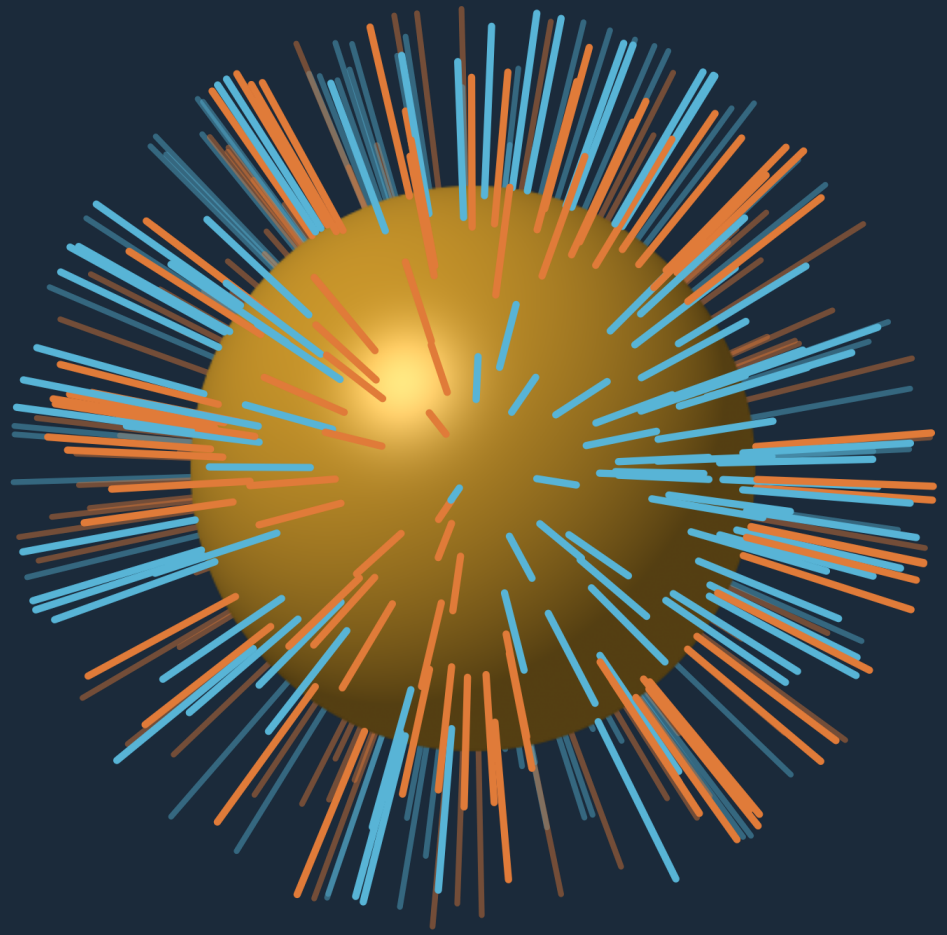
GUEST LECTURE 2 OF 3

Ligand-Coated Nanoparticles

What they are and how to characterize them



Francesco Stellacci · EPFL

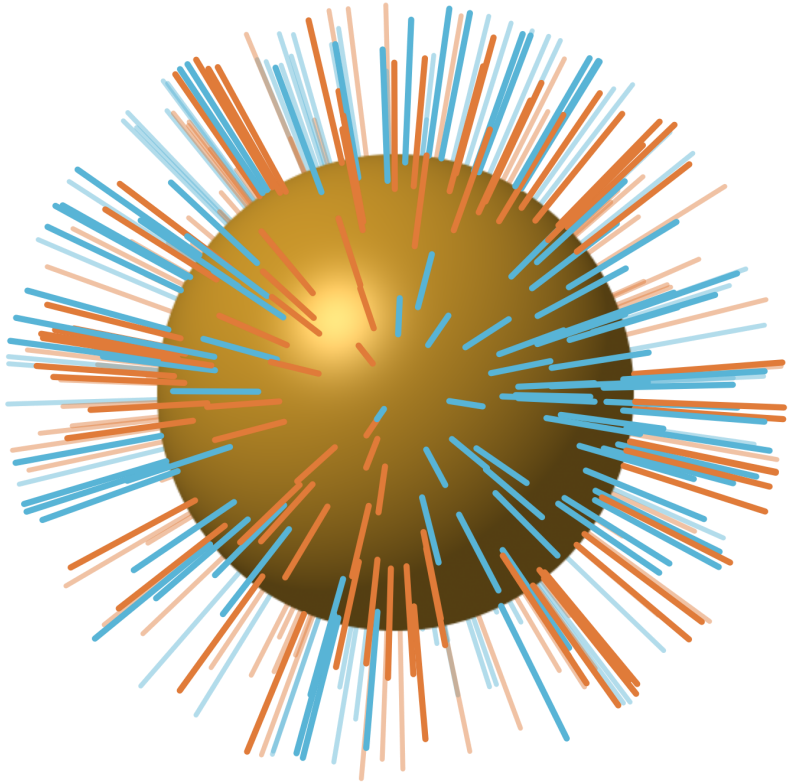
Outline

Part I · What they are

1. Anatomy and bonding
2. Synthesis
3. Mixed-ligand shells: morphology and why it matters

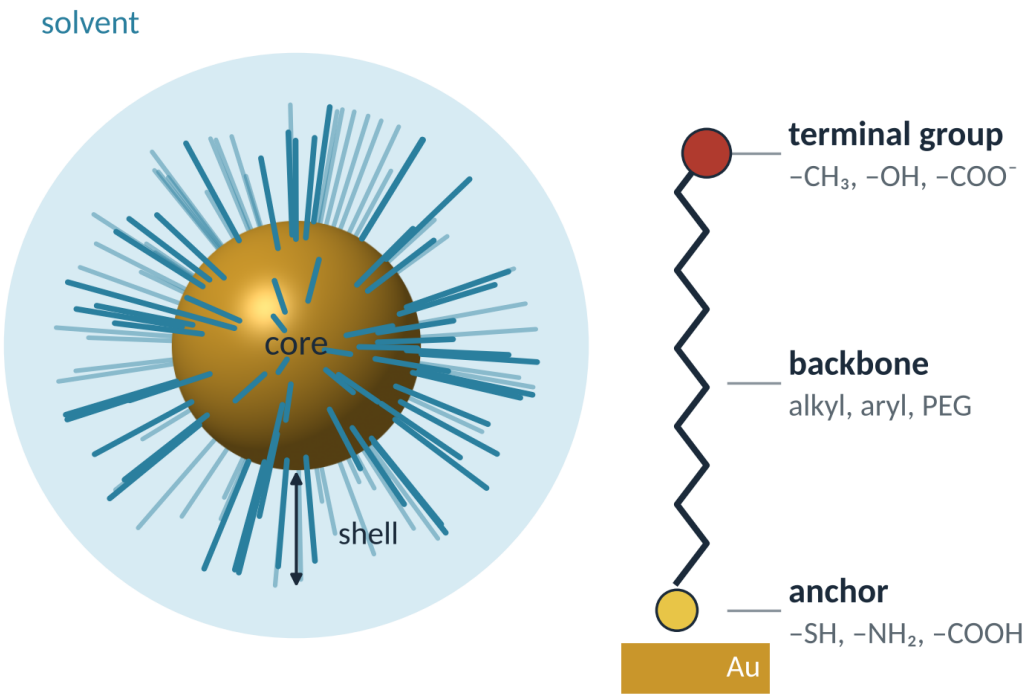
Part II · How to characterize them

4. Core, amount and composition
5. Shell morphology: microscopy
6. Spectroscopy: NMR and neutron scattering
7. Spectroscopy: mass spectrometry, EPR and probes
8. Simulation
9. Perspective: combining methods



Monolayer-protected nanoparticles

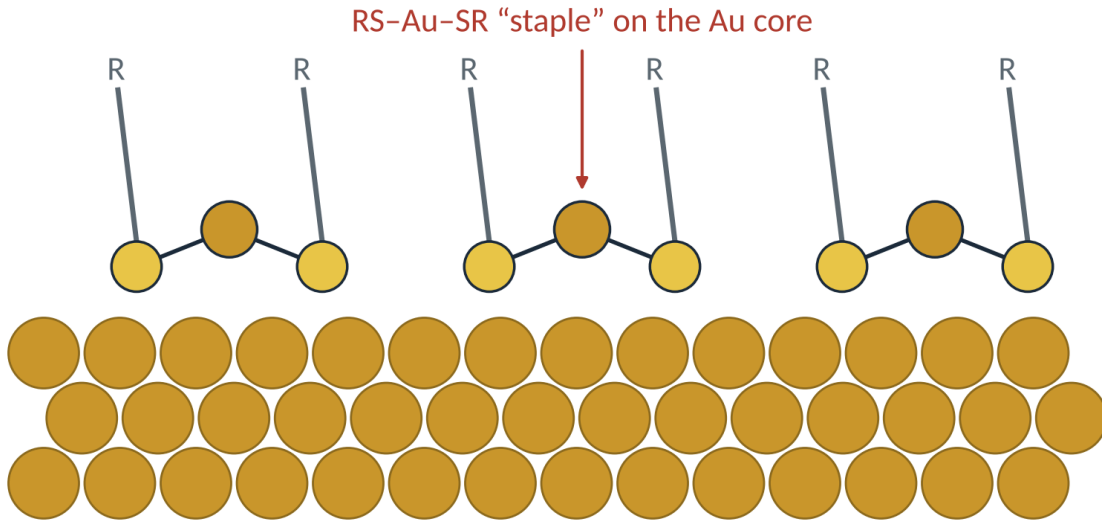
- A gold core a few nanometres across, covered by a monolayer of ligands bound through S–Au bonds
- Each ligand: **anchor** (binds the core), **backbone** (packs), **terminal group** (faces the solvent)
- Made by direct synthesis with thiols, or by ligand exchange afterwards
- Core and shell together set the properties, often non-additively



Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); Daniel & Astruc, Chem. Rev. 104, 293 (2004); Silvera Batista, Larson & Kotov, Science 350, 1242477 (2015)

The gold–thiolate interface

- Thiols bind gold as thiolates: a strong but dynamic bond
- Crystal structure of $Au_{102}(p\text{-}MBA)_{44}$: surface gold atoms form RS–Au–SR “staples”
- XPS S $2p_{3/2}$: ≈ 162 eV bound thiolate; ≈ 163.5 eV free thiol; ≈ 168 eV oxidized
- Bound thiolates exchange with free thiols and move on the surface

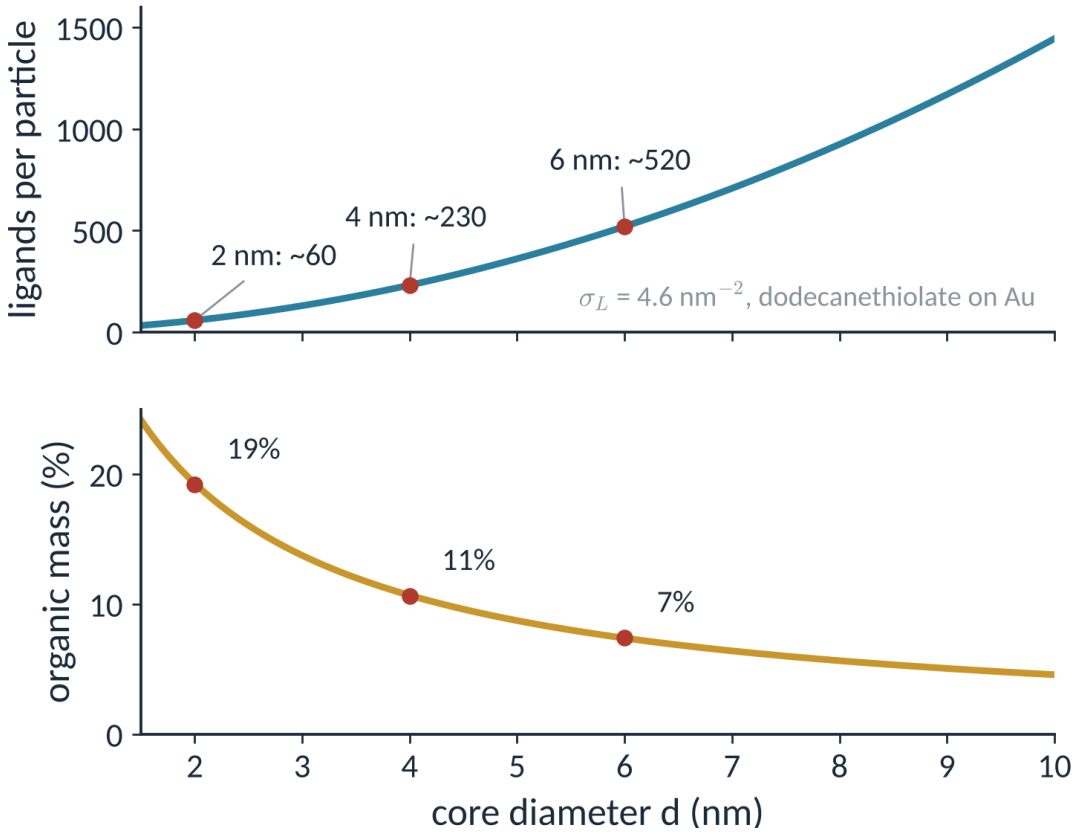


Jadzinsky et al., Science 318, 430 (2007); Häkkinen, Nat. Chem. 4, 443 (2012); Castner, Hinds & Grainger, Langmuir 12, 5083 (1996)

How many ligands per particle?

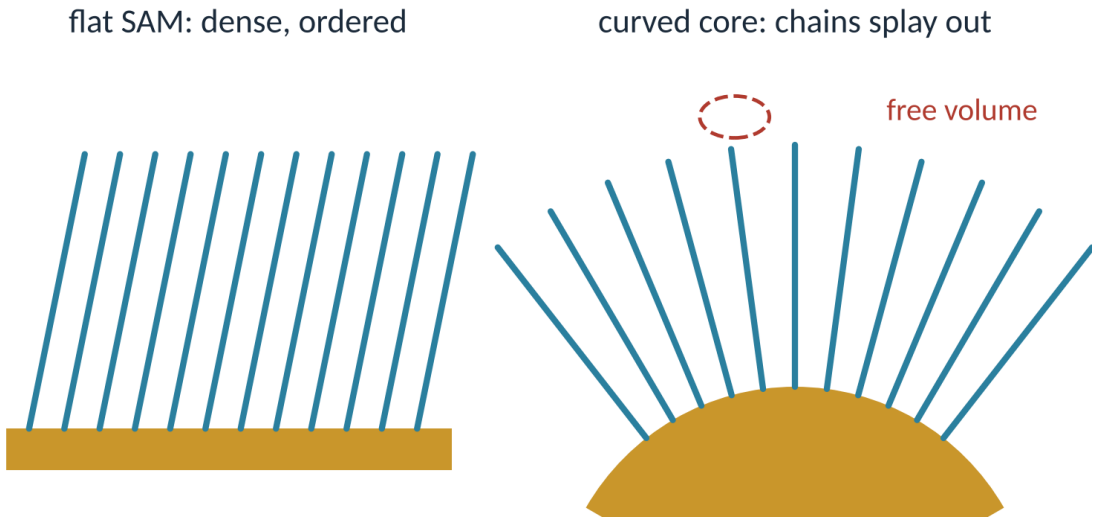
$$N_L = \sigma_L \pi d^2 \qquad (\sigma_L \approx 4.6\ \mathrm{nm}^{-2}\ \text{on Au(111)})$$

- Flat Au(111): one alkanethiol per 21.4 Å^2
- A 4 nm core: ~230 ligands, ~11% of the mass
- A 2 nm core: ~60 ligands, ~19% of the mass
- Ligand number and organic fraction are what TGA and NMR measure



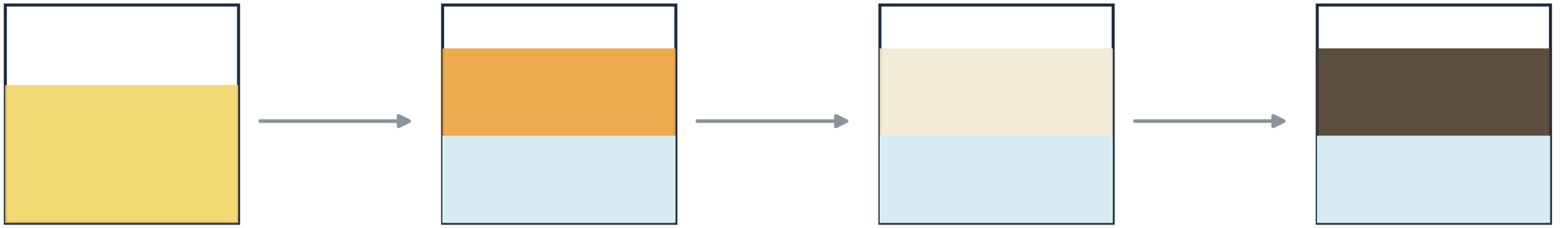
Packing and order in a curved monolayer

- On flat gold, alkanethiols form dense, nearly crystalline monolayers
- On a sphere the area per chain grows with distance from the core: chains splay out
- Order decreases outwards and on smaller cores
- FTIR CH_2 stretch: ~2918 cm^{-1} (ordered, all-trans) vs ~2924 cm^{-1} (liquid-like)



Hostetler, Stokes & Murray, Langmuir 12, 3604 (1996); Hostetler et al., Langmuir 14, 17 (1998)

Direct synthesis: the Brust–Schiffrin method



- Phase transfer of $AuCl_4^-$ into toluene by tetraoctylammonium bromide
- Thiol reduces Au(III) to Au(I)–thiolate
- $NaBH_4$ nucleates cores, capped as they grow
- Thiol:Au ratio sets the size (~1–5 nm)

Brust, Walker, Bethell, Schiffrin & Whyman, J. Chem. Soc., Chem. Commun. 801 (1994)

Other routes and ligand exchange

One-phase synthesis

Amine–borane reduction with the thiol mixture in one solvent (Stucky method)

Weak ligands, then exchange

Citrate gold (Turkevich), then incoming thiols displace citrate

Hot injection

Quantum dots and oxides with oleic acid, oleylamine, phosphines

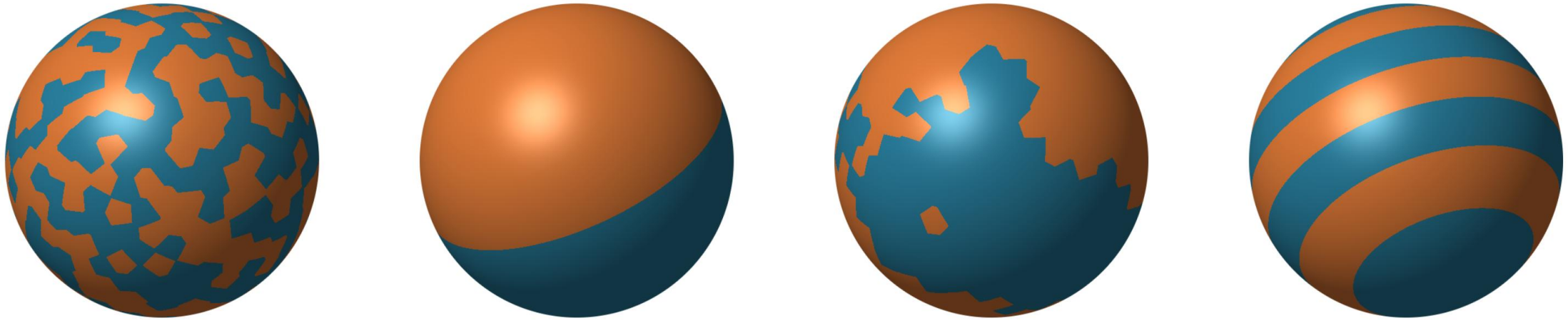
Place exchange

Free thiols replace bound ones; a route to mixed shells

Mixed shells: the composition on the particle differs from the feed, so it must be measured

Zheng, Fan & Stucky, J. Am. Chem. Soc. 128, 6550 (2006); Templeton, Wuelfing & Murray, Acc. Chem. Res. 33, 27 (2000)

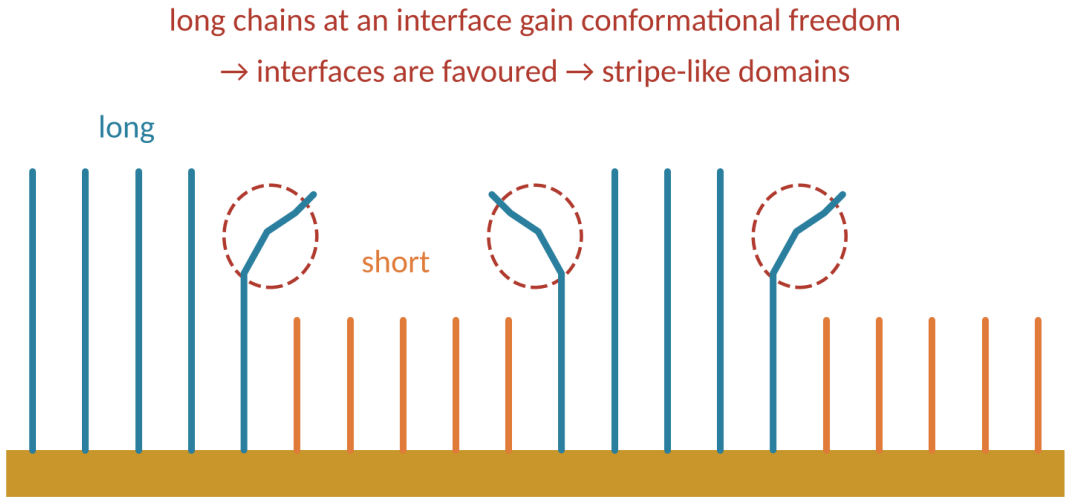
Mixed shells: four limiting morphologies



- Random: mixed at the molecular level
- Janus: two hemispheres
- Patchy and stripe-like: domains of ~0.5–2 nm
- The same composition can give any of the four

What decides the morphology?

- Enthalpy: unlike ligands prefer like neighbours → phase separation
- Interfacial entropy: a long ligand next to a short one gains conformational freedom → many interfaces → stripes
- Core size: ordered stripes only in a window (~2.5–8 nm for NT/MBT); Janus on smaller cores
- Branched ligands do not order → random mixing



Singh et al., Phys. Rev. Lett. 99, 226106 (2007); Carney et al., J. Am. Chem. Soc. 130, 798 (2008)

Why the shell structure matters

Wetting

Interfacial energy depends on domain size (Lecture 1)

Solubility

Non-monotonic with shell composition

Protein adsorption

Striped shells resist non-specific adsorption

Cell penetration

Striped particles enter cells without poration

Catalysis

Activity depends on shell composition and structure

Cation capture

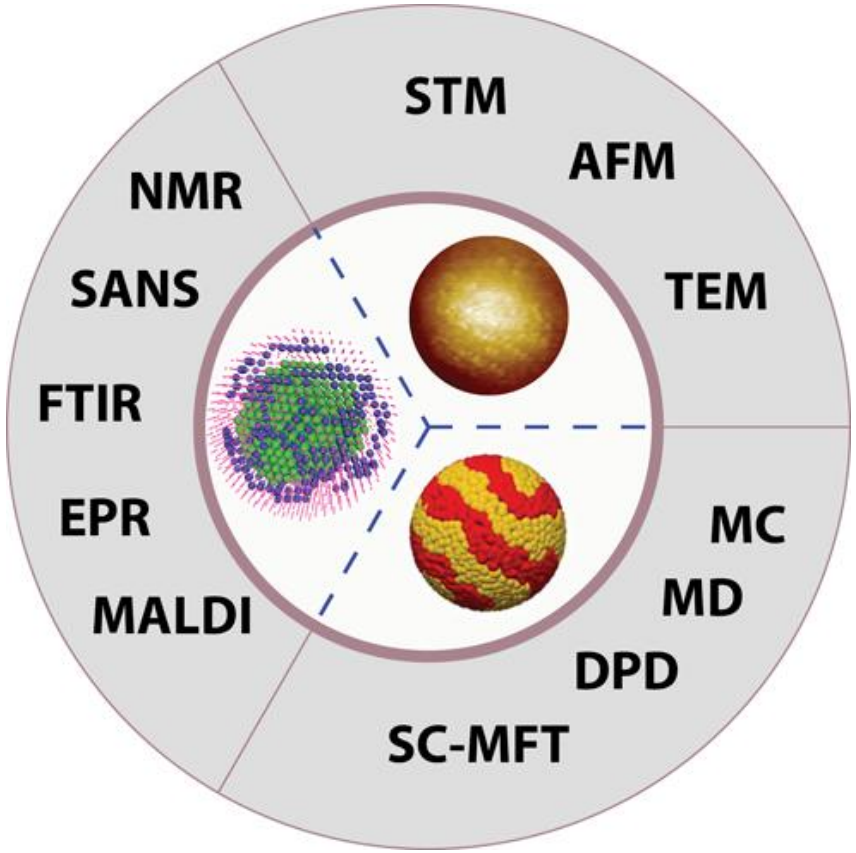
Films of striped particles detect toxic cations

Kuna 2009; Centrone 2008; Jackson 2004; Hung 2011; Verma 2008; Ghosh 2011; Cho 2012 (full references at the end)

The characterization challenge

~1 nm	2–6 nm	~10^2
domain size	core diameter	ligands per particle

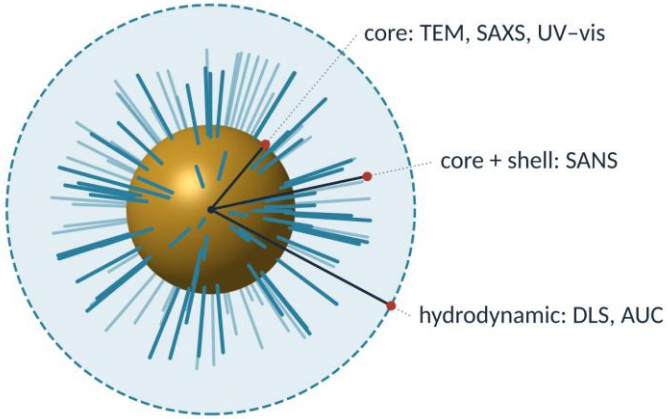
- Domains below the resolution of most imaging; shells soft and dynamic
- **Microscopy** (STM, AFM, TEM): real space, but a few particles
- **Spectroscopy** (NMR, MS, SANS, EPR): the whole ensemble, but averaged
- **Simulation**: why a morphology forms; what the data mean



Graphic: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017)

A characterization map

Question	Main techniques
Core size and shape	TEM, SAXS, AUC, UV–vis
Particle in solution	DLS, AUC, ζ-potential
Shell amount and composition	TGA, ^{1}H NMR after core etching, XPS
Morphology in real space	STM, AFM, S/TEM
Morphology of the ensemble	NMR, MS, SANS, EPR, FTIR, UV–vis, adsorption
Mechanism and interpretation	MD, Monte Carlo, DPD

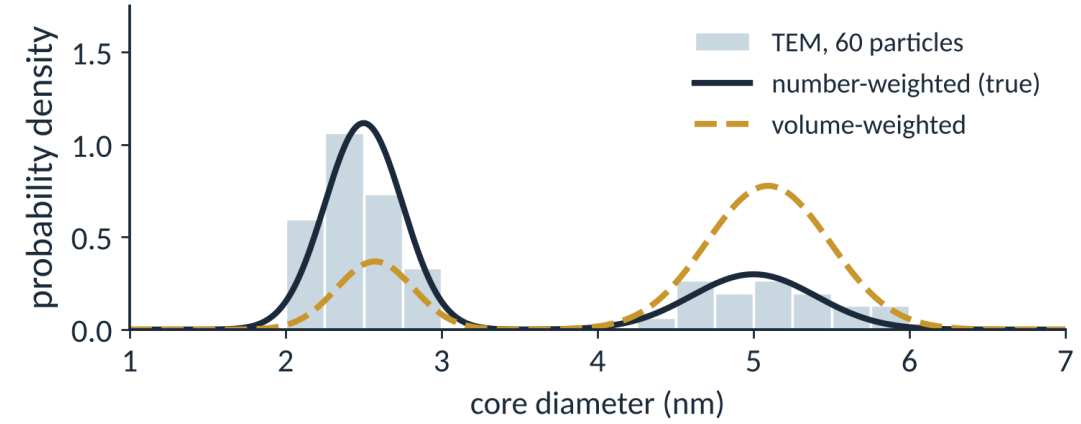


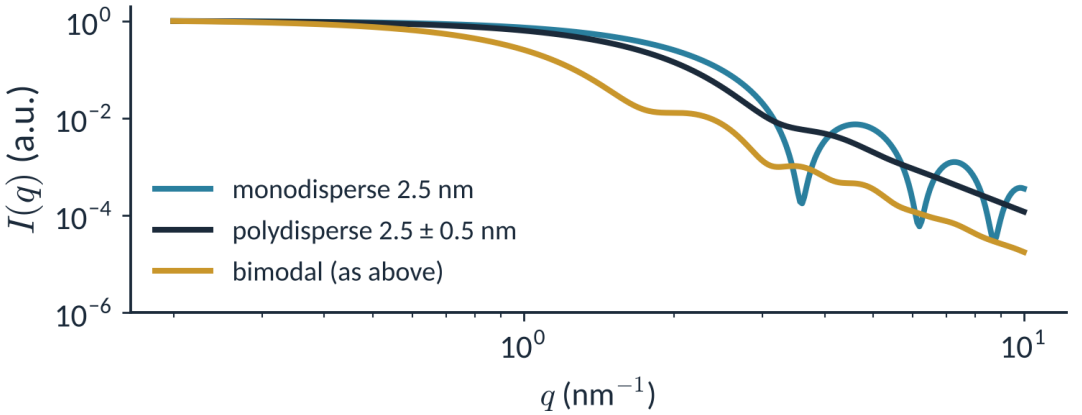
Core size: TEM and SAXS

- TEM: direct images of cores (ligands barely visible); shape, crystallinity
- Limits: hundreds of particles, drying artefacts, operator bias
- SAXS: the whole ensemble in solution

$$I(q) \propto \int N(R)\,(\Delta\rho)^2\,V(R)^2\,P(q,R)\,dR$$

- Large particles dominate; form-free Monte Carlo fitting recovers polydisperse and bimodal 2–7 nm Au populations



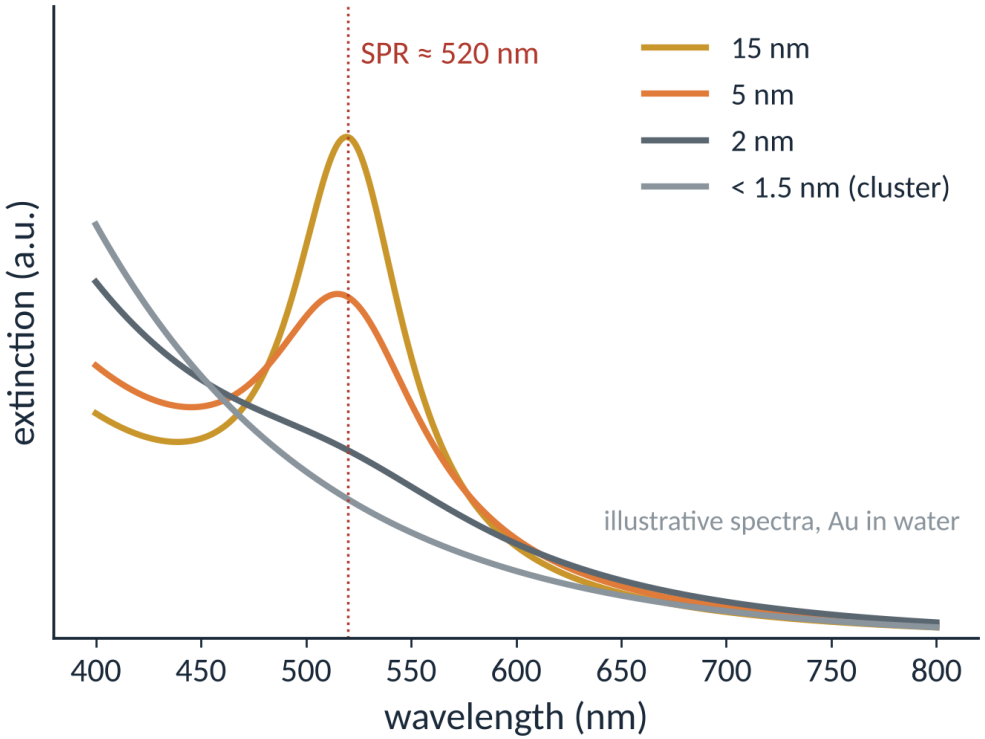


Yang, Liao, Luo, Qi, Mac Fhionnlaoich, Stellacci & Guldin, Nanoscale 12, 12007 (2020)

UV–vis, DLS and ζ-potential

$$R_h = \frac{k_B T}{6\pi\eta D}$$

- UV–vis: plasmon near 520 nm for Au cores > ~3 nm; damped below; clusters show molecular-like bands
- DLS: core + shell + solvation; intensity-weighted, biased to aggregates
- ζ-potential: surface charge, in the medium of use



Haiss, Thanh, Aveyard & Fernig, Anal. Chem. 79, 4215 (2007)

Analytical ultracentrifugation (AUC)

- Spin at up to ~10^5 g; optics record c(r, t); fit the Lamm equation → c(s, D)
- s: mass and density; D: size (Stokes–Einstein)

$$s = \frac{u}{\omega^2 r} = \frac{MD\,(1 - \rho_s/\rho_P)}{RT}$$

$$d_P = \frac{k_B T}{3\pi\eta_s D} \qquad \rho_P = \rho_s + \frac{18\,\eta_s\, s}{d_P^2}$$

- Together: density, mass and diameter of each population, with no standards

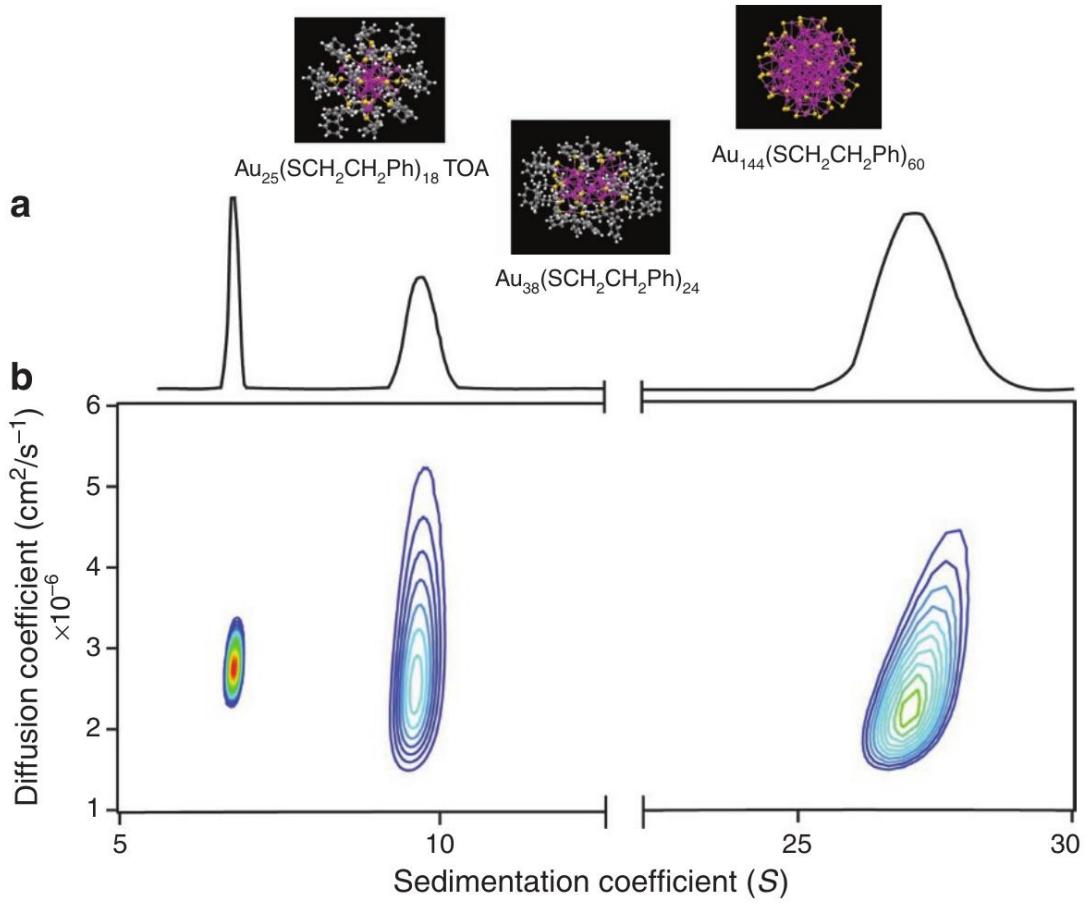


Figure and method: Carney, Kim, Qian, Jin, Mehenni, Stellacci & Bakr, Nat. Commun. 2, 335 (2011)

AUC: size, density and mass together

- Au_{25}, Au_{38}, Au_{144} in one run: mass within 2–4% of ESI-MS
- $Au_{144}(SR)_{60}$: ρ_P = 4.51 g cm^{-3}, d_P = 2.83 nm; shell density 1.2 g cm^{-3}
- 6.7 nm particles: two populations (6.68 and 6.82 nm) invisible to TEM
- Polydisperse MUS particles: discrete populations (figure)
- Limits: spheres assumed; rods need the aspect ratio

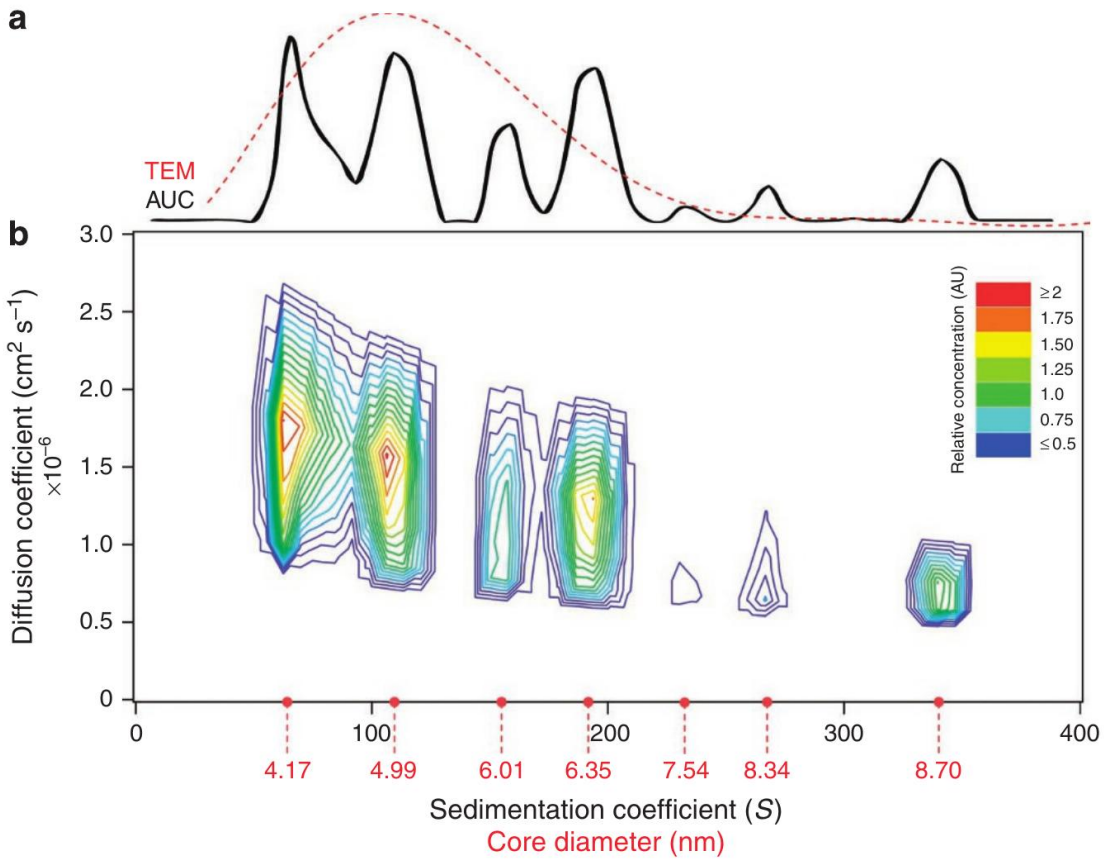
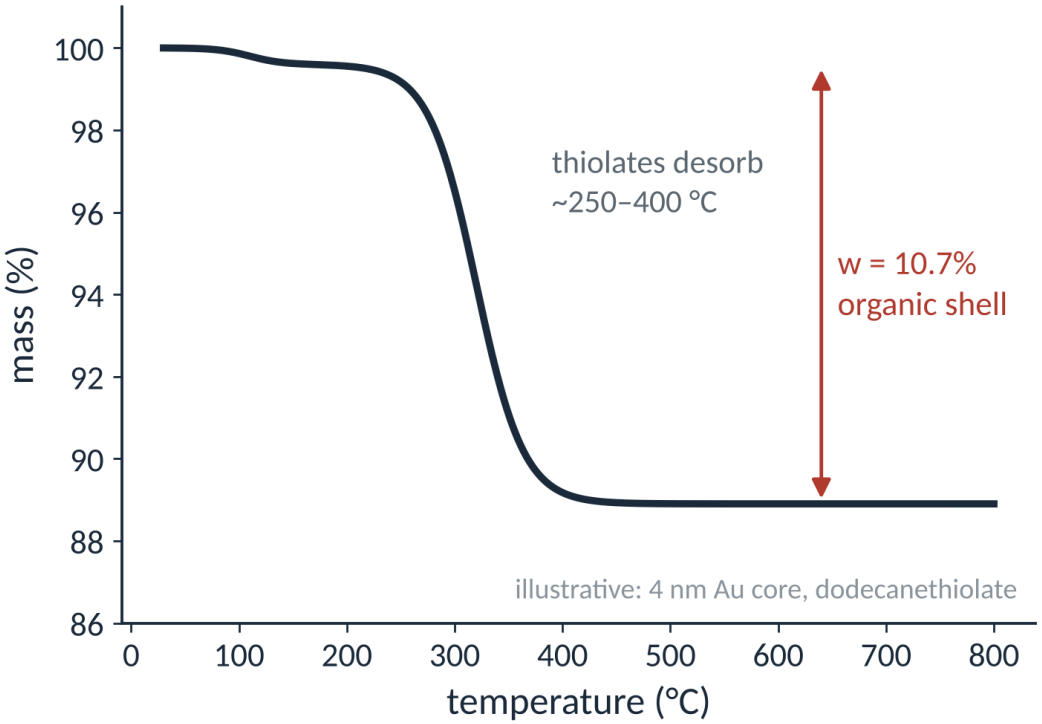


Figure: Carney et al., Nat. Commun. 2, 335 (2011) (TEM, red dashed; AUC, black)

TGA: how much organic shell?

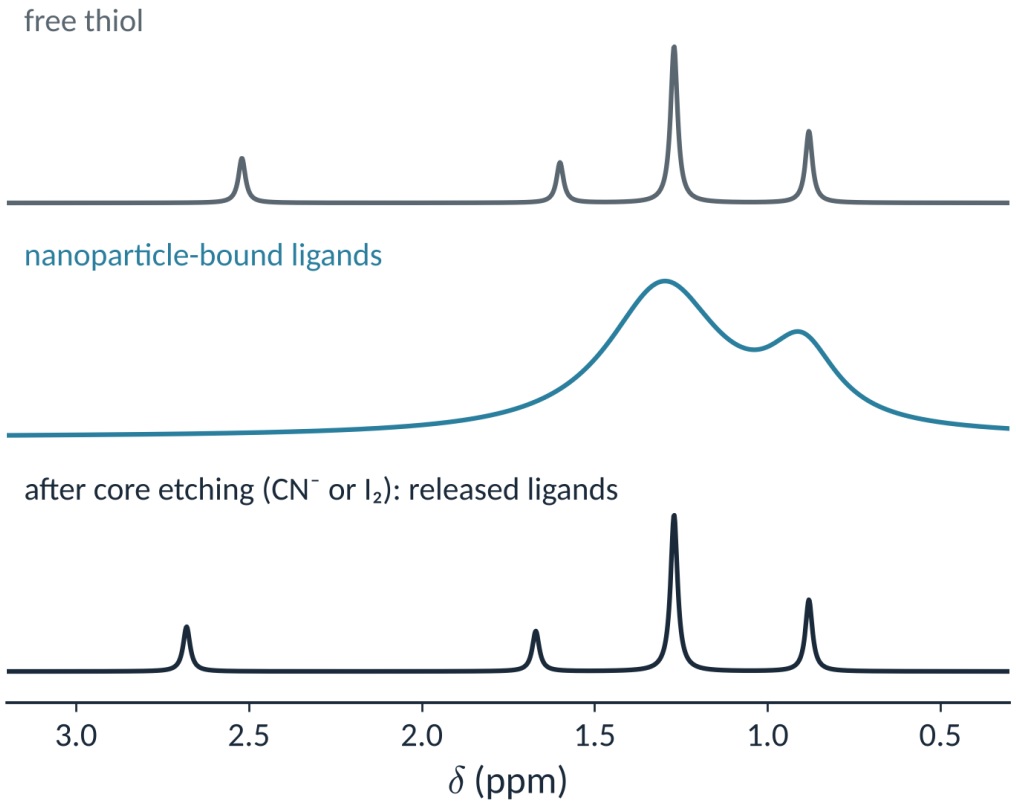
$$N_L = \frac{w}{1-w} \cdot \frac{\rho_{\mathrm{Au}} \frac{\pi}{6} d^3 N_A}{M_L}$$

- Heating desorbs and burns the shell; the residue is the core
- With the TEM core size, w gives ligands per particle
- Example: 4 nm Au, w = 10.7% → ~230 dodecanethiolates (4.6 nm^{-2})
- Free ligand or solvent inflates w: purify first



Purity and composition by NMR

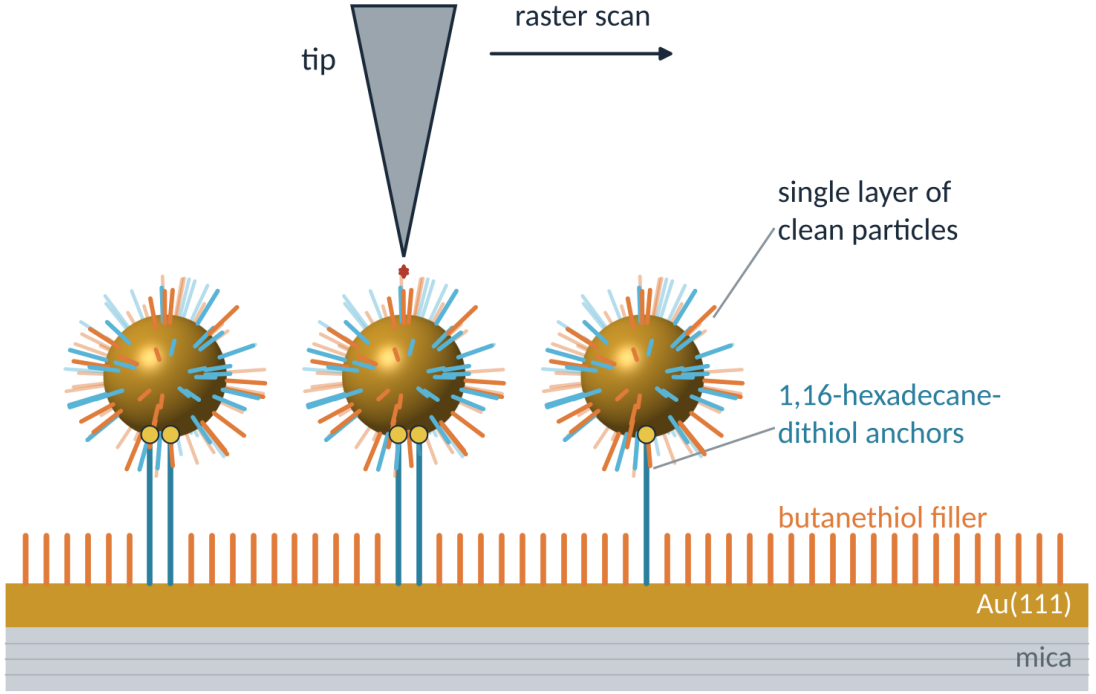
- Bound ligands: broad lines; sharp peaks reveal free ligand
- No sharp peaks: the entry ticket for STM imaging
- Composition: etch the core (CN^- or I_2) and integrate the released ligands
- DOSY separates bound and free species by diffusion



Marbella & Millstone, Chem. Mater. 27, 2721 (2015); Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017)

STM: three conditions for imaging a shell

- **Clean:** free ligand contaminates the tip; ^{1}H NMR with no sharp peaks
- **Anchored:** SAM of butanethiol and 1,16-hexadecanedithiol on Au(111)/mica; any motion blurs the image
- **Single layer:** Langmuir–Schaefer or drop-casting a dilute dispersion
- Contrast: height and conductivity differences between ligands

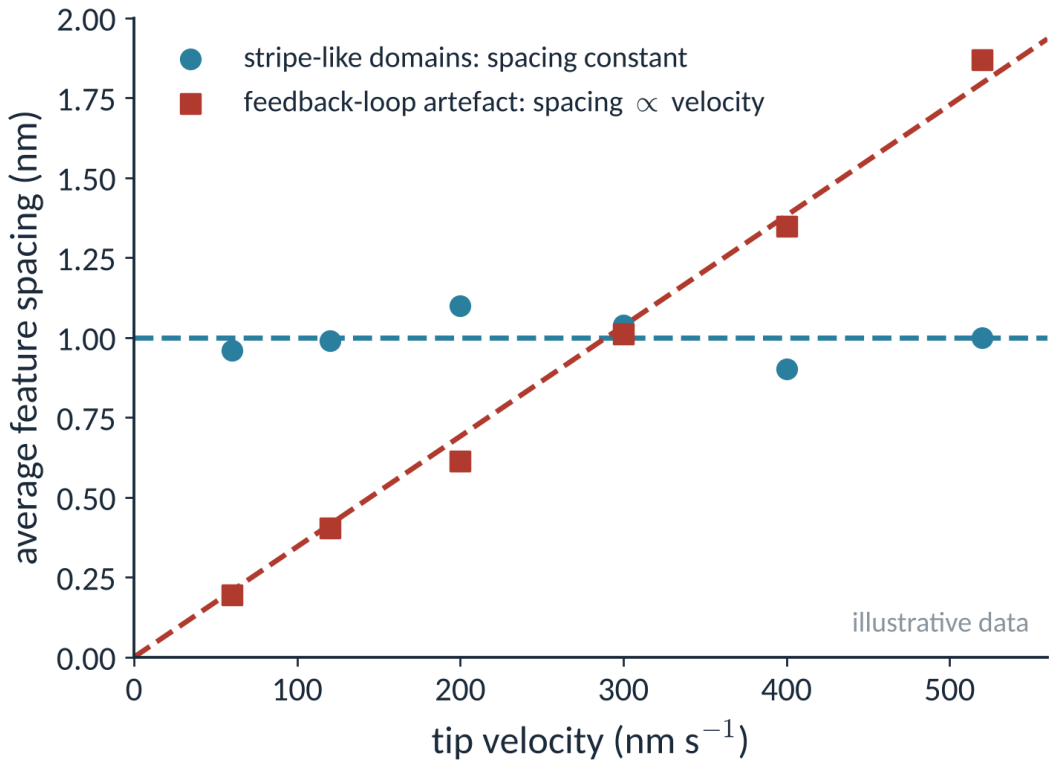


Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); Ong et al., ACS Nano 7, 8529 (2013)

Stripes or artefacts? Controls for STM

- 2004: stripe-like domains ~1 nm wide on OT/MPA (2:1) particles
- Badly set feedback gains also create parallel or wavy lines
- Controls: several tip velocities and scan angles, homoligand references

$$d_{\mathrm{artefact}} = \frac{v_{\mathrm{tip}}}{f_{\mathrm{osc}}} \qquad d_{\mathrm{domain}} \text{ independent of } v_{\mathrm{tip}}$$



Jackson et al., Nat. Mater. 3, 330 (2004); Hu et al., J. Scanning Probe Microsc. 4, 24 (2009); Cesbron et al., Small 8, 3714 (2012); Stirling et al., PLoS ONE 9, e108482 (2014); Ong & Stellacci, PLoS ONE 10, e0135594 (2015)

Quantitative STM: power spectral density

$$\mathrm{PSD}(k) = \frac{1}{L}\left| \int_0^L z(x)\, e^{-2\pi i k x}\, dx \right|^2$$

- I plateau → particle size; II decay → curvature, 1/f noise; III shoulder → stripe width; IV flat to the Nyquist limit
- Mixed shells: ~1 nm; homoligand shells: ~0.5 nm
- (b) NT/MBT: same PSD in air and in phenyloctane

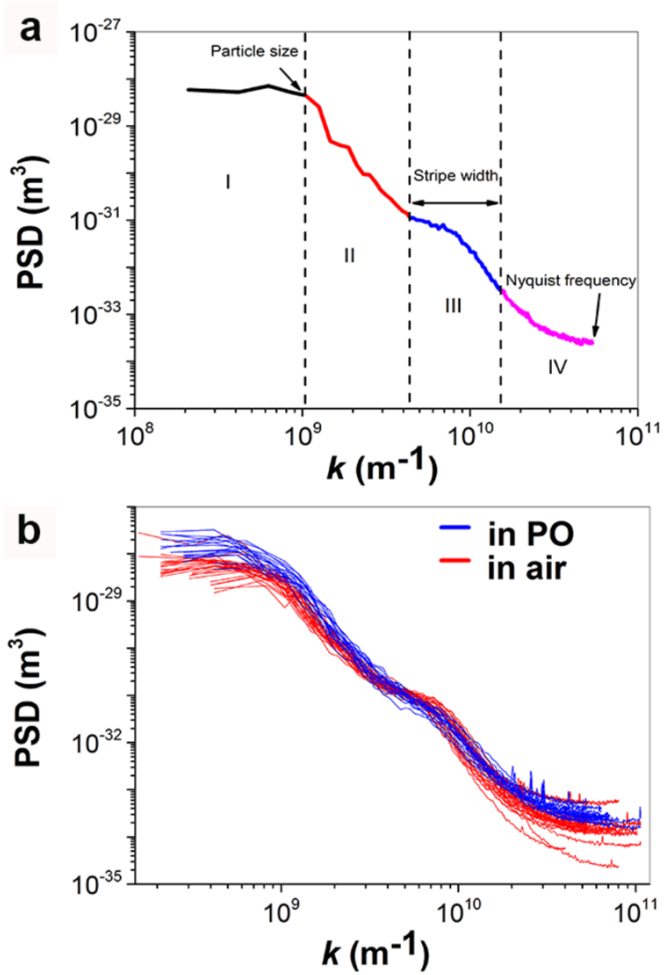


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Biscarini et al., Langmuir 29, 13723 (2013); Ong et al., Chem. Commun. 50, 10456 (2014)

Real STM images of mixed shells

- (a–c) C6/C12 in phenyloctane: clean tip, crisp stripes
- (d, e) MPA/OT at molecular resolution
- (g, h) C11OL/C4OL: molecules ~0.5 nm apart along, ~1 nm across stripes; (i) a Janus particle
- (f) coarse-grained model for comparison
- AFM in liquid: equivalent images of OT/MHol stripes

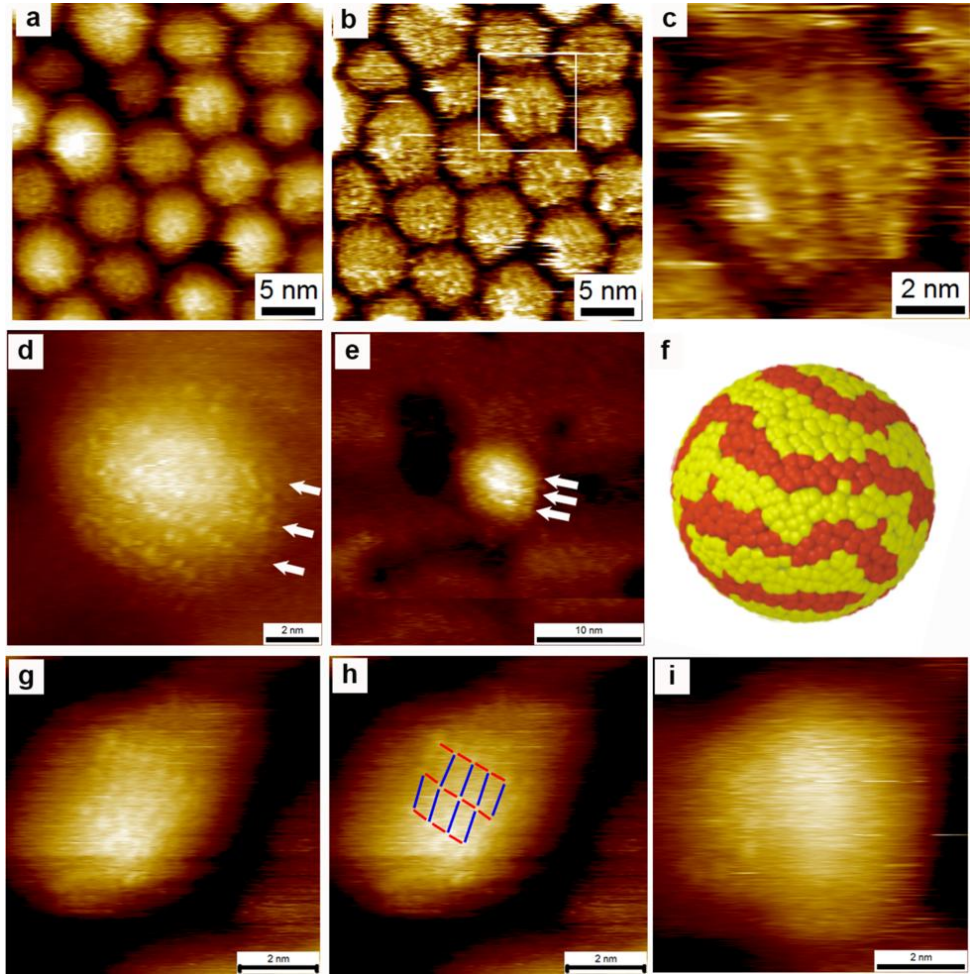


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Moglianetti et al., Chem. Sci. 5, 1232 (2014); Ong et al., ACS Nano 7, 8529 (2013); Kuna et al., Nat. Mater. 8, 837 (2009)

Electron microscopy of the shell

- Ligands are nearly invisible: light atoms, beam damage
- Graphene support + 80 kV aberration-corrected TEM: citrate shell seen
- OsO_4 staining: patchy lipid layers on large particles
- Polyoxometalate clusters replace citrate: 11-MU islands appear as gaps in cryo-TEM (figure)
- Large particles only; 2D projections

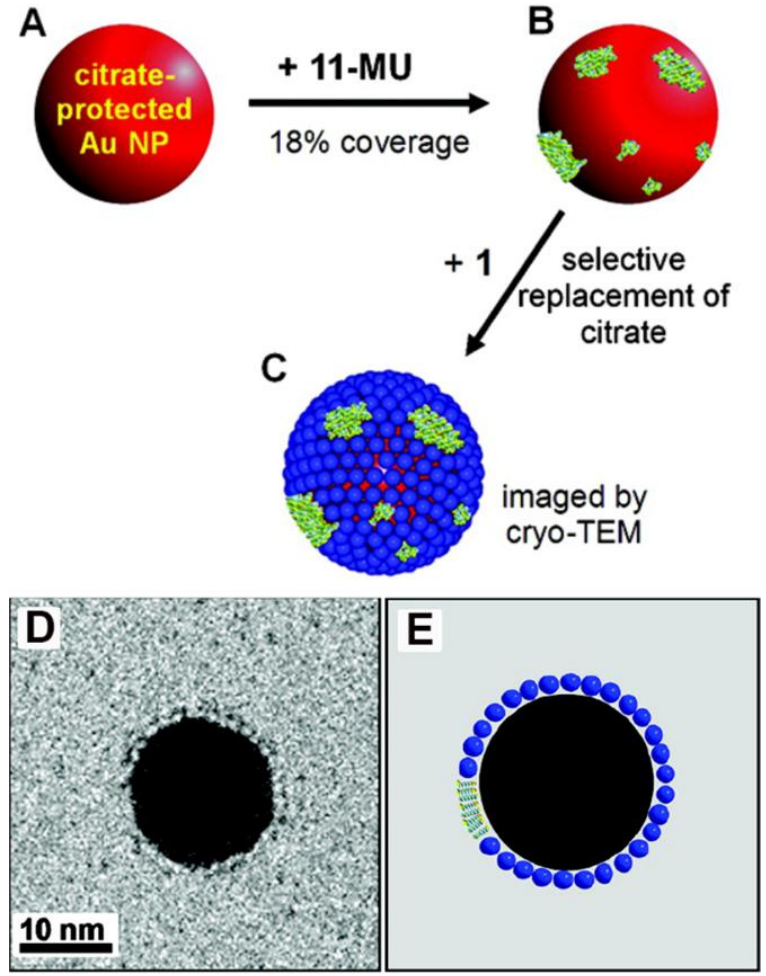


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Wang et al., ACS Nano 6, 629 (2012); Lee et al., Nano Lett. 9, 3365 (2009); Yang & Murphy, Langmuir 28, 5404 (2012)

NMR reads the neighbours

Shift of a ligand depends on its first neighbours

Random: local = global composition

$$\delta = B\,x_A + I\,(1 - x_A)$$

Janus: only an interfacial band of width t is mixed

$$\delta = B + \frac{(I - B)\,t}{2r\,x_A}$$

- Patchy and striped: sigmoidal trends
- NOESY: cross-peaks only between nuclei closer than ~0.5 nm

Morphology	1D shift vs x	NOESY
Random	linear	cross-peaks
Janus	∝ 1/x	none
Striped	plateau, then drop	cross-peaks

Liu, Yu, Kim, Mameli & Stellacci, Nat. Commun. 3, 1182 (2012)

NMR fingerprints of three morphologies

- (a, d, g) DPT–DMOT, 4–5 nm: linear, cross-peaks → random
- (b, e, h) DPT–DDT, 2–3 nm: 1/x (t = 0.4 nm), no cross-peaks → Janus
- (c, f, i) DPT–DDT, 4–5 nm: plateau, cross-peaks → stripes of 0.8 nm (STM 0.65 nm)

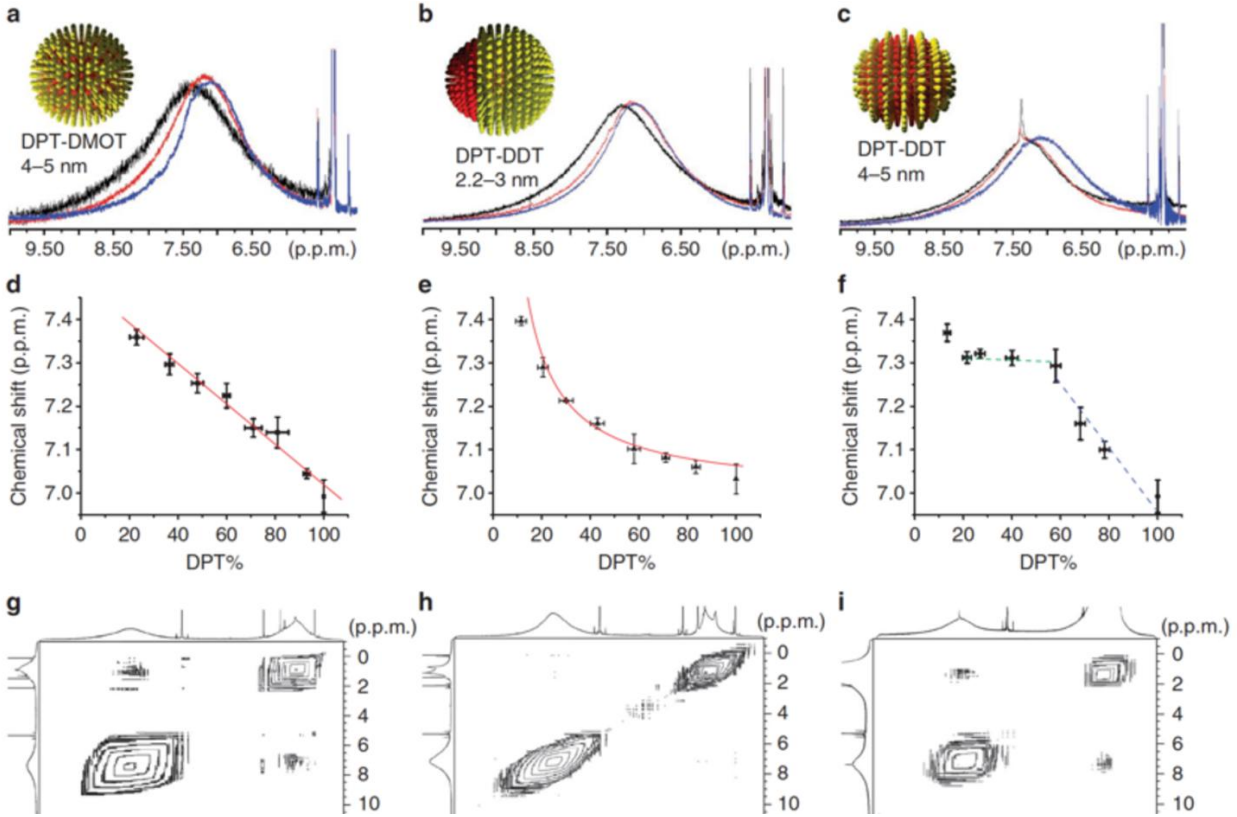


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Liu, Yu, Kim, Mameli & Stellacci, Nat. Commun. 3, 1182 (2012)

Fluorinated ligands, and where NMR goes next

- H and F chains are immiscible: strong drive to separate
- ^{19}F shift of CF_3 vs composition, with DPD snapshots: (j) random, (k) Janus, (l, m) stripe-like
- Equal length → Janus; large mismatch → stripes; small → patches; branched → random
- Next: ^{13}C, lanthanide labels, 2D NMR of clusters

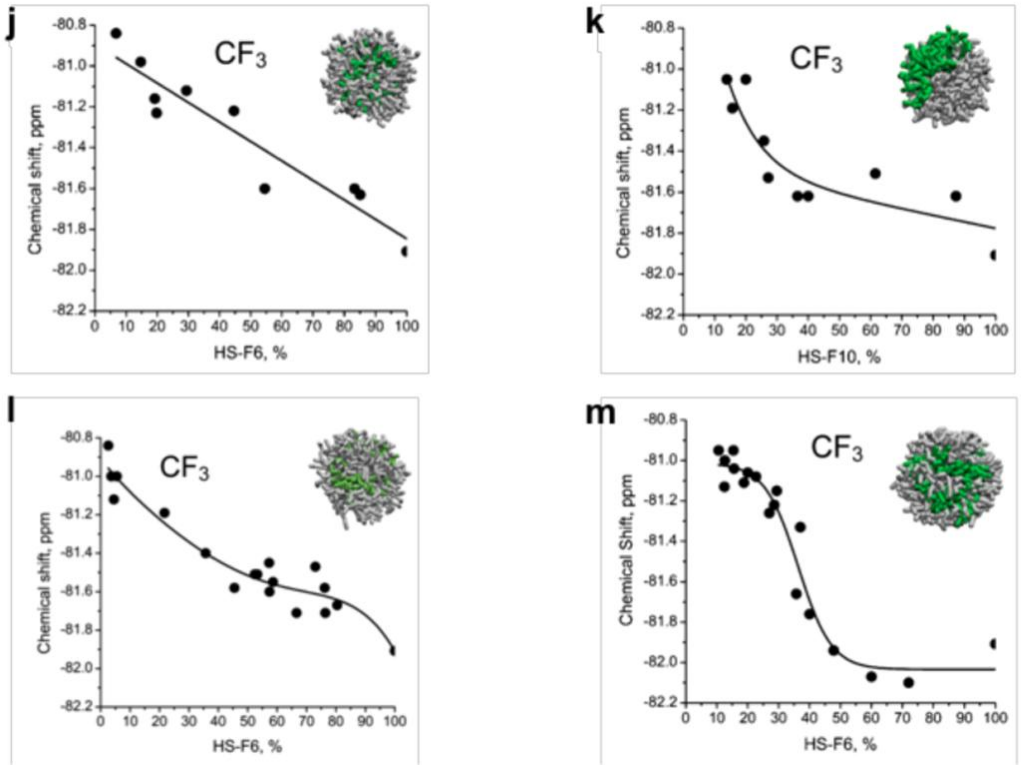
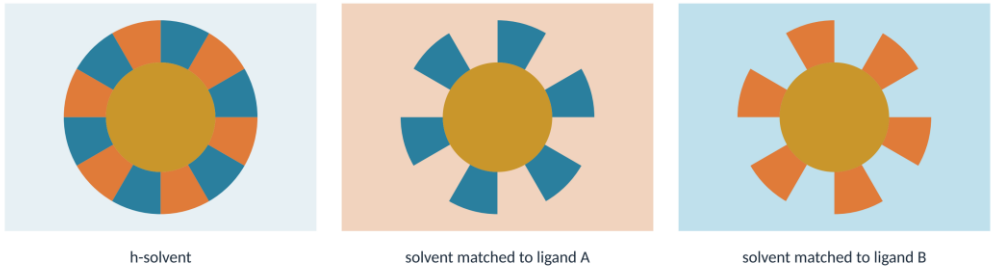


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Şologan et al., ACS Nano 10, 9316 (2016); also Guarino et al., JACS 134, 7200 (2012); Salorinne et al., Nat. Commun. 7, 10401 (2016)

SANS: seeing ligands with neutrons

$$\rho = \frac{\sum_i b_i}{V_{\mathrm{mol}}} \qquad b_{\mathrm{H}} = -3.74\ \mathrm{fm}, \quad b_{\mathrm{D}} = +6.67\ \mathrm{fm}$$

- Neutrons scatter from nuclei: H and D differ in sign
- Deuterate one ligand (or the solvent) to change what is visible
- (b) dPET–DDT vs PET–dDDT: different curves; (c) sizes 75 vs 58 Å
- (d, e) one 3D model fits both



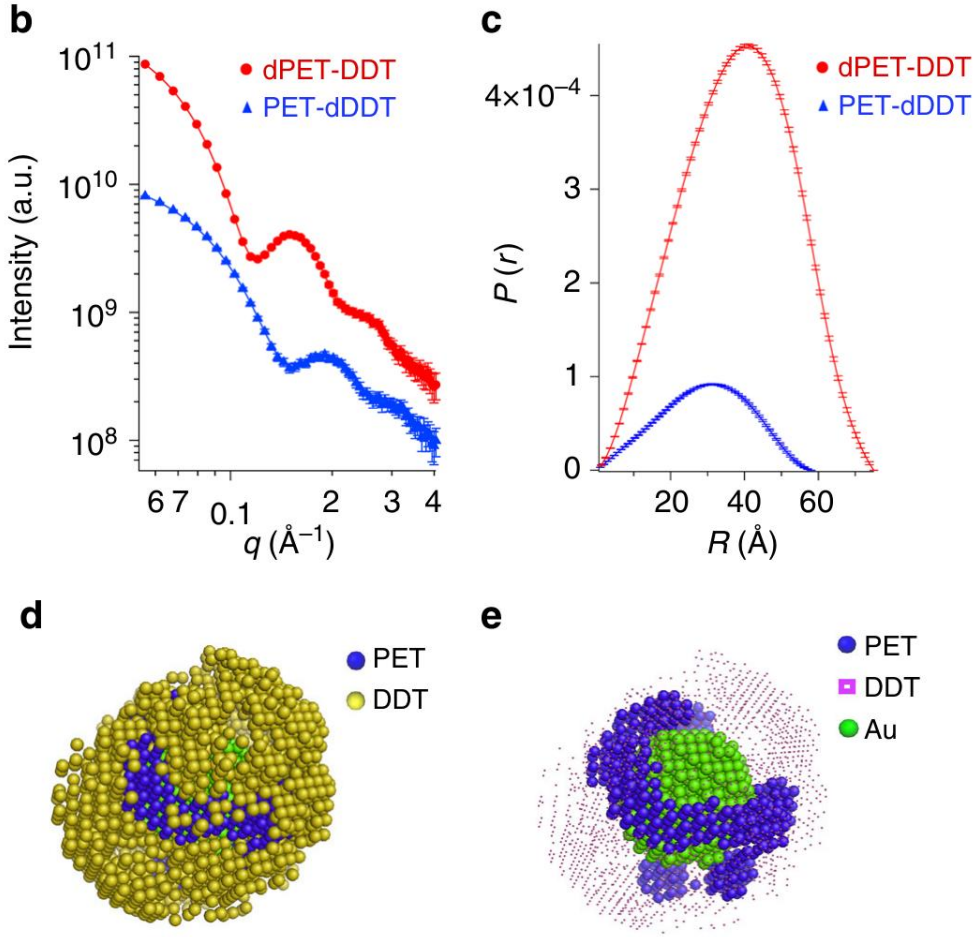


Figure: Luo et al., Nat. Commun. 9, 1343 (2018), CC BY 4.0; Moglianetti et al., Chem. Sci. 5, 1232 (2014)

From contrasts to a 3D model

- MONSA: simulated annealing fits all contrasts with one bead model
- Constraints: core from TEM, ratio from NMR/TGA
- (a, d) dDDT–DDT random; (b, e) MUA–DDT Janus; (c, f) MUA–BT stripe-like
- Resolves domain shape, not only the class
- Needs deuteration and monodisperse cores (< ~10%)

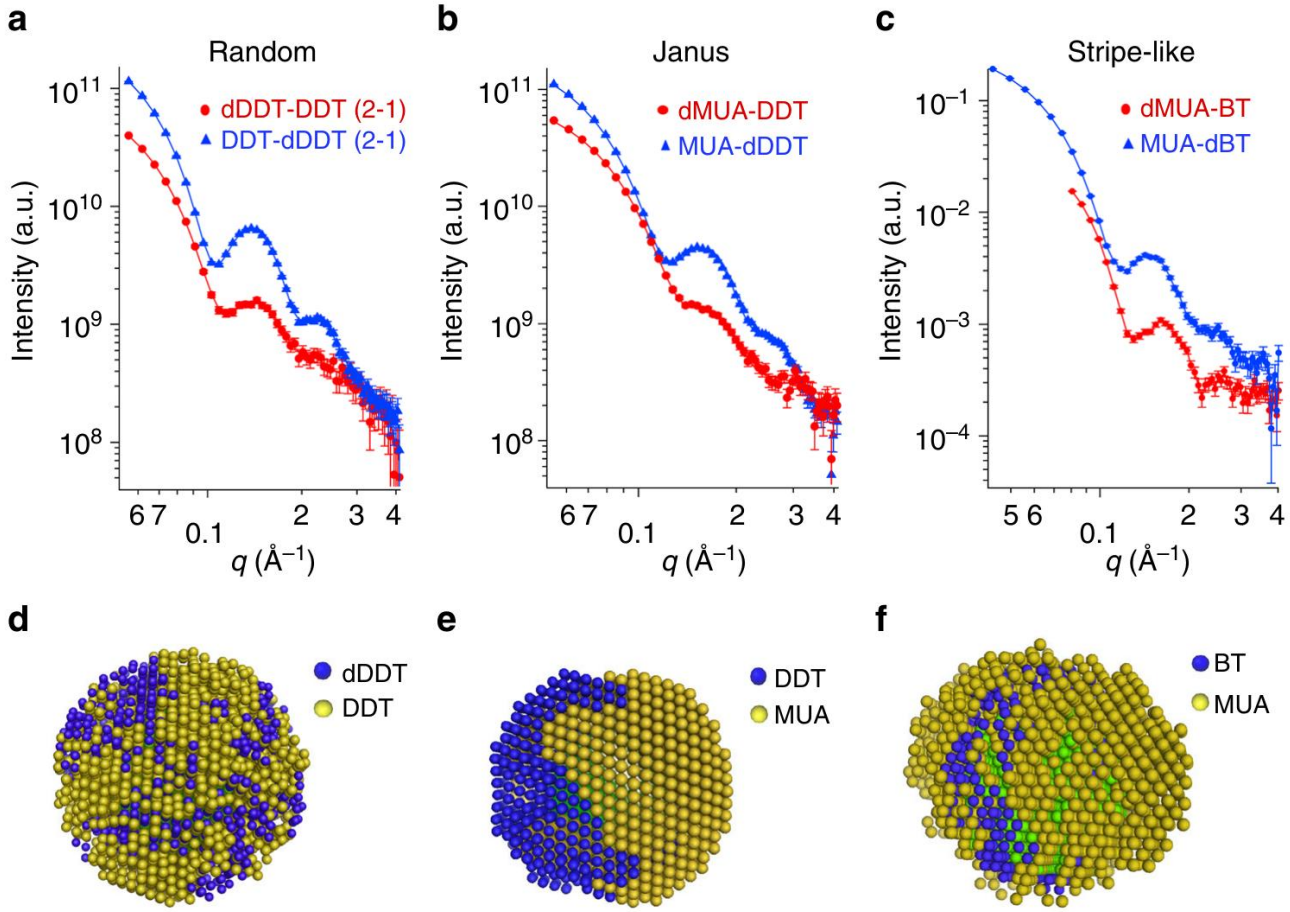


Figure: Luo et al., Nat. Commun. 9, 1343 (2018), CC BY 4.0; Svergun, Biophys. J. 76, 2879 (1999)

SANS series, checked against simulation

- (a–c) cores 3.2, 4.4, 5.5 nm: PET domains 1.6, 1.3, 1.2 nm thick
- (d–f) more PET:
  patches → stripes → percolated
- (m–r) DPD of the same particles;
  (s–x) overlays agree

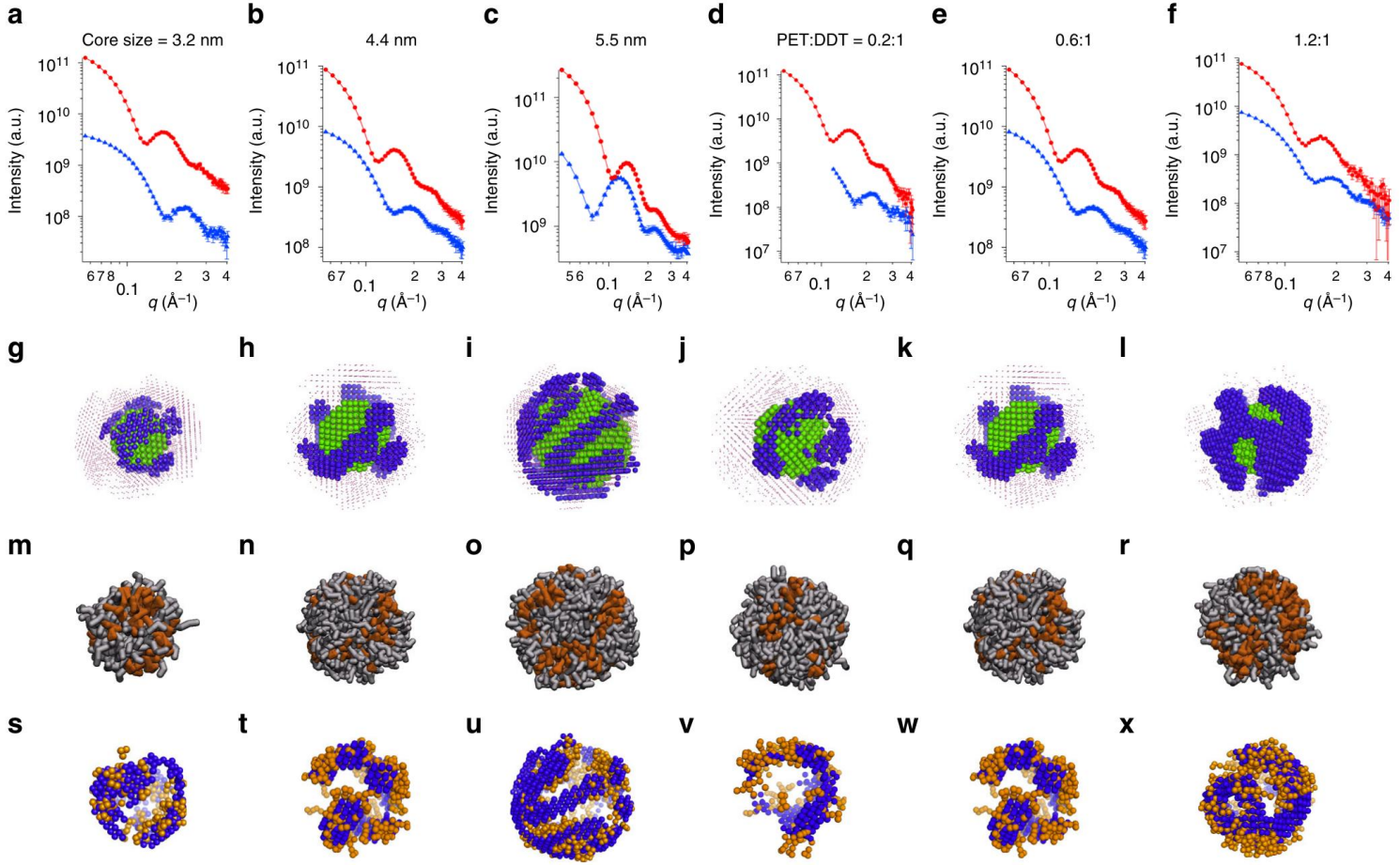


Figure: Luo, Marson, Ong, Loiudice, Kohlbrecher, Radulescu, Krause-Heuer, Darwish, Balog, Buonsanti, Svergun, Posocco & Stellacci, Nat. Commun. 9, 1343 (2018), CC BY 4.0

MALDI-TOF: the shell comes off in clusters

- LDI-MS: ligand identity and ratio
- MALDI: Au_4L_4 fragments keep neighbours together

$$P(x) = \binom{n}{x} \phi^x (1-\phi)^{n-x}$$

- Random → binomial (filled dots); measured: open circles
- OT/d-OT: none; tiopronin/glutathione: minimal; tiopronin/MUA: domains; tiopronin/MUTEG: Janus
- Same ratio, different synthesis → different separation

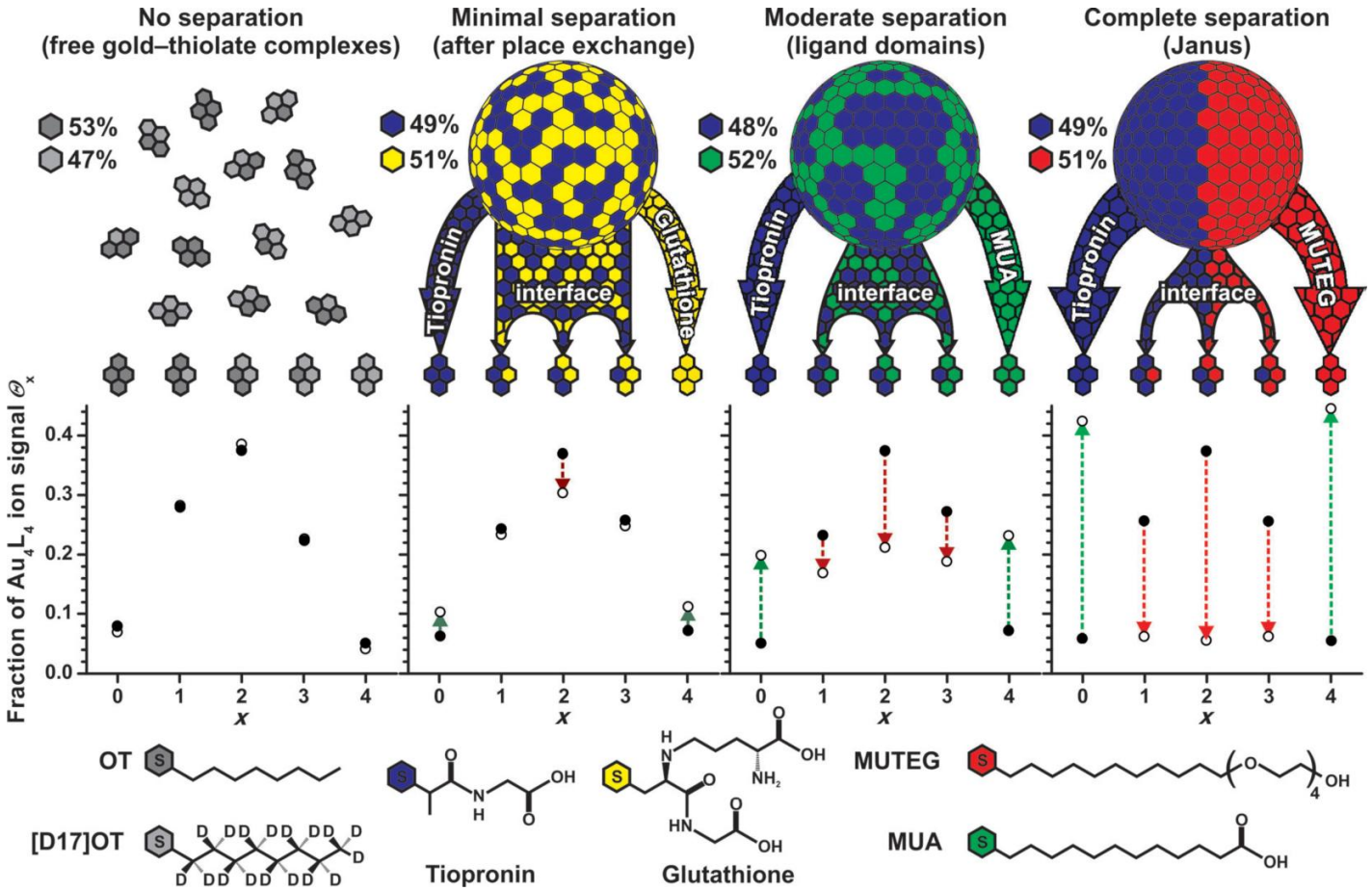
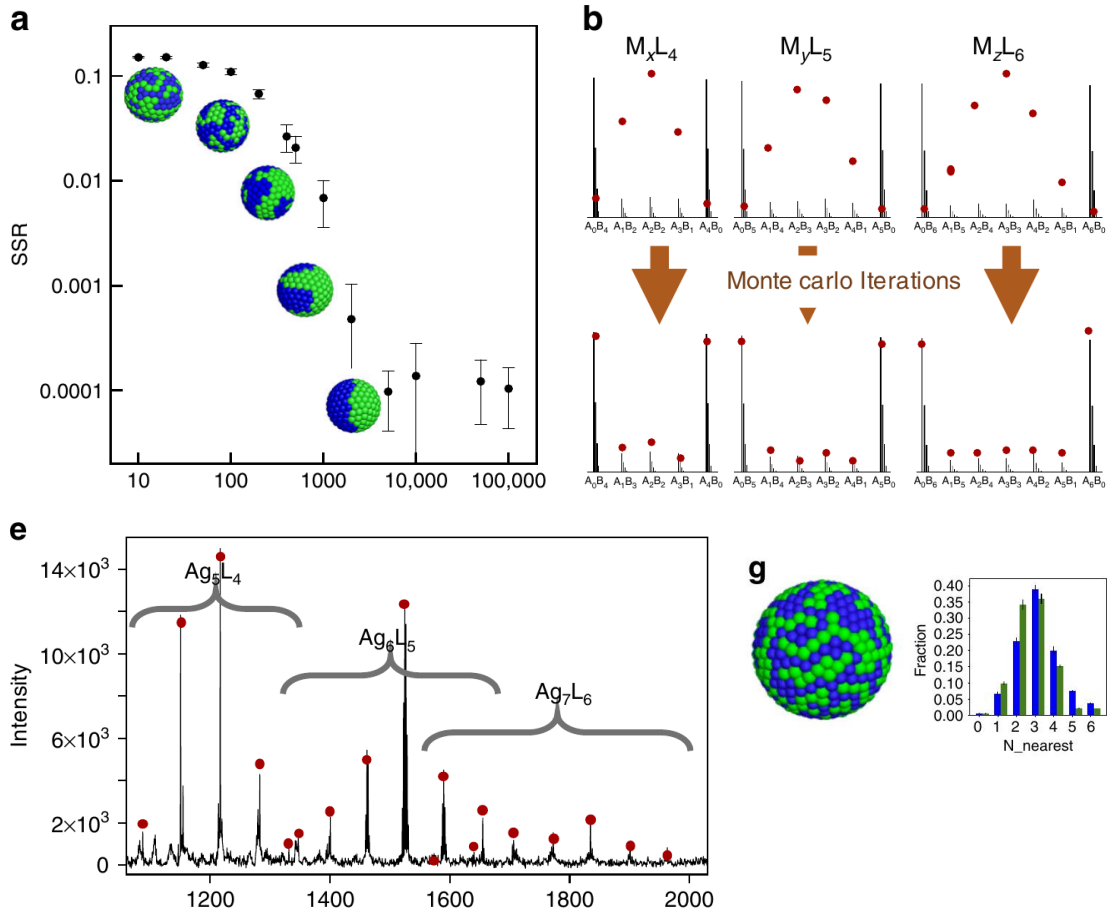


Figure: Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); data: Harkness, Balinski, McLean & Cliffel, Angew. Chem. Int. Ed. 50, 10554 (2011); Yan et al., Anal. Bioanal. Chem. 396, 1025 (2010)

From spectrum to 3D model

- N beads, random start; flip a bead, keep it if the SSR to the spectrum drops
- Converges in ~10^4 steps, minutes on a laptop (top)
- Ag PET–DDT: spectrum and model (bottom); PET domains 1.7 vs 1.9 nm by SANS
- Robust output: nearest-neighbour statistics
- Theory for Ag: self-consistent field, atomistic MC



Figures: Luo, Zhao, Darwish, Wang, Hou & Stellacci, Nat. Commun. 9, 4478 (2018), CC BY 4.0; Farrell et al., Angew. Chem. 54, 6479 (2015); Merz et al., ACS Nano 10, 9871 (2016)

MALDI beyond ligands: bimetallic surfaces

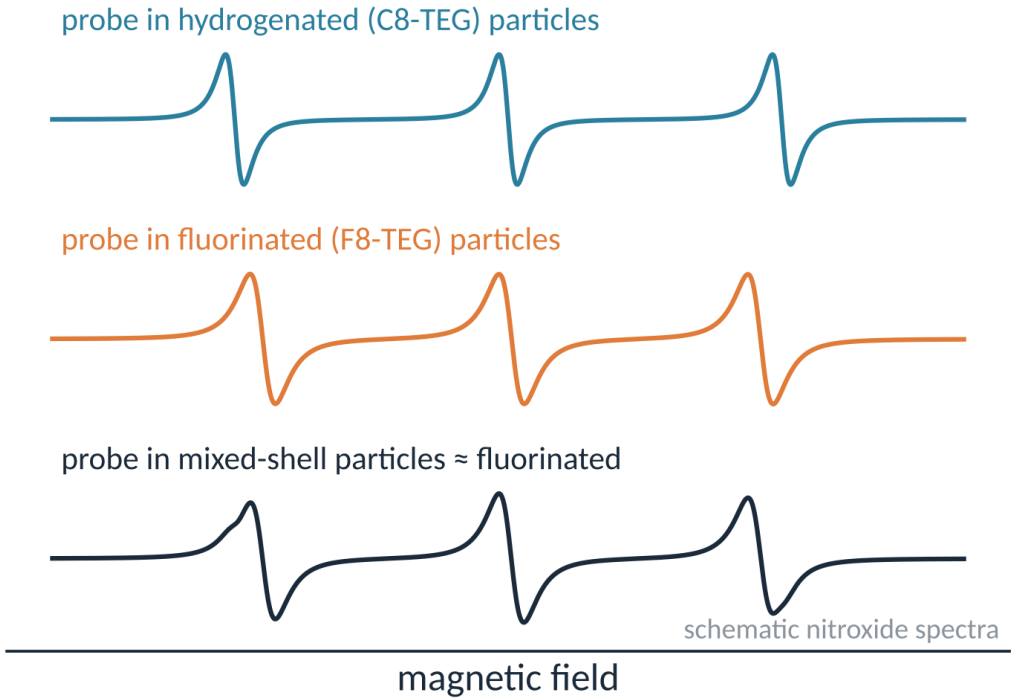
- AuAg alloy particles (2.4–3.8 nm) capped with dodecanethiol
- Fragments $(Au_xAg_{n-x})L_{n-1}$ sample surface atoms
- Surfaces are Ag-enriched vs bulk; Au and Ag mix randomly
- MALDI also tracks shell evolution during ligand exchange

Sample	Au feed (%)	Au surface, MALDI (%)	Au bulk, ICP (%)
A	10	13.9	24
B	20	11.2	28
C	30	23.0	41
D	40	46.8	53
E	50	30.4	32

Liao, Luo, Metternich, Zenobi & Stellacci, Nanoscale 12, 22639 (2020); Luo et al., Angew. Chem. Int. Ed. 56, 13521 (2017)

EPR with spin probes

- Nitroxide radicals: in the shell (mobility, lateral diffusion) or as partitioning probes
- F8-TEG/C8-TEG shells: the probe sits near fluorinated ligands
- Mixed shells give the all-F spectrum → fluorinated patches
- Needs strong uptake and very different domains; resolution unknown



Ionita et al., Anal. Chem. 80, 95 (2008); Gentilini et al., Angew. Chem. Int. Ed. 48, 3060 (2009); Lucarini & Pasquato, Nanoscale 2, 668 (2010); Posocco et al., ACS Nano 6, 7243 (2012)

Other ensemble probes

FTIR

CH_2 shifts vs composition: linear if random, sigmoidal if phase-separated

UV–vis

Phosphinine replaced by thiols: plasmon blue shift, assigned to a Janus shell

Fluorescence titration

ATP uptake peaks at 50–70% cationic ligand; mixed homoligand particles stay flat → patches

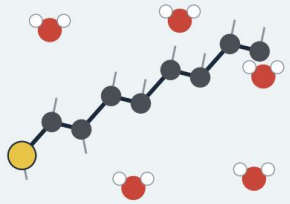
SERS

Ag pentanethiol/MPS shells bind a cationic porphyrin best at 1:1 → domains of both

Centrone et al., Small 3, 814 (2007); Vilain et al., J. Mater. Chem. 17, 3509 (2007); Bonomi, Cazzolaro & Prins, Chem. Commun. 47, 445 (2011); Stewart et al., ACS Nano 6, 3718 (2012)

Simulation: the third family of tools

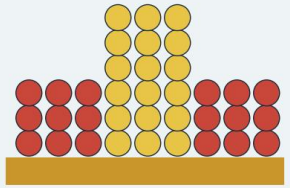
- Why a morphology forms, and whether it is stable
- What a measurement means: NMR, SANS, MALDI, EPR, STM
- Methods across scales: atomistic MD and Monte Carlo, coarse-grained DPD, lattice and mean-field models
- Parameters pass between scales; experiments validate



Atomistic MD, Monte Carlo

atomic detail, often explicit solvent

chemical detail; ~10 nm, ns–µs



Coarse-grained DPD

beads of a few atoms, soft forces

whole particle in solvent



Lattice and mean-field models

one site per ligand

fast; fits experimental data

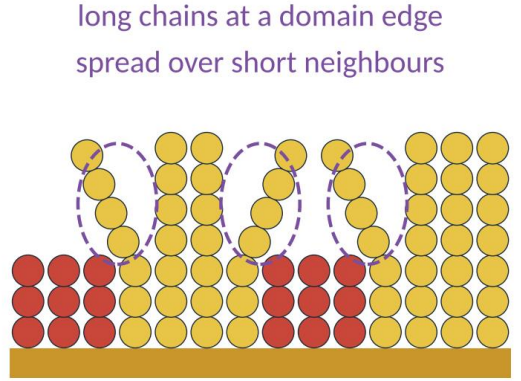
Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); Pengo et al., Eur. Biophys. J. 46, 749 (2017)

Glotzer: entropy-mediated stripes

- Coarse-grained DPD: bead-spring ligands, heads confined to the surface; atomistic MD as a check
- Two immiscible ligands of different length or bulkiness
- A long ligand next to short ones gains conformational entropy: interfaces pay for themselves
- Stripes have lower free energy than full separation; also on flat surfaces and rods



coarse-grained striped particle

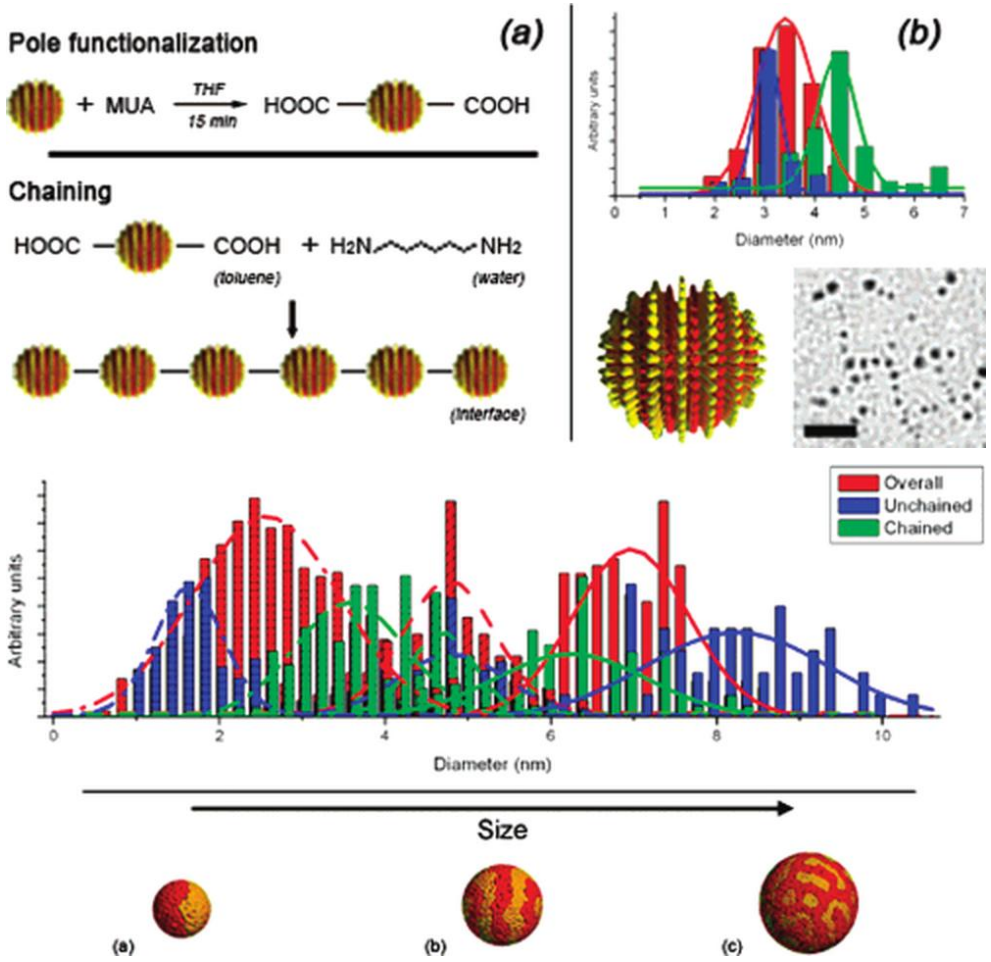


red: short · yellow: long

Singh, Ghorai, Horsch, Jackson, Larson, Stellacci & Glotzer, Phys. Rev. Lett. 99, 226106 (2007); Ghorai & Glotzer, J. Phys. Chem. C 114, 19182 (2010); Singh et al., Nanoscale 3, 3244 (2011); model image: Ong et al. 2017, Fig. 1f

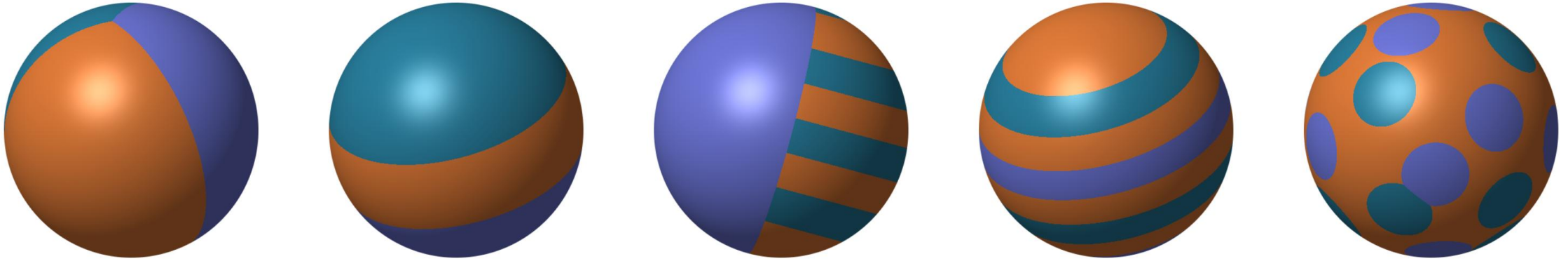
Prediction and test: a size window for stripes

- Simulation (a–c): small → two phases;
  larger → ordered ripples; larger still → disordered
- Ordered ripples have two reactive polar defects (hairy-ball theorem)
- Test: MUA at the poles, diamine coupling → only rippled particles chain (top)
- NT/MBT 2:1: chained (green) only from ~2.5–8 nm cores (bottom)



Figures: Carney, DeVries, Dubois, Kim, Kim, Singh, Ghorai, Tracy, Stiles, Murray, Glotzer & Stellacci, J. Am. Chem. Soc. 130, 798 (2008); DeVries et al., Science 315, 358 (2007)

Glotzer: designing patchy particles



Cerberus

small radius

Neapolitan

strong repulsion

striped Janus

larger radius

alternating stripes

weak repulsion, 1:1:1

spotted

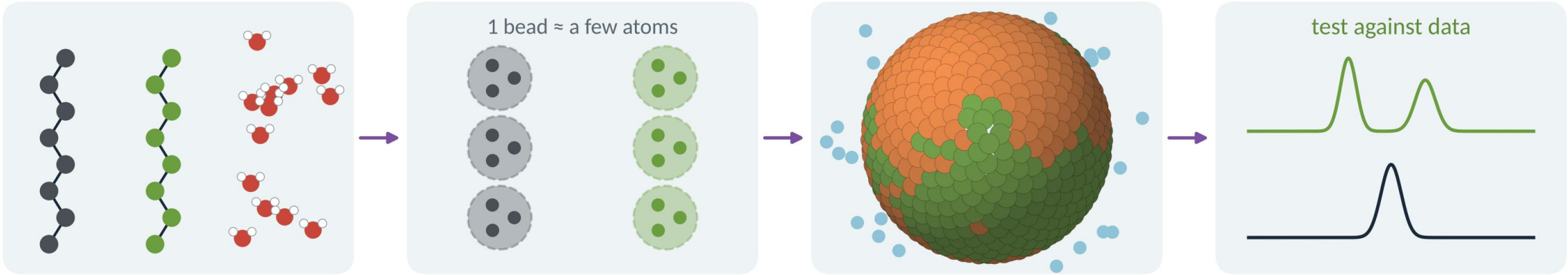
one ligand > ~70%

- DPD of ternary and quaternary monolayers
- Ligands: short (orange), medium (blue), long (teal)

- Knobs: radius, immiscibility, length mismatch, stoichiometry
- Equilibrium patterns, driven by conformational entropy

Pons-Siepermann & Glotzer, Soft Matter 8, 6226 (2012); Pons-Siepermann & Glotzer, ACS Nano 6, 3919 (2012)

Posocco and Pasquato: multiscale simulation



From atoms to beads (Groot–Warren)

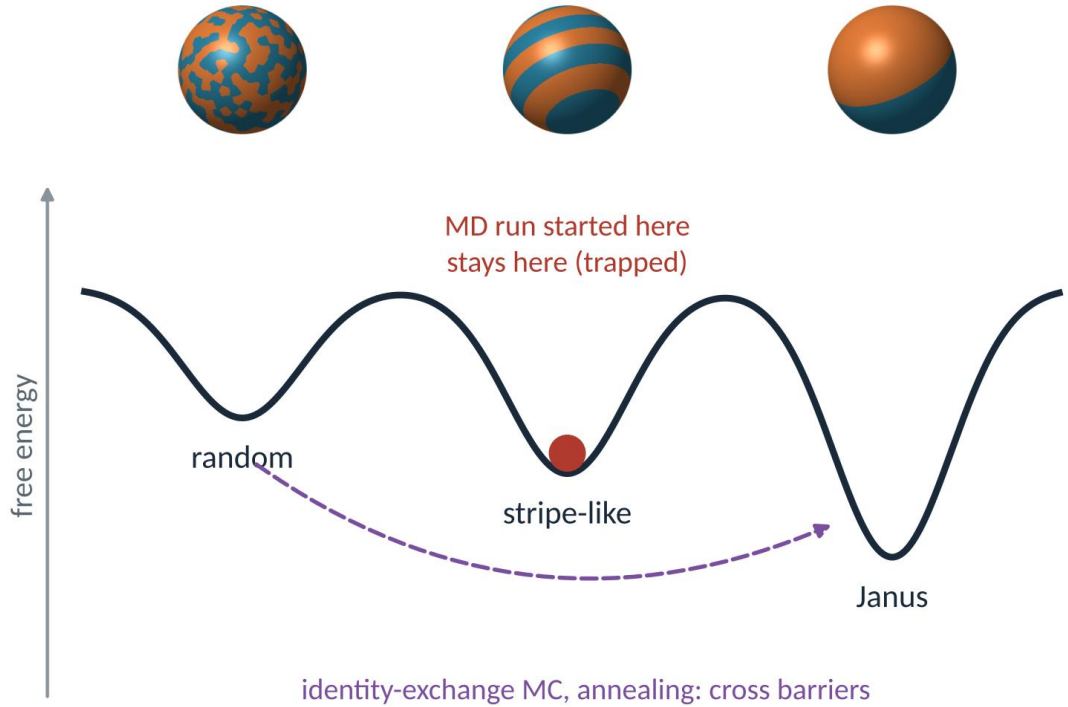
$$a_{ij} \approx a_{ii} + 3.27\,\chi_{ij} \qquad (\rho r_c^3 = 3)$$

- F/H thiolates: patches and stripes, consistent with EPR and ^{19}F NMR
- Same approach tested the SANS shell models

Posocco et al., ACS Nano 6, 7243 (2012); Şologan et al., ACS Nano 10, 9316 (2016); Luo et al., Nat. Commun. 9, 1343 (2018); Groot & Warren, J. Chem. Phys. 107, 4423 (1997)

Equilibrium or kinetically trapped?

- Ligands diffuse slowly on the surface: simulations can get stuck
- Discrete MD from random, striped and Janus starts → different end states
- Monte Carlo with identity swaps: C6/C14 ends Janus; stripes transient
- In salt water, ligand fluctuations blur differences between morphologies
- Experiments agree: synthesis route and annealing change domains



Ge et al., Small 11, 4894 (2015); Fetisov & Siepmann, J. Phys. Chem. B 120, 1972 (2016); Van Lehn & Alexander-Katz, J. Phys. Chem. C 117, 20104 (2013)

Simulation and experiment together

Technique	What simulation adds	Example
STM	coarse-grained model of the imaged stripes	Singh 2007
NMR	DPD morphologies behind ^{19}F shifts and HOESY	Şologan 2016
EPR	MD/DPD place the probe in fluorinated domains	Posocco 2012
SANS	DPD tests the bead reconstructions	Luo 2018
MALDI-MS	MC fitting; field theory and atomistic MC predict spectra	Luo 2018; Merz 2016
Adsorption	patch size and spacing behind the ATP maximum	Bonomi 2011

Limit: one particle at a time, so a homogeneous sample is implicitly assumed

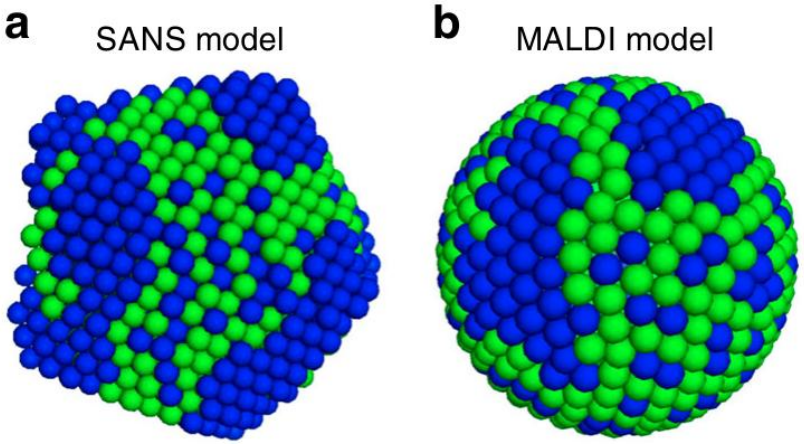
Comparing the morphology methods

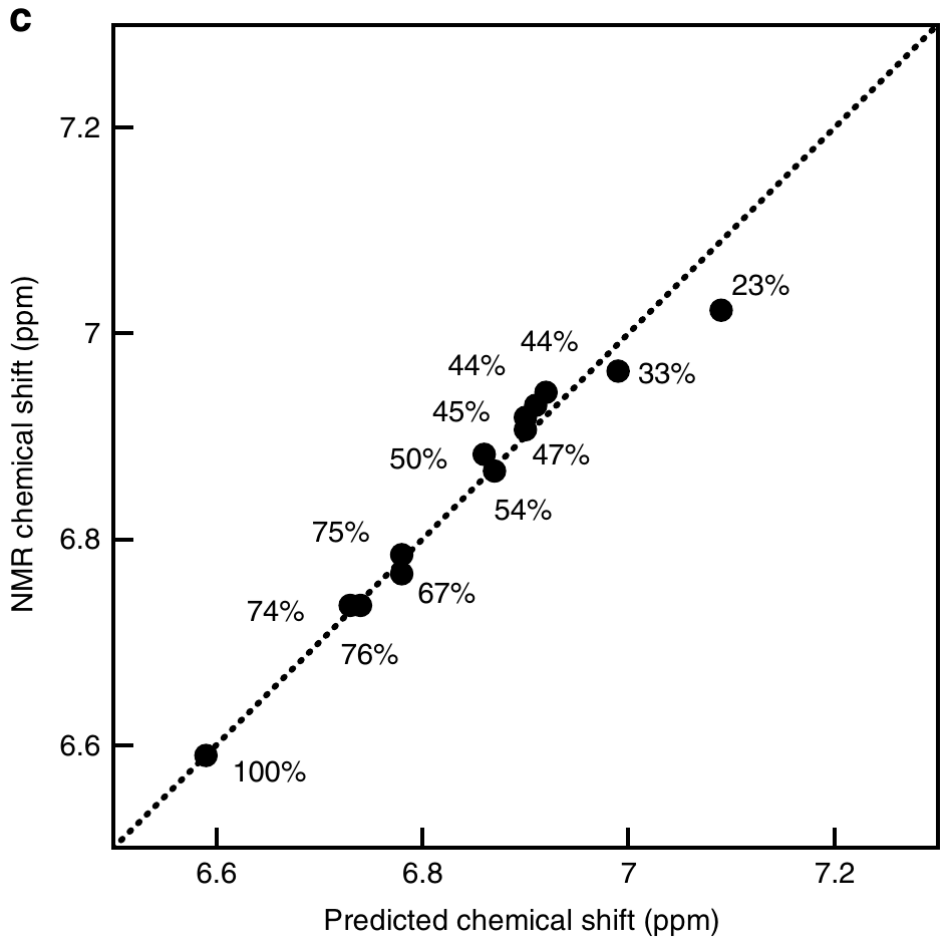
Method	Gives	Main limits
STM / AFM	real-space domains, top of the shell	few particles; artefacts; cannot prove absence
S/TEM	shell of large particles	contrast agents; 2D projection
NMR	neighbours; class of morphology	composition series; choice of ligands
MALDI-MS	fragment statistics → 3D model	uniform samples; Au_4L_4 yield
SANS	3D domain shape	deuteration; monodisperse cores
EPR, adsorption	probe environment	indirect; resolution unknown
Simulation	mechanism; interpretation	one particle; equilibration

Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017)

Cross-validation between techniques

- SANS and MALDI on Ag PET–DDT: same patches; domains 1.9 vs 1.7 nm (left)
- MALDI neighbour statistics predict the NMR shift of 12 samples (right)
- STM and SANS on C12/C6 particles: the same stripes, in solution
- NMR stripe width 0.8 nm vs STM 0.65 nm

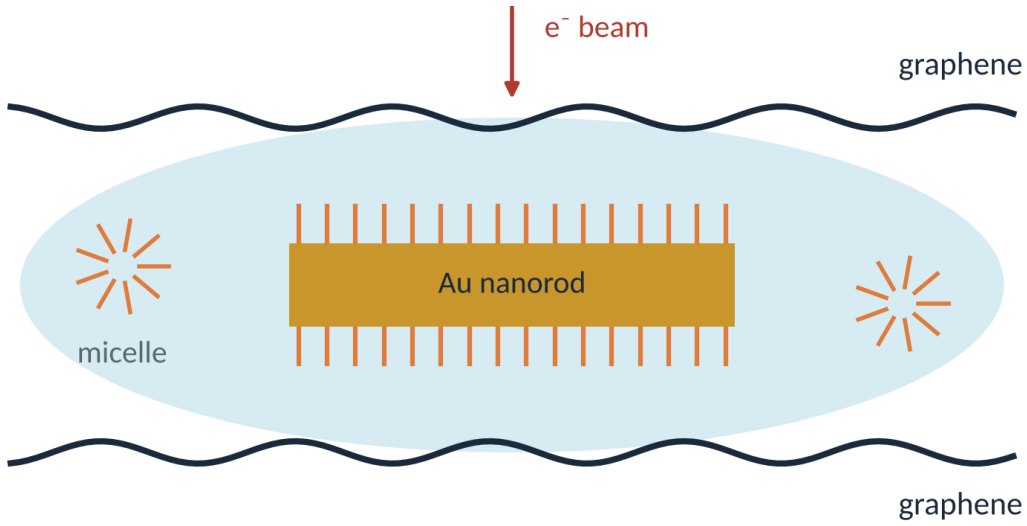




Figures: Luo et al., Nat. Commun. 9, 4478 (2018), CC BY 4.0; also Moglianetti et al., Chem. Sci. 5, 1232 (2014); Liu et al., Nat. Commun. 3, 1182 (2012)

Open problems and the way forward

- Ensemble methods need uniform samples, but uniformity cannot be measured directly
- Goal: quantitative cross-comparison, e.g. SANS vs MALDI, many STM images vs SANS
- Obstacle: STM, SANS and MALDI need different samples
- Dynamics: shells in biological media or catalysis; liquid-cell TEM is a start



Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017); Pedrazo-Tardajos et al., Nat. Chem. (2024), doi:10.1038/s41557-024-01574-1

A practical checklist

1 Core

TEM + SAXS or AUC; UV–vis; DLS and ζ in the medium of use

2 Purity

NMR: no sharp free-ligand peaks (DOSY)

3 Amount

TGA → ligands per particle

4 Composition

^{1}H NMR after core etching

5 Morphology

NMR series + MALDI; SANS or STM when possible

6 Interpretation

Simulate the proposed structure; seek two methods that agree

Summary

1 The object

Core + chemically bound monolayer; ~10^2 ligands

2 Mixed shells

Random, Janus, patchy, stripes; enthalpy vs interfacial entropy

3 Why it matters

Wetting, membranes, proteins, catalysis, sensing

4 Routine

TEM, SAXS, AUC, UV–vis, DLS, TGA, NMR after etching

5 Morphology

STM, NMR, MALDI, SANS, EPR; simulation to explain and interpret

6 Rule

Trust structures confirmed by independent methods

Key references (1/4): the object and its properties

- Ong, Luo & Stellacci, Acc. Chem. Res. 50, 1911 (2017)
- Brust et al., J. Chem. Soc. Chem. Commun. 801 (1994)
- Zheng, Fan & Stucky, JACS 128, 6550 (2006)
- Jadzinsky et al., Science 318, 430 (2007)
- Silvera Batista et al., Science 350, 1242477 (2015)
- Jackson, Myerson & Stellacci, Nat. Mater. 3, 330 (2004)
- Centrone et al., PNAS 105, 9886 (2008)
- Verma et al., Nat. Mater. 7, 588 (2008)
- Kuna et al., Nat. Mater. 8, 837 (2009)
- Hung et al., JACS 133, 1438 (2011)
- Ghosh et al., Angew. Chem. 50, 7900 (2011)
- Cho et al., Nat. Mater. 11, 978 (2012)

Key references (2/4): routine methods and microscopy

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- Marbella & Millstone, Chem. Mater. 27, 2721 (2015)
- Jackson et al., JACS 128, 11135 (2006)
- Ong et al., ACS Nano 7, 8529 (2013)
- Biscarini et al., Langmuir 29, 13723 (2013)
- Ong et al., Chem. Commun. 50, 10456 (2014)
- Stirling et al., PLoS ONE 9, e108482 (2014)
- Ong & Stellacci, PLoS ONE 10, e0135594 (2015)
- Moglianetti et al., Chem. Sci. 5, 1232 (2014)
- Lee et al., Nano Lett. 9, 3365 (2009)
- Wang et al., ACS Nano 6, 629 (2012)
- Carney et al., Nat. Commun. 2, 335 (2011)

Key references (3/4): spectroscopy and mass spectrometry

- Liu et al., Nat. Commun. 3, 1182 (2012)
- Şologan et al., ACS Nano 10, 9316 (2016)
- Centrone et al., Small 3, 814 (2007)
- Luo et al., Nat. Commun. 9, 1343 (2018)
- Gentilini et al., Angew. Chem. 48, 3060 (2009)
- Lucarini & Pasquato, Nanoscale 2, 668 (2010)
- Bonomi et al., Chem. Commun. 47, 445 (2011)
- Stewart et al., ACS Nano 6, 3718 (2012)
- Harkness et al., Angew. Chem. 50, 10554 (2011)
- Merz et al., ACS Nano 10, 9871 (2016)
- Luo et al., Nat. Commun. 9, 4478 (2018)
- Liao et al., Nanoscale 12, 22639 (2020)

Key references (4/4): simulation and outlook

- Singh et al., Phys. Rev. Lett. 99, 226106 (2007)
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- Pons-Siepermann & Glotzer, ACS Nano 6, 3919 (2012)
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- Van Lehn & Alexander-Katz, J. Phys. Chem. C 117, 20104 (2013)
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- Pengo et al., Eur. Biophys. J. 46, 749 (2017)
- Groot & Warren, J. Chem. Phys. 107, 4423 (1997)
- Pedrazo-Tardajos et al., Nat. Chem. (2024)