



THE UNIVERSITY
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$$D = \frac{k_B T}{6\pi\eta r} \quad \tau = \frac{1}{k^{-1} + (0.62)nFAD^{2/3}\omega^{1/2}v^{-1/6}C_o'^{1/3}} \quad C = C_o' \left[\frac{1 - \theta}{1 + \theta} \right] \quad k^o = \frac{1}{E^{\alpha} [C_{O,0} e^{-\alpha F E^{\circ}/RT} + C_{R,0} e^{(1-\alpha) F E^{\circ}/RT}]} \quad \text{Research Group}$$

Electrochemistry + Analysis \rightleftharpoons Nanoscience + $n e^-$ \rightleftharpoons Cell Biology

www.nanoelectrochemistry.com

Single Entity Electrochemistry: Reaching the Ultimate Sensitivity in Measurement Science

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Advances, Challenges, and Long-Term Opportunities for Electrochemistry

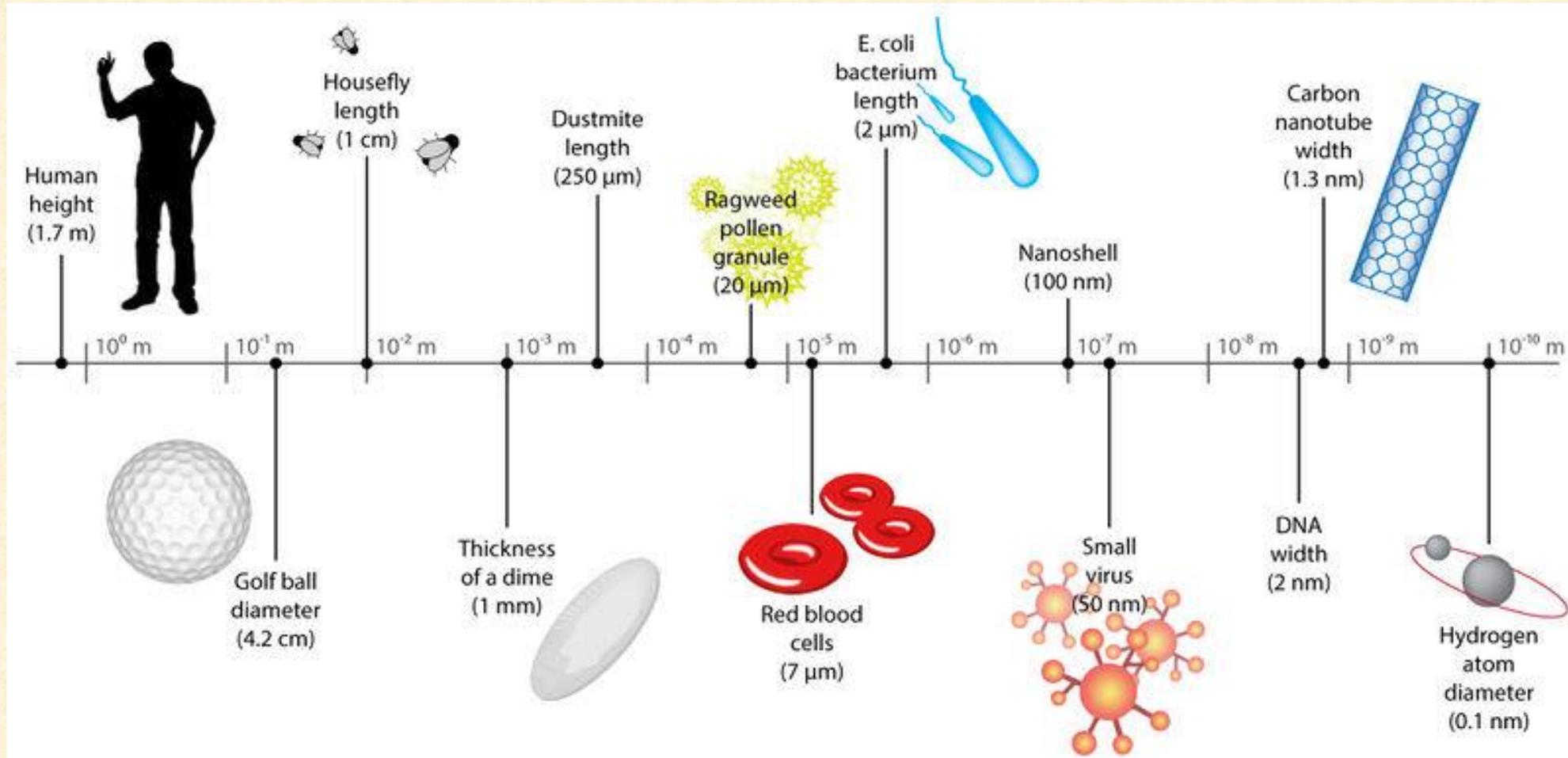
Washington, DC

19 November 2019

Outline

- What is an entity?
- What is measurement science?
- Why study single entities?
- Examples and a story of single atoms
- Frontiers & final thoughts

What is an entity?



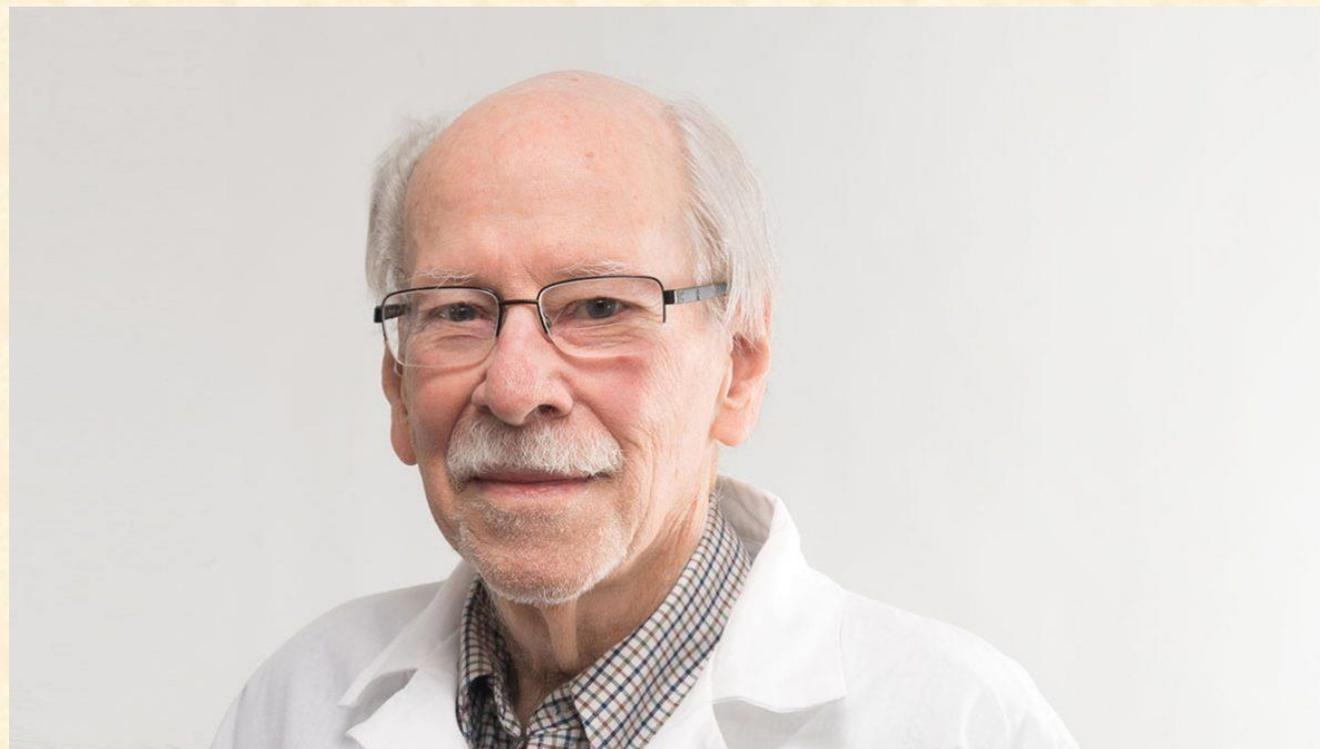
What is measurement science?

The original version of this editorial was written in 1991, 3 months after I became Editor of *Analytical Chemistry*.

The definition of what *is* the discipline of analytical chemistry, and thus what should be published in the field's leading journal, was then, to many, a topic of debate. Because I was concerned about that debate, I wanted to explicitly state that the journal would take a broad view of its scope, based on the criterion of *measuring important chemical things*.

Attitudes and impressions can, however, be slow to change, and to this day we still receive questions from authors, "Is this measurement appropriate for the journal?" and comments from reviewers, "The authors did not measure a concentration, so it is not appropriate for the journal."

In this editorial, I wish to firmly reiterate that the journal's scope remains that of describing the fundamental and practical applications of how to *measure important chemical things*, which include concentrations, rate constants, lifetimes, and whatever—as long as what is measured is a *chemically* important parameter. I believe that this is a critically important viewpoint in modern chemistry as subdisciplines, and indeed disciplines, grow closer together in what researchers investigate as important subjects. I would like to see *Analytical Chemistry* report all original descriptions of what a *xxxxx* (name your area) chemist, *xxxxx* (again, name your area) biochemist, geochemist, atmospheric chemist, forensic chemist, art historian, etc., etc., would consider is an important measurement capability.



Royce Murray, NAS Member, Professor Emeritus, UNC Chapel Hill
Written while Editor of *Analytical Chemistry*

Why study single entities?

Imagine you've never heard of fireflies



Firefly

Your Colleague Asks a Favor...

- She places varying amounts of fireflies in 3 large jars...

Think of This



But the Size of This



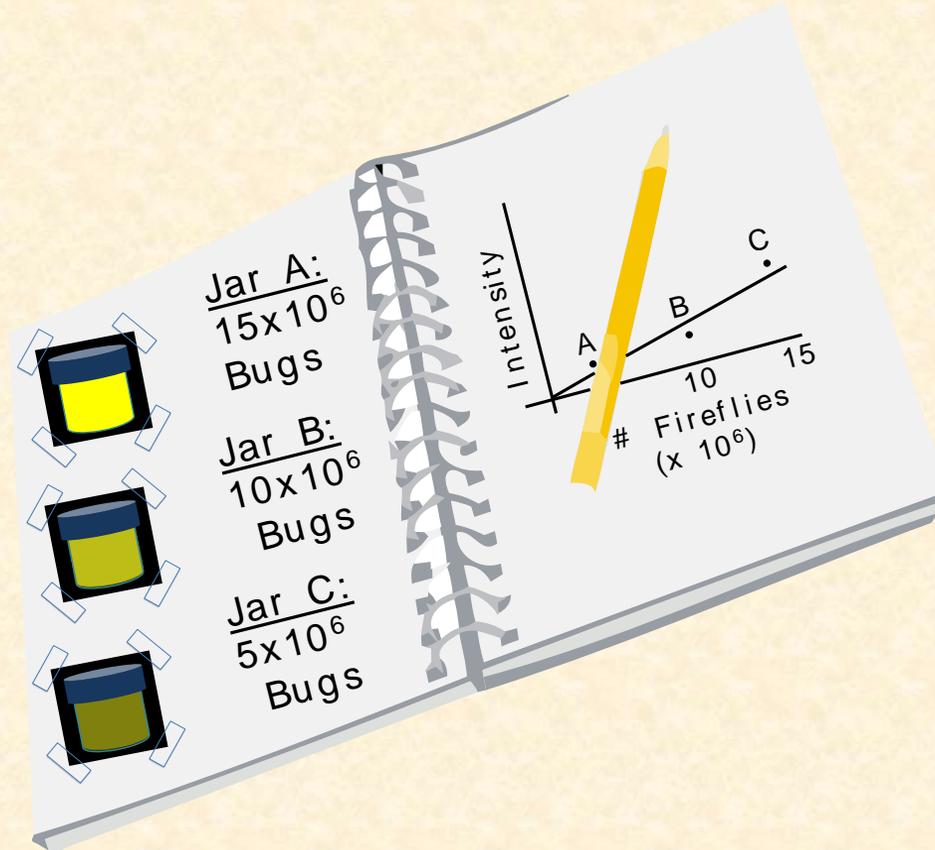
World's Largest Bottle for Whiskey

Your Colleague Asks a Favor...

- And she asks you to come to some general conclusion about the light generated by a firefly.



Your Lab Notebook



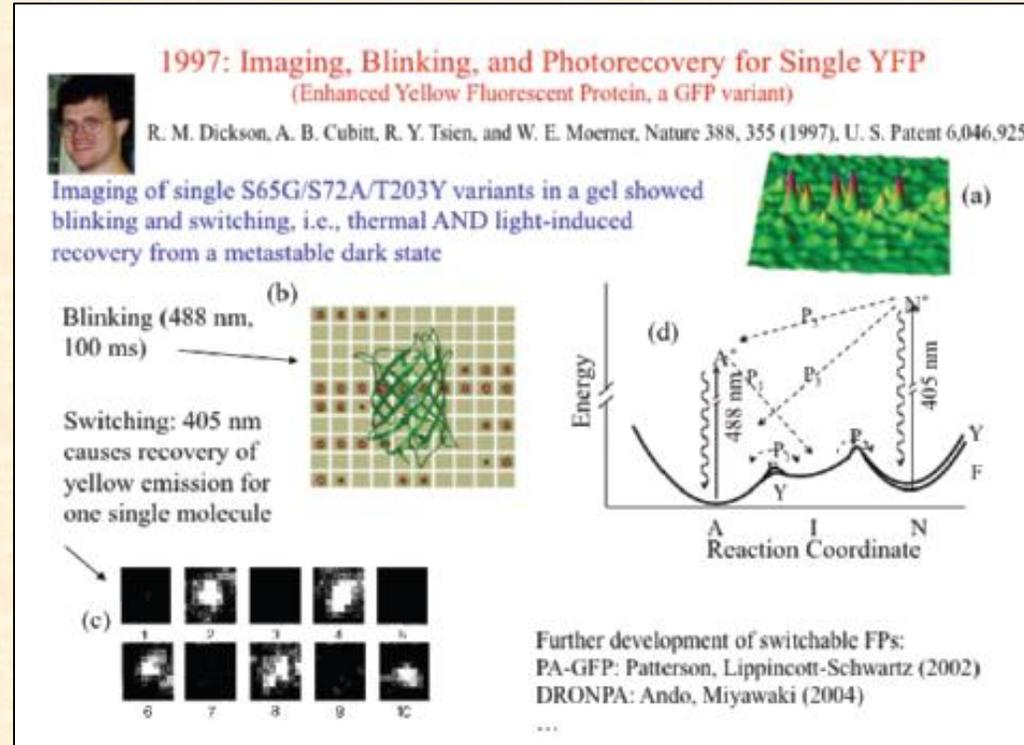
The intensity of light doesn't vary greatly with time and scales linearly with the number of fireflies. You conclude fireflies *continuously* light due to bioluminescence.

Misconceptions of nature arise when careful measurements are not taken on single entities.

Why Single Molecule Science?



W. E. Moerner



- Not until scientists like W. E. Moerner studied the fluorescence of single molecules did we know that single molecules actually blink when giving off fluorescence!

Why Single Molecule?



W. E. Moerner



Eric Betzig



Stefan W. Hell



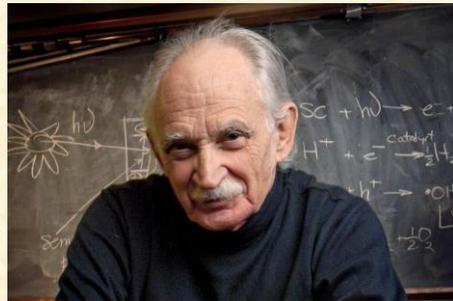
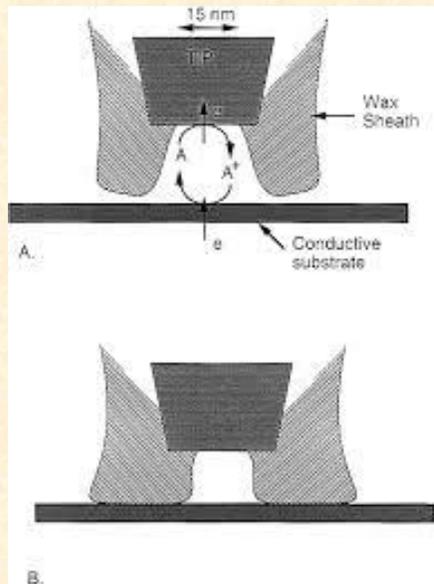
- Moerner further used this blinking phenomenon to invent super resolution microscopy, for which he shared the 2014 Nobel Prize in Chemistry.

Two Exciting Ramifications of These Experiments

1.) We can now develop techniques to study the chemical and physical properties of single entities.

2.) Takes measurement science toward a digital era: Detecting analyte species one at a time;
LOD = one!

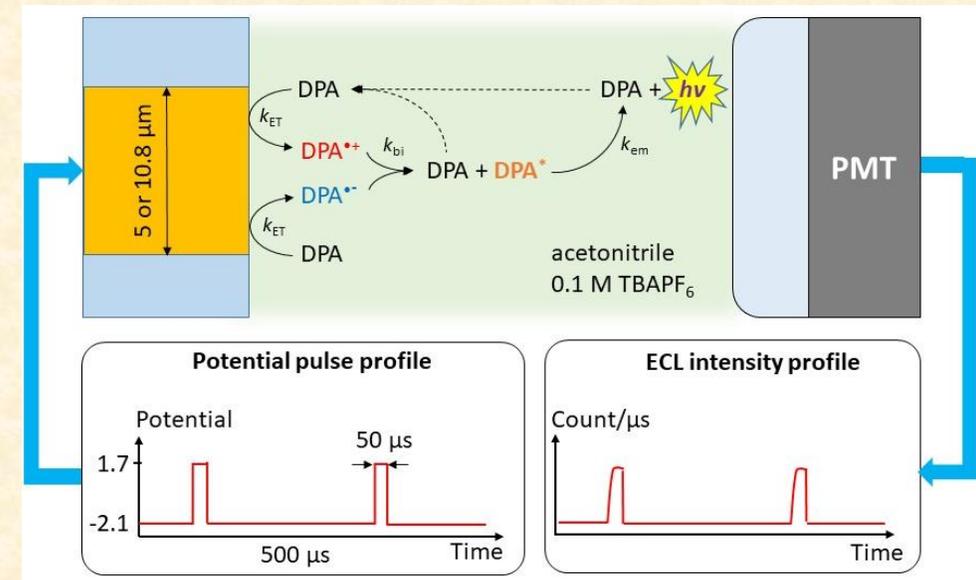
1995 – Single Molecule Electrochemistry & Electrogenenerated Chemiluminescence



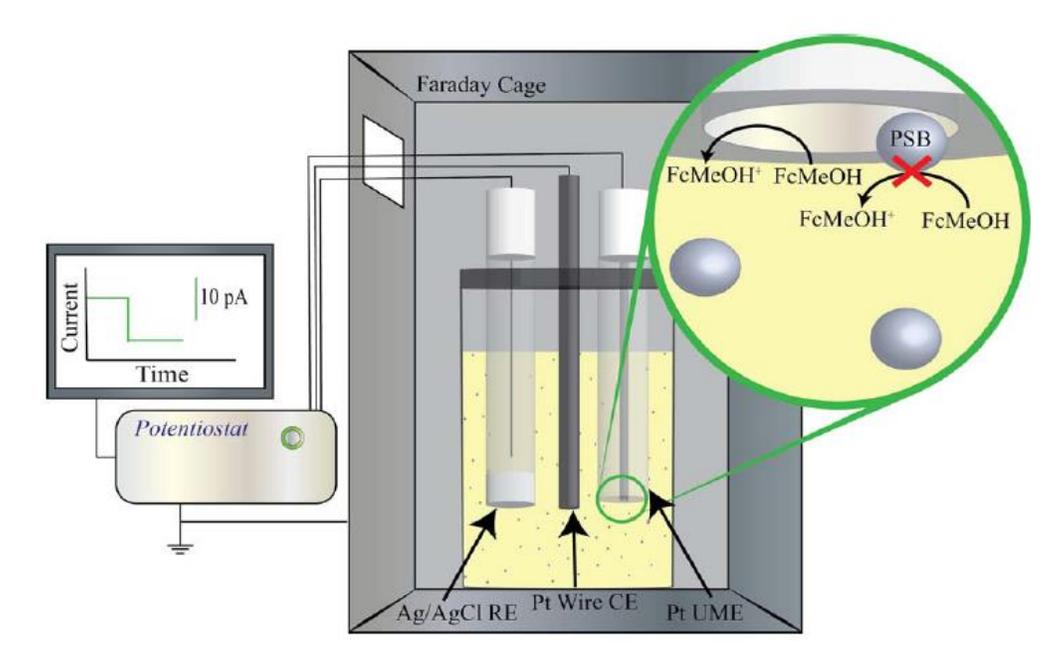
Allen J. Bard, NAS Member,
Professor, UT Austin



R. Mark Wightman
Professor Emeritus,
UNC Chapel Hill



A variety of techniques to study single entities colliding with electrodes

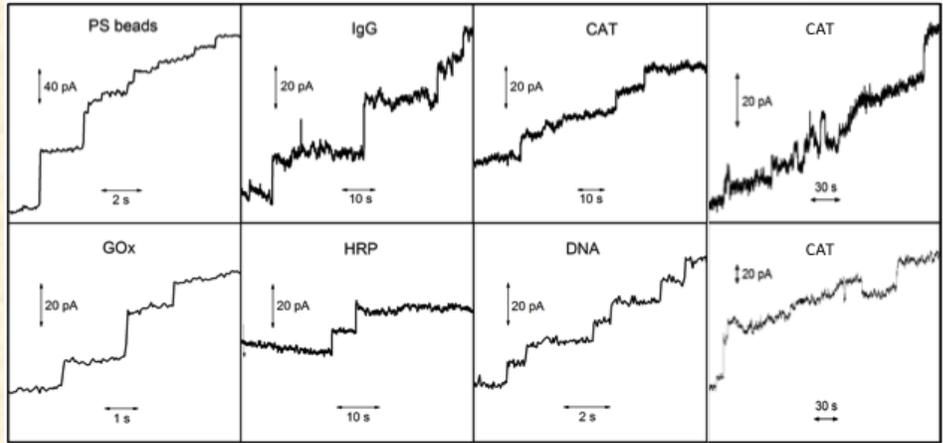
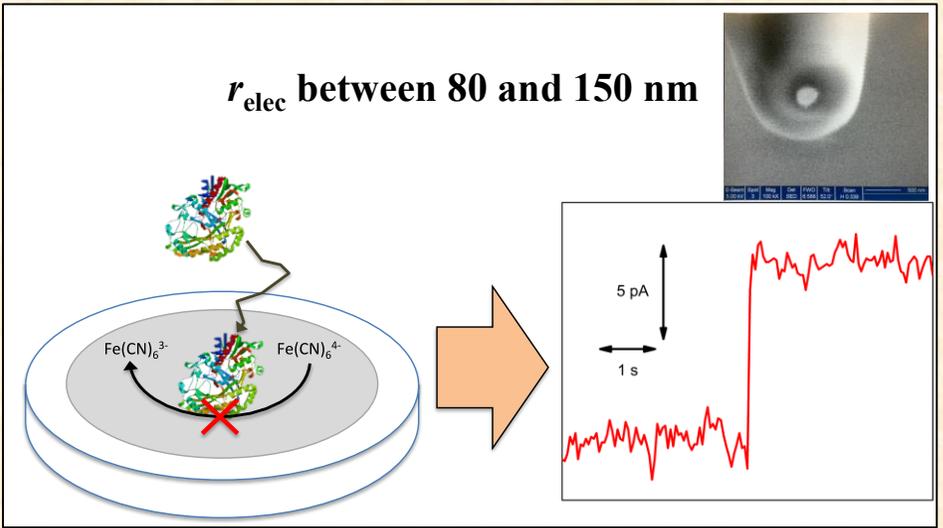
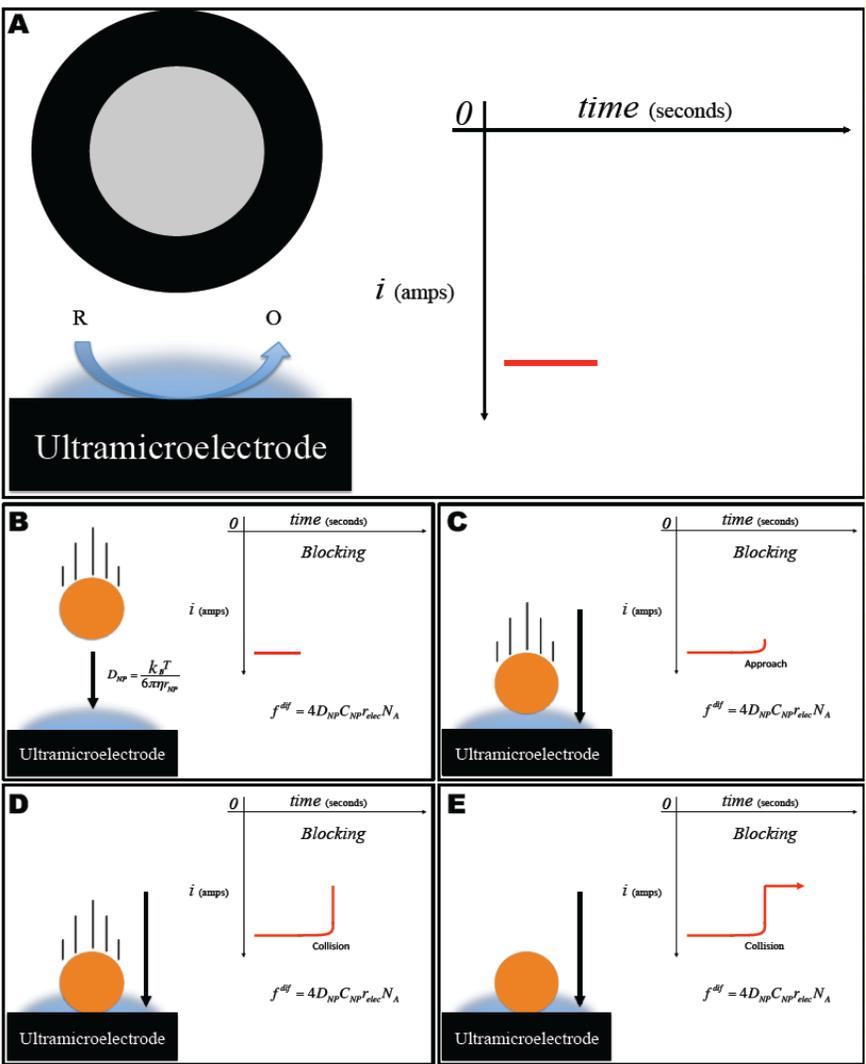


Technique	Schematic	Amperometric Response & Current Magnitude	Benefits	Limitations
<i>Blocking</i>		Current vs Time graph showing a step-down response. Scale bar: 10 pA.	<ul style="list-style-type: none"> - Robust - Size-selective on hemispherical UME - Wide variety of entities give response 	<ul style="list-style-type: none"> - Uneven current distribution on disk UME - Specific only to insulating or kinetically unfavorable entities - Prone to false-positives
<i>Electrocatalytic Amplification</i>		Current vs Time graph showing a step-up response. Scale bar: 100 pA.	<ul style="list-style-type: none"> - Highly selective - Low background current - Can use solvent to amplify signal 	<ul style="list-style-type: none"> - Requires inner-sphere reactant for signal - High dependence on electrode/particle material - Particles may deactivate
<i>Material Dissolution</i>		Current vs Time graph showing a peak response. Scale bar: 1 nA.	<ul style="list-style-type: none"> - Highest S/N - Does not require other reactants - Independent of UME material 	<ul style="list-style-type: none"> - Limited to metals that easily oxidize - Oxidation product cytotoxicity - Particles may deactivate before fully reacting
<i>Droplet, Vesicle, Micelle</i>		Current vs Time graph showing a peak response. Scale bar: 10 pA.	<ul style="list-style-type: none"> - Reactions may be confined to sub-femto-liter environments - Wide range of sizes - Simple to generate 	<ul style="list-style-type: none"> - Must consider charge balance mechanism - S/N is low - Difficult to use as tags for biomarkers
<i>Enzymatically Enhanced</i>		Current vs Time graph showing a step-up response. Scale bar: 1 pA.	<ul style="list-style-type: none"> - Entity specific detection - ELISA literature precedence 	<ul style="list-style-type: none"> - Low S/N - Electrode fouling/enzyme non-specific adsorption - Complex mechanism

... cells, bacteria, mitochondria

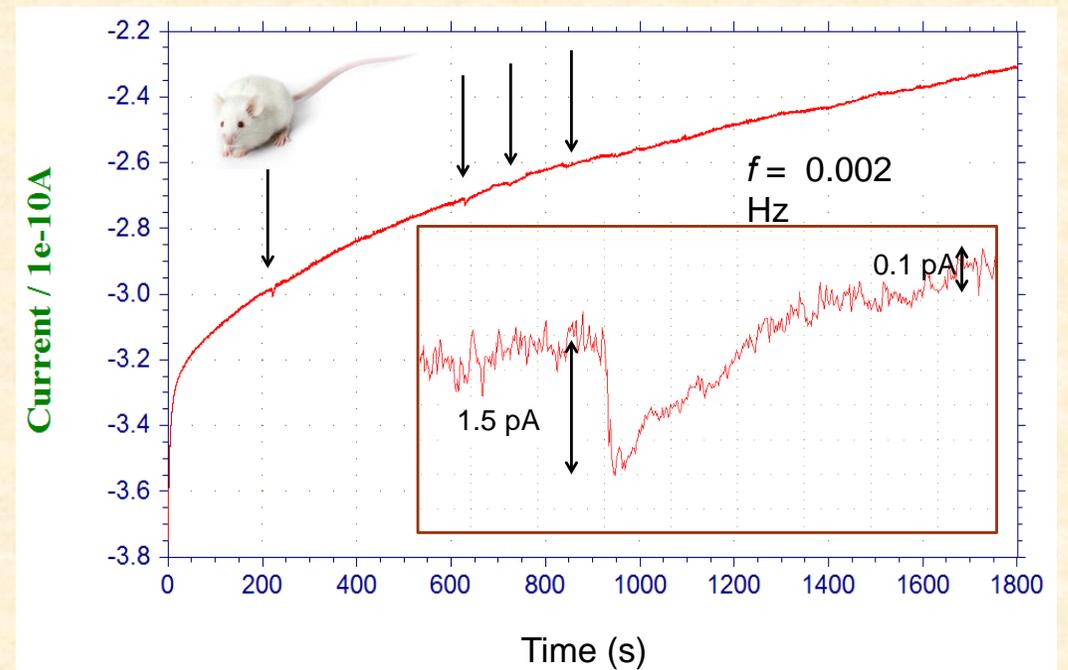
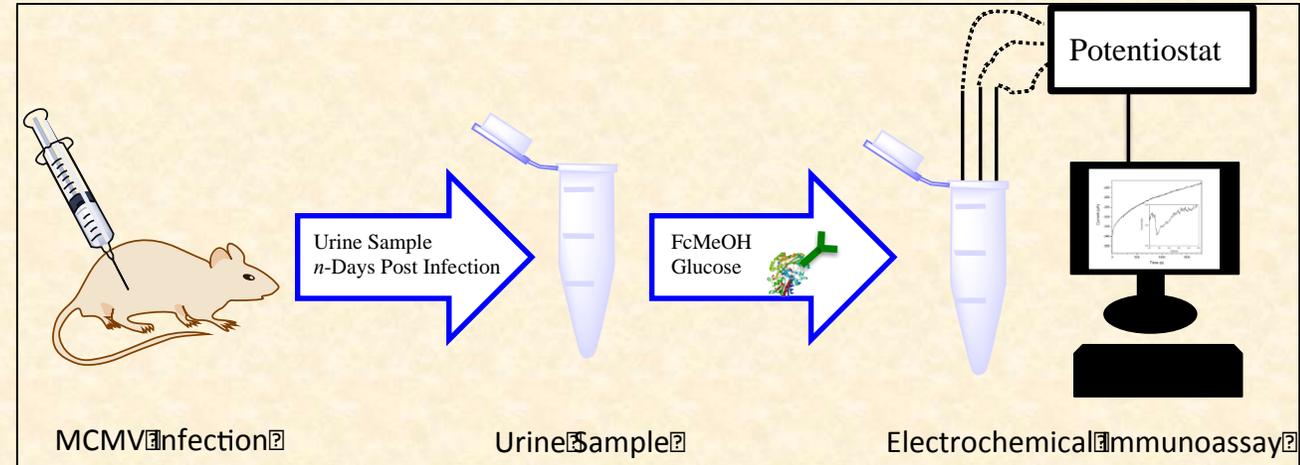
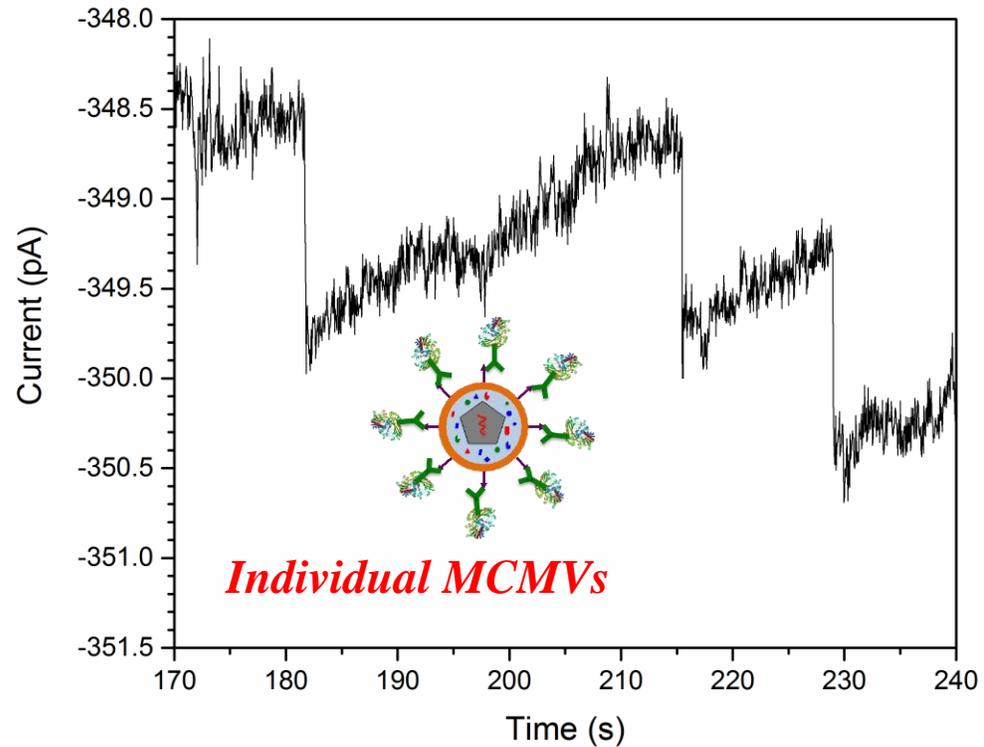
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Single Entity Electrochemical Detection

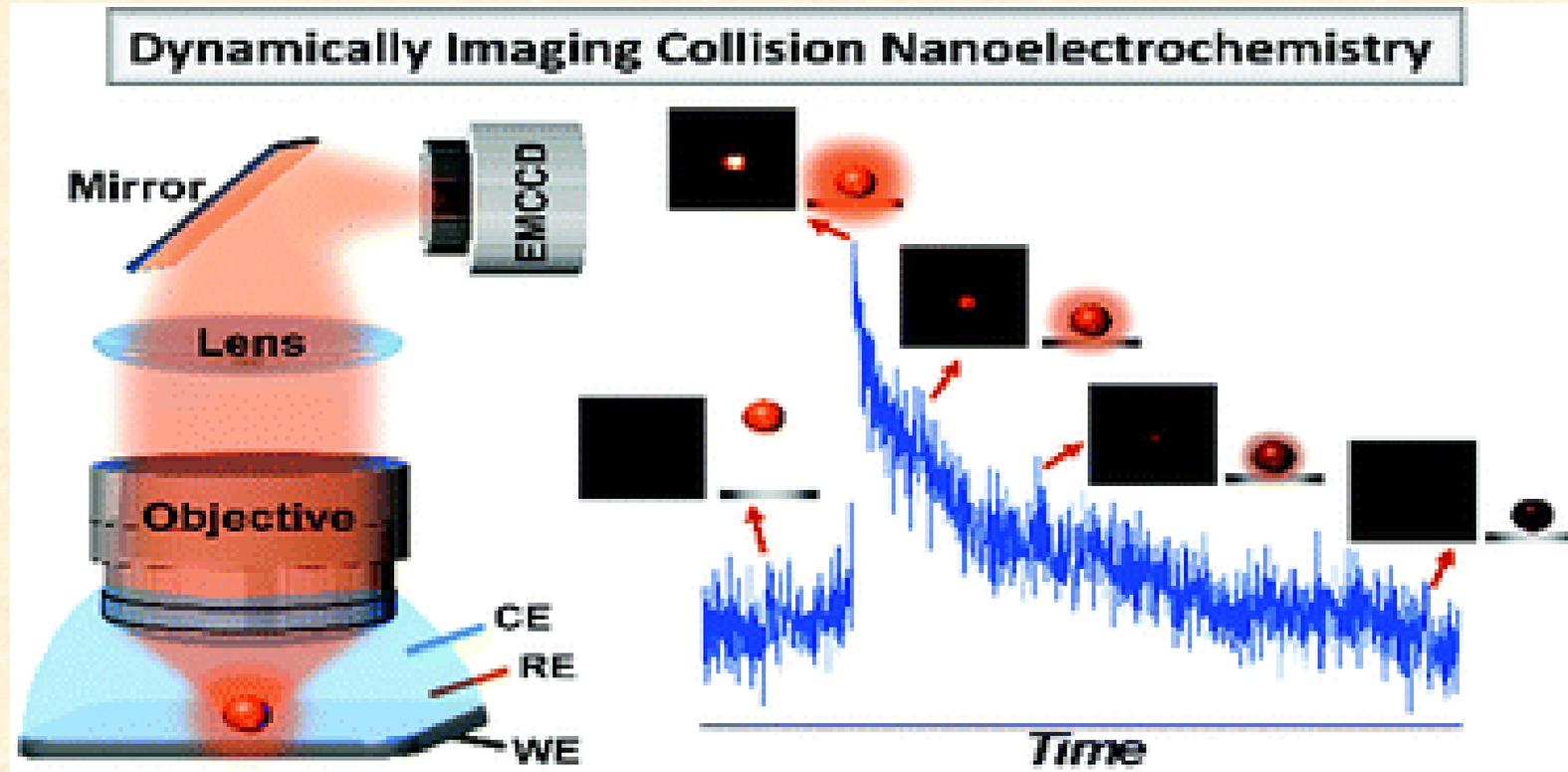


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Enzymatic Enhancement: Specific Detection



... but seeing is believing. **It's important moving forward to correlate collisions to diagnose reactivity.**



Electrocatalytic Amplification

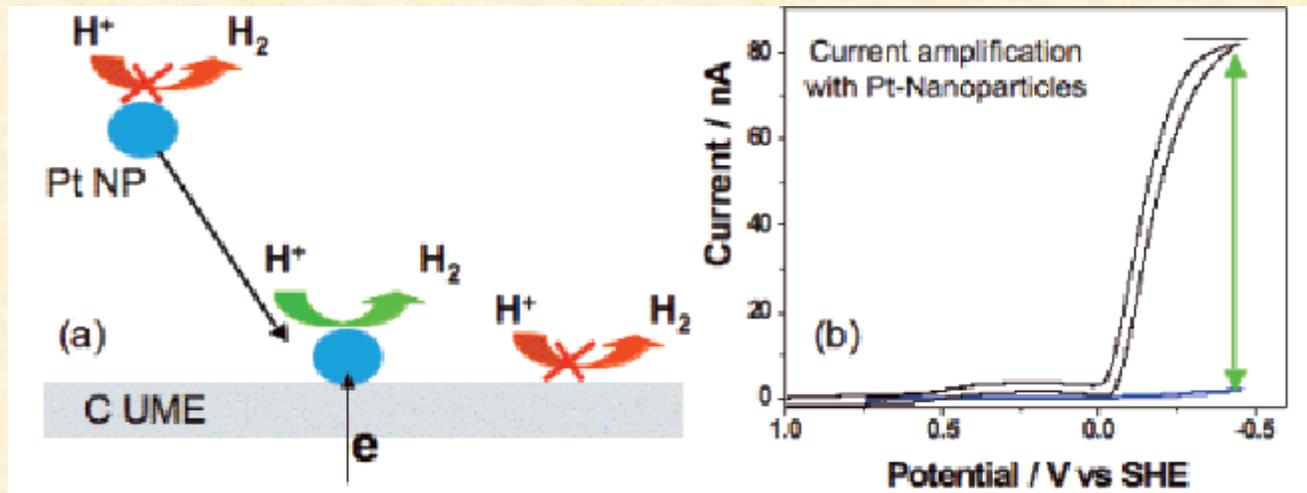


Figure 1 (a) Schematic of a single platinum nanoparticle collision event.

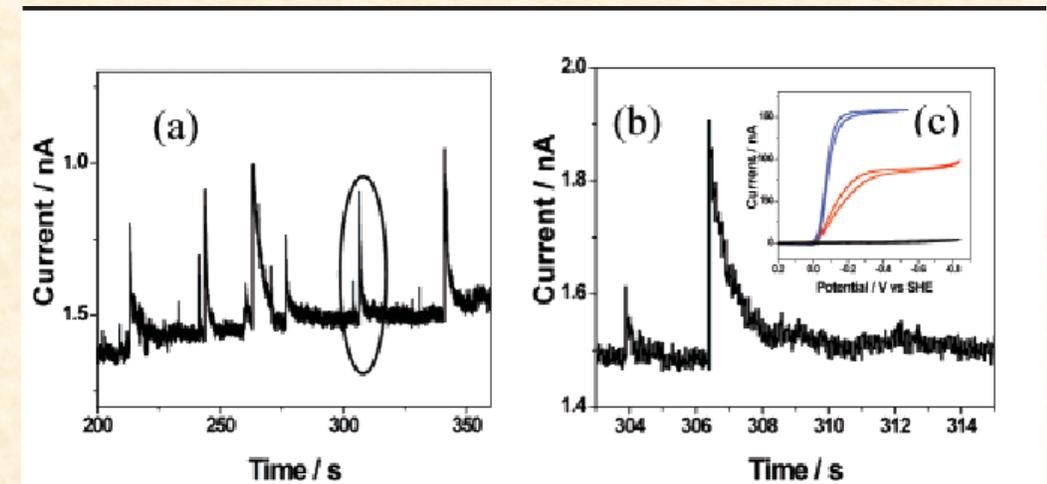
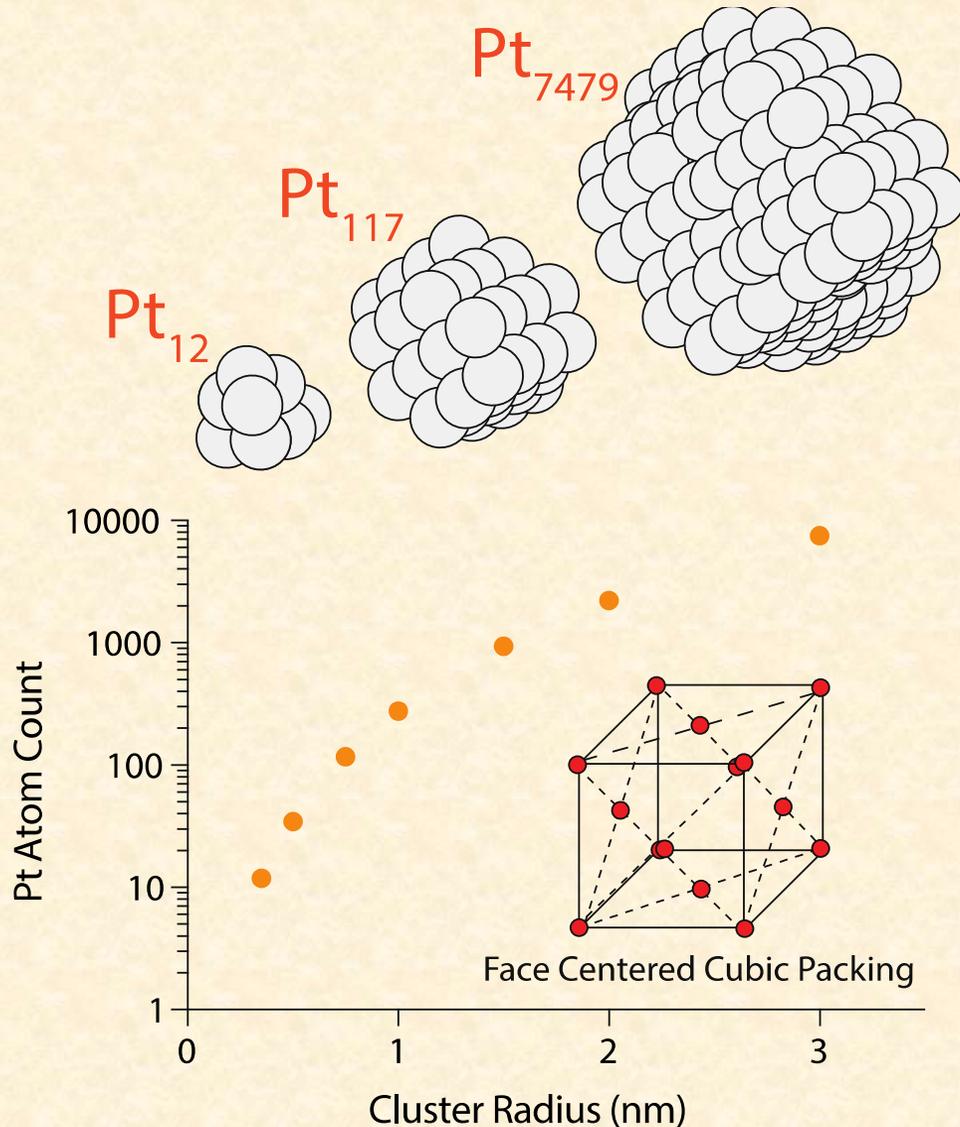


Figure 3 (a) Current transient at a C UME in 10 mM perchloric acid and

How small of a NP can we observe?



If current to a sphere on a plane is given by:
$$i_{ss} = 4nFDCr_{NP}\ln(2)$$

The current for an electrode the size of a single atom ($r \sim 250$ pm) in a .05M acid

Current is on the order of **>10 picoamperes**.

The noise on most electrochemical instruments is plus or minus 100 femtoamperes in a well grounded system, so S/N should be $\sim 120!!!$

Single Atom Predictions

Electrodeposition and electrocatalysis: the deposition and dissolution of single catalyst centres *

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^c Department of Chemistry, West Chester University, West Chester, PA 19383 (USA)

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Abstract

It is confirmed that it is possible to obtain a mathematical solution to the problem of the nucleation and three-dimensional growth at constant potential of single growth centres of a new phase on a microelectrode substrate under all conditions ranging from kinetic to diffusion control of the growth process under the assumption that diffusion is in a quasi-steady state. The results are extended to double-potential-step experiments and it is shown that similar complete descriptions can be derived for experiments where the growth centre acts as a catalyst site for an electrocatalytic reaction.

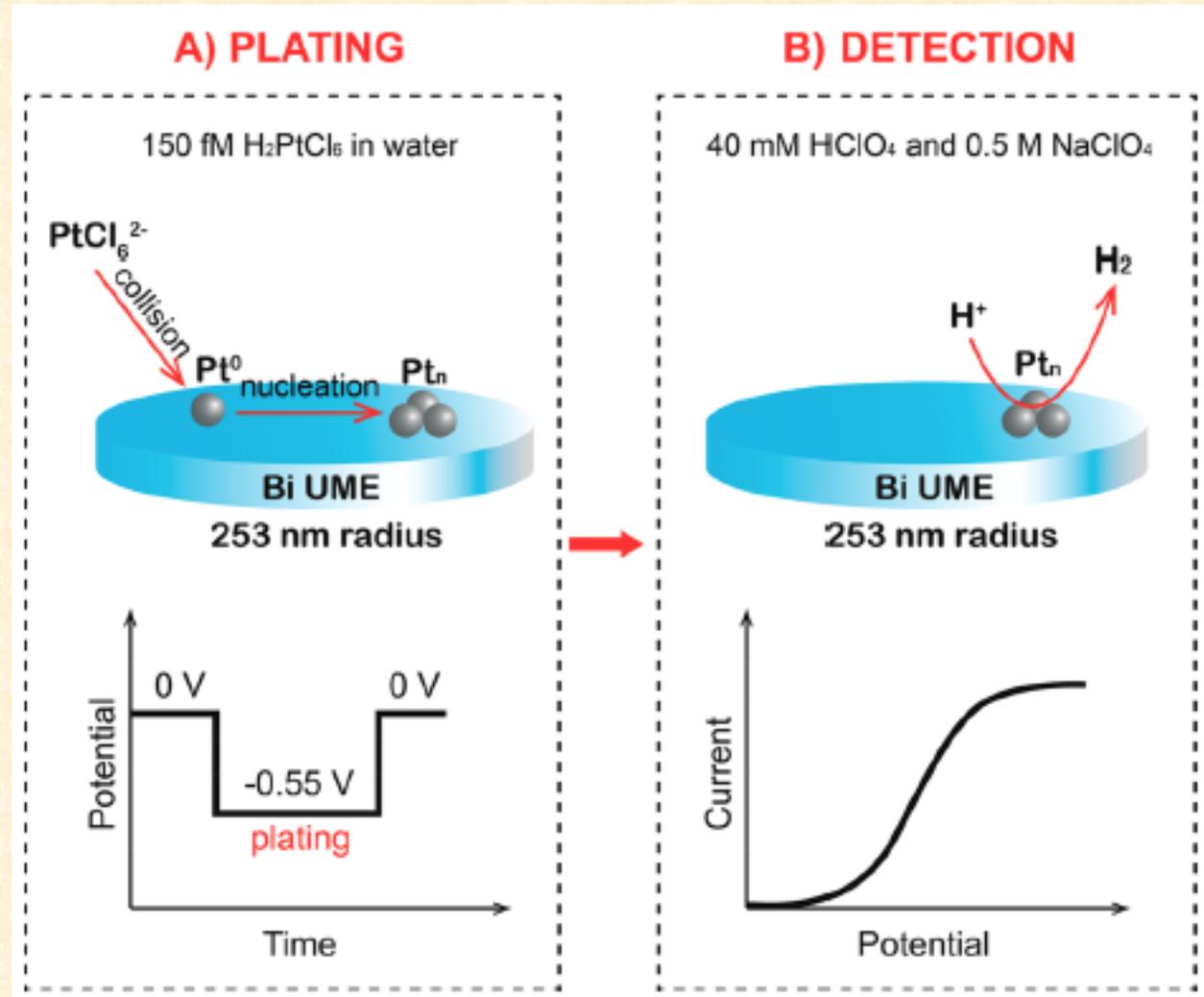
Cyclic voltammetry of the two types of processes is discussed for a more restricted range of conditions, namely pure kinetic or diffusion control of the growth of the catalyst centre.

It is shown that it should be possible to detect catalytic reactions at a single atom of the new phase.



Stan Pons (left) & Martin Fleischmann

Measurements on Isolated, Single Atoms & Clusters



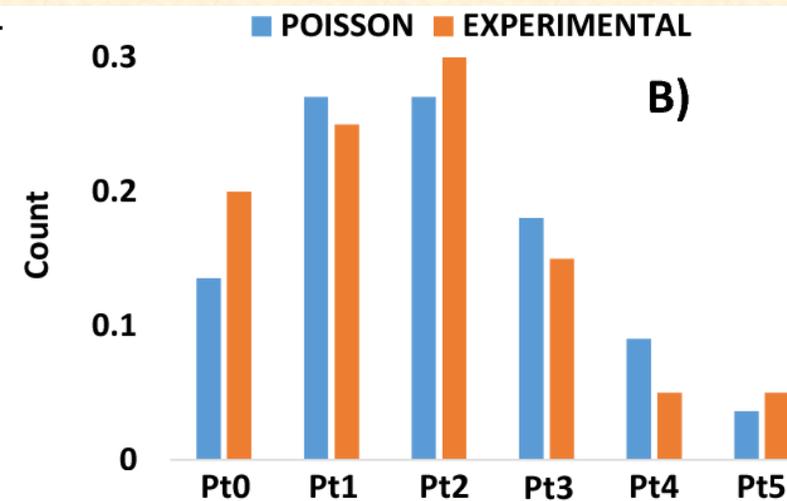
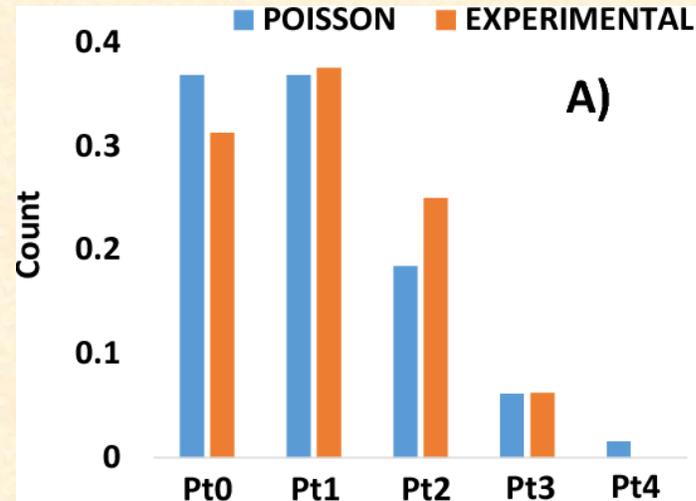
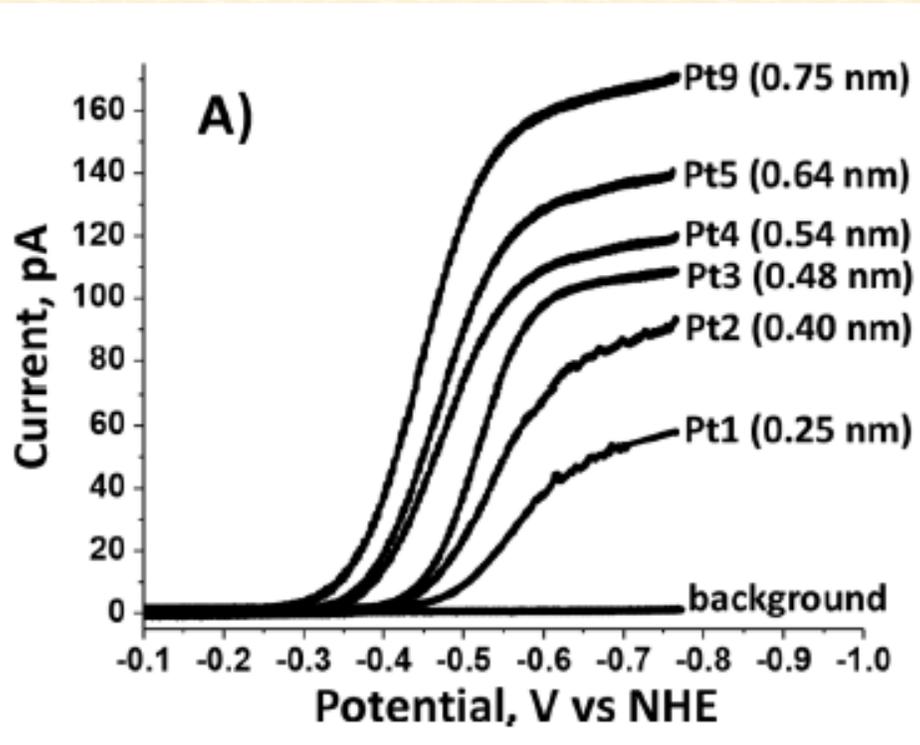
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Measurements on Isolated, Single Atoms & Clusters



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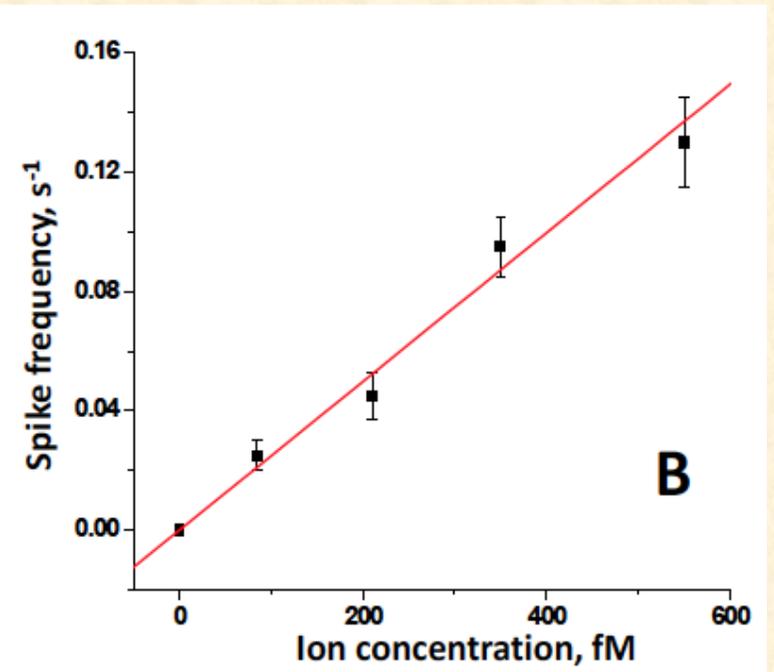
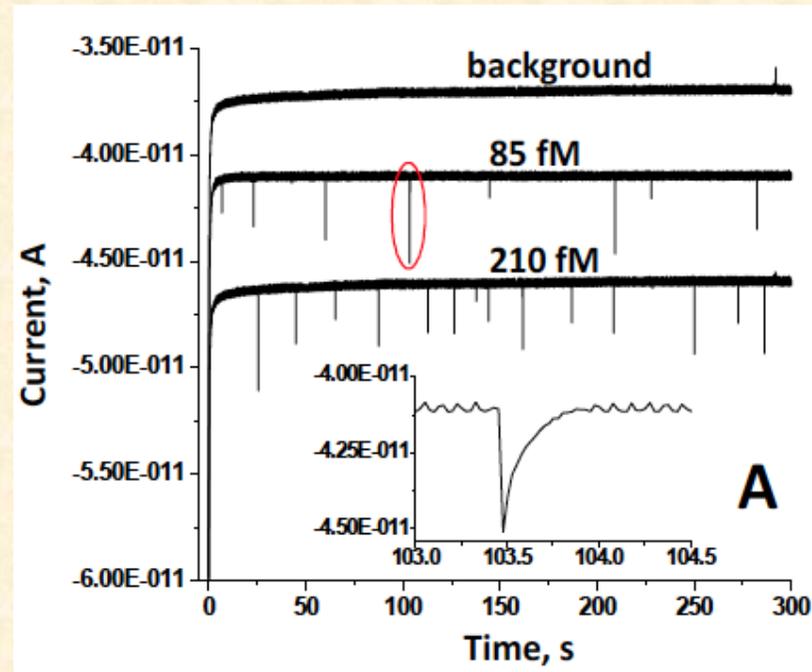
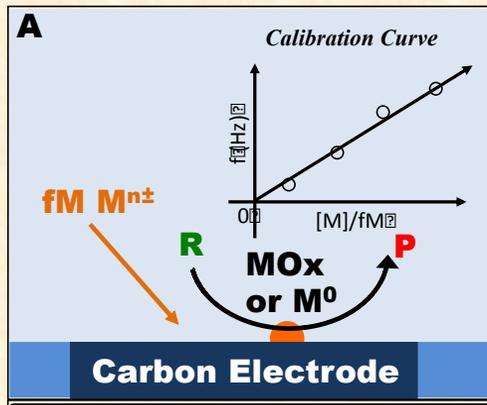
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Zhou, M.; Bao, S.; Bard, A. J. *J. Am. Chem. Soc.*, **2019**, *141*, 7327.

Glasscott, M. W.; Dick, J. E. *Anal. Chem.*, **2018**, *90*, 7804.

Detecting femtomolar amounts of ions

Parts per quadrillion detection



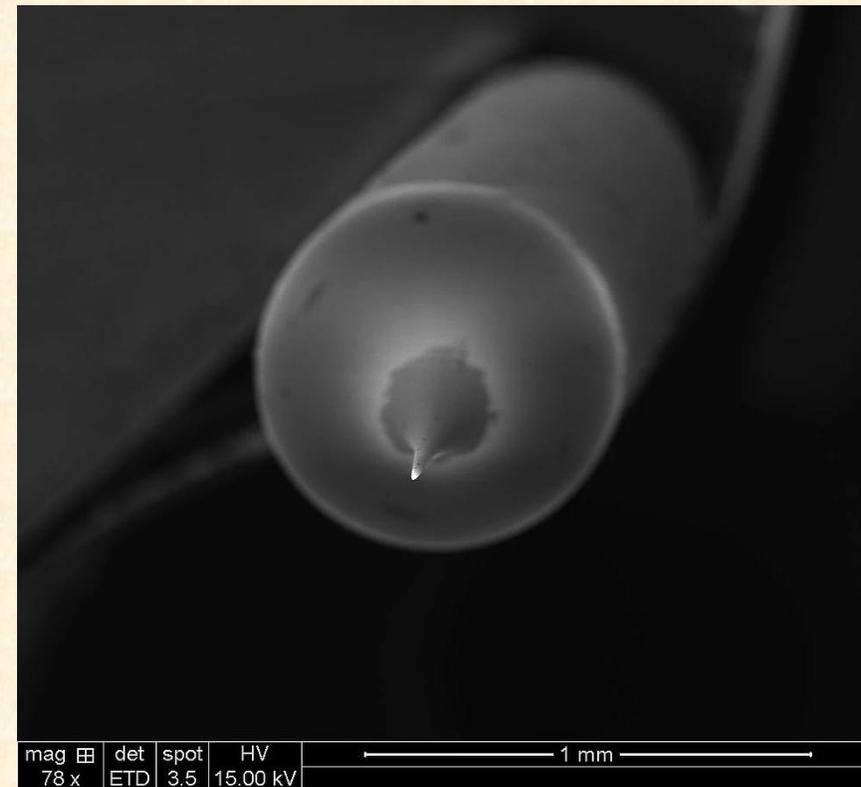
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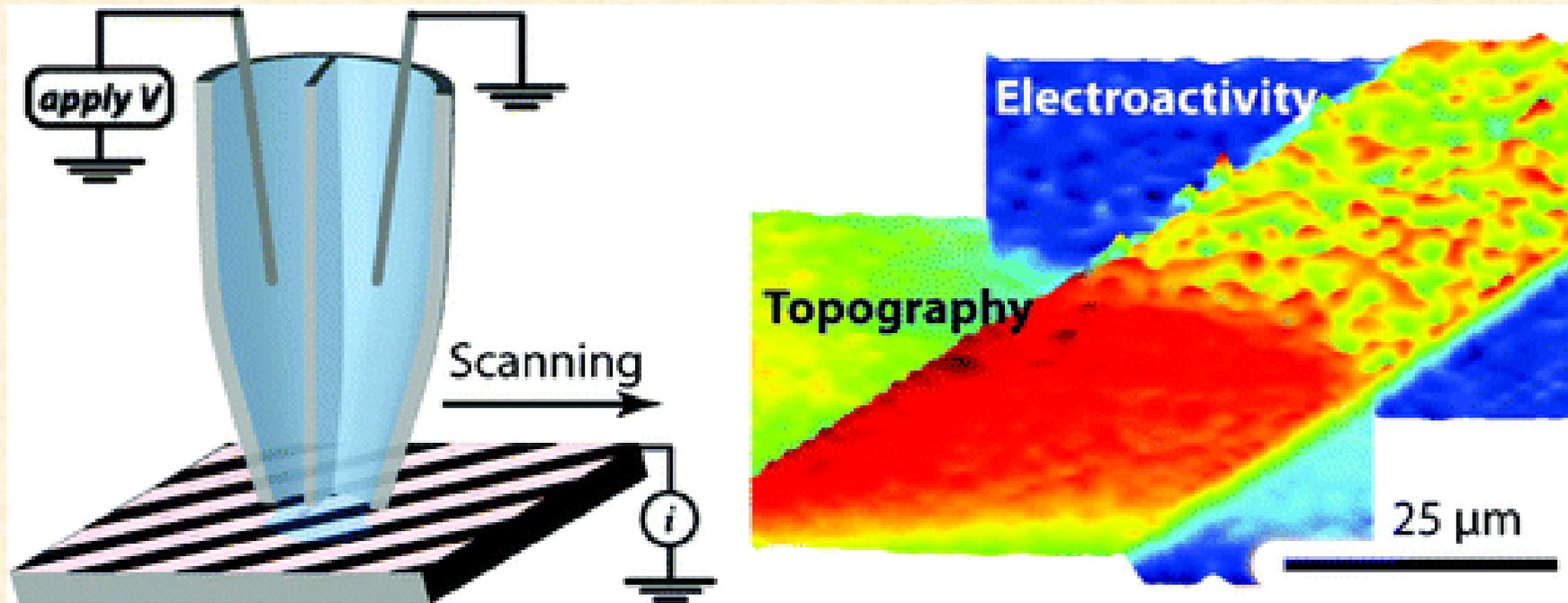
Zhou, M.; Dick, J. E.; Bard, A. J. *Anal. Chem.*, **2017**, *90*, 1142.

**Many of these experiments require
nanoelectrodes to enhance sensitivity**

Different ways of making nanoelectrodes: Laser pulling



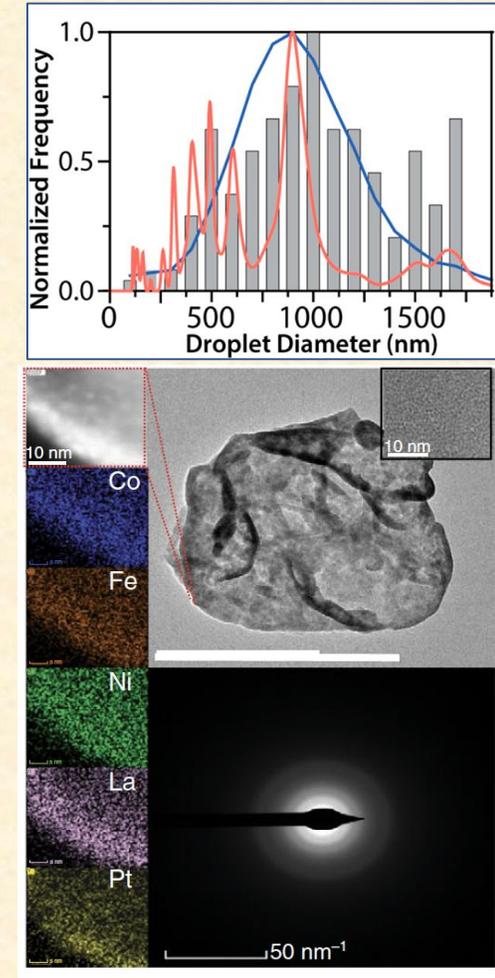
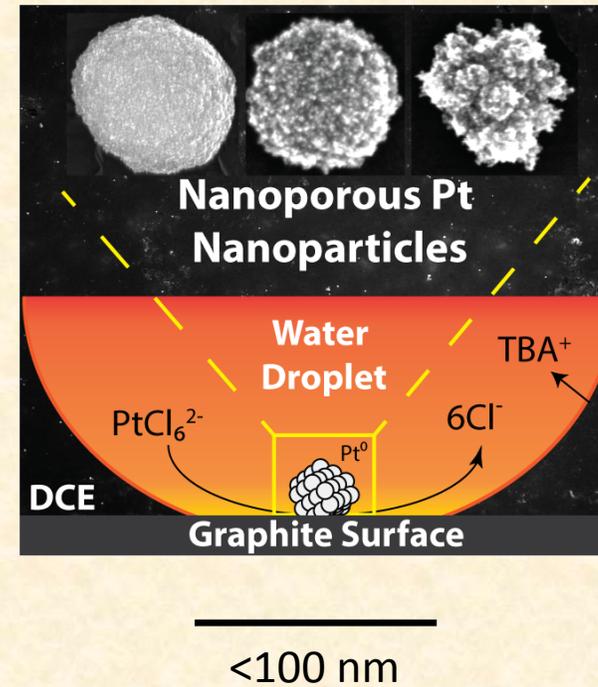
Different ways of making nanoelectrodes: Scanning Electrochemical Cell Microscopy



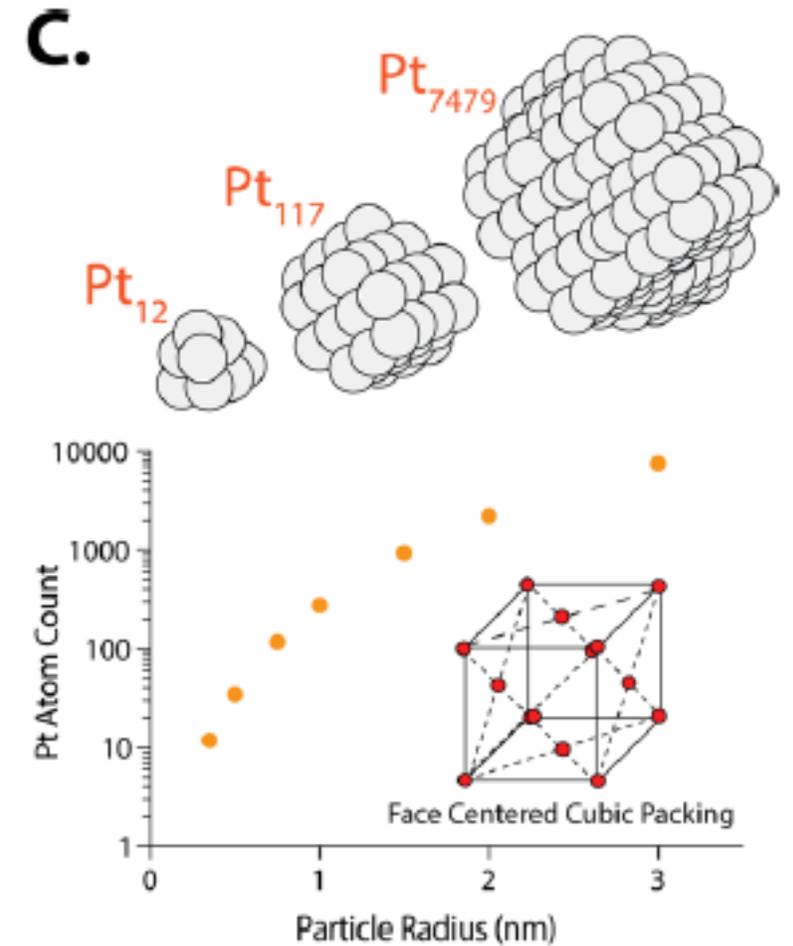
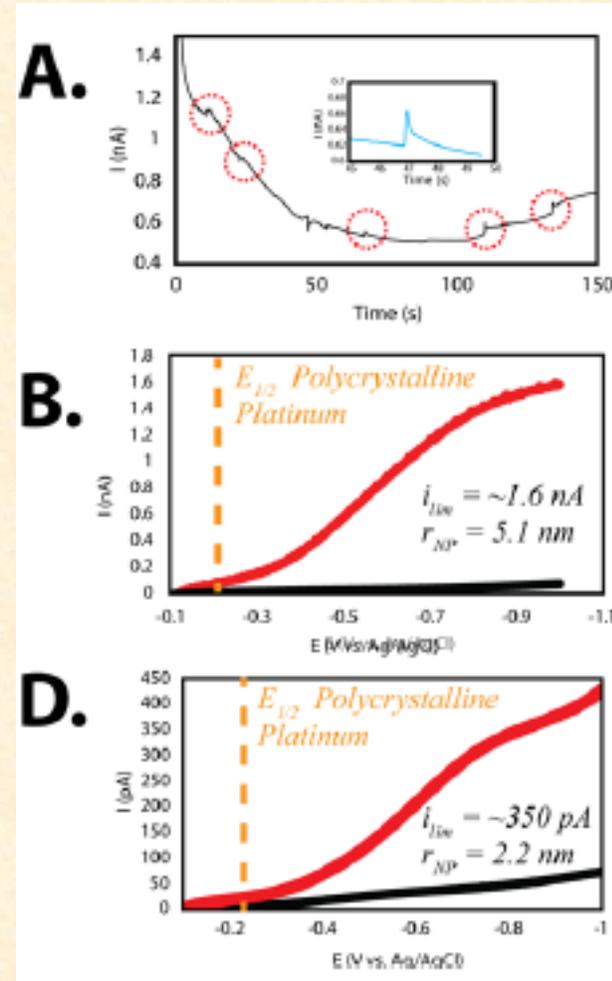
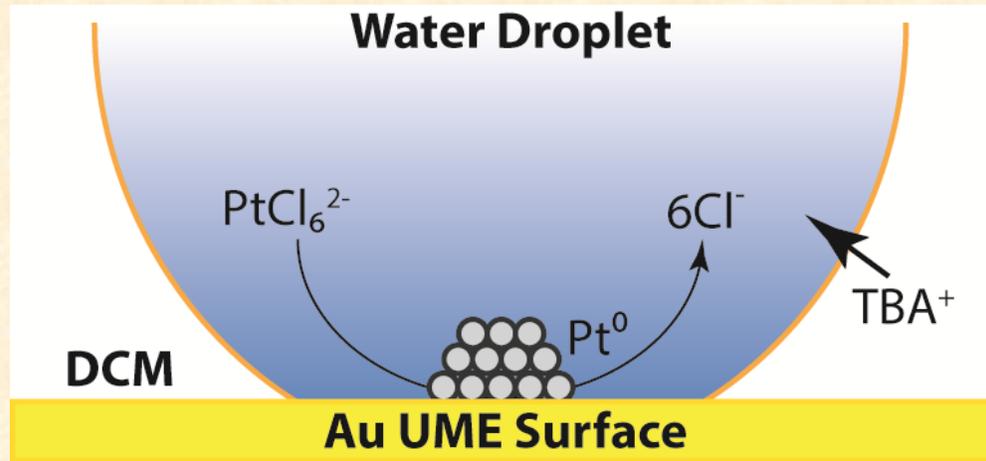
Different ways of making nanoelectrodes: Confining contents to nanodroplets

Electrodeposition from water nanodroplets:

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- Glasscott, M. W.; Pendergast, A. D.; Goines, S.; Bishop, A.; Hoang, A.; Renault, C.; Dick, J. E. *Nat. Commun.*, **2019**.



Single Cluster Electrocatalysis



Final Thoughts:

- Elephant in the room is the inner-sphere reaction, and gaining a fundamental understanding of these reactions on the most basic level is of great importance for all applications (energy storage and conversion, electrosynthesis).
- We have entered an era where the limit of detection in electrochemical measurements is a single atom, molecule, or nanoparticle. We are poised to learn new truths of nature at this level. Correlated measurements will enhance understanding.
- Resolution in electrochemistry is not limited by a fundamental limit (i.e., diffraction limit), but rather the smallest electrode one can make. A single atom. Need more effort to image with this resolution.
- One can electrosynthesize many organic compounds (Baizer, M. Organic Electrochemistry: An Introduction and Guide, 1973, M. Dekker.) While Nobel Prizes have been won for creating bonds, one can also break bonds with electrogenerated radical species (i.e., perfluoroalkyl substances).

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Michael Daniele, NC State
Henry White, Utah
Christophe Renault, CNRS
Caleb Hill, Wyoming
David Sinclair, Harvard
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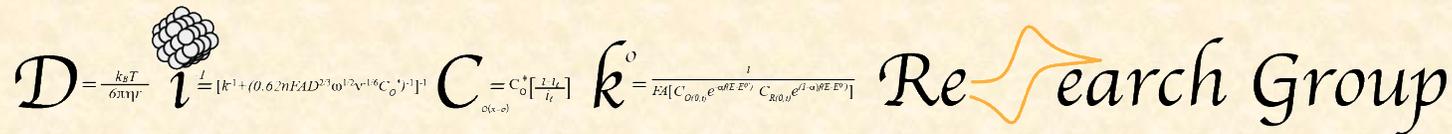
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