First-phase release and model of pore space network in a sustained release system

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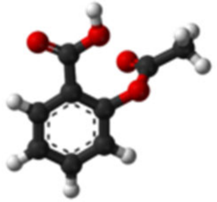
Student Presenter for Rigaku X-ray Computed Tomography Seminar

University of Delaware

Biopharmaceutical & drug delivery systems

Small molecule

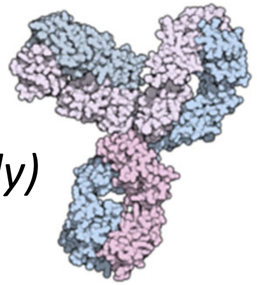
Aspirin
(180 Da)



$\sim 0.5\ nm$

Biopharmaceutical

Pembrolizu*mab (antibody)*
(150,000 Da)

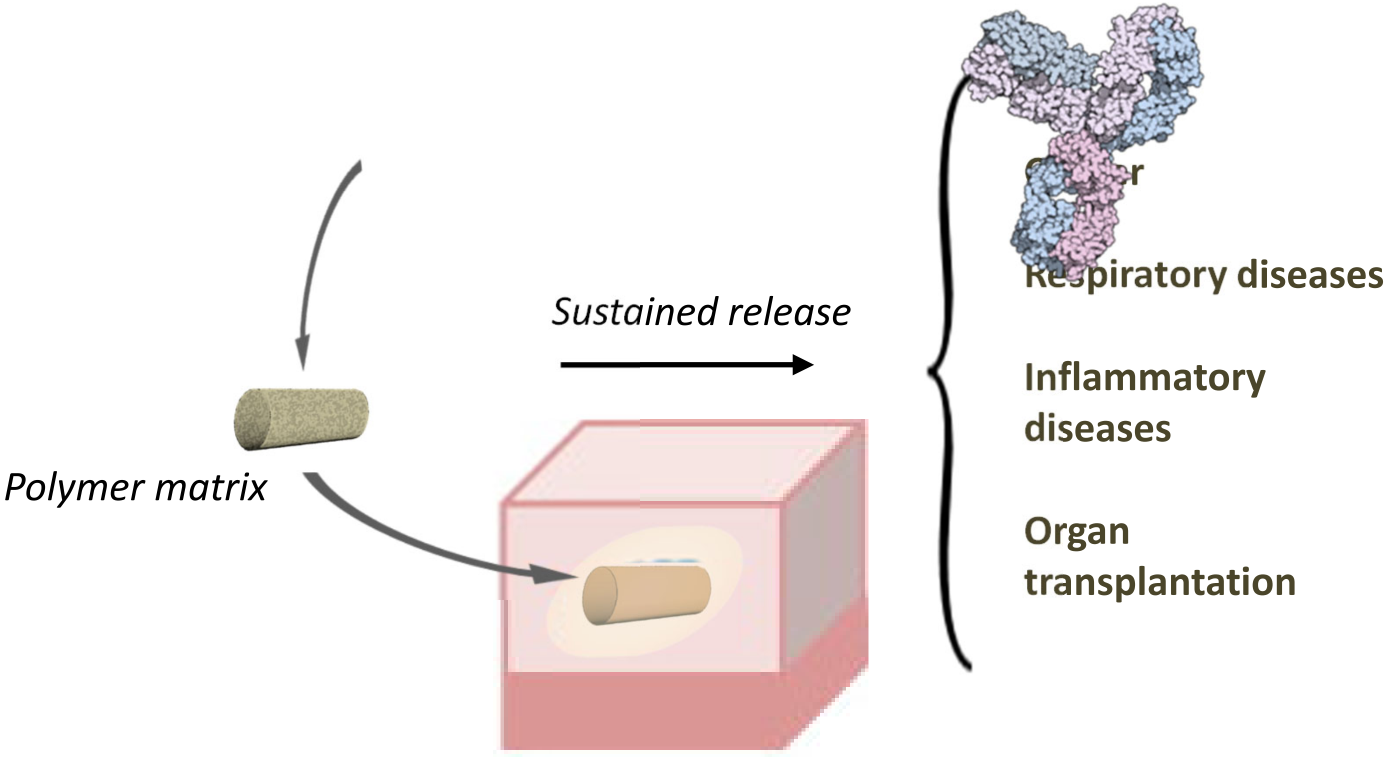


$\sim 15\ nm$

Biopharmaceutical & drug delivery systems

Advantages:

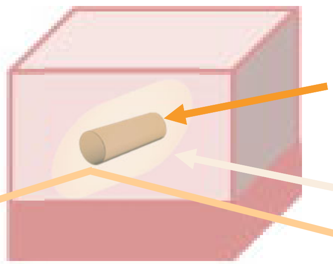
- Protection against drug degradation/denaturation
- High specificity
- Less frequent administration
- Long-term bioavailability
- Improved patient compliances

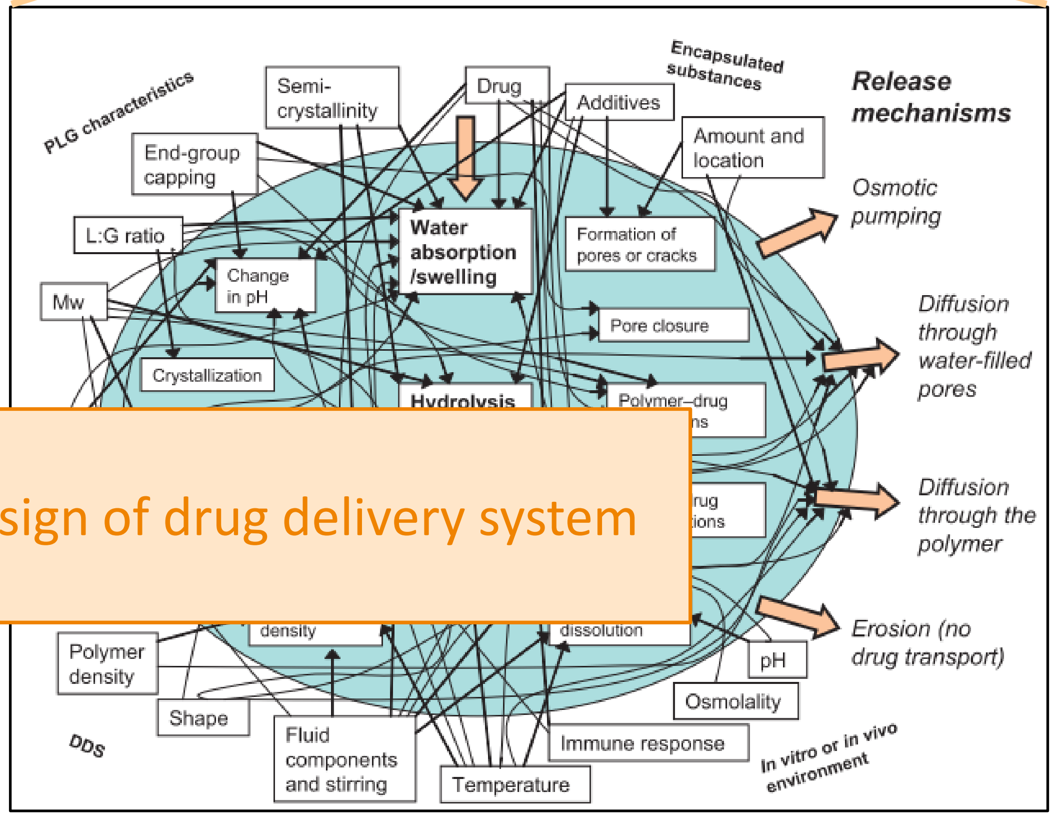


Sung YK, Kim SW. *Biomater Res*. 2020;24(1):12.
Ding D, Zhu Q. *Mater Sci Eng C*. 2018;92(December 2017):1041-1060.
Mitragotri S, Burke PA, Langer R. *Nat Rev Drug Discov*. 2014;13(9):655-672.

Motivation & research question

- Release process is dictated by complex interactions between delivery systems and environment
- Tight control of the release profile is a major challenge in the design of delivery systems
- A physically-based model can enable prediction outside experimentally verified behavior





Research question:

How well can we understand/inform the design of drug delivery system using a physically-based model?

Release process of poly(lactic-co-glycolic acid)-based (PLGA) delivery systems

University of Delaware

Fredenberg S, Wahlgren M et al. *Int J Pharm*. 2011;415(1-2):34-52.
Peppas NA, Narasimhan B. *J Control Release*. 2014;190:75-81.
Mitragotri S, Burke PA, Langer R. *Nat Rev Drug Discov*. 2014;13(9):655-672.

Experimental design

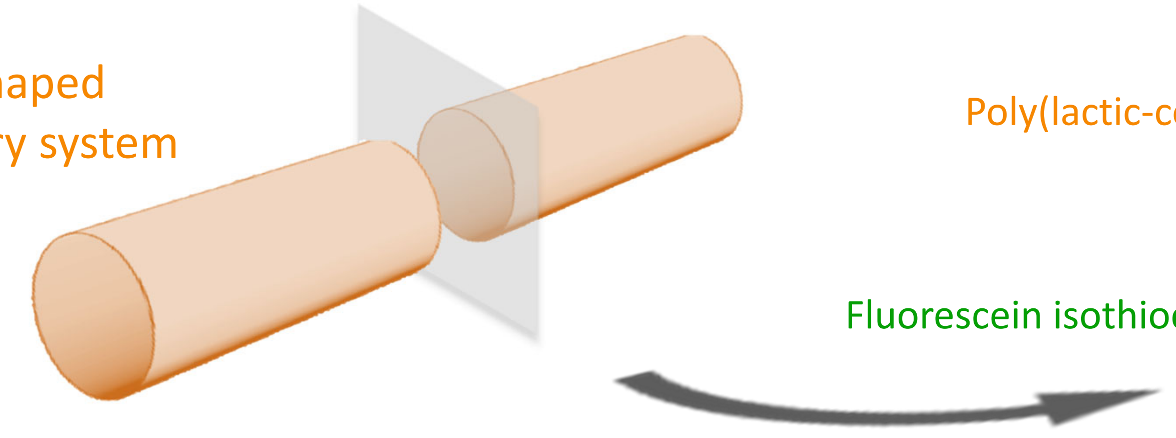
Parameter space
- 5 design factors (level varied around A)
- Mostly one factor at a time approach

Parameter space (partial)

Design Parameter	Formula A	Formula D	Formula E	Formula F	Formula I
Polymer initial MW [kDa]	60	**110**	60	60	60
Drug loading [wt%]	15	15	**5**	**25**	15
L:G ratio	75:25	75:25	75:25	75:25	**85:15**
Polymer grade & end-group*	5S	6S	5S	5S	**5A**

*Number: Intrinsic viscosity/MW; S: ester; A: acid

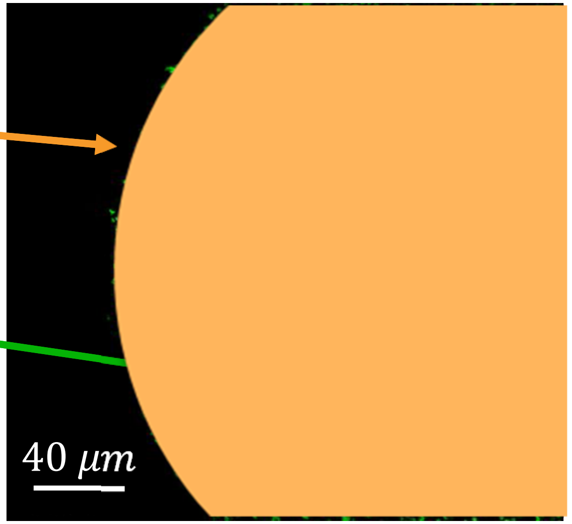
Rod-shaped delivery system



Cross-section view

Poly(lactic-co-glycolic acid) (PLGA)

Fluorescein isothiocyanate (FITC)-dextran



Confocal fluorescence microscopy (CFM) of rod cross-section

Problem Statement

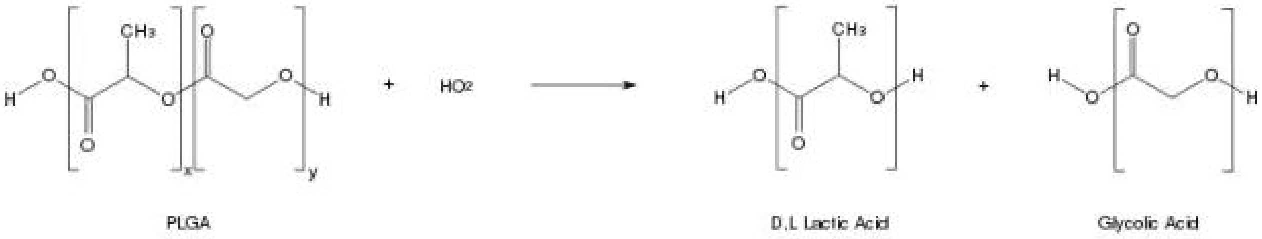
Implantable polymer rods that release bio-agents via **physic-chemical processes**

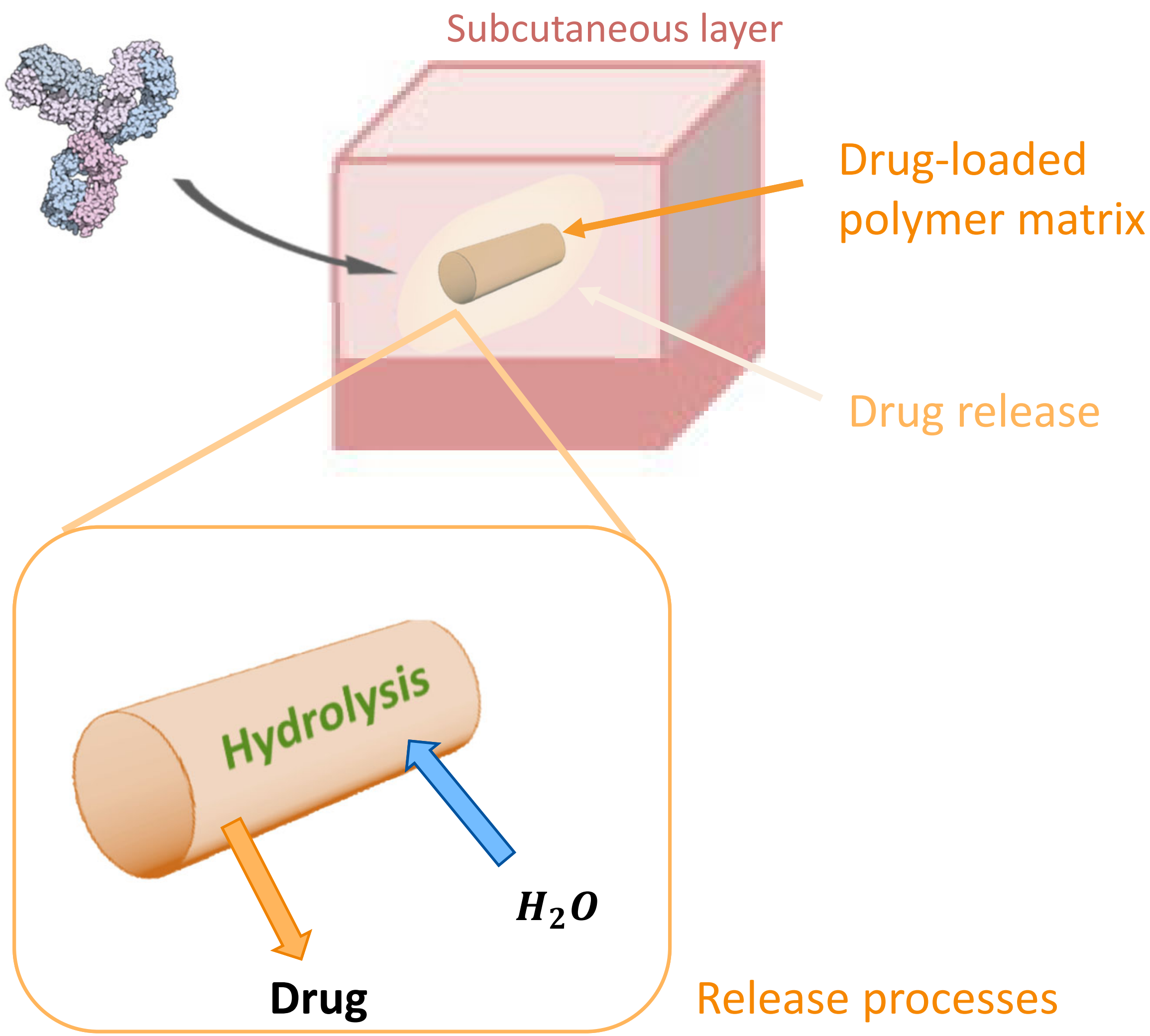
Processes:

- Drug diffusion out
- Water diffusion in
- Matrix degradation

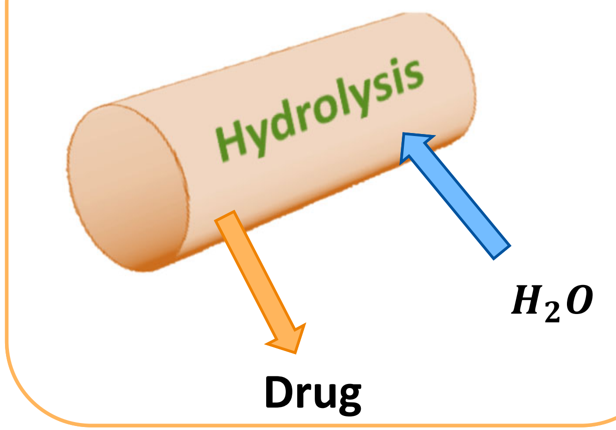
Degradative reaction

- PLGA hydrolysis





Methods – modeling approach



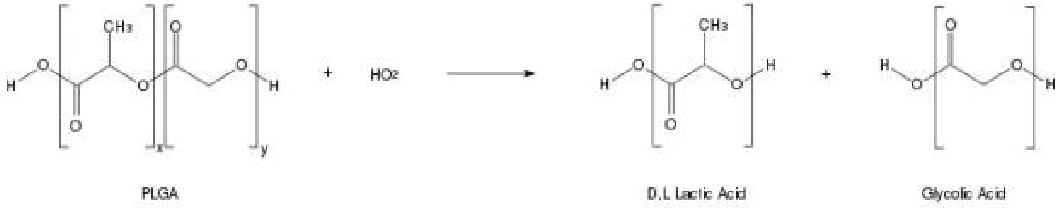
Modeled uptake and release mechanisms:

- Drug: $$\frac{\partial C_D}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}D_D(r,t)C_D\right)$$
- Water: $$\frac{\partial C_W}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}D_W C_W\right) - k[E]C_W$$
- Polymer: $$\frac{\partial C_E}{\partial t} = -kC_E C_W \qquad C_E = \rho\left(\frac{1}{M_0} - \frac{1}{MW}\right)$$

Model Parameter	Variable	Method
Drug diffusion coefficient	$D_{D,0}$	Heuristic
Drug initial concentration	$C_{D,0}$	Design
Water diffusion coefficient	D_w	Estimation
Water maximum concentration	$C_{w,0}$	Estimation
Occlusion radius	R_{occ}	Heuristic
Radius of cylinder	R	Design
Initial polymer MW	MW_0	Design
Polymer MW at release	MW_r	Estimation
Polymer degradation rate constant	k_{deg}	Fit
Polymer degradation variance	σ_r^2	Estimation

Previous rate law $$\frac{\partial MW}{\partial t} = -kMWC_w$$

PLGA hydrolytic degradation



Rothstein SN, Federspiel WJ, Little SR. *J Mater Chem*. 2008;18(16):1873.
Antheunis H, van der Meer J-C et al. *Biomacromolecules*. 2010;11(4):1118-1124.

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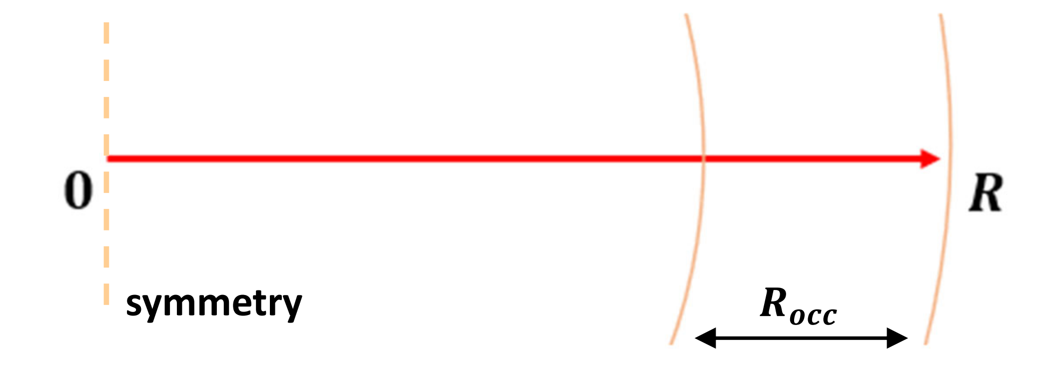
Position-dependent

$$D_D(r,t) = \begin{cases} D_{D,0}; & if\ r > (R - R_{occ}) \\ D_{D,0}\cdot\epsilon\big(MW(r,t)\big); & if\ r \le (R - R_{occ}) \end{cases}$$

MW-dependent

$$\epsilon\big(MW(r,t)\big) = 1 - \frac{1}{2}\left[1 + \mathrm{erf}\left(\frac{MW(r,t) - MW_r}{\sqrt{2\sigma_r^2}}\right)\right]$$

Cylindrical 1D domain



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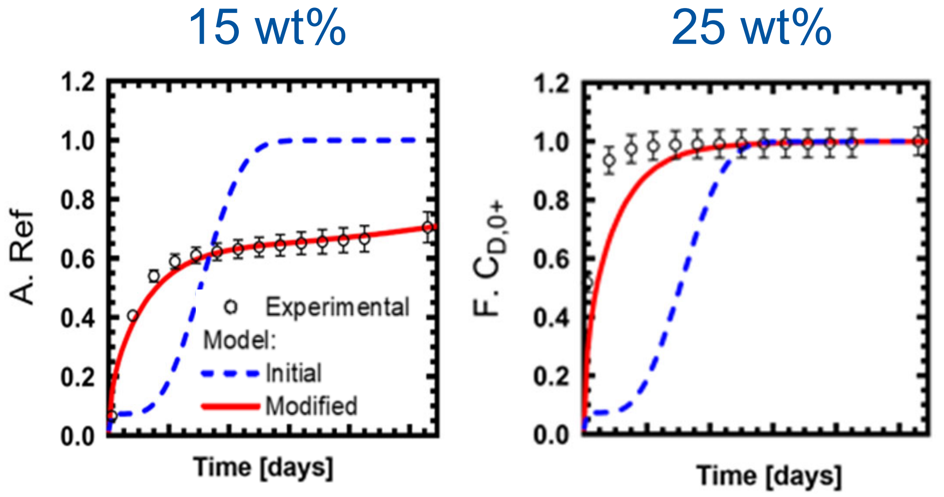
First-phase release

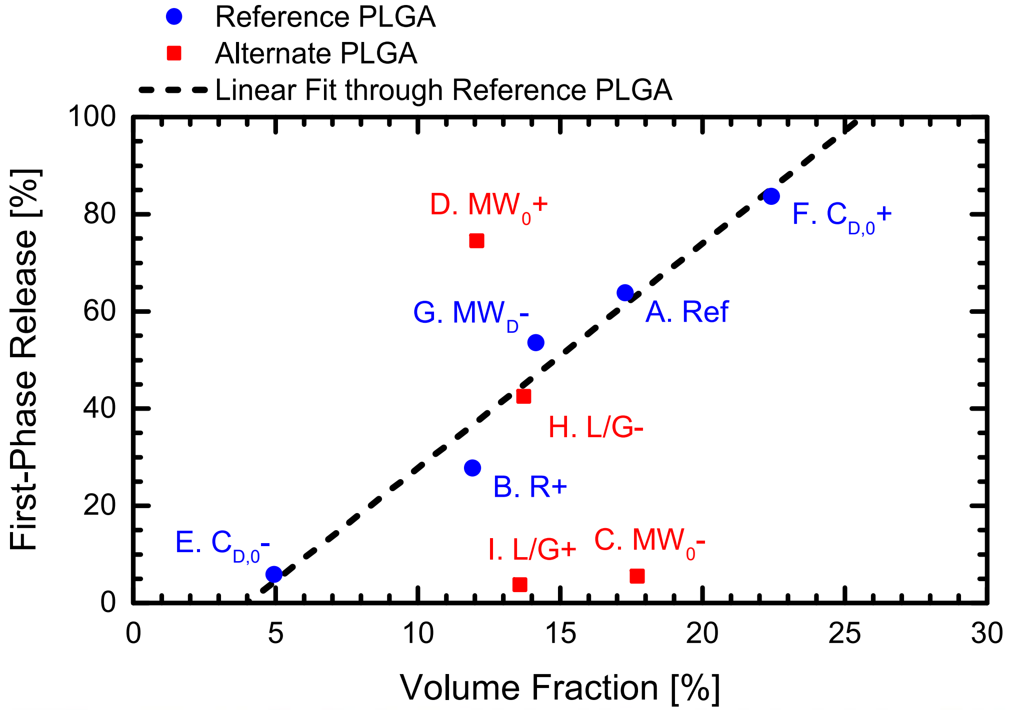
Hypothesis to be investigated:

- Percolation of drug particles within the polymer rods (threshold ~ 0.2; spheres; jammed)
- Faster water penetration and pore formation

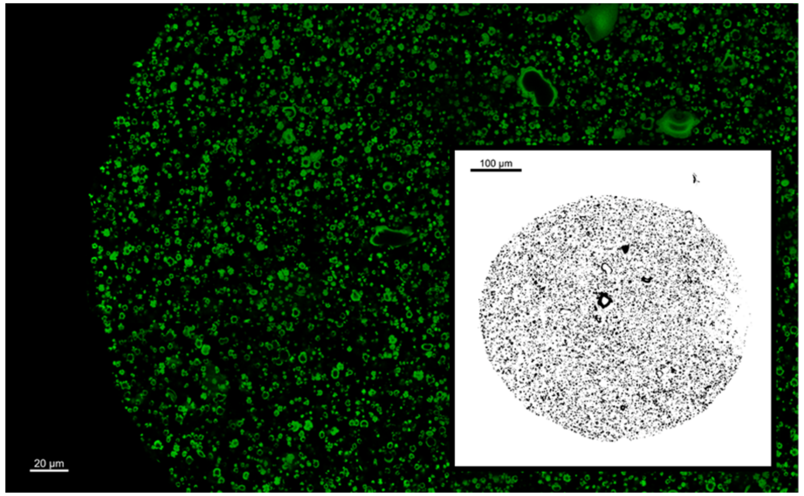
Supporting evidence:

- CFM images of FITC-dextran particles
- Apparent particle volume percent from binary transformation





CFM image of formulation A (Inset is binary transformation)



Koshari SHS. Dissertation. 2018
Rintoul MD, Torquato S. *J Phys A Math Gen*. 1997;30(16):L585-L592.
Ziff RM, Torquato S. *J Phys A Math Theor*. 2017;50(8).

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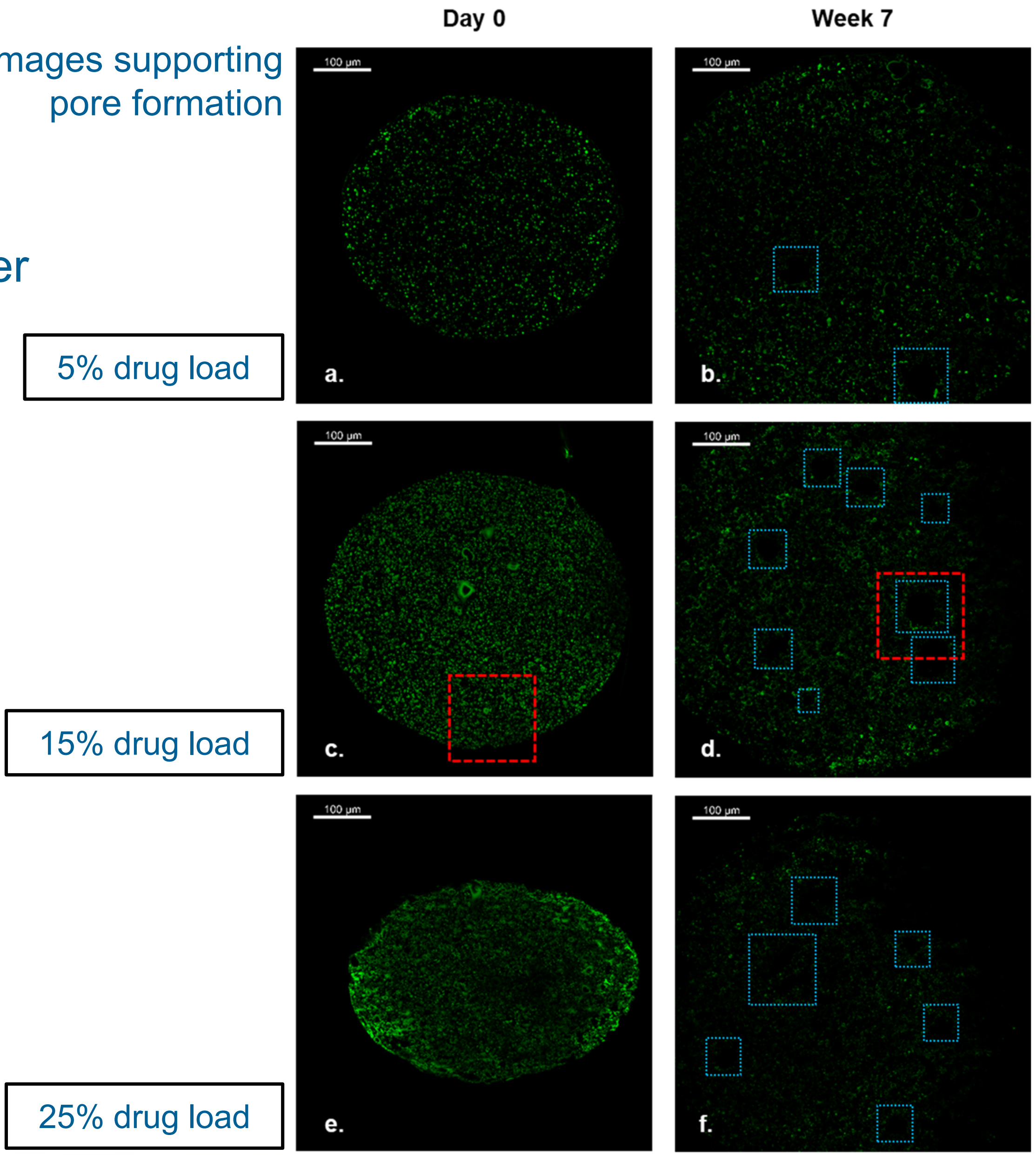
CFM images supporting pore formation



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Ziff RM, Torquato S. *J Phys A Math Theor*. 2017;50(8).

Limitations of CFM

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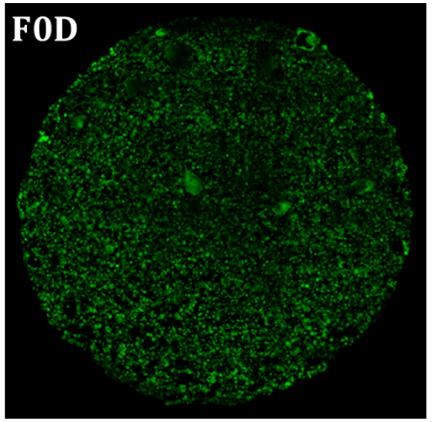
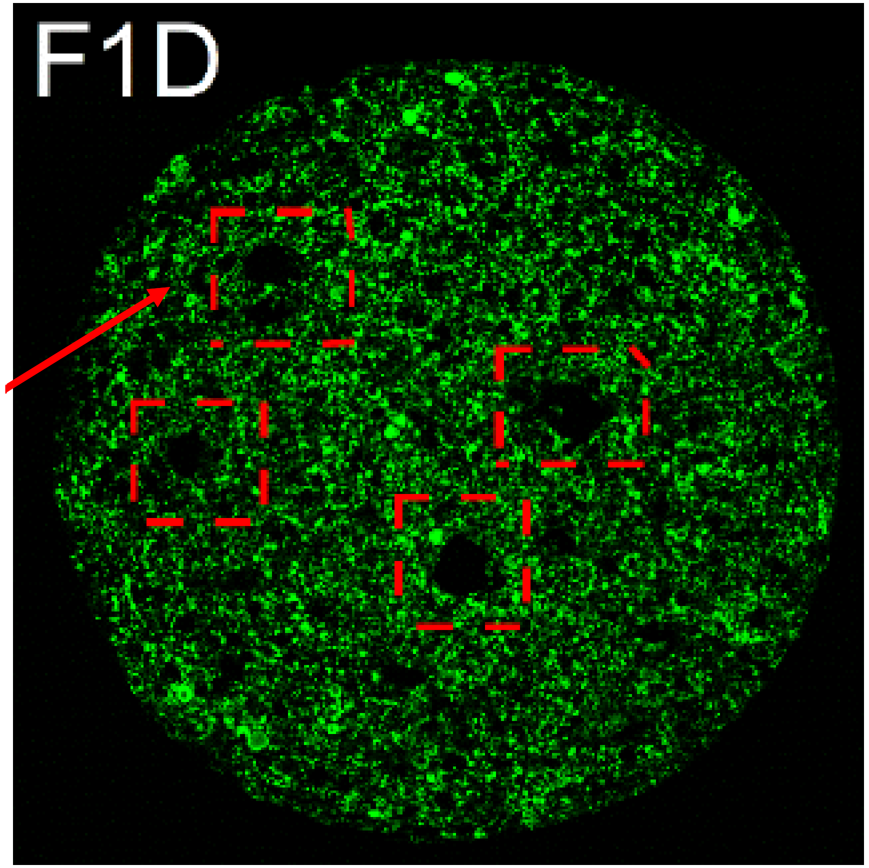


Microscopy - CFM results



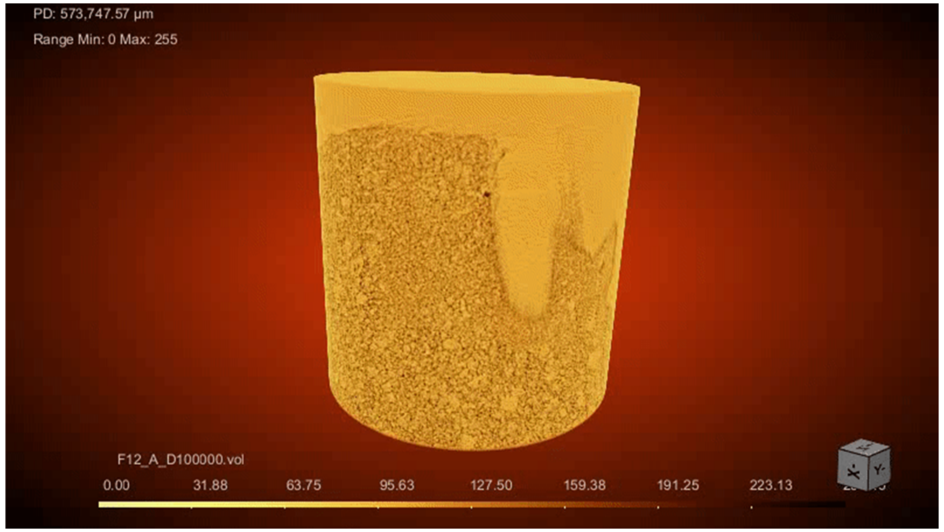
CFM disadvantages:

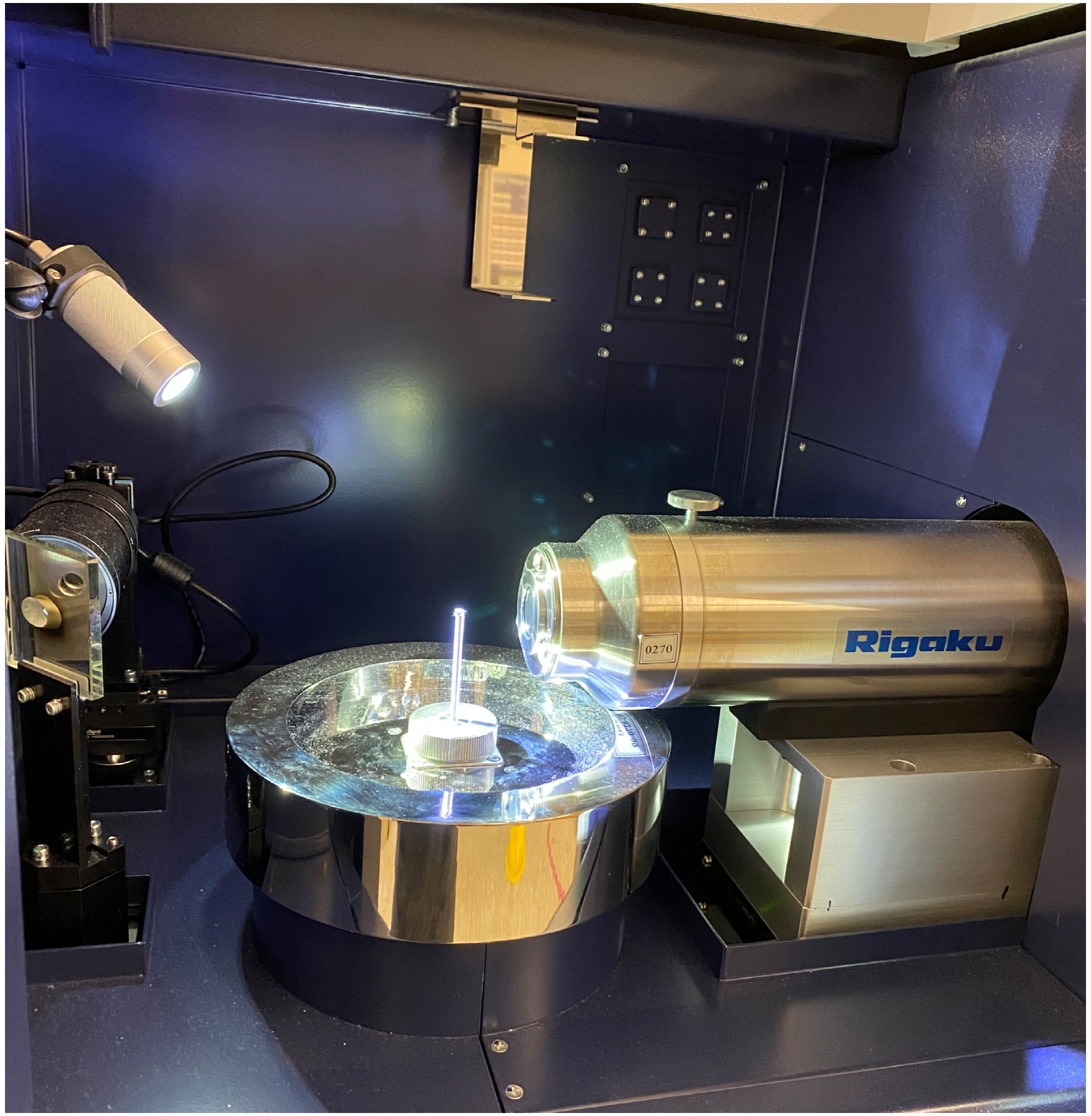
1. *Only recognize discrete FITC distr.*
2. *Very destructive*
   → *Evolution is unavailable*
3. *Restricted to 2D*
   → *Network analysis is limited*

X-ray CT Nano3Dx

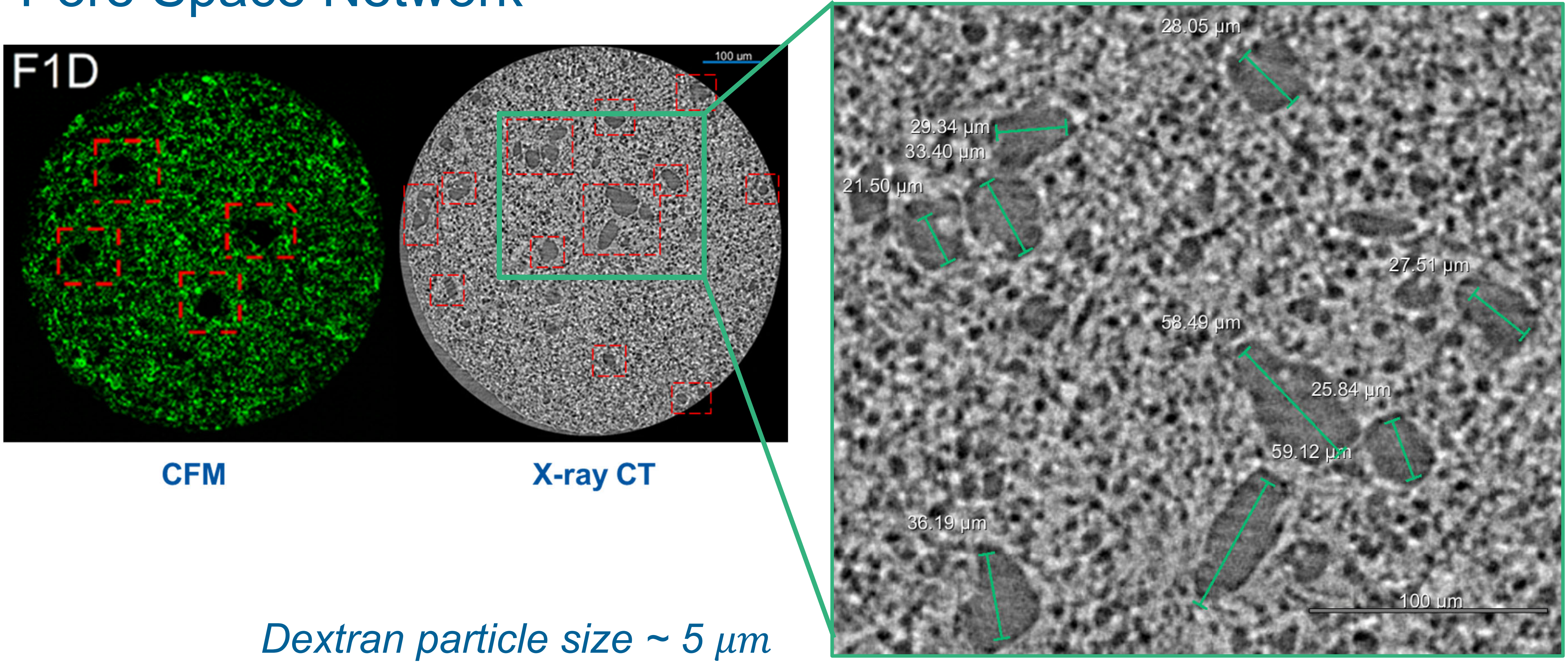
Advantages:

1. *Contrast based on density*
2. *Non-destructive loading*
3. *Optical resolution* $0.325\ \mu m/px$
4. *3D reconstruction*
5. *Image segmentation (Dragonfly)*



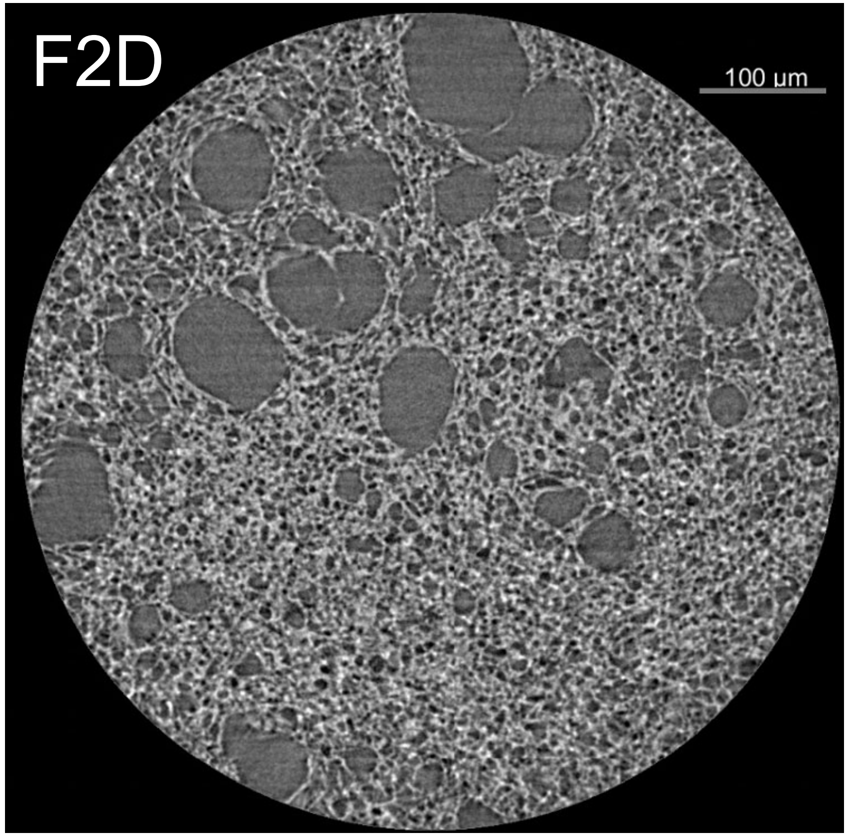


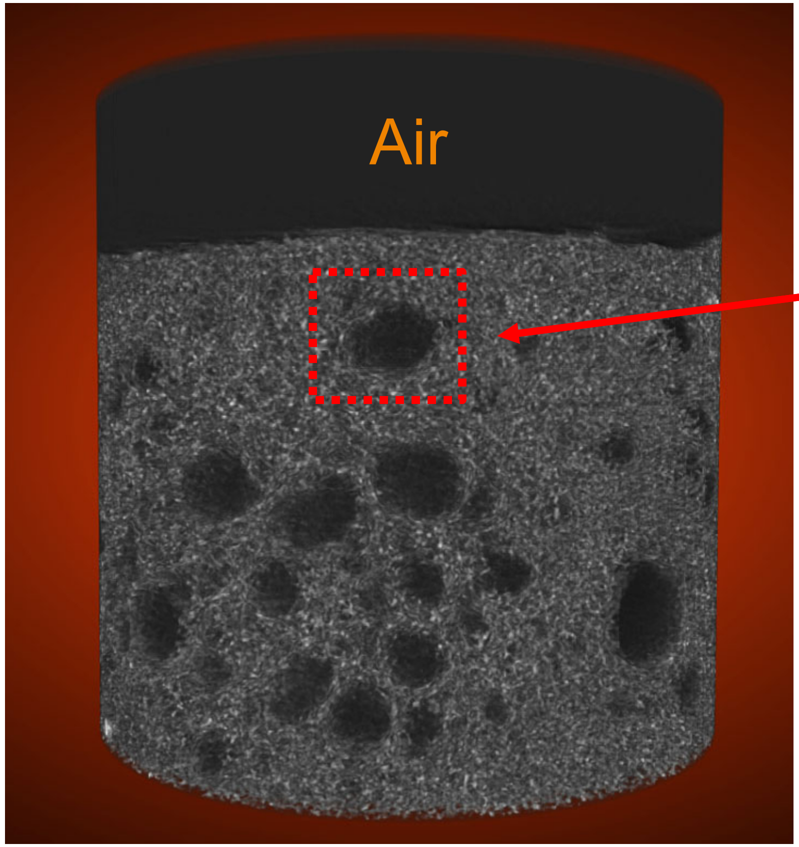
Pore Space Network



Dextran particle size ~ 5 μm

Pore Space Network

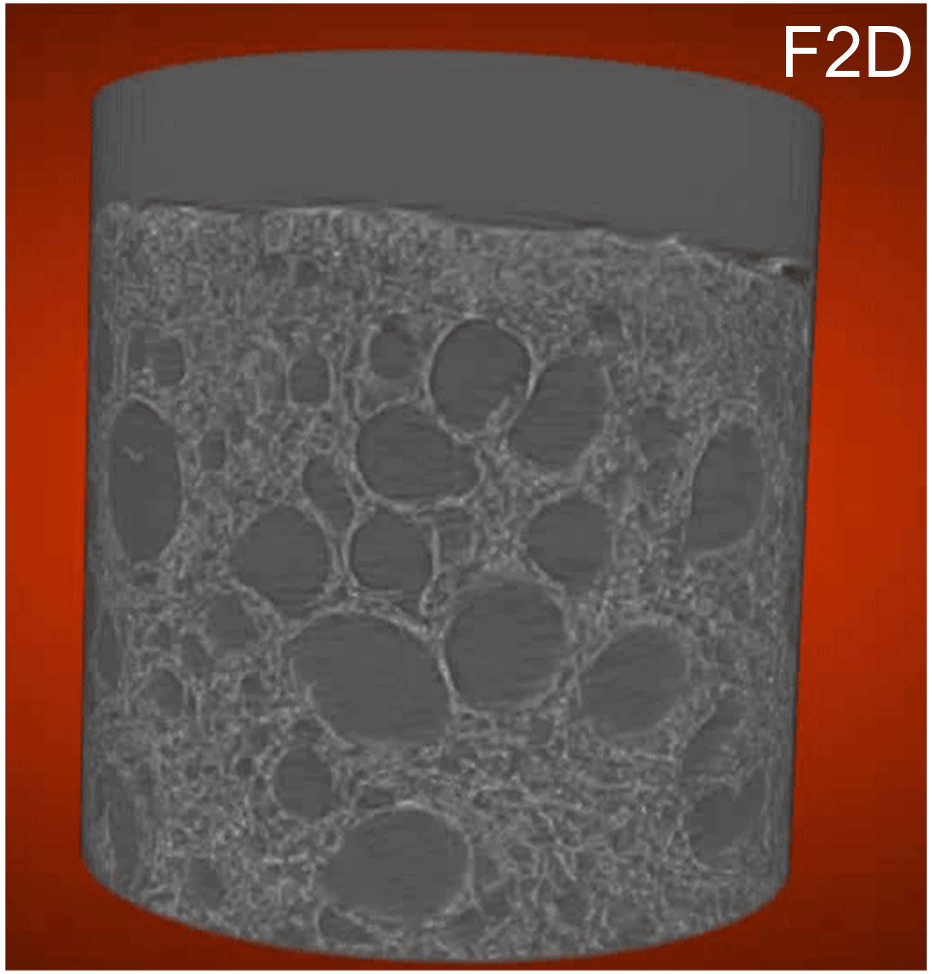




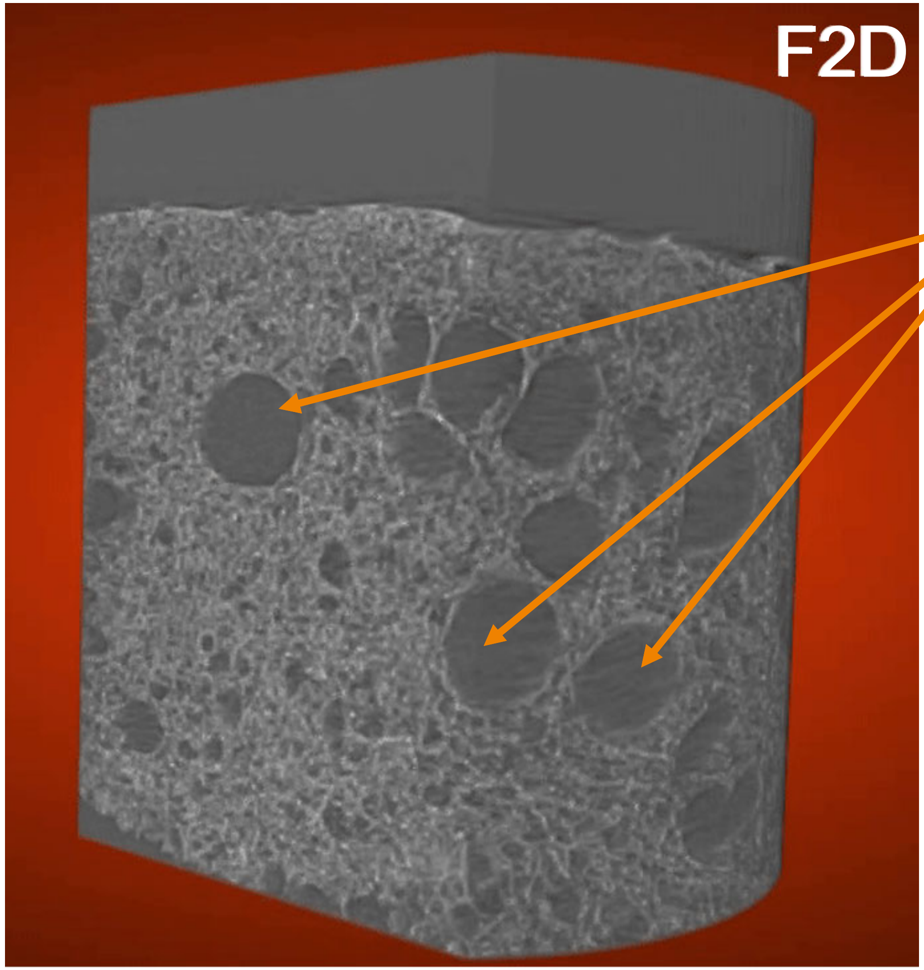
Cross-section

3D reconstruction

Pore Space Characterization



Pore Space Characterization



Pore dynamics:

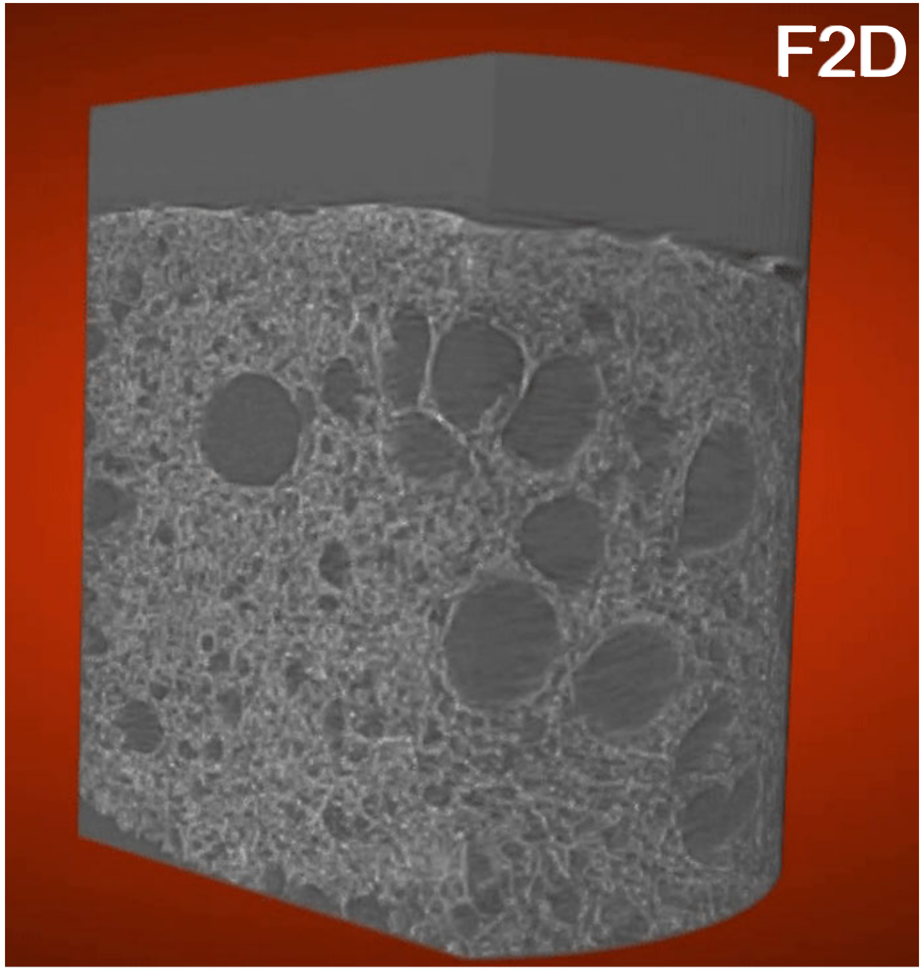
Spherical

Growing

Merging

Population Balance

Pore Space Characterization



Population balance (PBM)

$$\underbrace{\frac{\partial V n(v,t)}{\partial t}}_{\text{Accumulation}} = \underbrace{\dot{Q}_{in} n_{in}(v,t)}_{\text{Inlet}} - \underbrace{\dot{Q}_{out} n_{out}(v,t)}_{\text{Outlet}} - \underbrace{\frac{\partial V G n(v,t)}{\partial v}}_{\text{Growth}} + \overbrace{\underbrace{V\dot{b}}_{\text{Birth}} - \underbrace{V\dot{d}}_{\text{Death}}}^{\text{Coalescence}}$$

Coalescence

Assumption:

- No breakage
- Volume basis
- Time-independent growth kernel: $G = G_0 v^{\xi}$
- Nucleation: $\dot{b} = \dot{B}_{nuc}\delta(v - 0.27)$
- V does not change significantly (ROI boxing)
- Initial condition: $n(v,0) = 0$ *or* $n(v, D0)$
- Continuum Brownian collisional kernel:
  $\beta(\phi, \Phi) = \beta_0\left(\phi^{\alpha}\Phi^{\lambda-\alpha} + \phi^{\lambda-\alpha}\,\Phi^{\alpha}\right)$

Pore Space Characterization

Population balance – moment method

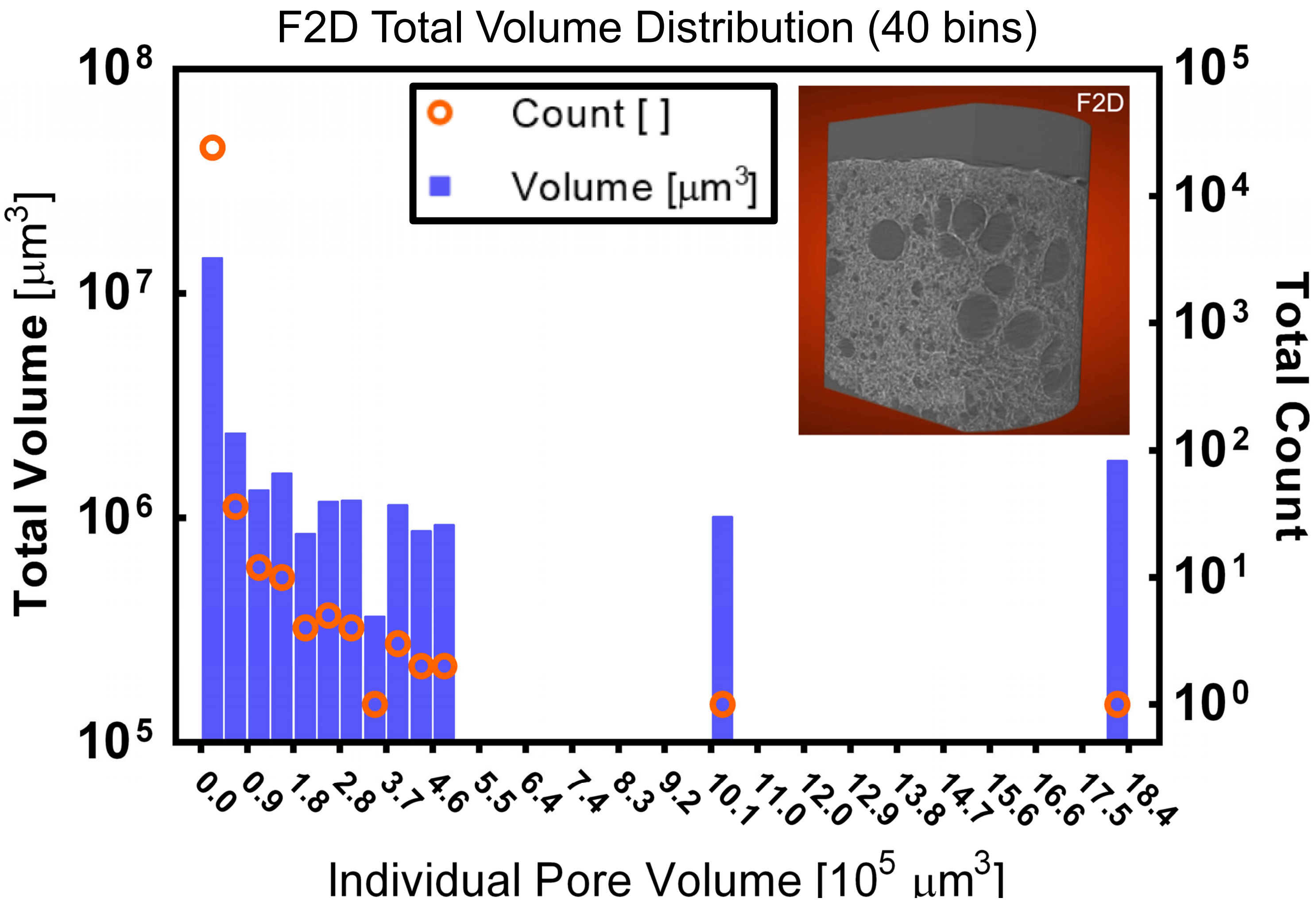
$$\frac{dv_j}{dt} = \dot{B}V_0^j + jG_0 v_{j-1/3} + \beta_0 \left[\sum_{k=0}^{j} \binom{j}{k} \left(v_k v_{j-k} + v_{k+1/3} v_{j-k-1/3} \right) - v_{1/3+j} v_{-1/3} - v_{1/3} v_{j-1/3} - 2 v_0 v_j \right]$$

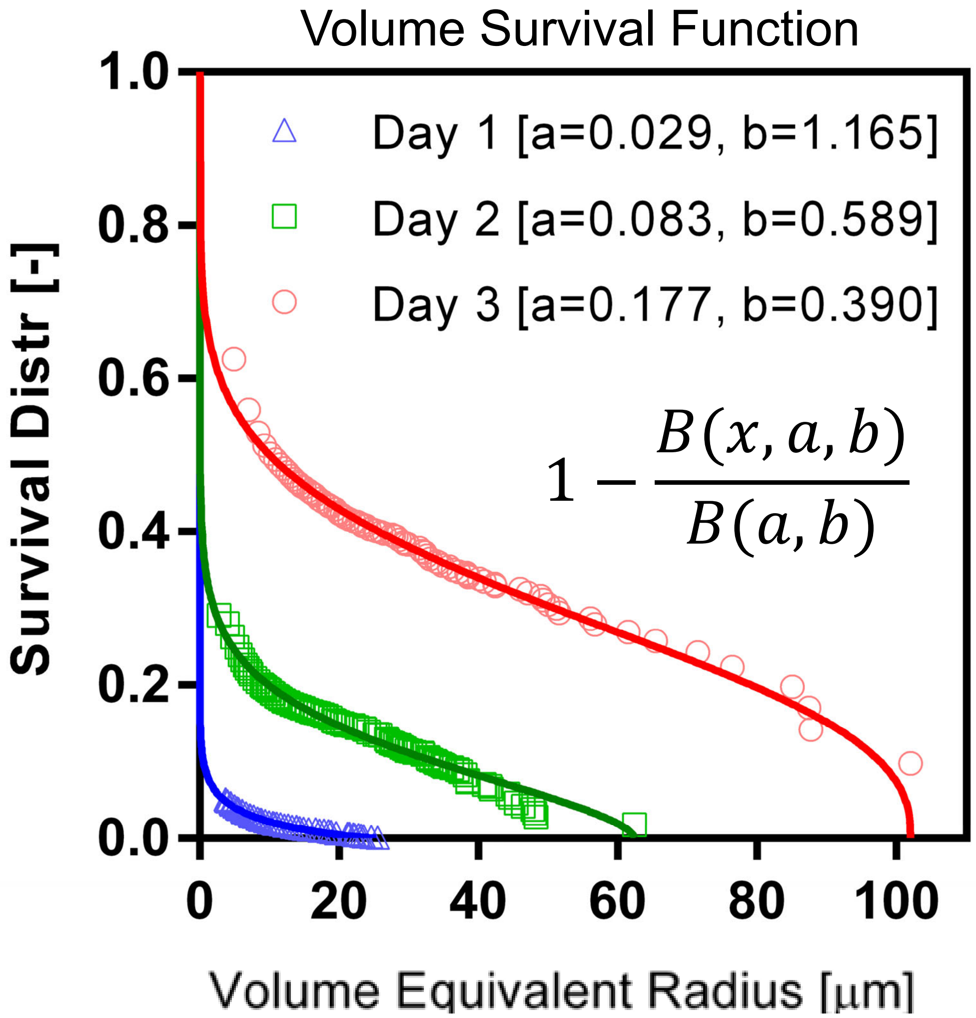
Special moments:

- Number balance: $$\frac{\partial v_0}{\partial t} = \dot{B} - \beta_0 \left[-v_0 v_0 - v_{1/3} v_{-1/3} \right]$$
- Mass balance: $$\frac{\partial v_1}{\partial t} = \dot{B}V_0 + G_0 v_{2/3}$$
- Variance balance: $$\frac{\partial v_2}{\partial t} = \dot{B}V_0^2 + 2G_0 v_{5/3} + 2\beta_0 \left[v_1 v_1 + v_{4/3} v_{2/3} \right]$$

Non-integer moment closure by distribution/MOMIC

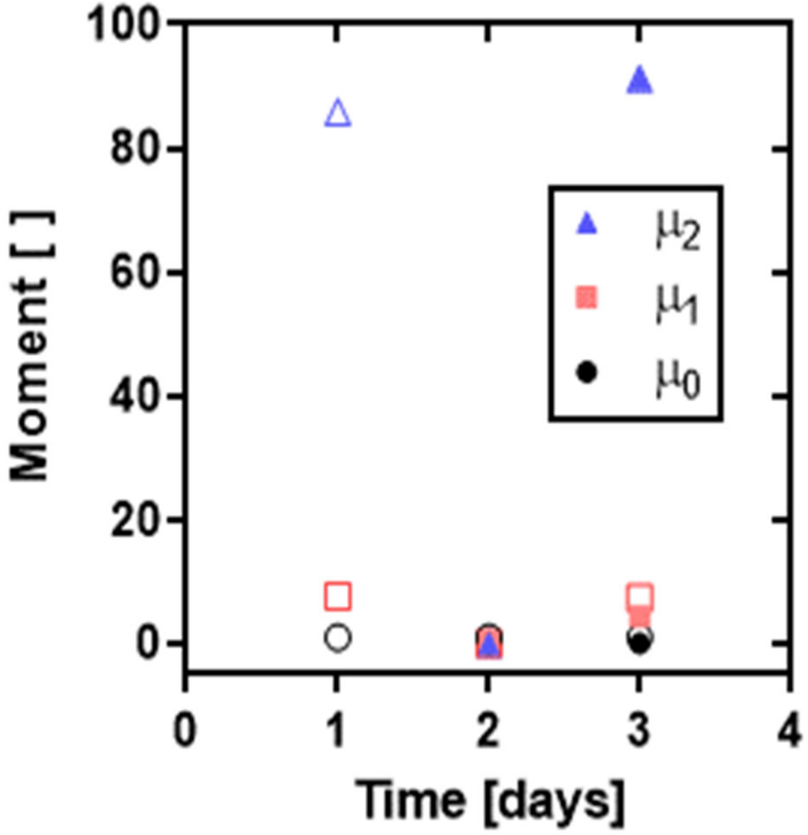
Pore Space Characterization





Pore Space Characterization

PBM Moment Fit



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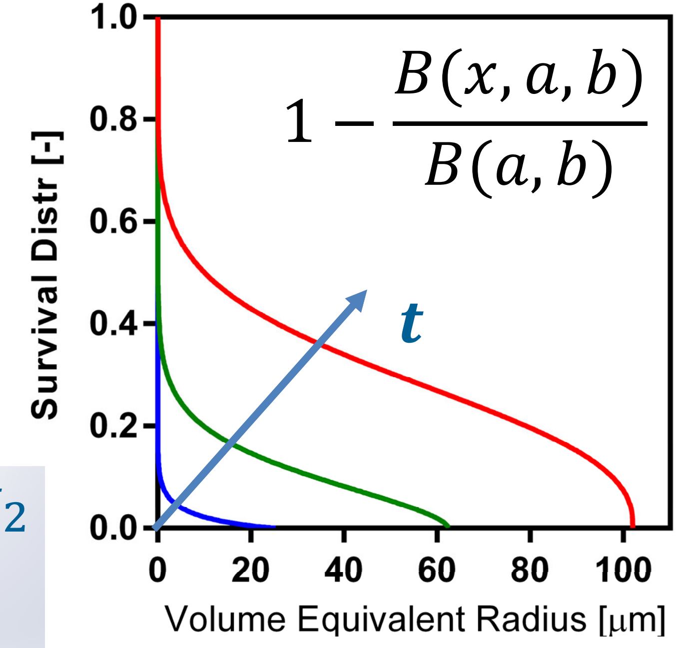
Pore Space Characterization

Pore domain utility:

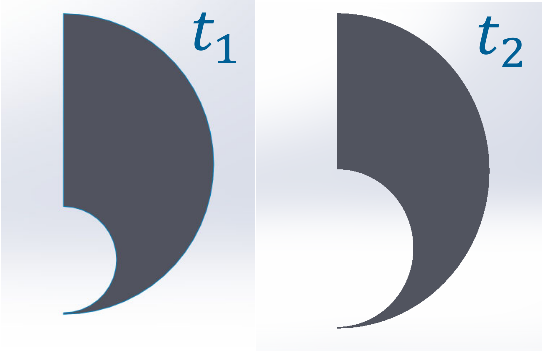
1. Refit beta distribution using PBM-predicted moments
2. Reconstruct porous domains in evolution
3. Implement Little/Antheunis model with moving pore mesh

$$\begin{bmatrix}\mu_1\\ \mu_2\\ \mu_3\end{bmatrix}$$

1



2



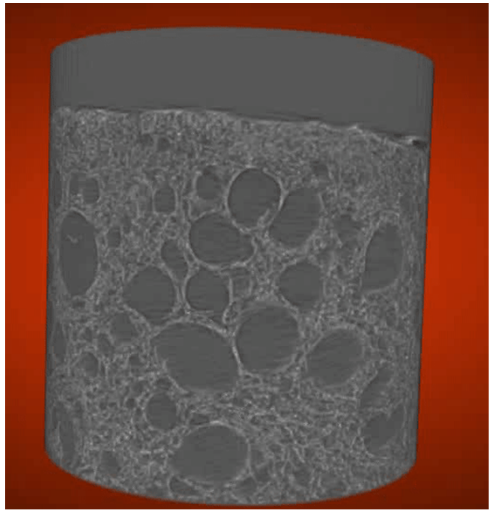
3

2D Transport/kinetics model*

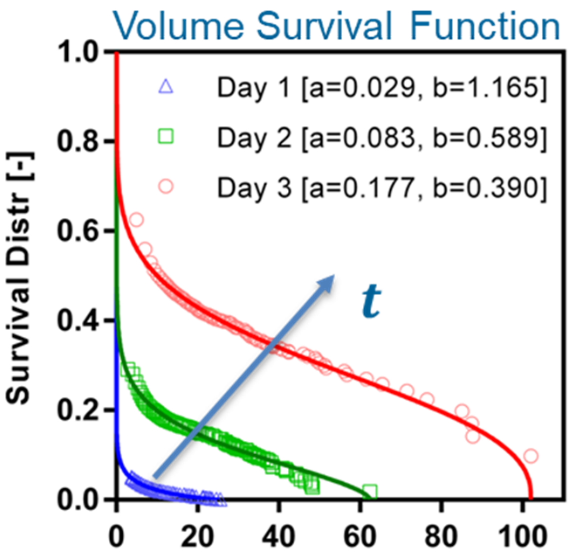
- Drug: $\xi_0 \frac{\partial}{\partial\tau} y_1 - \frac{\partial}{\partial\eta_1}\left[\xi \frac{\partial}{\partial\eta_1} y_1\right] - \frac{\partial}{\partial\eta_2}\left[\xi \frac{\partial}{\partial\eta_2} y_1\right] = 0$
- Water: $\xi_0 \frac{\partial}{\partial\tau} y_2 - \frac{\partial}{\partial\eta_1}\left[\frac{\partial}{\partial\eta_1} y_2\right] - \frac{\partial}{\partial\eta_2}\left[\frac{\partial}{\partial\eta_2} y_2\right] + D_a y_2 y_3 = 0$
- MW: $\xi_0 \frac{\partial}{\partial\tau} y_3 + \varphi D_a y_2 y_3 = 0$
- $y_3 = \frac{\rho_R}{[E]_0}\left(\frac{1}{MW_O} - \frac{1}{MW}\right)$

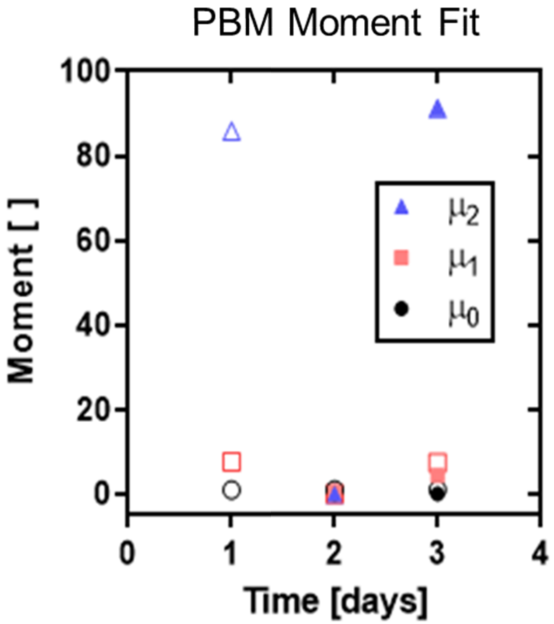
Conclusion & Recap.

F2D 3D Reconstr.



- Mechanistic model & First-phase release
- Hypothesis: Percolation in pores
- XRCT: confirm early-stage pore formation
- Evolution of pore space distribution
- Population balance model





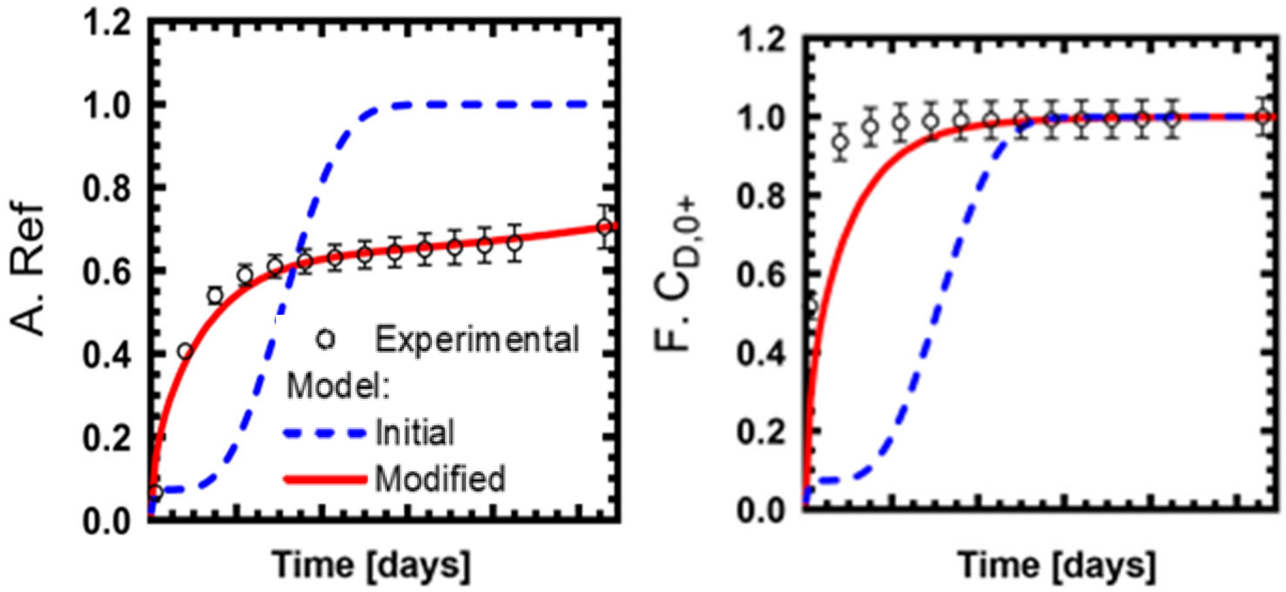
Acknowledgements

Genentech
Advanced Materials Characterization Lab
DELAWARE BIOTECHNOLOGY INSTITUTE®

University of Delaware

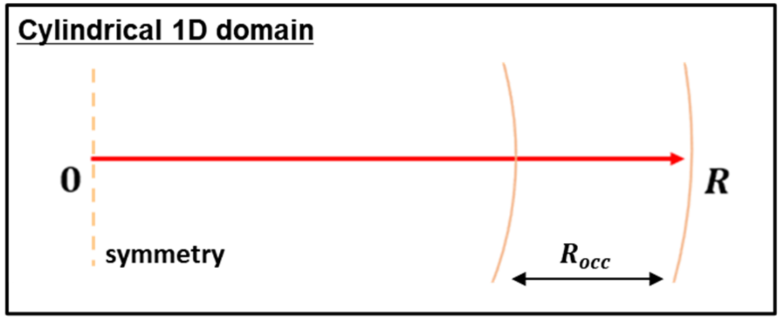
Modified model prediction

Design Parameter	Formula A			Formula F	
Polymer initial MW [kDa]	60			60	
Drug loading [wt%]	15			**25**	
L:G ratio	75:25			75:25	
End-group	S			S	



With fitted occlusion radius:

- Close fit in MW profiles
- Capturing first-phase release
- Occlusion radius spans differently based on extent of burst release

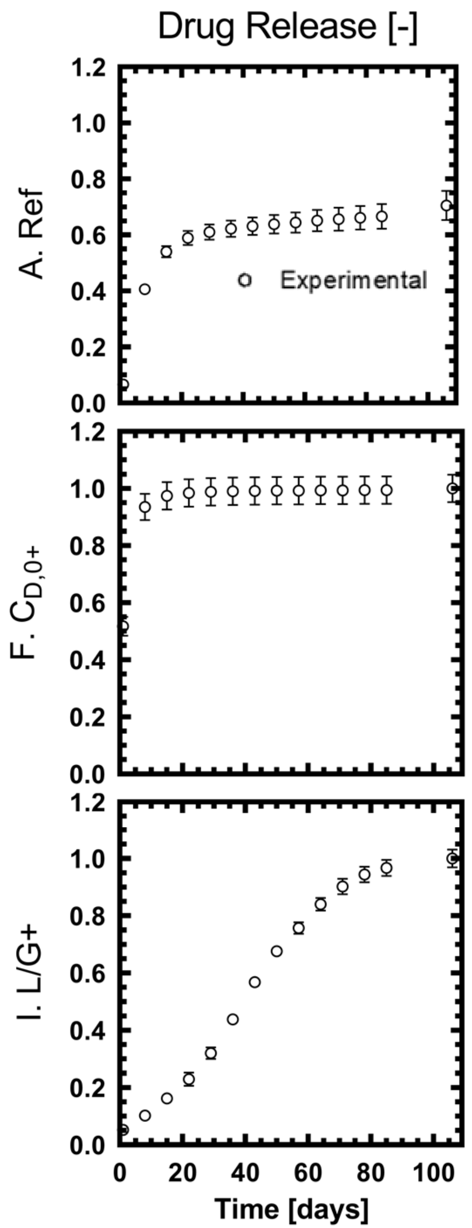


High drug load & High L:G

Experimental observations:

- Formulation A and F show significant first-phase release
- Reference does not reach complete release
- Higher L:G ratio (I) alone does not lead to slow degradation, indicating strong influence by the acid end-group.
- Water uptake occurs quickly and remains constant

Design Parameter	Formula A	Formula F	Formula I
Polymer initial MW [kDa]	60	60	60
Drug loading [wt%]	15	**25**	15
L:G ratio	75:25	75:25	**85:15**
End-group	S	S	**A**



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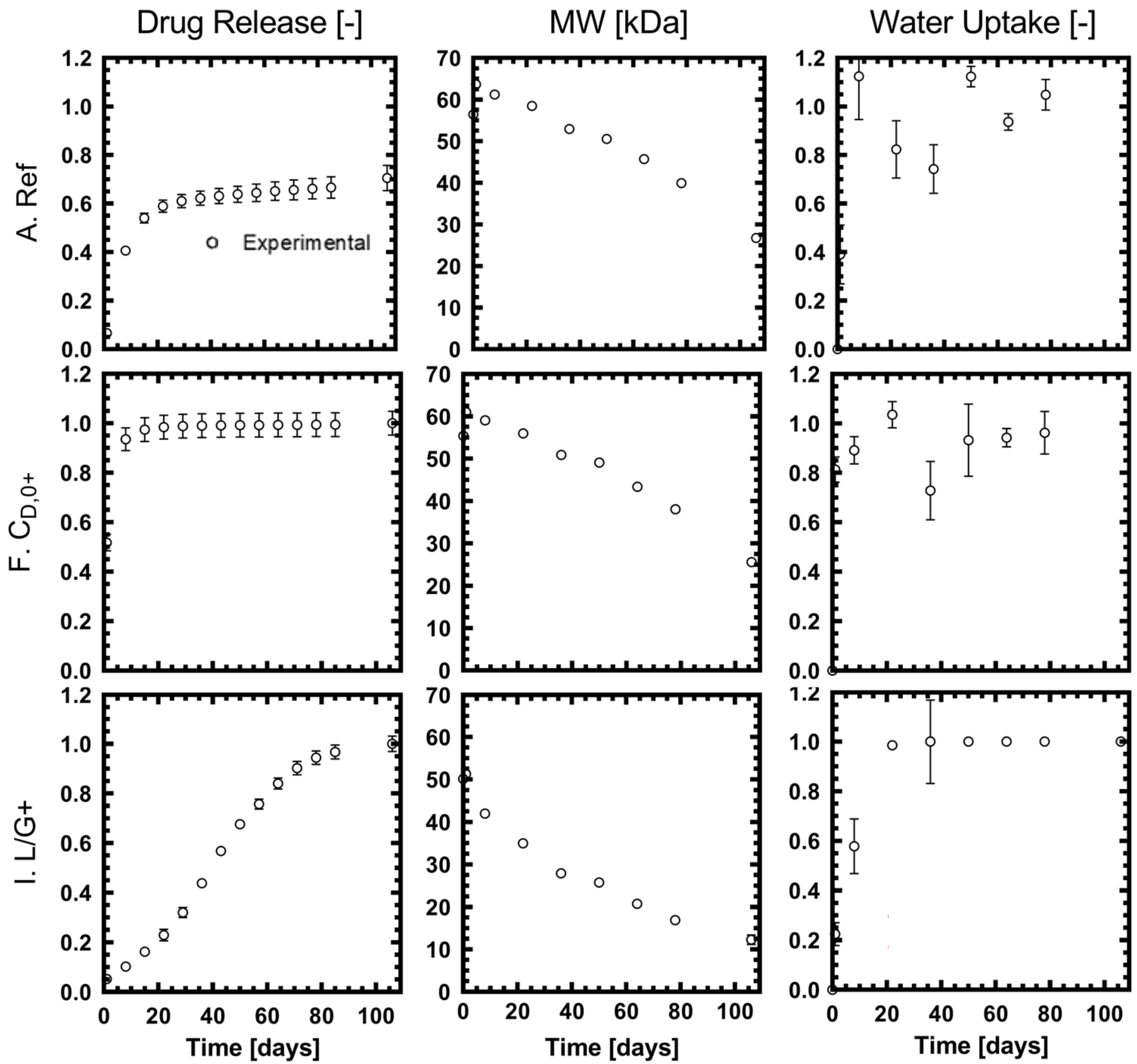


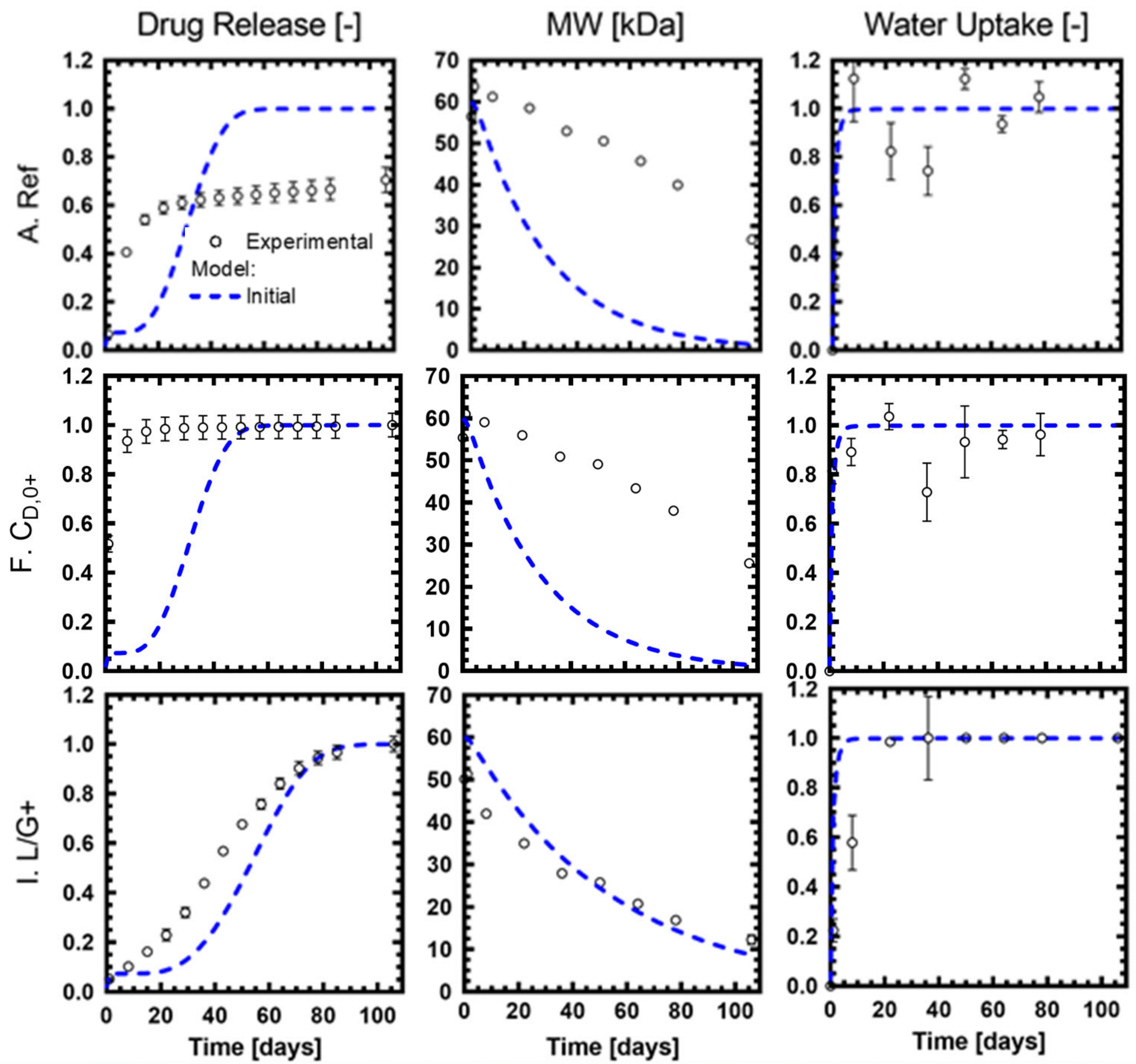
High drug load & High L:G

Design Parameter	Formula A
Polymer initial MW [kDa]	60
Drug loading [wt%]	15
L:G ratio	75:25
End-group	S

Formula F	Formula I
60	60
25	15
75:25	**85:15**
S	**A**

Model predictions (initial):

- Sigmoidal drug release profile
- Higher drug loading only affects the absolute amount of release (not the relative shape)
- Does not capture first-phase release
- Discrepancy in drug release from MW profiles



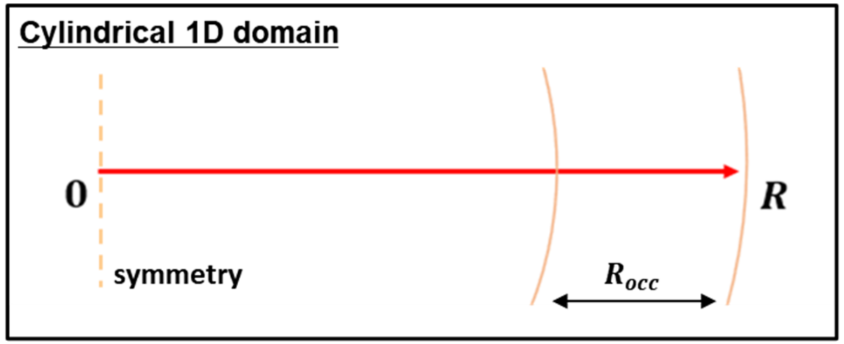
First-phase release

Supporting evidence:

- CFM images of FITC-dextran particles
- Apparent particle volume percent from binary transformation

- Pore formation motivates occlusion radius fitting

*Not drawn to scale

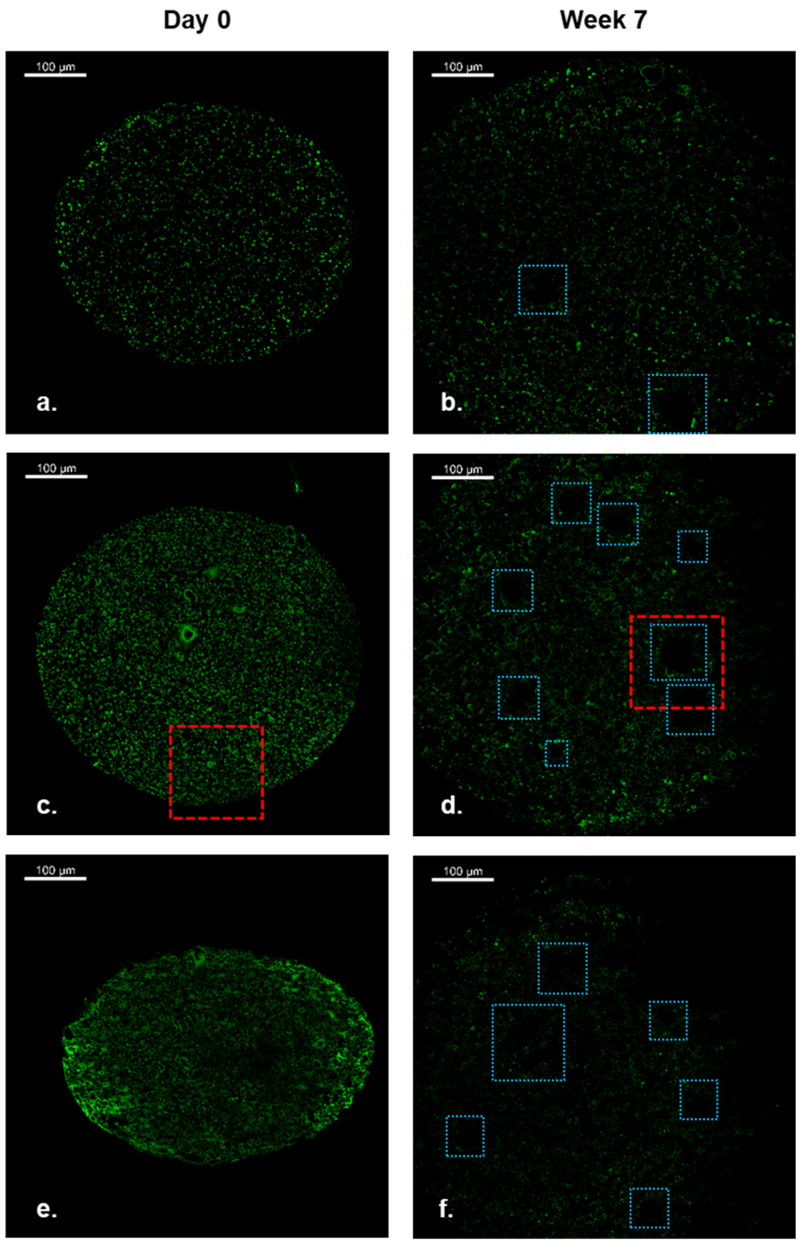


CFM images supporting pore formation

5% drug load

15% drug load

25% drug load



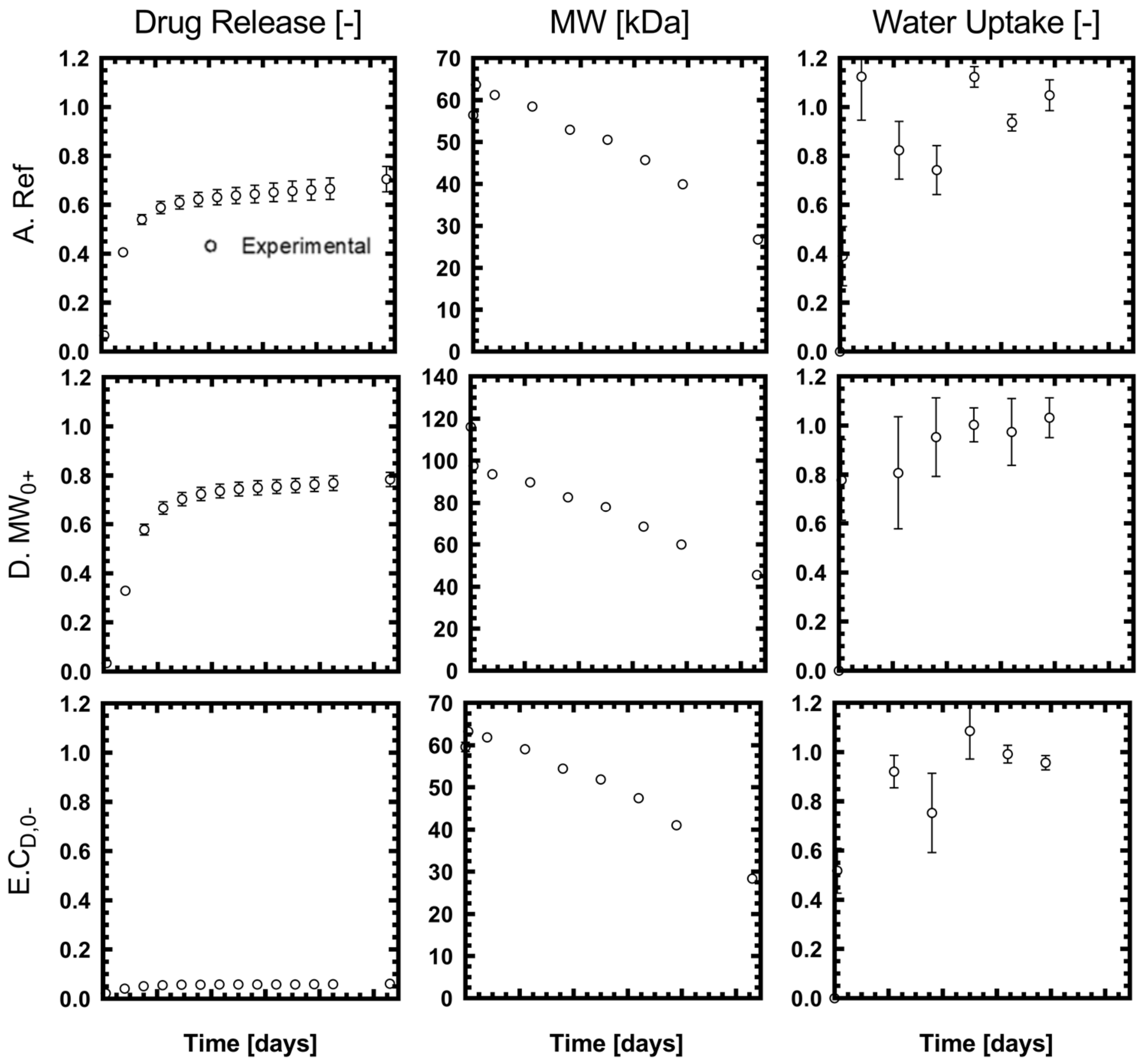
Koshari SHS. Dissertation. 2018
Rintoul MD, Torquato S. *J Phys A Math Gen*. 1997;30(16):L585-L592.
Ziff RM, Torquato S. *J Phys A Math Theor*. 2017;50(8).

Low drug load & High MW

Experimental observations:

- Formulations A and D show significant first-phase release
- All 3 formulations show incomplete release
- Similar rate of polymer degradation, indicating un-affected hydrolysis at higher polymer MW and lower drug loading

Design Parameter	Formula A	Formula D	Formula E
Polymer initial MW [kDa]	60	**110**	60
Drug loading [wt%]	15	15	**5**
L:G ratio	75:25	75:25	75:25
End-group	S	S	S



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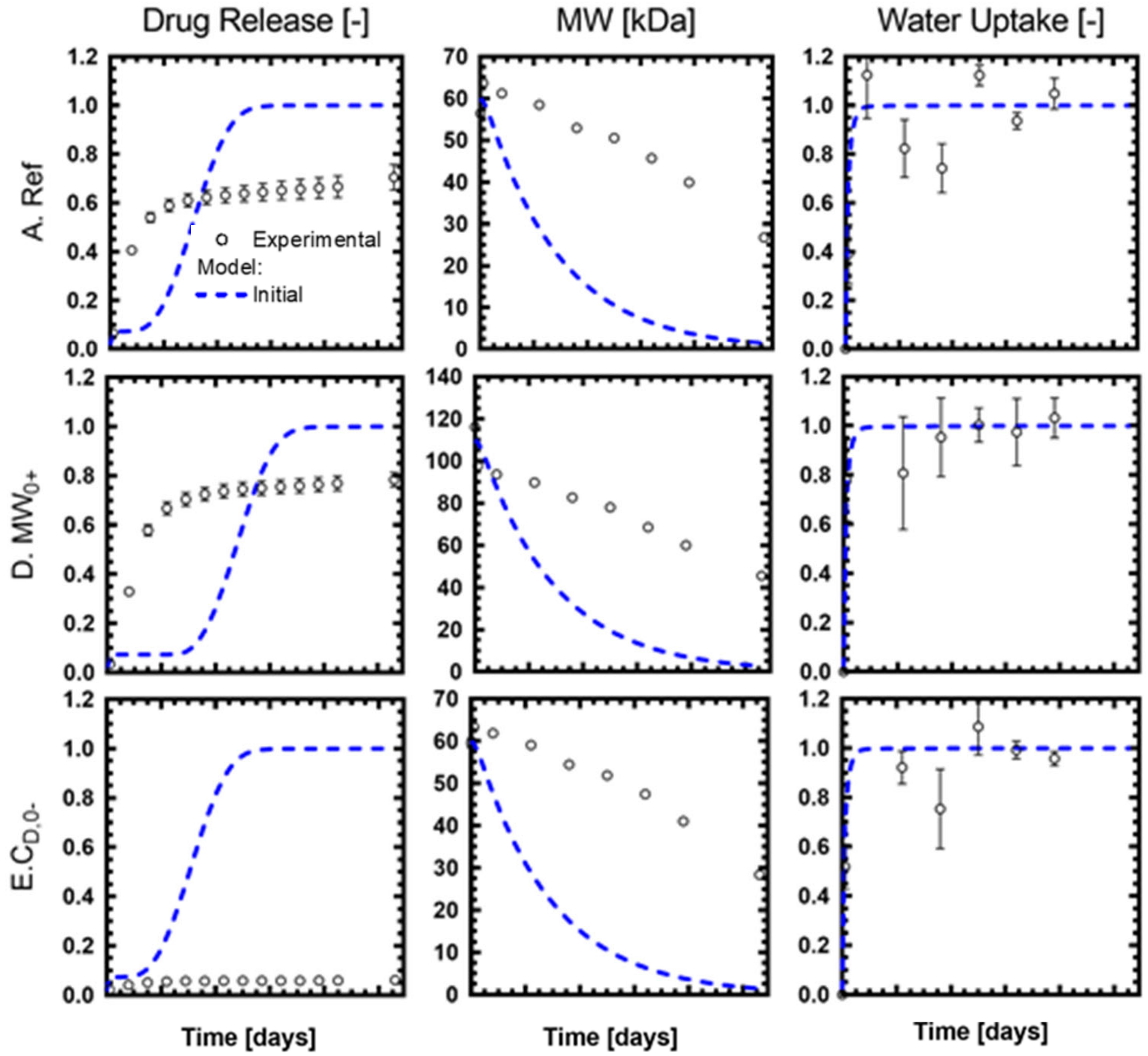
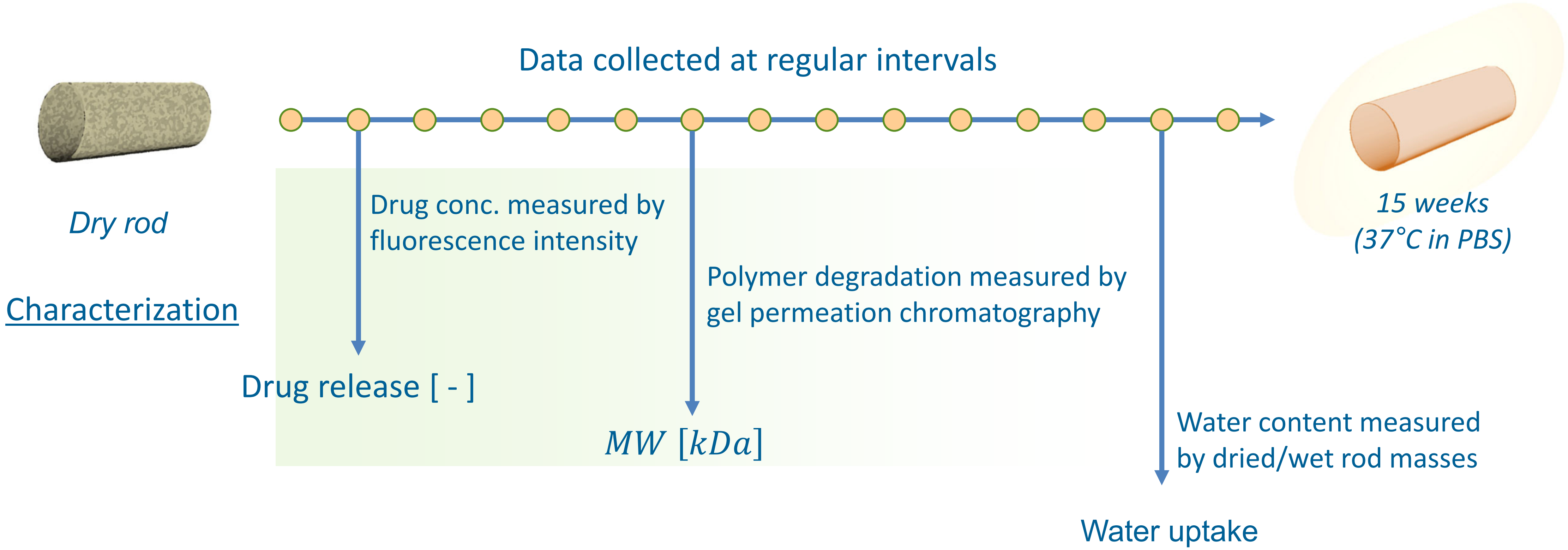
Model predictions (initial):

- Sigmoidal drug release profile
- Higher polymer molar mass/lower drug loading does not affect predicted rate of degradation
- Does not capture first-phase release
- Discrepancy in drug release from MW profiles



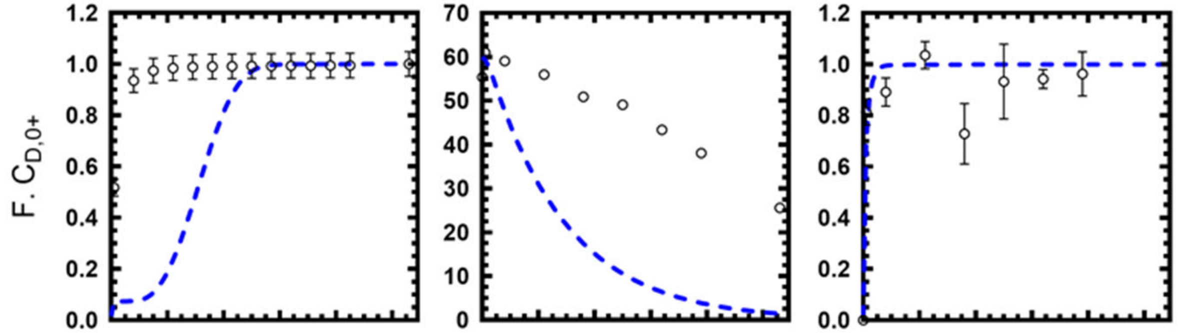
Methods – release characterization



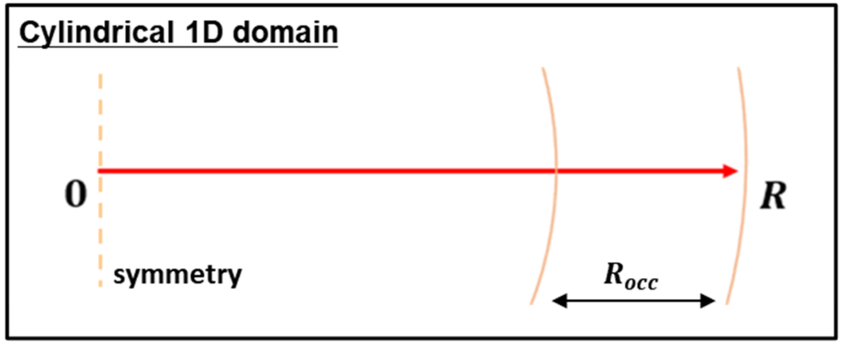
First-phase release

Preliminary explanations:

- Rapid erosion due to polymer $\sigma_{MW} >> MW_0$



- Occlusion radius (~ 2% of rod radius)



*Not drawn to scale

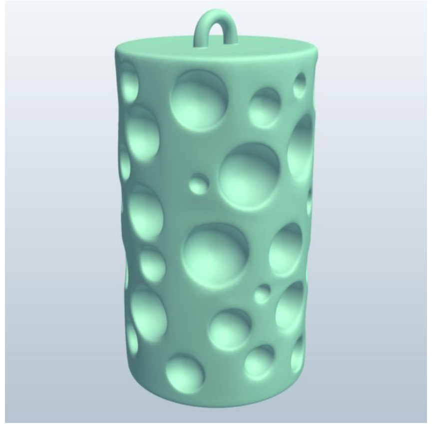
Limitations/Hypothesis

Features:

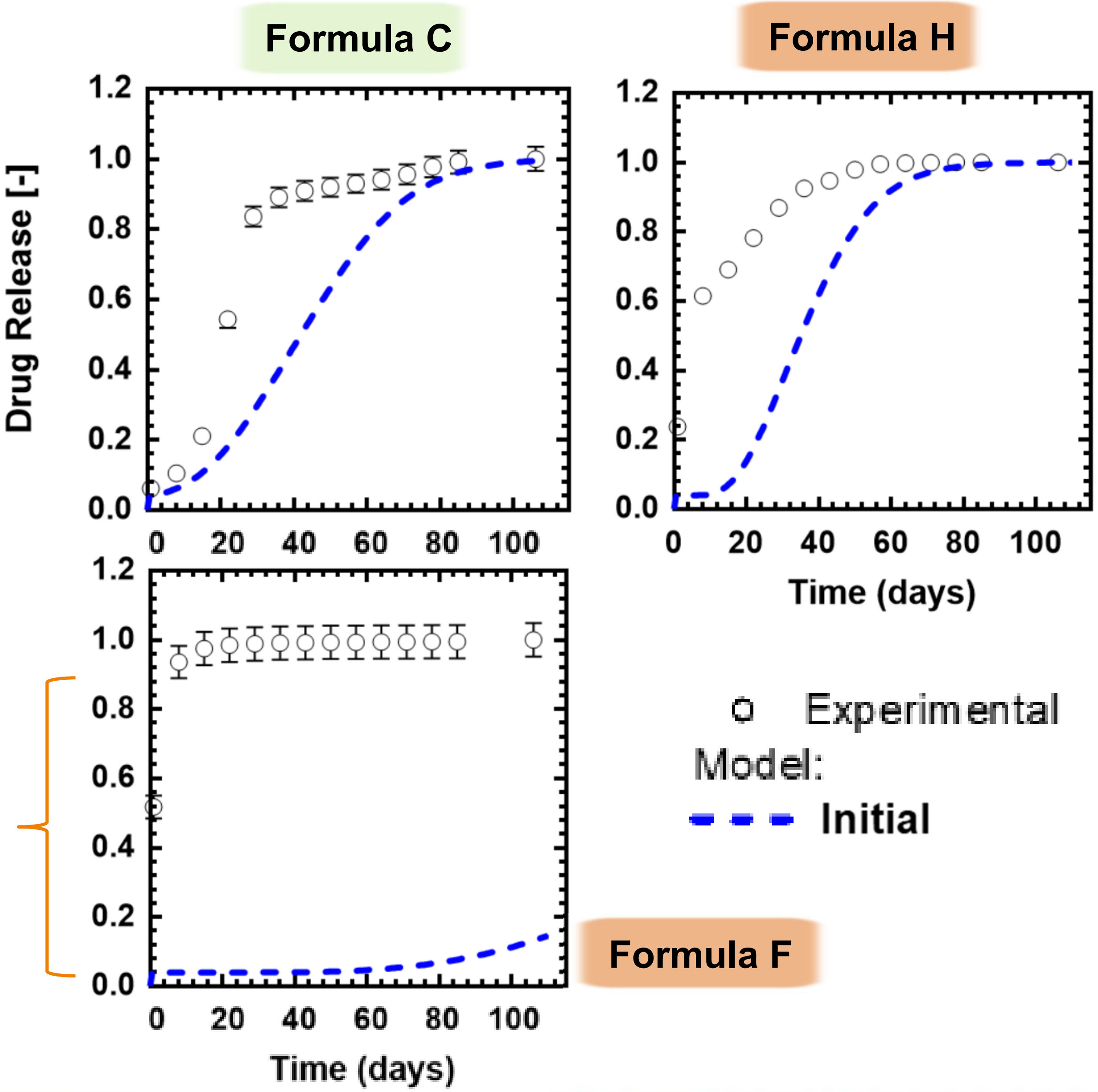
- Burst release
- Incomplete release
- End-phase degradation lag

Hypothesis

Early pore formation



Potential drug dumping



* Koshari S.H.S. (2018). Ph.D. Dissertation, University of Delaware, Newark, DE.

Limitations/Hypothesis

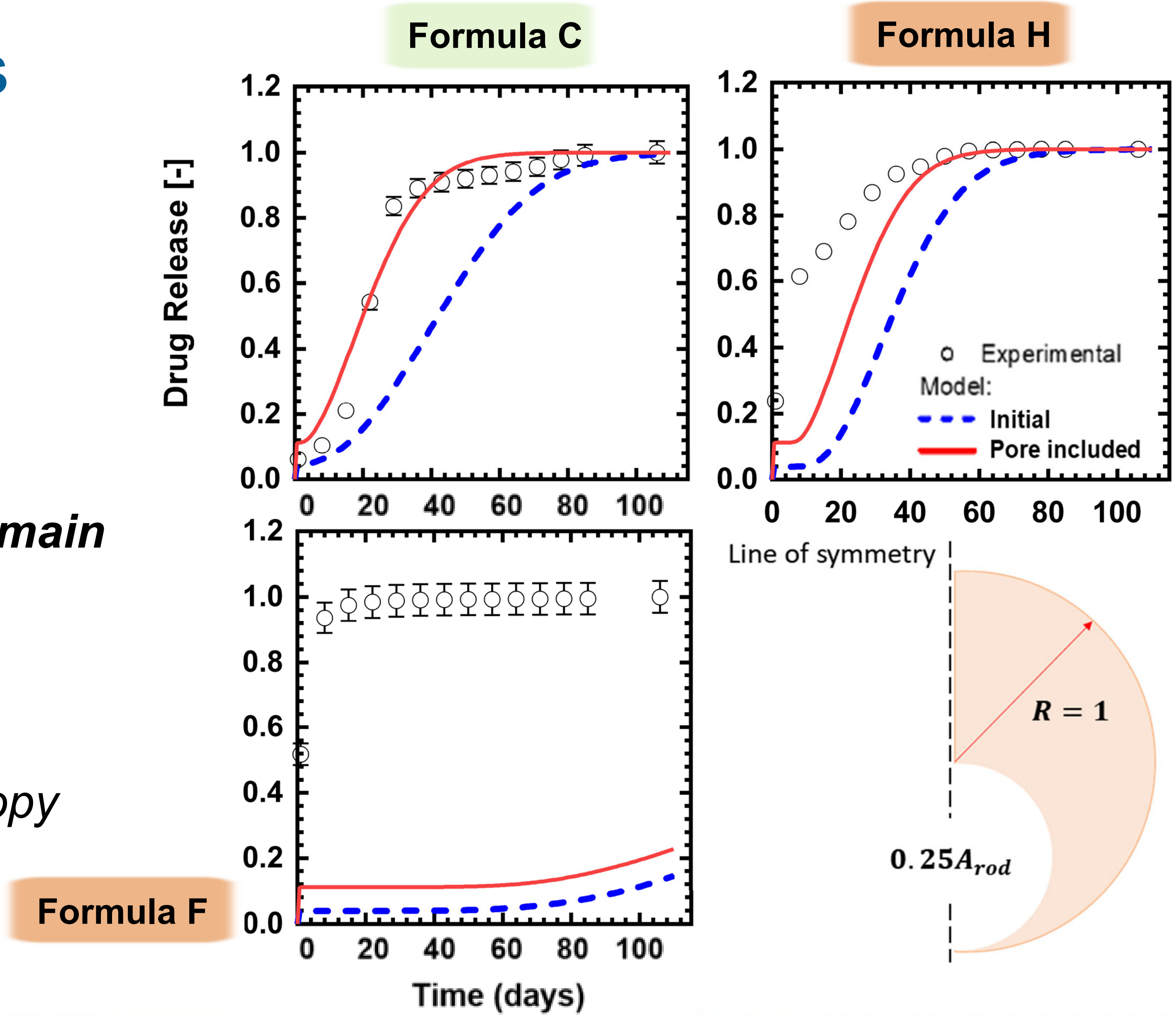
Hypothesis

Early pore formation

Preliminary Evidence

Pore domain

Microscopy



* Koshari S.H.S. (2018). Ph.D. Dissertation, University of Delaware, Newark, DE.