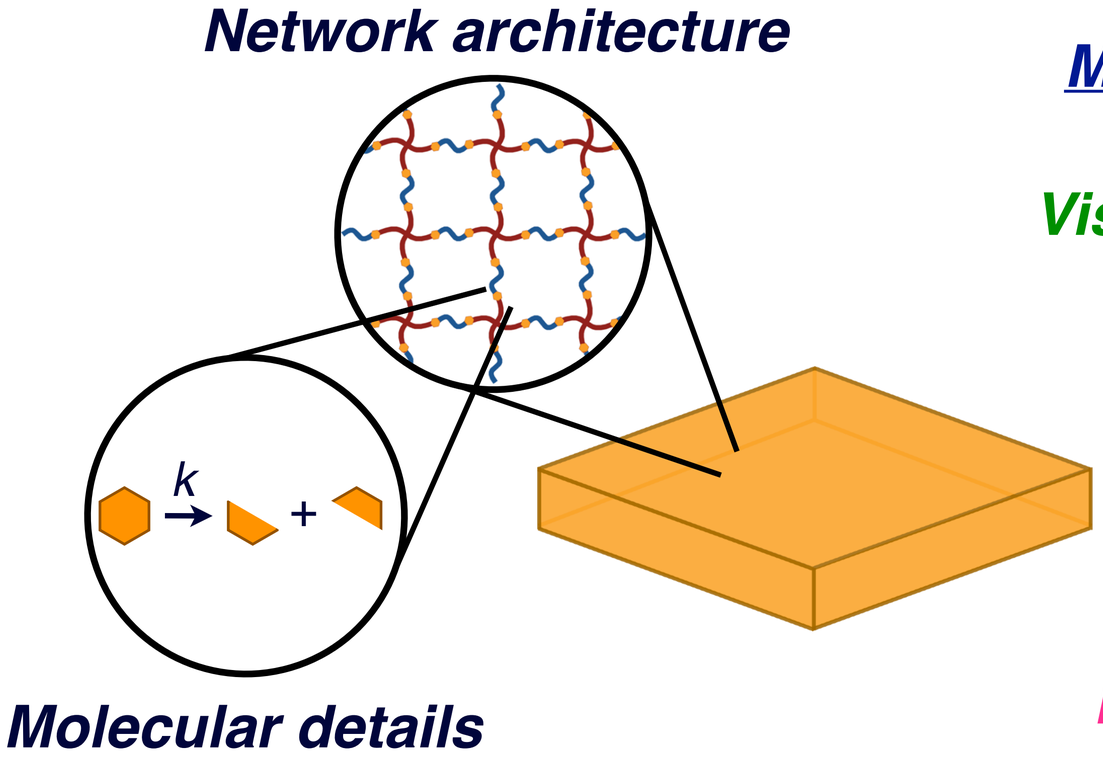
ETH zürich

Macromolecular Engineering: Networks and Gels

Lecture 19: Diffusion

Prof. Dr. Mark W. Tibbitt, 03. May 2022

Macroscale properties are controlled by molecular details



Macroscale Properties

Viscoelasticity

Diffusivity

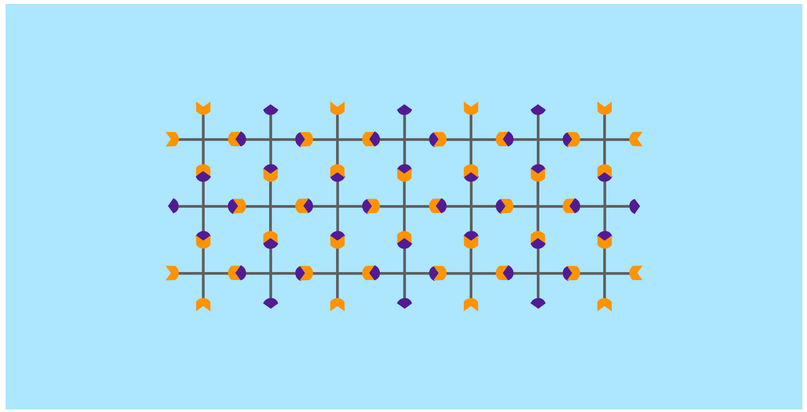
Surface chemistry

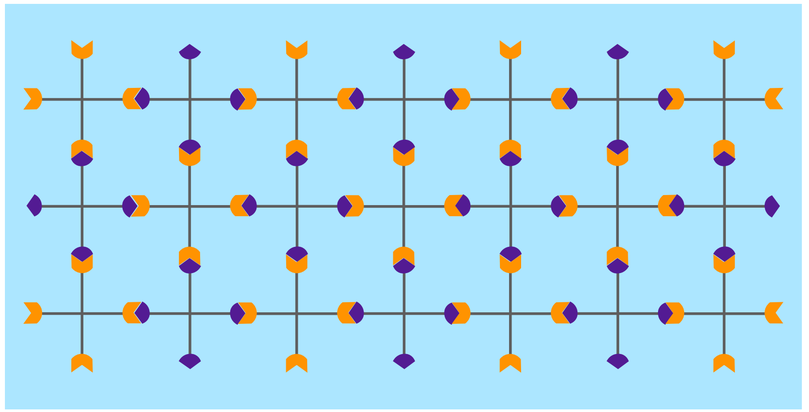
Swelling

Degradation

Macromolecular details inform material properties and provide a tunable handle in their design.

Solute diffusion





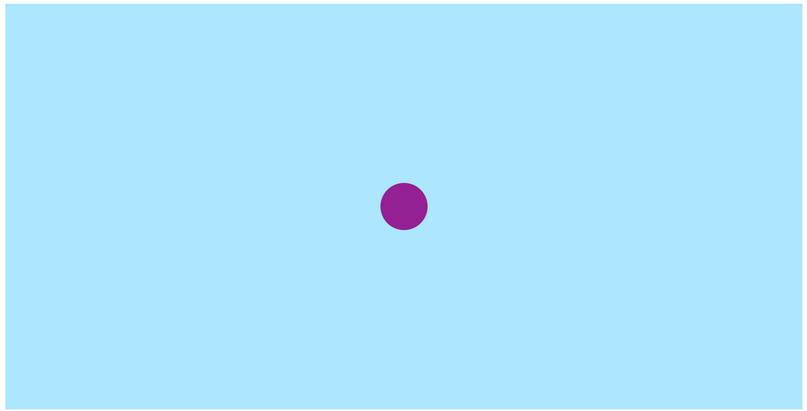
We are interested in the rate at which solutes pass through the network or gel.

$$Q \equiv \frac{V_p + V_s}{V_p}$$ swelling ratio

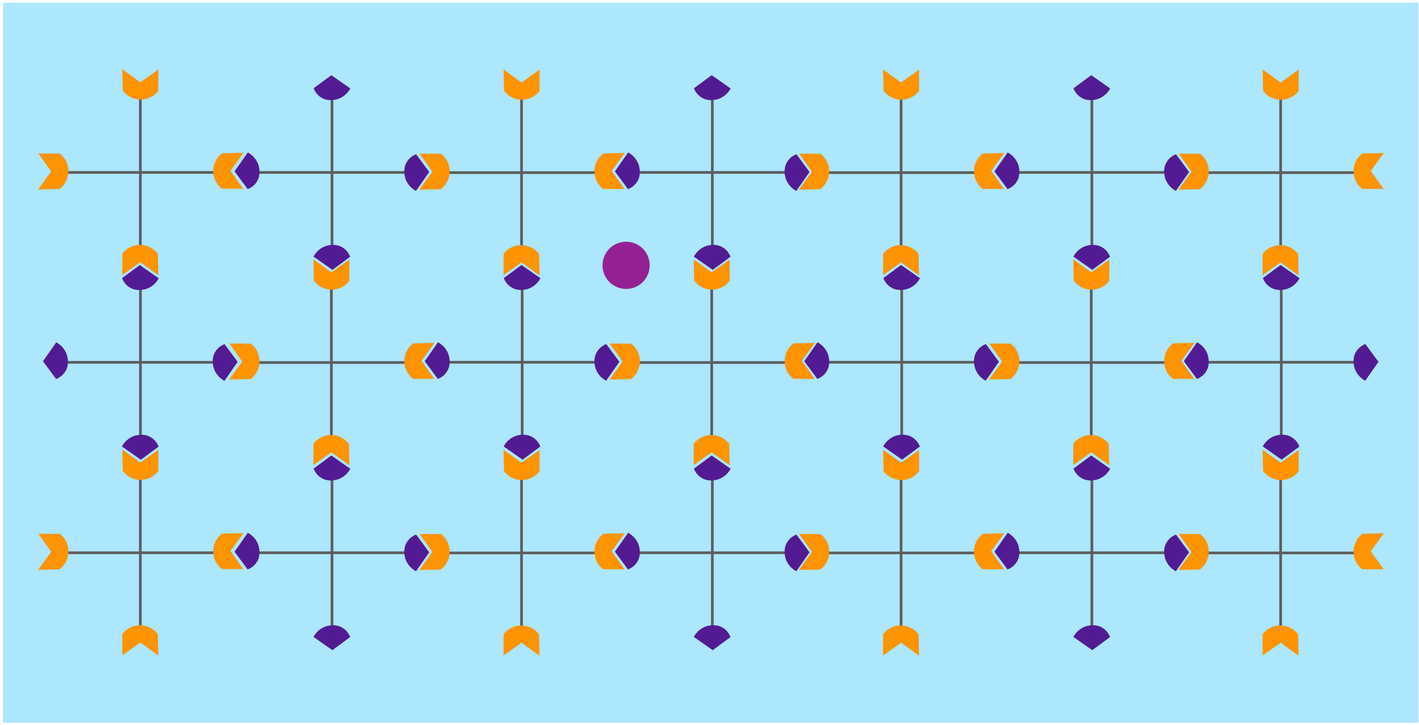
Stokes-Einstein Diffusion

$$D_0 = \frac{k_B T}{6\pi\eta r_s}$$

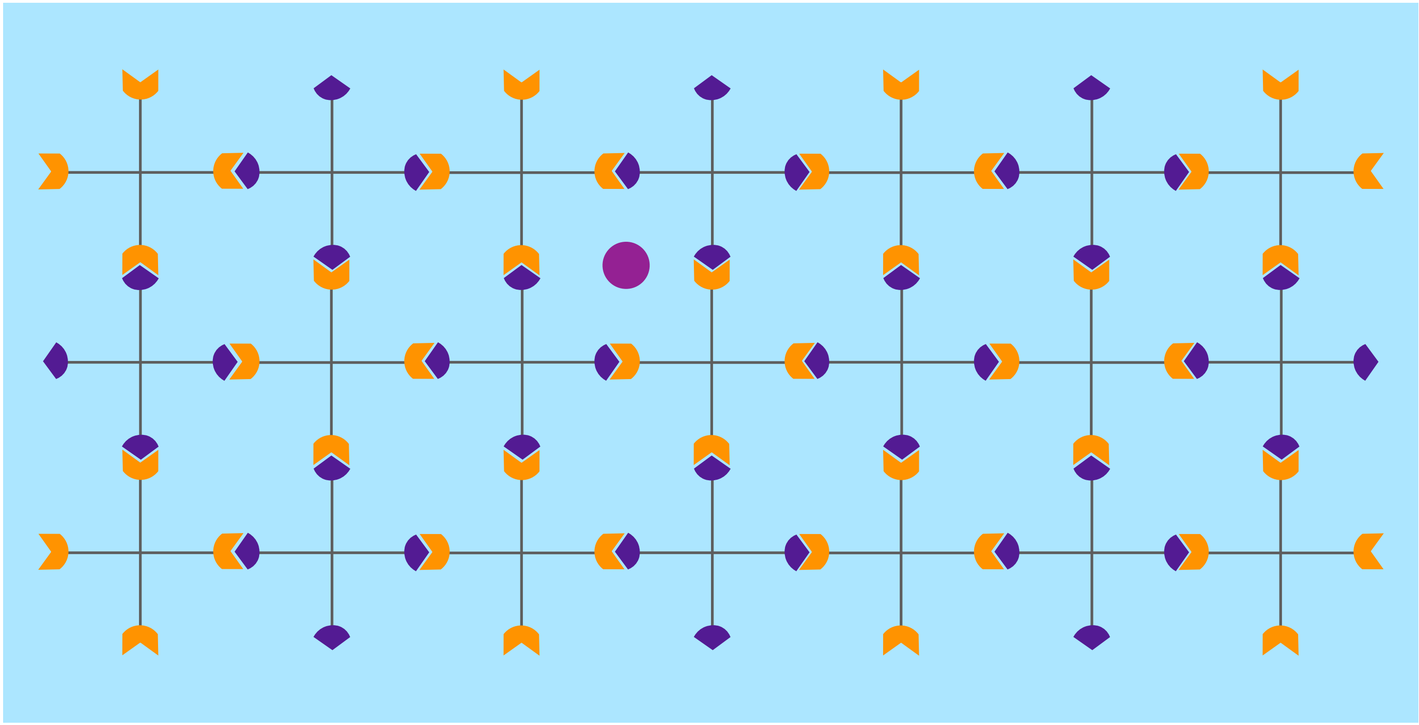
$$r_s = \frac{k_B T}{6\pi\eta D_0}$$



Solute diffusion in a gel



Solute diffusion in a gel



$$\xi = Q^{1/3} \left\langle r_0^2 \right\rangle^{1/2} = Q^{1/3} \ell \left(N C_\infty \right)^{1/2}$$

Solute diffusion in a gel

Table 1. Summary of Diffusion Models and the Hydrogels for Which They are Suited

model	expression	ref	hydrogel class
free volume theory	$\frac{D_g}{D_0} = (1 - k_1 r_s \varphi^{0.75}) \exp\left(-k_2 r_s{}^2 \left(\frac{\varphi}{1-\varphi}\right)\right)$	Lustig and Peppas[16]	homogeneous
hydrodynamic	$\frac{D_g}{D_o} = \exp(-k_C r_s \varphi^{0.75})$	Cukier[23]	homogeneous
hydrodynamic	$\frac{D_g}{D_o} = \left[1 + \left(\frac{r_s{}^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s{}^2}{k}\right]^{-1}$	Phillips et al.[24]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp\left[-\frac{(r_s + r_f)}{r_f}\sqrt{\varphi}\right]$	Ogston et al.[31]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp(-0.84\alpha^{1.09})$	Johansson et al.[30]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1}$	Tsai and Streider[34]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp\left[-\pi\left(\frac{r_s + r_f}{k_s \varphi^{1/2} + r_f}\right)^2\right]$	Amsden[35]	heterogeneous
combined	$\frac{D_g}{D_o} = \frac{\exp[-0.84\alpha^{1.09}]}{\left[1 + \left(\frac{r_s{}^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s{}^2}{k}\right]}$	Johnson et al.[38]	heterogeneous
combined	$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1} \exp(-\pi\varphi^{0.174\ln(59.6 r_f/r_s)})$	Clague and Phillips[39]	heterogeneous

Amsden *Macromolecules* **1998** *31, 8382*

Solute diffusion in a gel

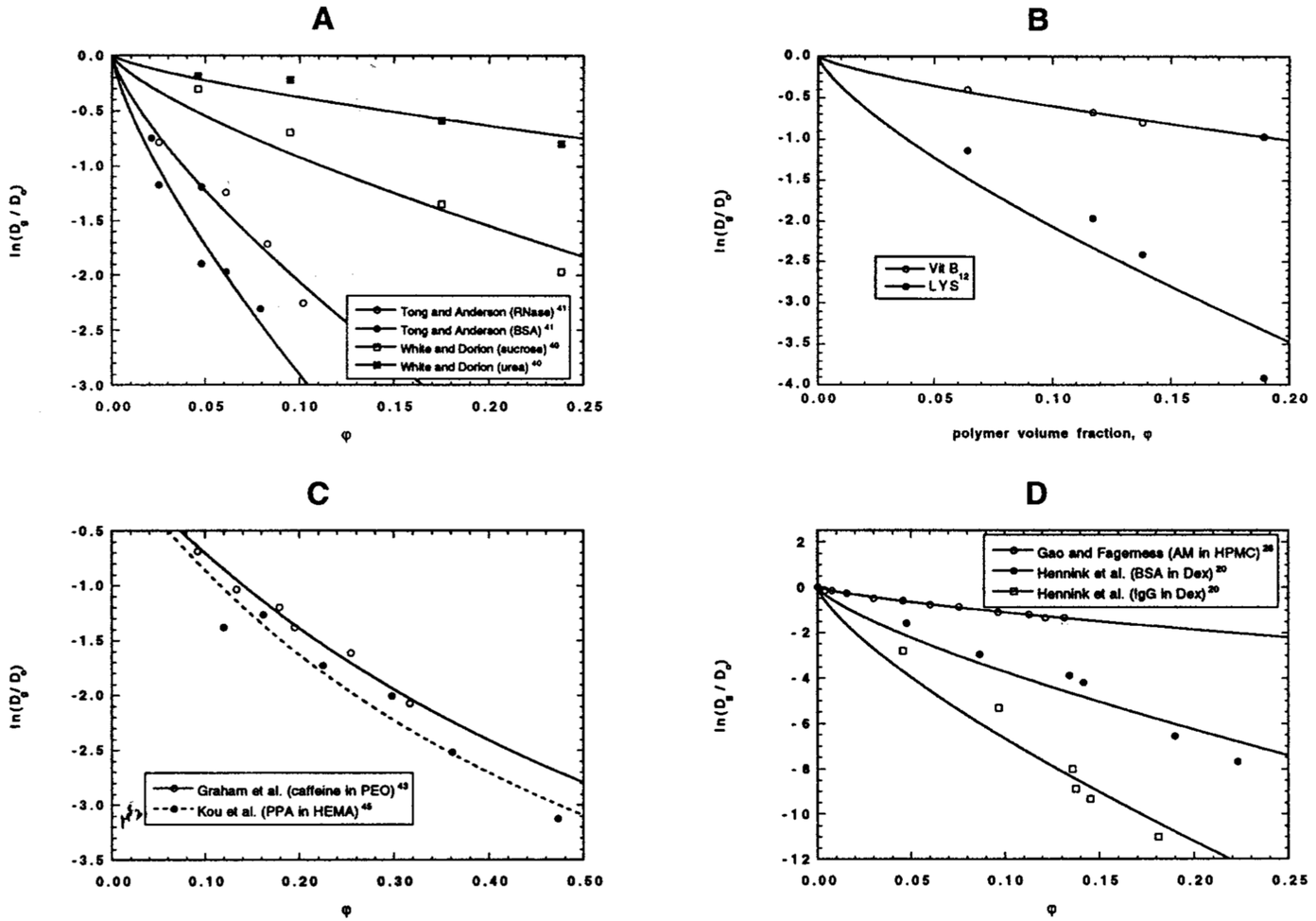


Figure 2. Application of the Cukier hydrodynamic-scaling model[23] to literature data showing the effect of polymer volume fraction on solute diffusivity within various homogeneous hydrogels: (A) polyacrylamide gels; (B) poly(vinyl alcohol) gels;[42] (C) poly-(ethylene oxide) (PEO) and poly(hydroxyethyl methacrylate) gels (HEMA); (D) dextran (Dex) and hydroxypropyl methylcellulose (HPMC) gels. The lines represent regression results.

Amsden *Macromolecules* **1998** *31, 8382*

Multiscale model for solute diffusion in hydrogels

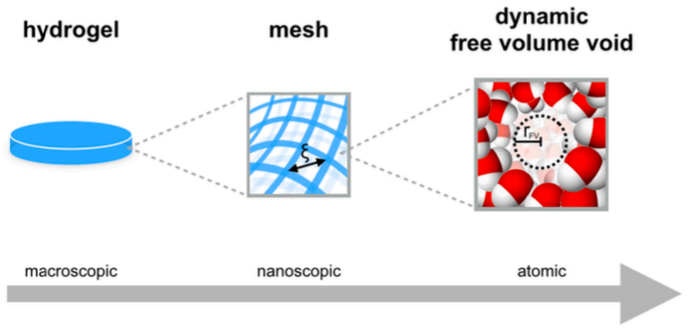
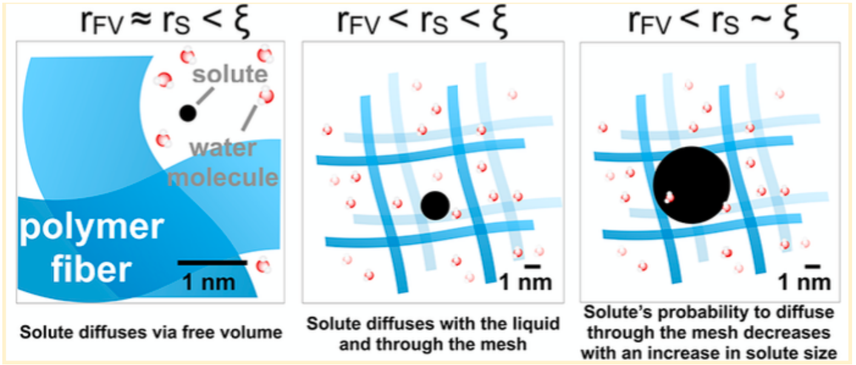
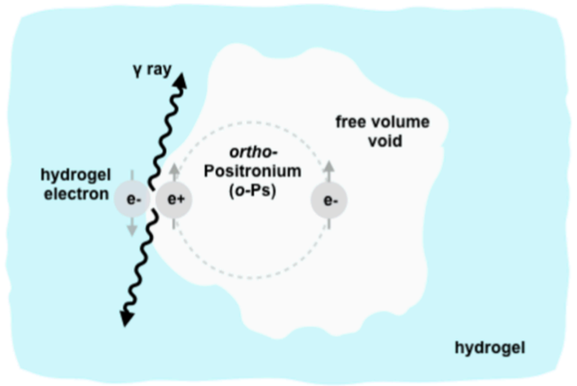


Figure 1. Scale effects in solute diffusion in hydrogels. The diffusion of a solute within a hydrogel occurs via aqueous solution and through liquid-filled, nano- to microscopic open spaces between the polymer fibers or free volume (dynamic, subnanoscopic, empty voids between the molecules). Which of these mechanisms dominates diffusion depends on the ratio between the hydrodynamic radius of the solute and the radius of the free volume voids in the hydrogel.



PALS to measure free volume

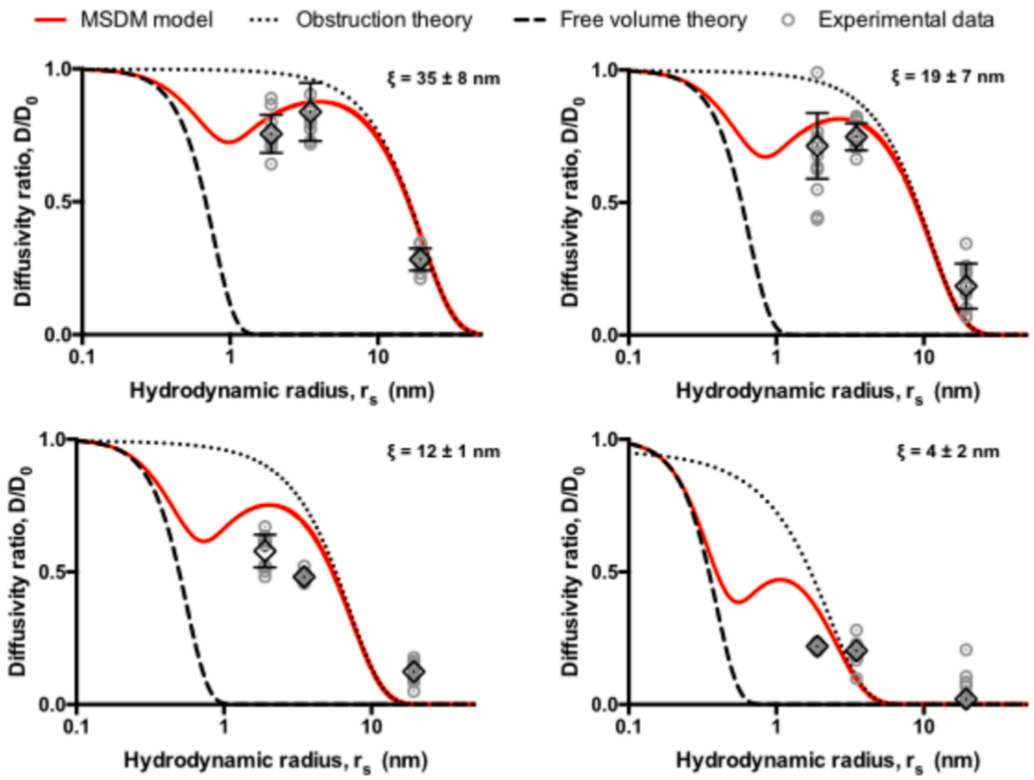


Multiscale model

$$\frac{D}{D_0} = \left[\operatorname{erf}\left(\frac{r_{FV}}{r_s}\right) \exp\left(-\left(\frac{r_s}{r_{FVW}}\right)^3 \left(\frac{\phi_p}{1-\phi_p}\right)\right) + \operatorname{erfc}\left(\frac{r_{FV}}{r_s}\right) \exp\left(-\pi\left(\frac{r_s + r_f}{\xi + 2r_f}\right)^2\right)\right]$$

Axpe et al. *Macromolecules*, **2019**, *52*, 6889.

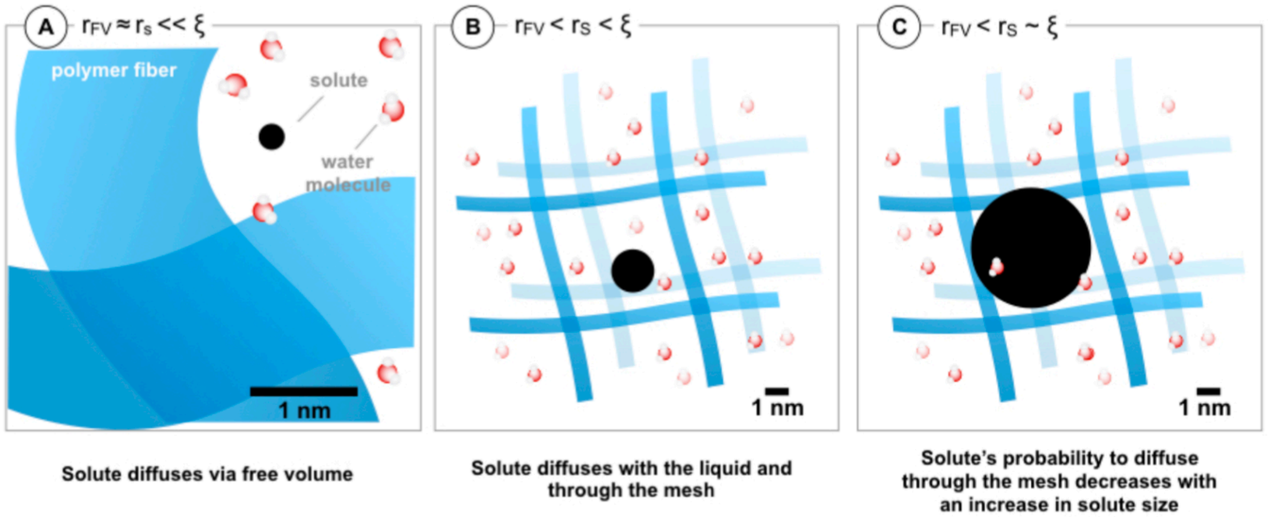
Multiscale model for solute diffusion in hydrogels



A combined theory that accounts for free volume and obstruction effects describes anomalies in observed diffusion as a function of solute size.

Axpe et al. *Macromolecules*, **2019**, *52*, 6889.

Multiscale model for solute diffusion in hydrogels



One needs to consider the molecular landscape that a solute encounters when considering solute diffusion.

Axpe et al. *Macromolecules*, **2019**, *52*, 6889.

Solute diffusion in a gel

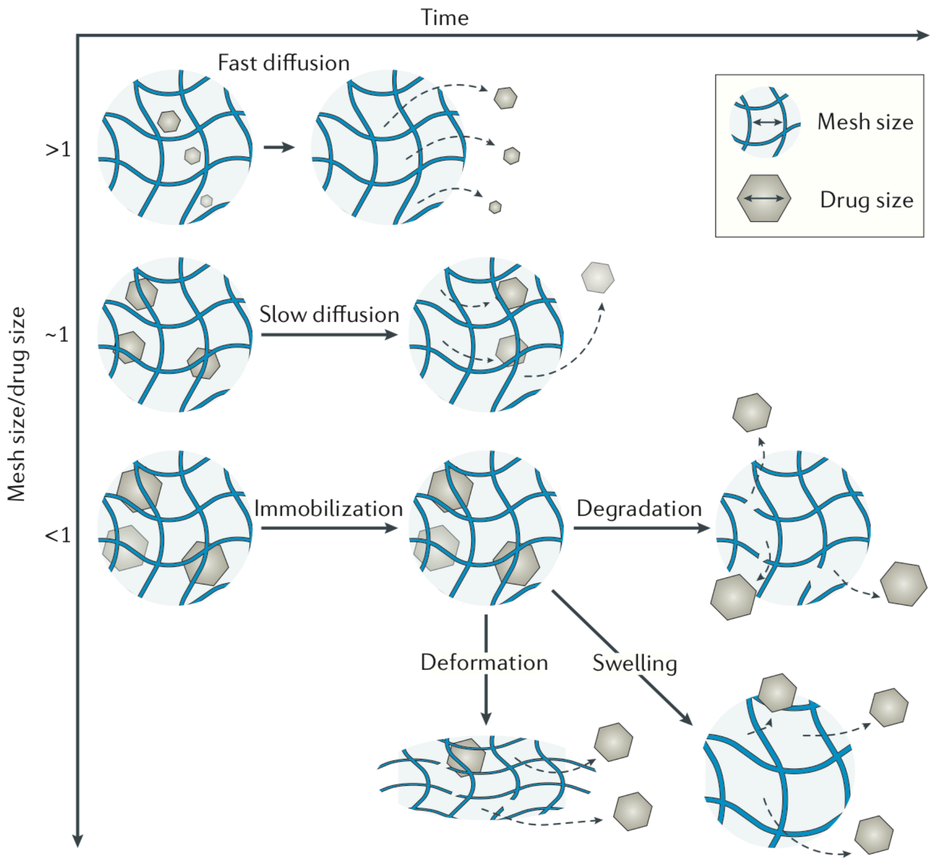
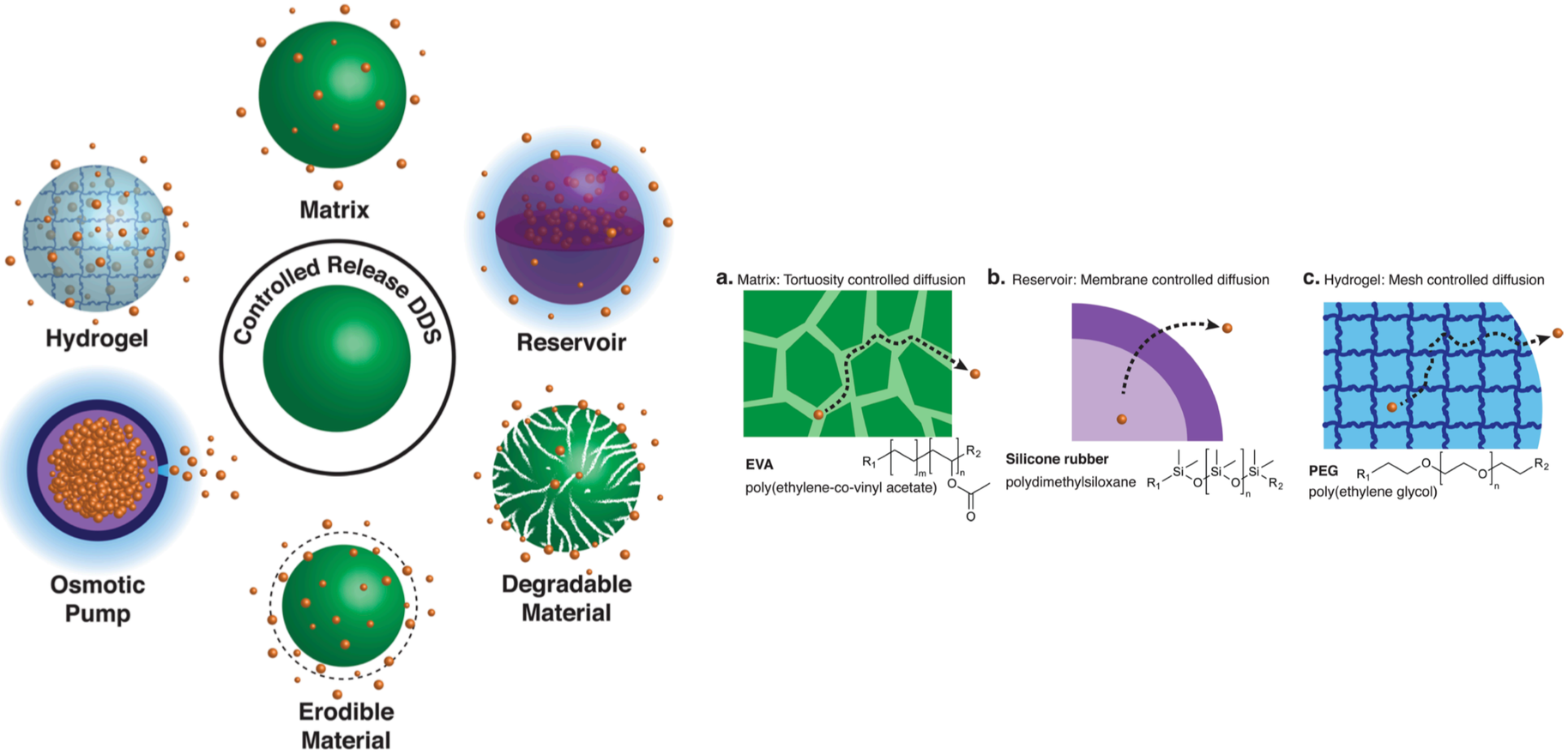


Figure 3 | **Mesh size mediates drug diffusion.** A small drug relative to the mesh size diffuses rapidly through the hydrogel, resulting in a short release duration. When the size of a drug approaches the mesh size ($r_{mesh}/r_{drug} \approx 1$), drug release is dramatically slowed. When the drug is larger than the mesh size ($r_{mesh}/r_{drug} < 1$), drugs are physically entrapped inside the network. To release the originally immobilized drugs, the mesh size can be enlarged through network degradation or swelling, or by applying deformation to disrupt the network. The dashed lines refer to the diffusion pathway of drugs.

Li and Mooney *Nat Rev Materials* **2016** *1*, 1

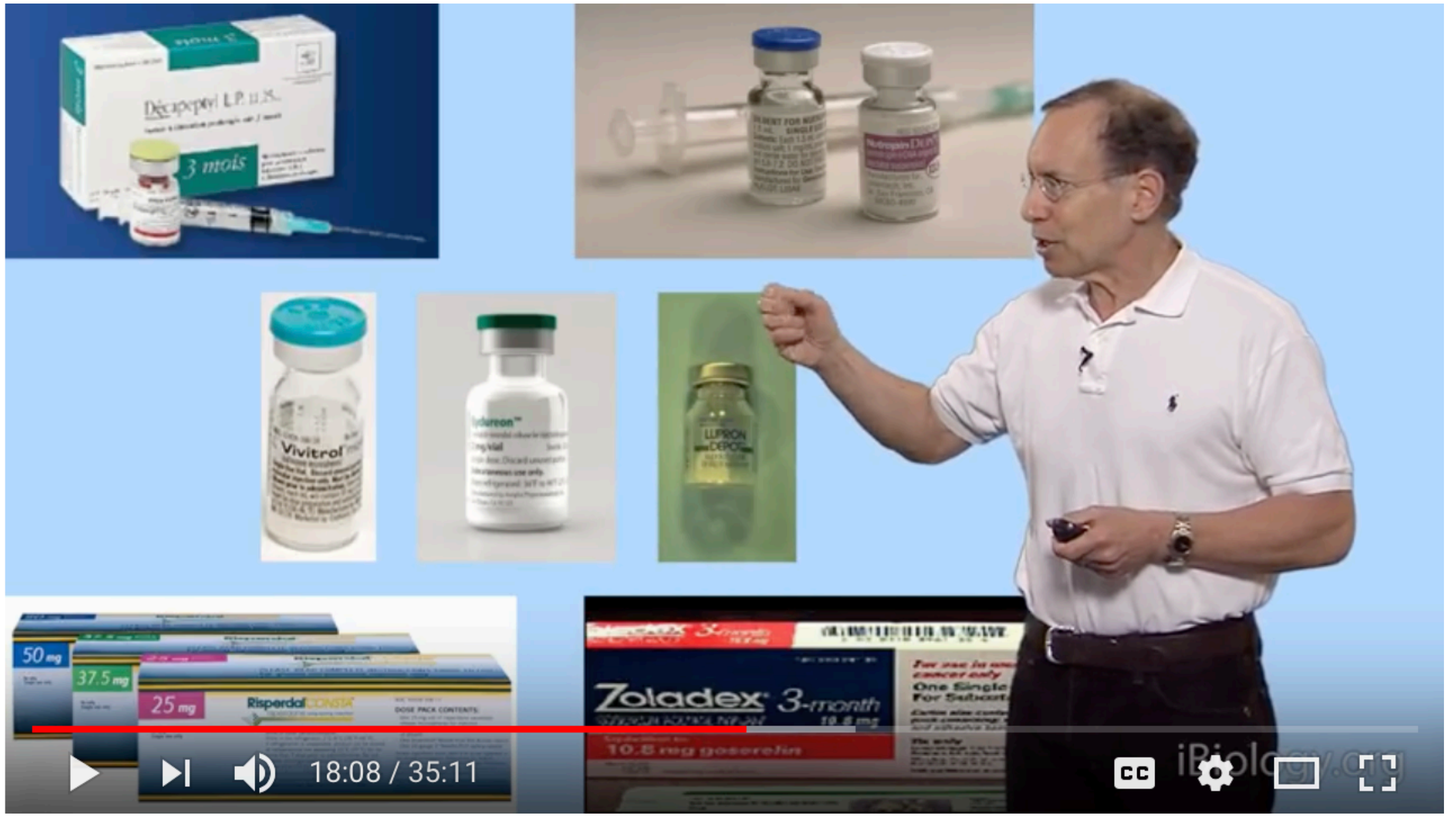
Controlled drug delivery



Materials and methods for controlled drug delivery from biomedical materials - swelling, diffusion, degradation

Tibbitt et al. *JACS*, **2016**, *138*, 704

Drug delivery products



There are numerous marketed products that rely on the controlled drug delivery - polymeric materials as well as networks and gels

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Clinically used hydrogel drug delivery systems

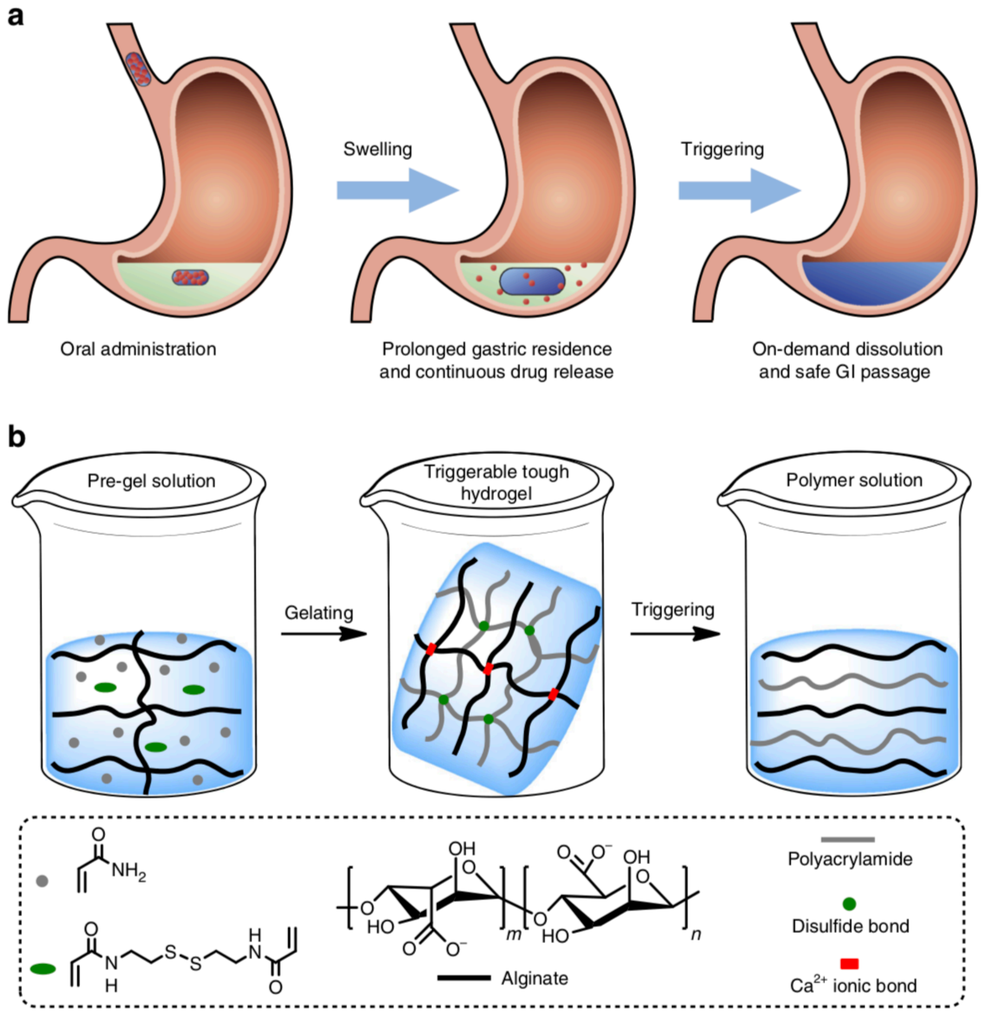
Table 1 | **Clinically used hydrogel drug delivery systems**

Product	Type of hydrogel	Drug	Therapeutic application
INFUSE	Collagen	Recombinant human BMP2	• Bone fracture • Oral maxillofacial reconstruction • Spinal fusion
MASTERGRAFT	Calcium phosphate and collagen	BMP2	Spinal fusion
OP-1, OP-1 Putty	Collagen	BMP7	• Long bone fracture • Spinal fusion
VANTAS	Poly(2-hydroxyethyl methacrylate), poly(2-hydroxypropyl methacrylate)	Histrelin acetate	Subdermal implant for the treatment of prostate cancer
SUPPRELIN LA	Poly(2-hydroxyethyl methacrylate)	Histrelin acetate	Subcutaneous implant for the treatment of children's central precocious puberty
AzaSite	Poly(acrylic acid)	Azithromycin	Bacterial conjunctivitis
Besivance	Poly(acrylic acid)	Besifloxacin	Bacterial conjunctivitis
Cervidil	PEG or urethane polymer	Dinoprostone	Vaginal insert for cervical ripening to induce labour
Differin	Carbomer 940	Adapalene	Topical treatment of acne vulgaris
AndroGel	Carbomer 980	Testosterone	Topical gel for hypogonadism treatment
Calamine-zinc gelatin	Gelatin	Calamine zinc oxide	Wound dressing to lessen pain and itching
ALGICELL Ag, Suprasorb A + Ag	Alginate	Silver	Wound dressing with antimicrobial silver
Prontosan	Hydroxyethylcellulose	Polyhexanide	Antiseptic wound dressing
REGRANEX	Carboxymethylcellulose	Becaplermin, a recombinant human platelet-derived growth factor	Topical gel for the treatment of diabetic foot ulcers

BMP, bone morphogenetic protein; PEG, poly(ethylene glycol).

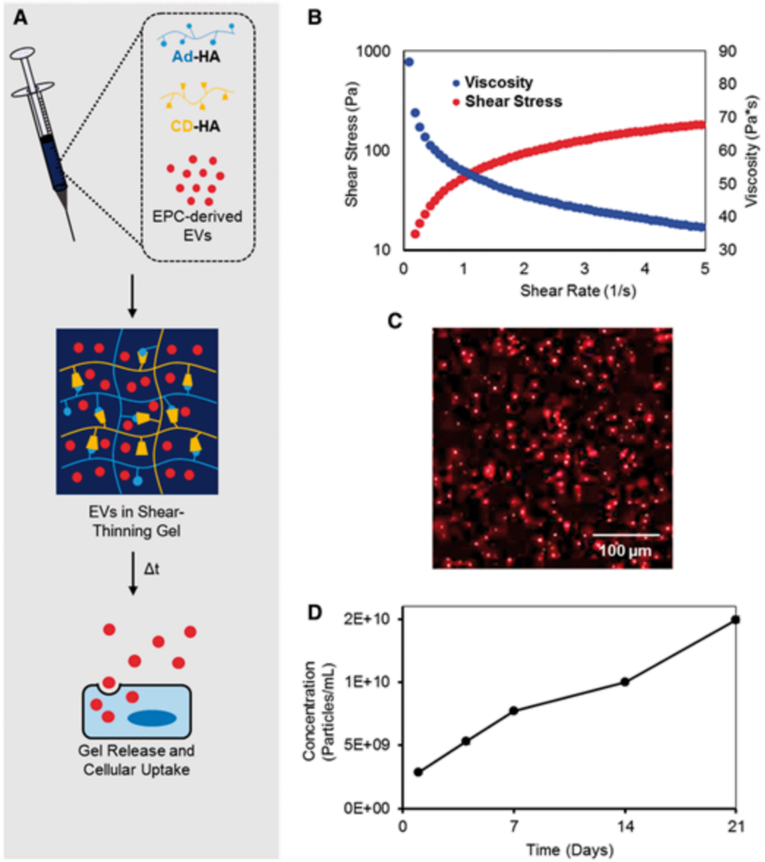
Li and Mooney *Nat. Rev. Mater.*, **2016**, *1*, 1

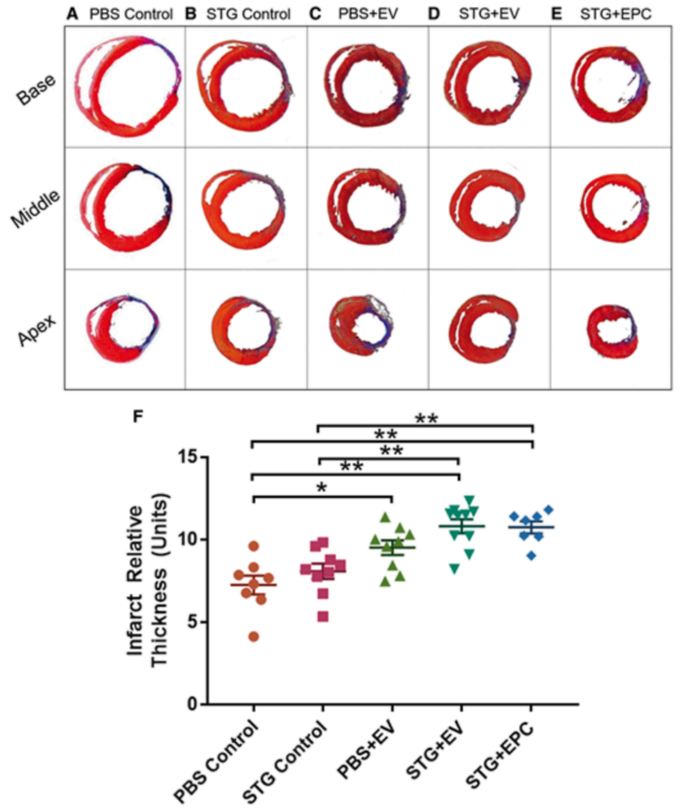
Triggerable tough hydrogels for gastric resident dosage forms



Liu et al. *Nature Communications.*, **2017**, *8*, 124

Injectable hydrogels for localized drug delivery





Chen et al. *Cardiovascular Research*, **2018**, 10.1093/cvr/cvy067

Diffusion also matters for tissue engineering

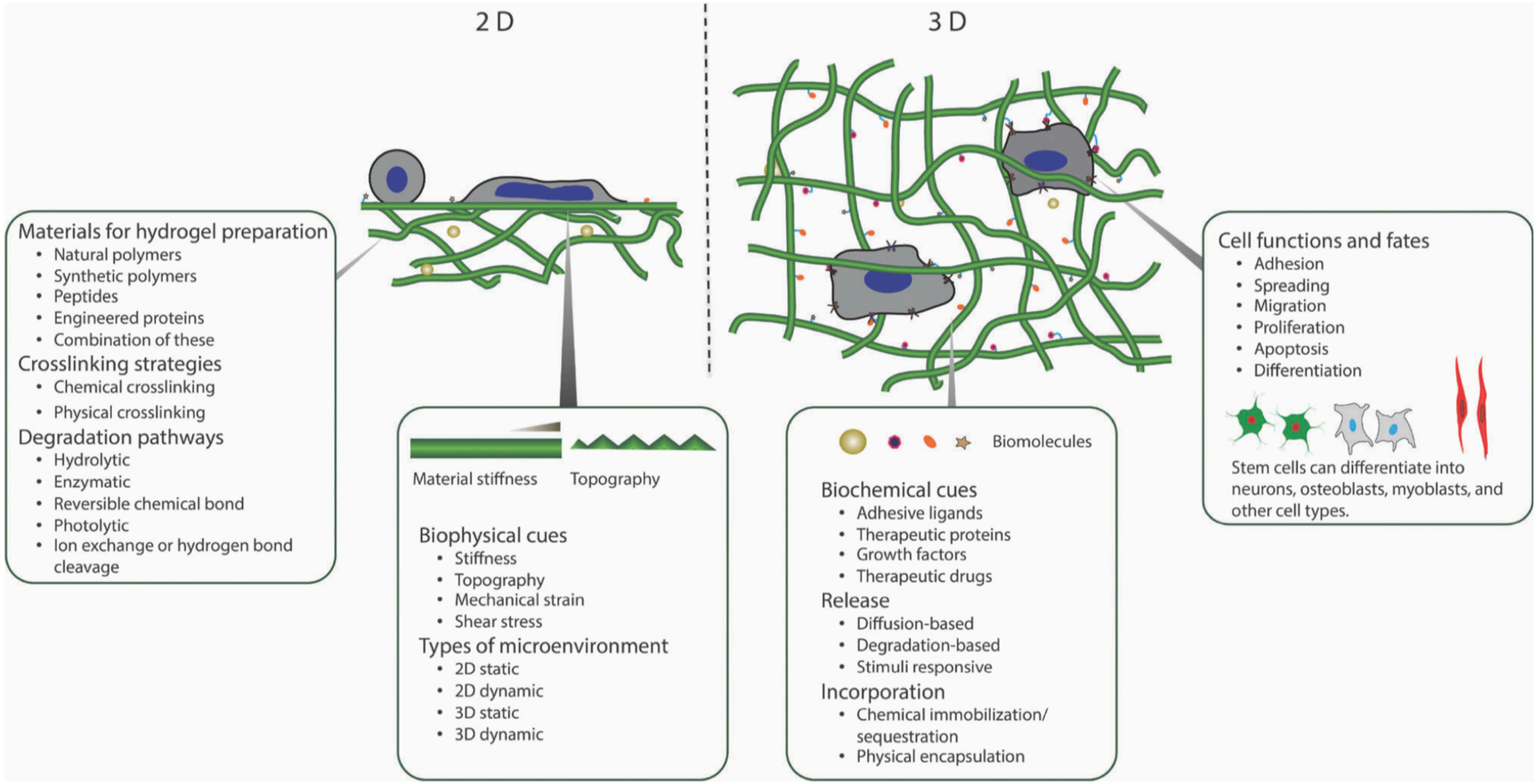


Fig. 1 Overview. Degradable hydrogels can be used for orthogonal control of multiple properties in both two- and three-dimensional (2D and 3D) cellular microenvironments.

Kharkar et al. *Chem Soc Rev* **2013** *42,* 7335

Encapsulated islets for diabetes therapy

nature materials

ARTICLES

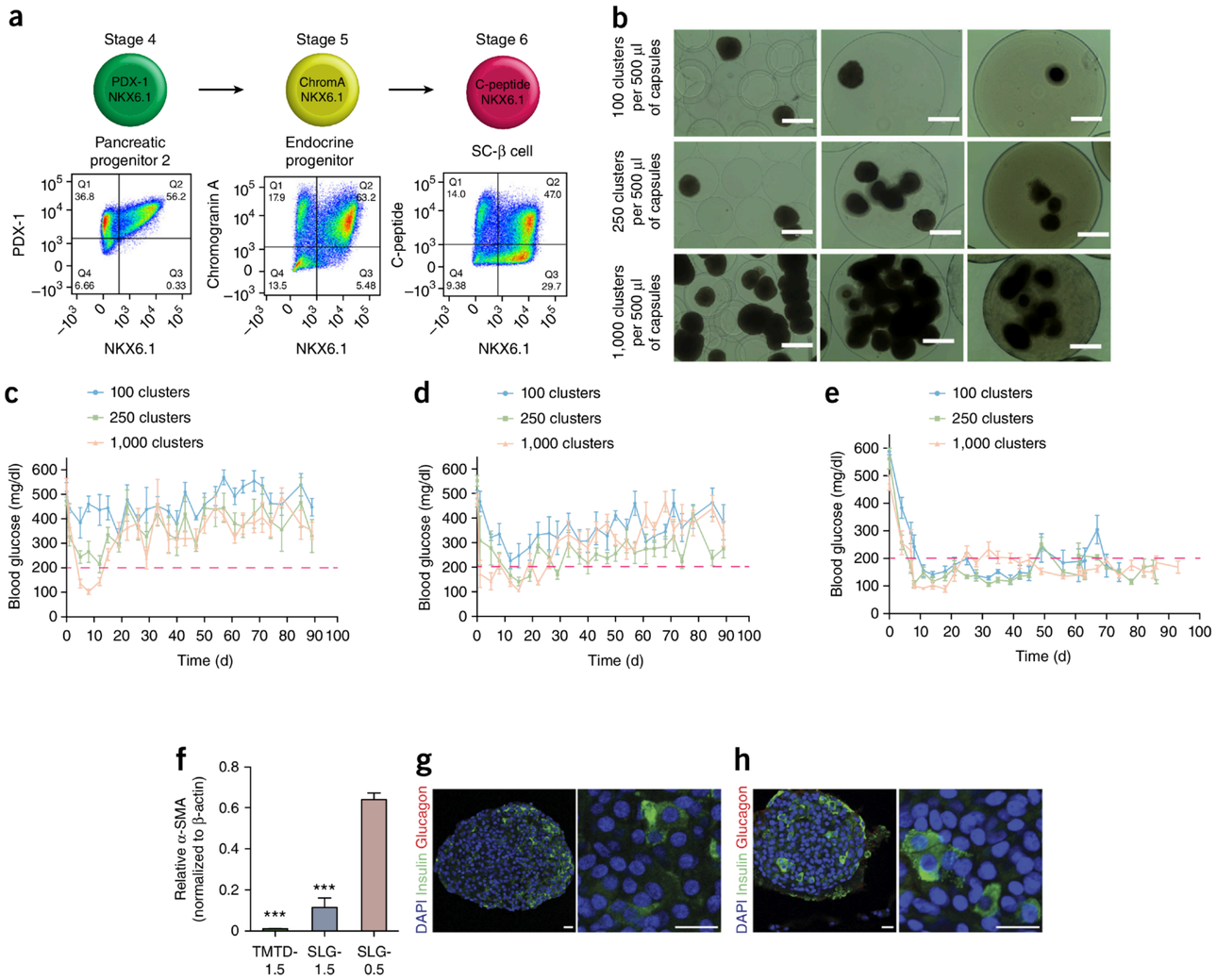
PUBLISHED ONLINE: 18 MAY 2015 | DOI: 10.1038/NMAT4290

Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates

Omid Veiseh[1,2,3†], Joshua C. Doloff[1,3†], Minglin Ma[1,3,4†‡], Arturo J. Vegas[1,3], Hok Hei Tam[1,2], Andrew R. Bader[1,3], Jie Li[1,3], Erin Langan[1,3], Jeffrey Wyckoff[1], Whitney S. Loo[2], Siddharth Jhunjhunwala[1,3], Alan Chiu[1,3], Sean Siebert[1,3], Katherine Tang[1,3], Jennifer Hollister-Lock[4], Stephanie Aresta-Dasilva[1,3], Matthew Bochenek[5], Joshua Mendoza-Elias[5], Yong Wang[5], Merigeng Qi[5], Danya M. Lavin[1,3], Michael Chen[1,3], Nimit Dholakia[1,3], Raj Thakrar[1,3], Igor Lacík[6], Gordon C. Weir[4], Jose Oberholzer[5], Dale L. Greiner[7], Robert Langer[1,2,3,8,9,10] and Daniel G. Anderson[1,2,3,8,9,10★]

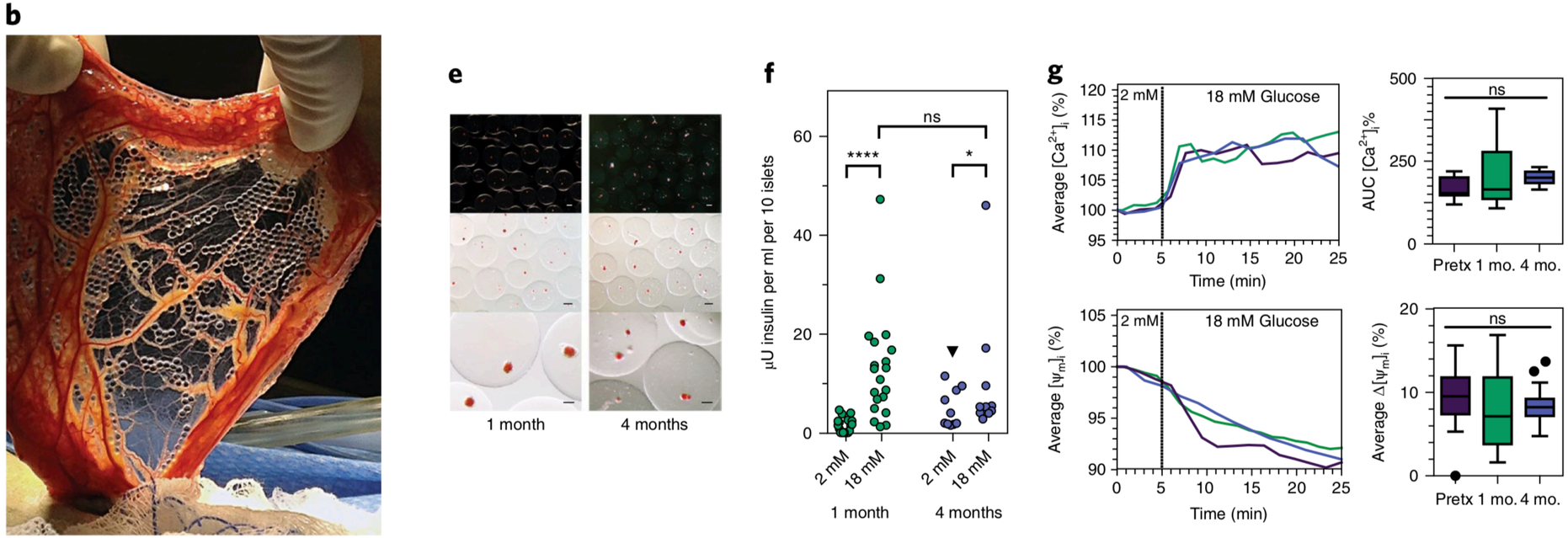
The efficacy of implanted biomedical devices is often compromised by host recognition and subsequent foreign body responses. Here, we demonstrate the role of the geometry of implanted materials on their biocompatibility *in vivo*. In rodent and non-human primate animal models, implanted spheres 1.5 mm and above in diameter across a broad spectrum of materials, including hydrogels, ceramics, metals and plastics, significantly abrogated foreign body reactions and fibrosis when compared with smaller spheres. We also show that for encapsulated rat pancreatic islet cells transplanted into streptozotocin-treated diabetic C57BL/6 mice, islets prepared in 1.5-mm alginate capsules were able to restore blood-glucose control for up to 180 days, a period more than five times longer than for transplanted grafts encapsulated within conventionally sized 0.5-mm alginate capsules. Our findings suggest that the *in vivo* biocompatibility of biomedical devices can be significantly improved simply by tuning their spherical dimensions.

Encapsulated islets for diabetes therapy



Vegas et al. *Nat. Med*, **2016**, *3*, 306.

Encapsulated islets for diabetes therapy



Alginate microbeads enable nutrient diffusion and limit host rejection to enable survival of implanted islets for diabetes therapy.

Bochenek et al. *Nat. Biomed. Eng.*, **2018**, *2*, 810.

Solute diffusion in a gel

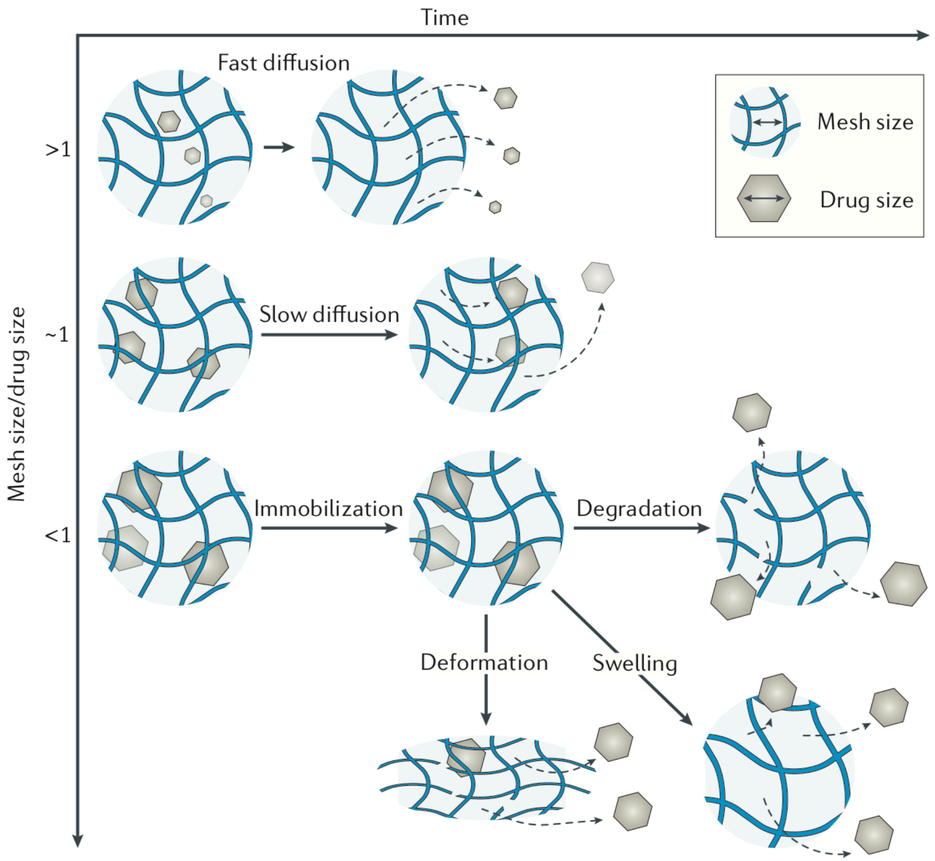


Figure 3 | **Mesh size mediates drug diffusion.** A small drug relative to the mesh size diffuses rapidly through the hydrogel, resulting in a short release duration. When the size of a drug approaches the mesh size ($r_{mesh}/r_{drug} \approx 1$), drug release is dramatically slowed. When the drug is larger than the mesh size ($r_{mesh}/r_{drug} < 1$), drugs are physically entrapped inside the network. To release the originally immobilized drugs, the mesh size can be enlarged through network degradation or swelling, or by applying deformation to disrupt the network. The dashed lines refer to the diffusion pathway of drugs.

Li and Mooney *Nat Rev Materials* **2016** *1*, 1