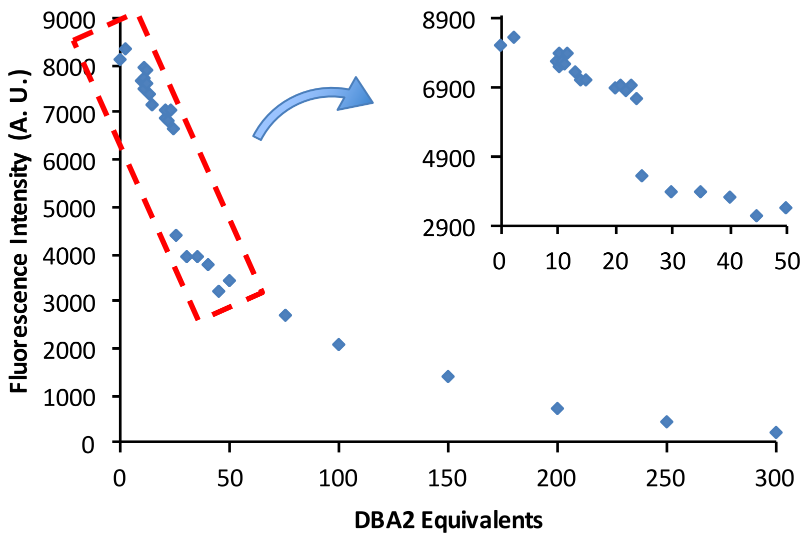
Fluorescence OFF

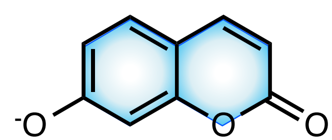
Two-Component Sensing in Solution – Fluorescence Quenching





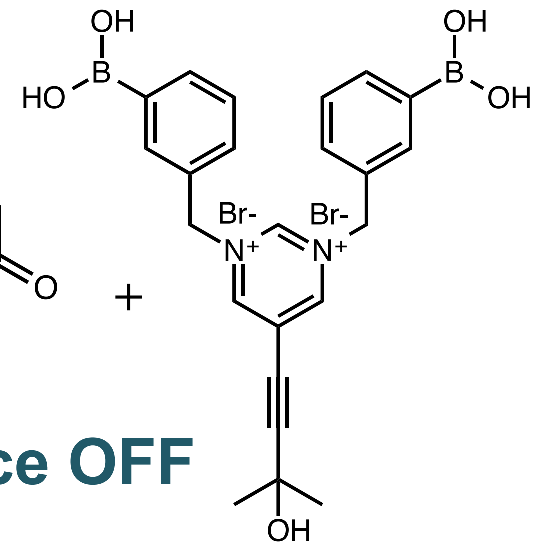
Excitation and emission spectra of 4 µM 7HC in pH 7.4:MeOH (1:1) (pH 8.6) with increasing DBA2 concentrations up to 1.2 mM (300 eq.); Medium sensitivity; 2.5 nm bandwidth





7HC

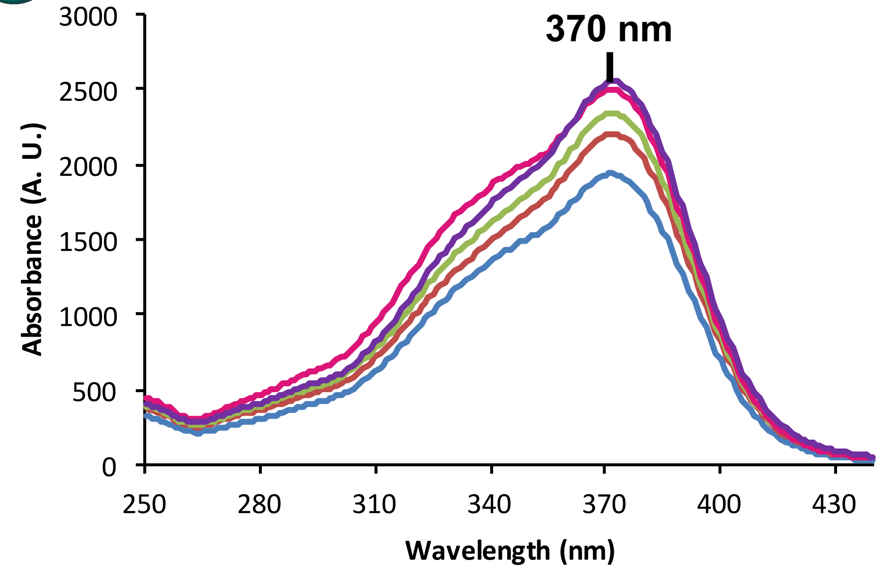
+

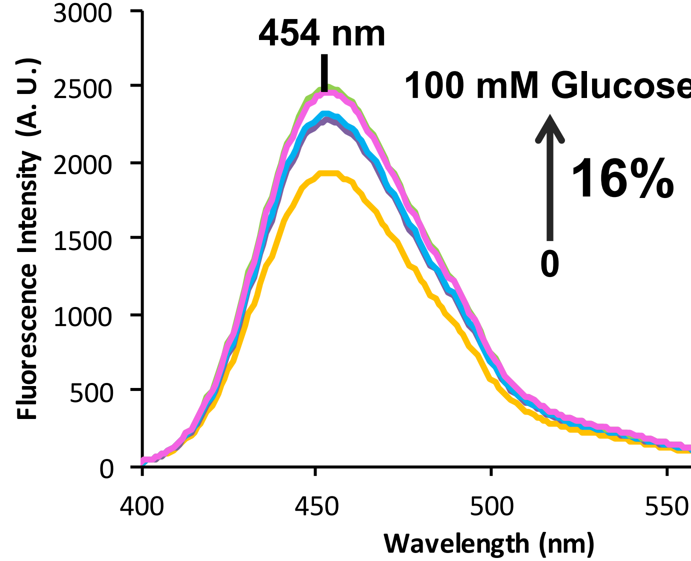


DBA2

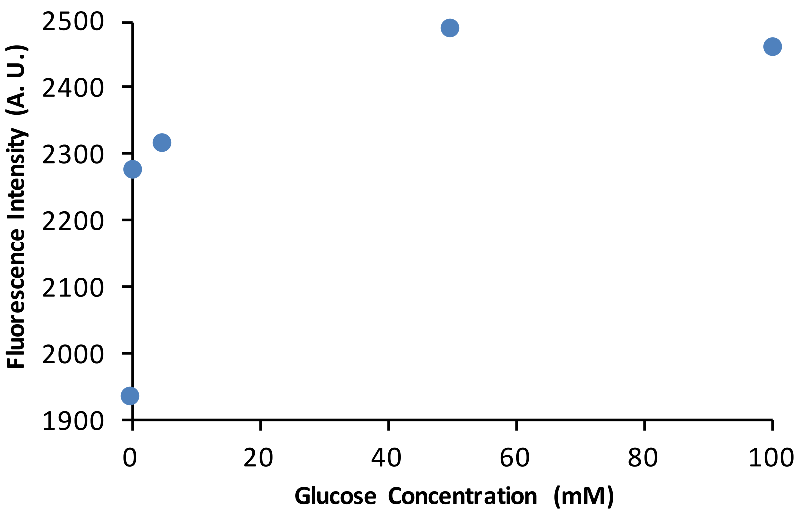
Fluorescence OFF

Two-Component Sensing in Solution – Fluorescence Recovery

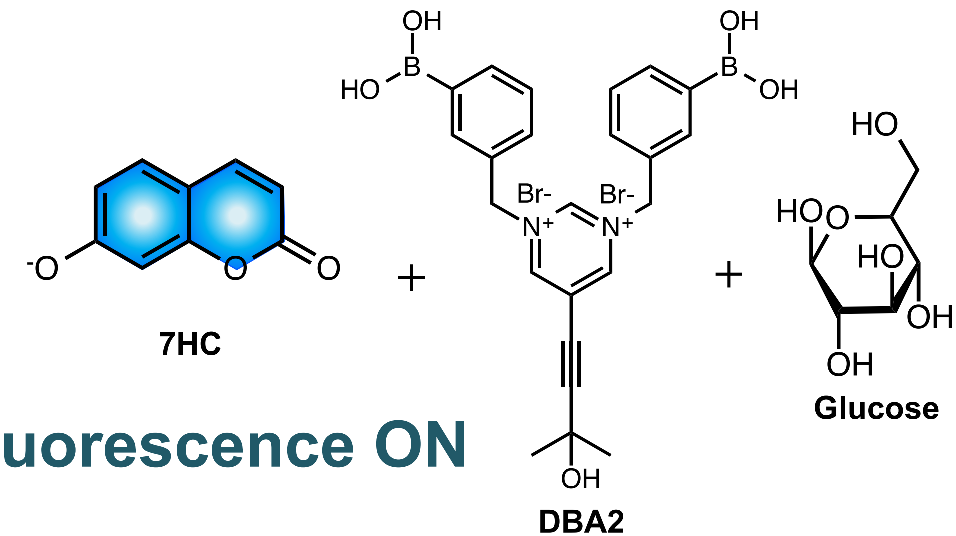




Excitation and emission spectra of 7HC (4 µM) and DBA2 (80 µM) (1:20 eq.) in pH 7.4:MeOH (1:1) (pH 8.6) with increasing concentrations of glucose up to 100 mM; Medium sensitivity; 2.5 nm bandwidth

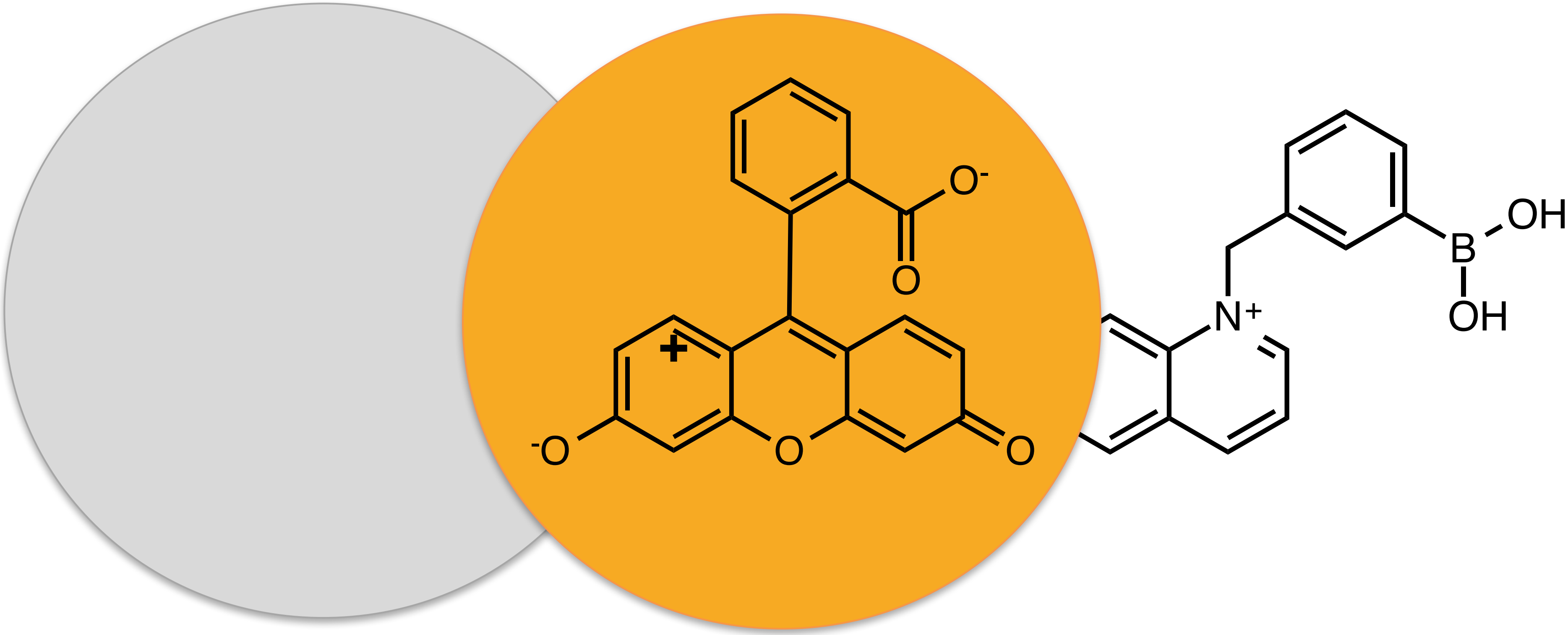


Fluorescence ON



Indirect Sensing in Ionogels

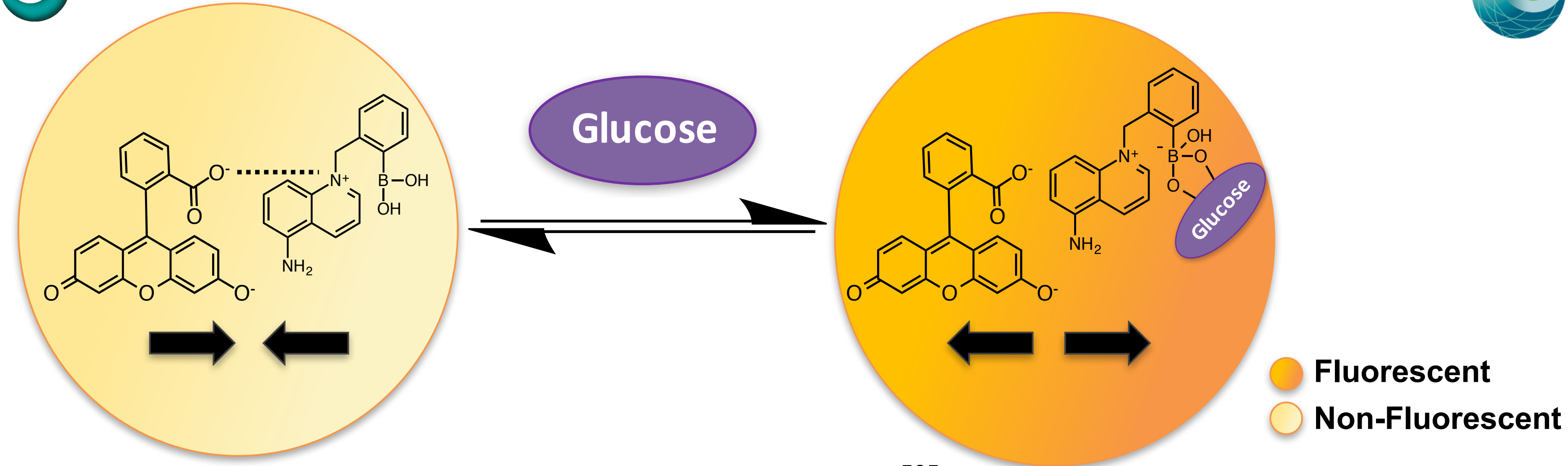
Two-Component Sensing in Ionogel 1

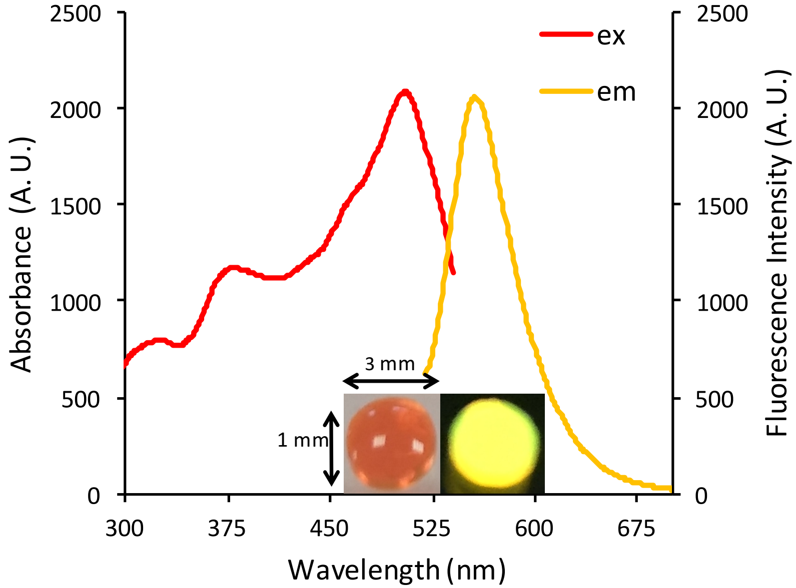


Non-Fluorescent

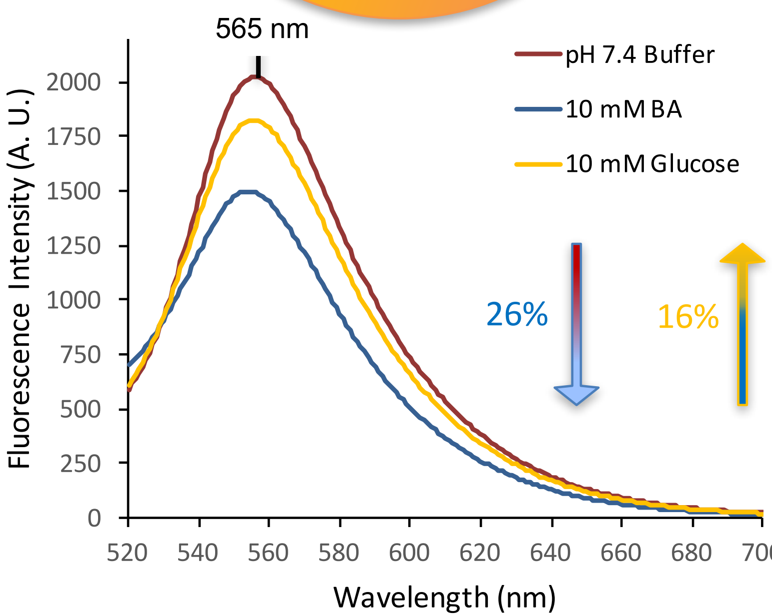
Fluorescent

Two-Component Sensing in Ionogel 1



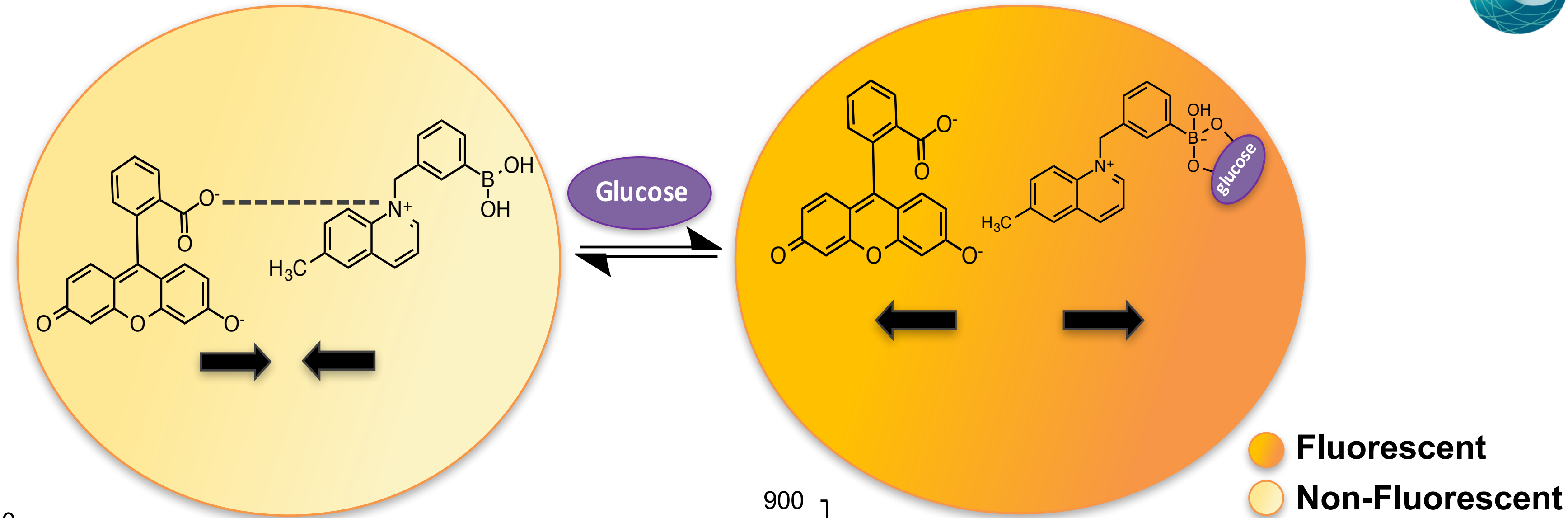


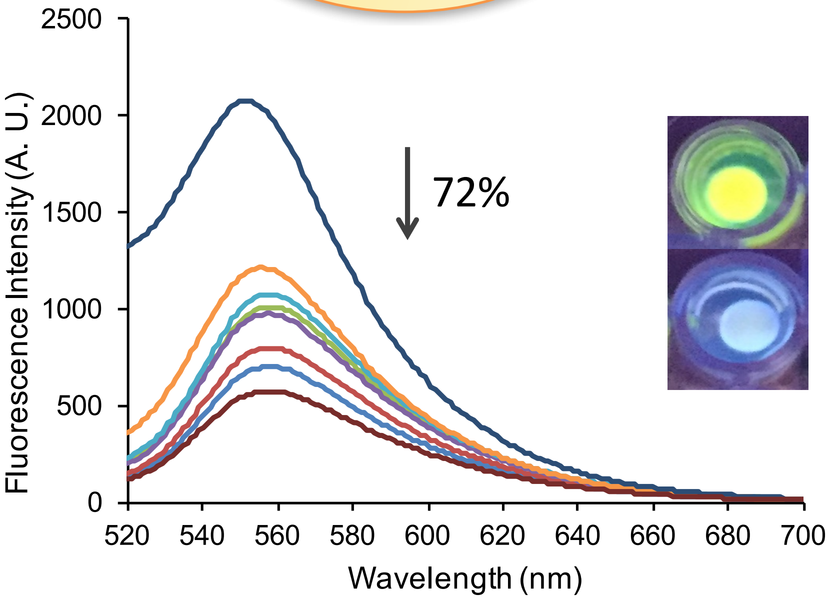
Excitation and emission spectrum of Ionogel 1 in pH 7.4 phosphate buffer solution.



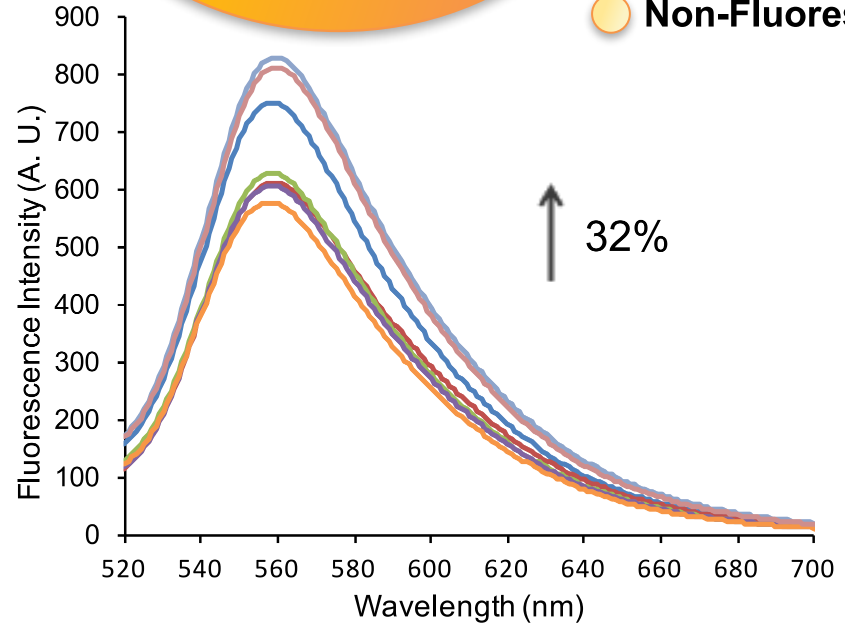
Emission spectrum of Ionogel 1, when immersed in a BA (10 mM) solution (blue) over 12h and then in a glucose solution (10 mM) (yellow) over 12h.

Two-Component Sensing in Ionogel 1





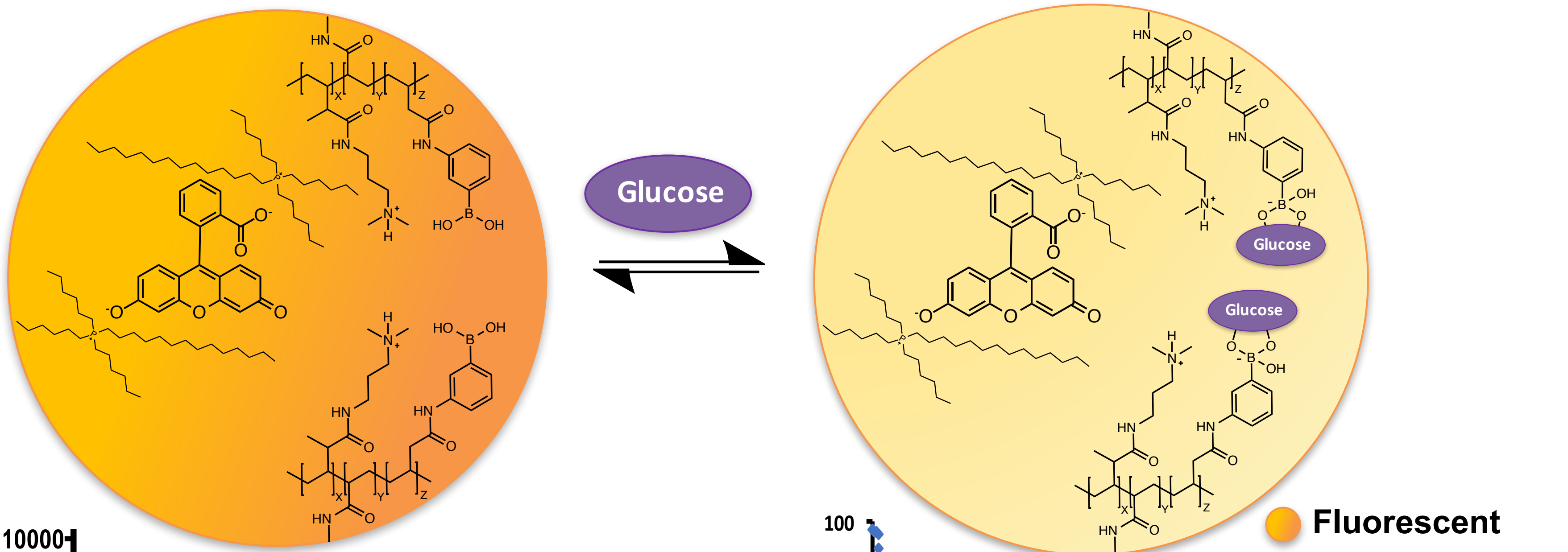
Emission spectrum of Ionogel 1, when immersed in a BA solution (10 mM) over 4h.

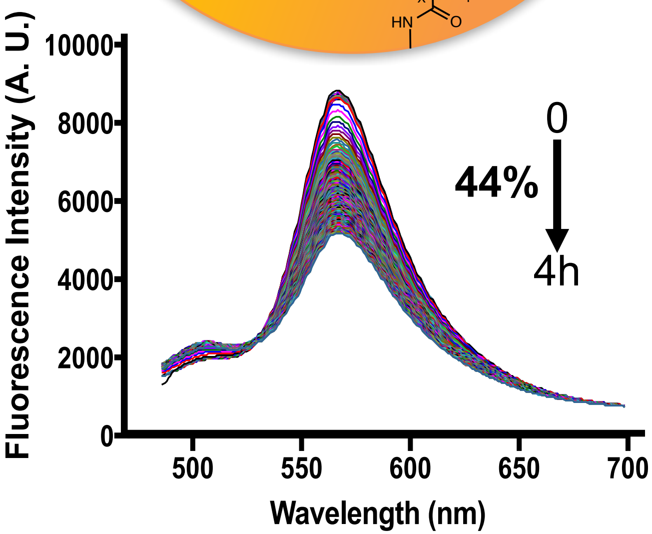


Emission spectrum of Ionogel 1 when immersed in a glucose solution (44 mM) over 4h.

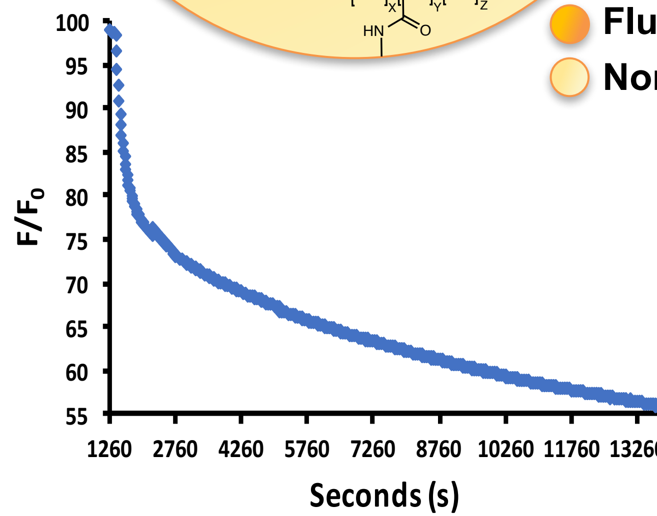
Two-Component Sensing in Ionogel 2

Fluorophore and BA immobilised inside non-fluorescent ionogel matrix





Emission spectrum of Ionogel 2, when immersed in a glucose solution (100 mM) over 4h.



Fluorescence quenching of Ionogel 2, when immersed in a glucose solution (100 mM) over 4h.

Conclusions

Direct Sensing

- Increased glucose concentrations causes fluorescence quenching in BA.
- -COOH substituent is desired for future anchoring possibilities.

Indirect Sensing

In Solution

- Cationic BA derivative quenches fluorescence of anionic fluorophore and on glucose addition fluorescence can be restored.
- Two-Component Sensing depends on the pK_a of the fluorophore and hence, the pH of the buffer solution.

In Ionogel 1

- Both fluorescein and BA are electrostatically immobilised: fluorescence decreases on BA addition and is restored on glucose addition.
- EWGs attached to BA play a role in the quenching efficiency.

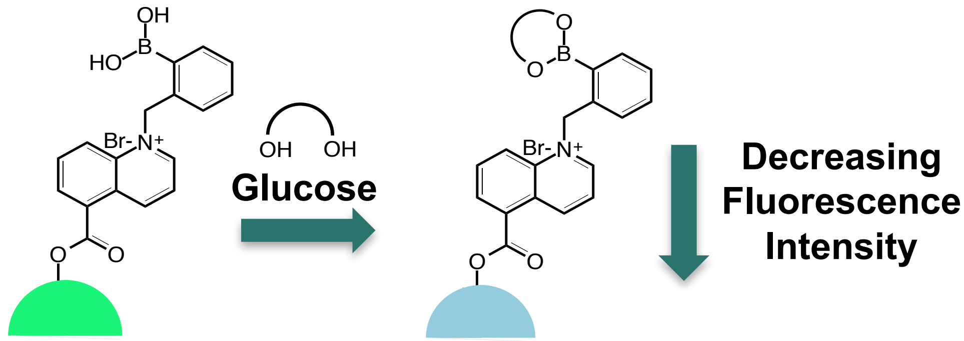
In Ionogel 2

- Quenched fluorescence by 44%, with increased concentrations of glucose (100 mM)

Future Work

Direct Sensing

- Immobilisation of the COOHBA sensors on to a lens-like platform.

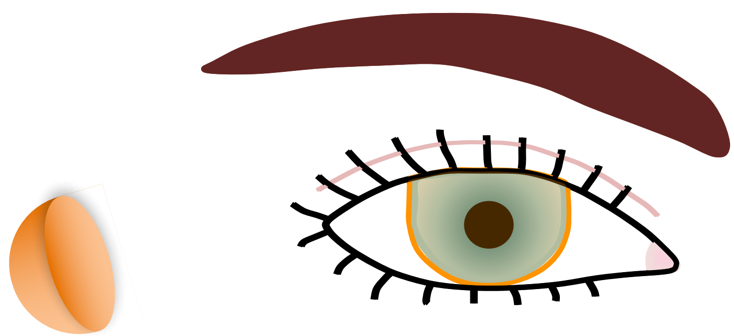


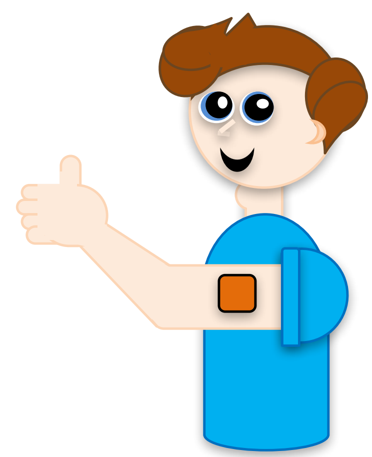
pK$_a$ 9
Fluorescent

pK$_a$ 6
Non-Fluorescent

Indirect Sensing

- The incorporation of the two component sensing ionogels in to a sensing platform, such as a hydrogel patch or contact lens, to allow for non-invasive and continuous monitoring of glucose levels in diabetic patients.





Other Presentations from the D. Diamond Group….

POSTER

Aishling Dunne

"Bipedal Hydrogels Walking in the Light"

ORAL PRESENTATION

Wayne Francis

"Droplets with Life-like Behaviour"

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Thank You for Your Attention!

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Materials and Advanced Sensor Knowledge Exchange