Systems Nanotechnology: Moving from Nano-science to Nano-products

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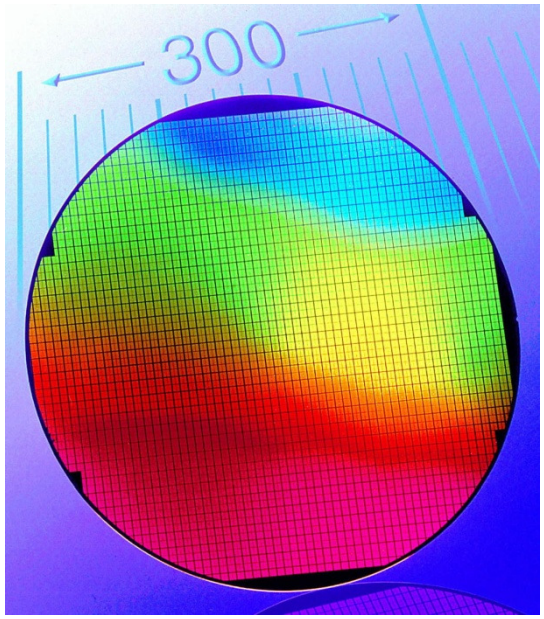
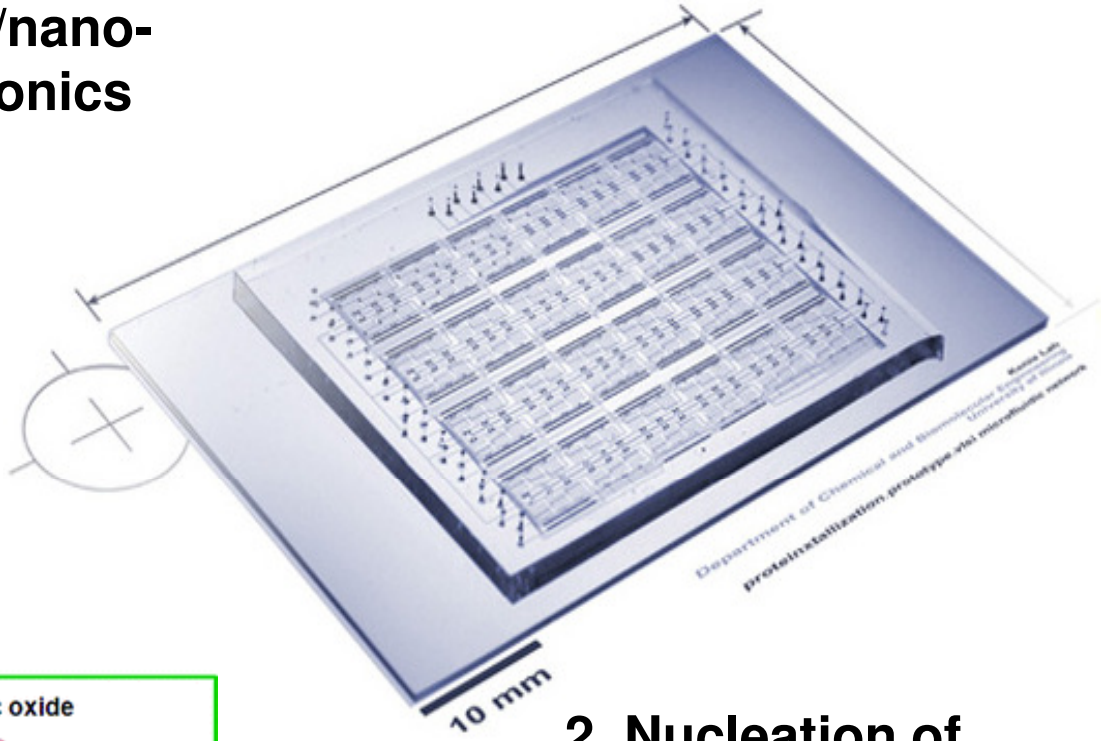
Outline

- Introduction
- Challenges and questions
- Some approaches
- Some more questions

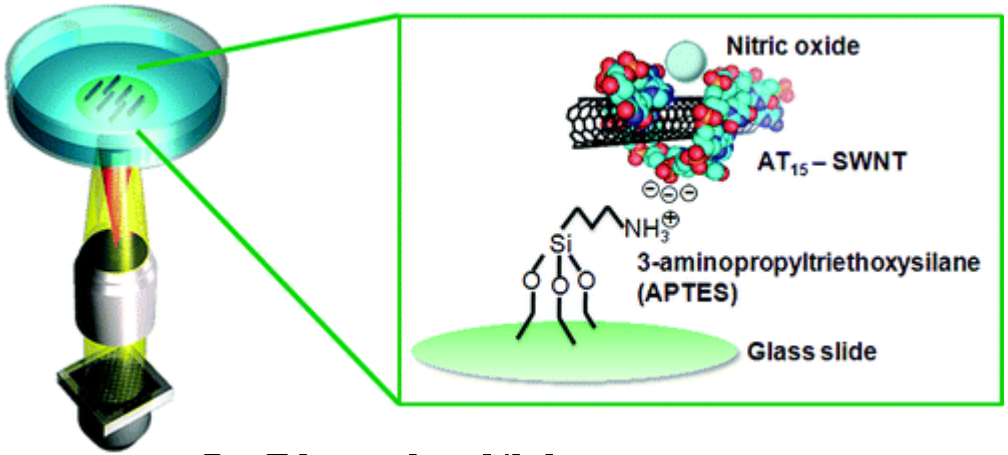
Control of events at the molecular scale has become critical to product quality in many applications



1. Micro/nano-electronics



2. Nucleation of proteins & drugs



3. Chemical/bio sensors

Images courtesy of Intel, Michael S. Strano, and Paul J. A. Kenis

Motivation for Systems Nanotechnology

- **An established field? An ISI search of "nano*" and "design or control" listed 100,000+ papers**
  - **Interpretation: The need for systems technology is high**
- **How many papers apply systematic tools?**
  - **Very few**
- **Motivates efforts to generate systems/control methods**
- **Let's explore some challenges/questions in systems nanotechnology & some approaches for addressing these challenges (with some example applications)**

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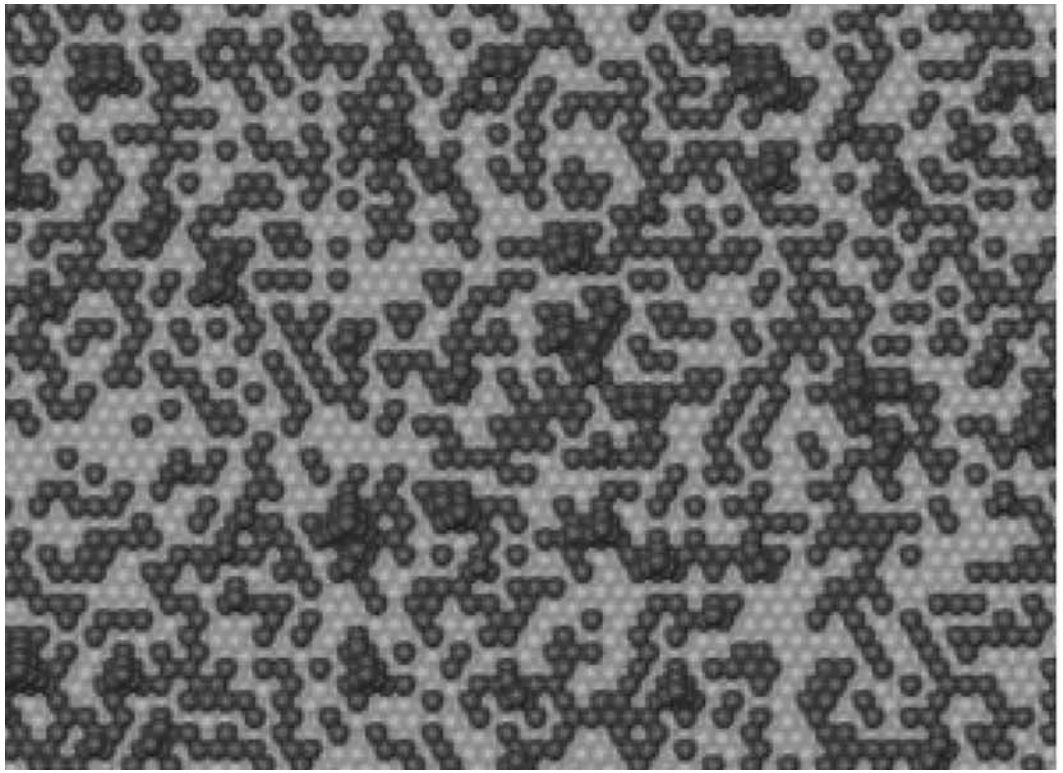
Typical Challenges, and Some Questions

1. **High state dimensionality and inherent stochasticity of molecular events**
   - Q: How do we formulate tractable approaches to address systems with these characteristics?
2. **Sparsity of on-line measurements available for process identification**
   - Q: How do we abstract the most information from the data, and redesign systems to obtain more data?
3. **Sparsity of manipulated variables available for process identification and control**
   - Q: How do we redesign systems to have more manipulated variables, and formulate tractable approaches to dealing with some of these new modes of manipulation?

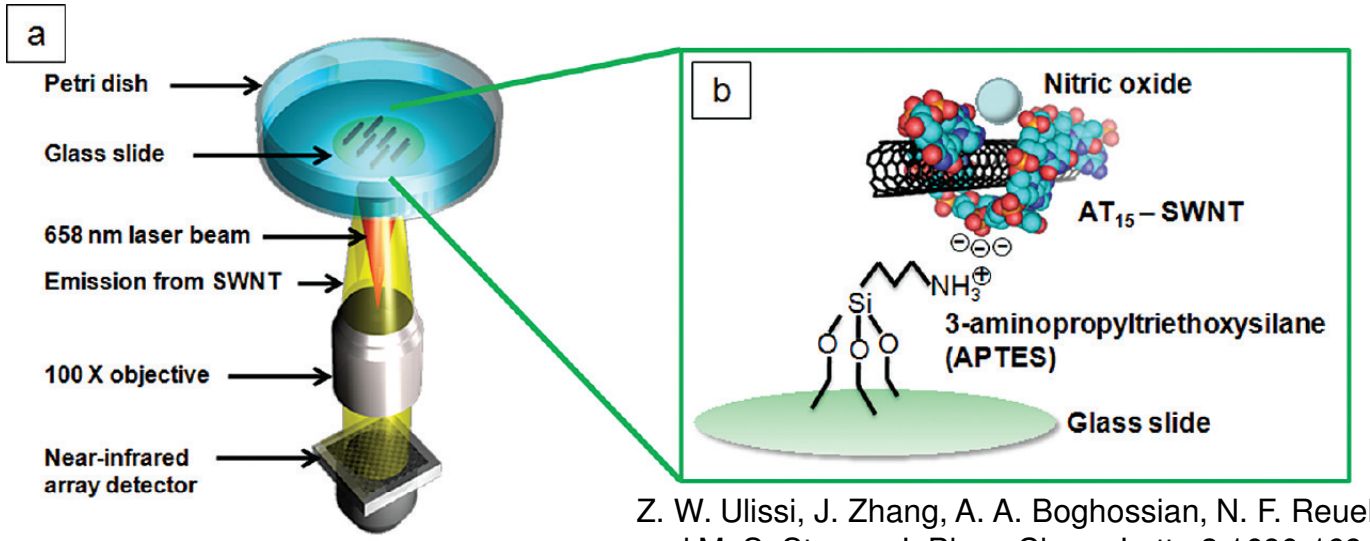
1. High state dimensionality and inherent stochasticity of molecular events

- **The dynamics of molecular events are often modeled by Chemical Master equations (up to 100s of seconds)**
- **In CME the *configuration* of the process is defined by the identity and positions of atoms or molecules on a lattice**
- **A lattice can be defined by spatial position (right) or non-spatially such as the # of molecules adsorbed on a carbon nanotube**



T. O. Drews, A. Radisic, J. Erlebacher, R. D. Braatz, P. C. Searson, and R. C. Alkire. J. Electrochem. Soc., 153:C434-C441, 2006

Example: Single-molecule carbon nanotube sensor arrays



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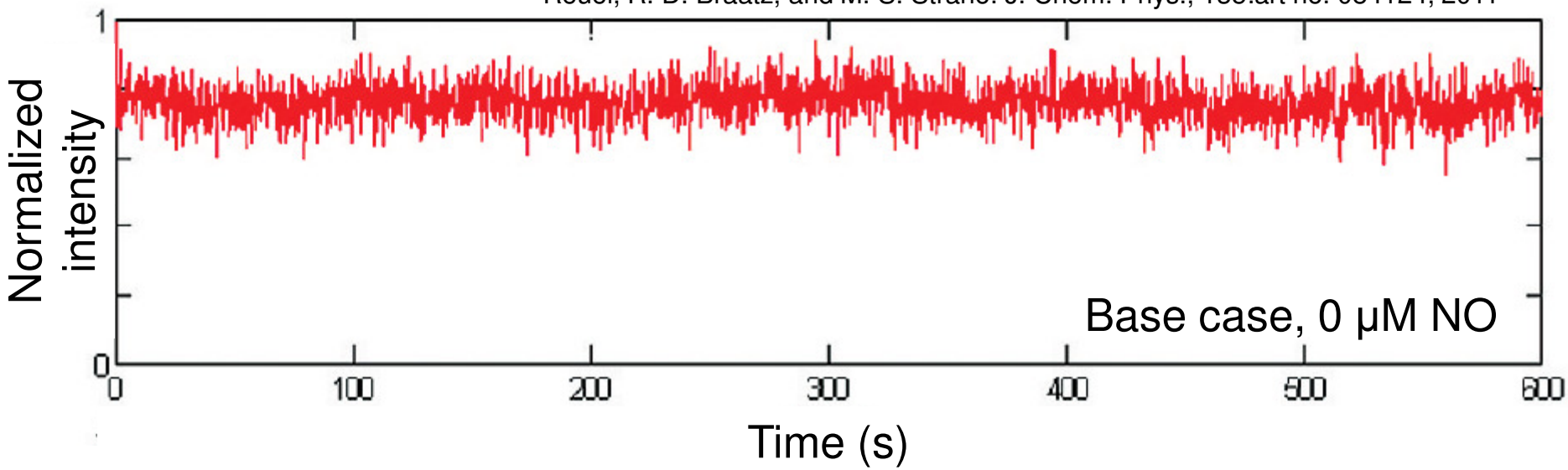

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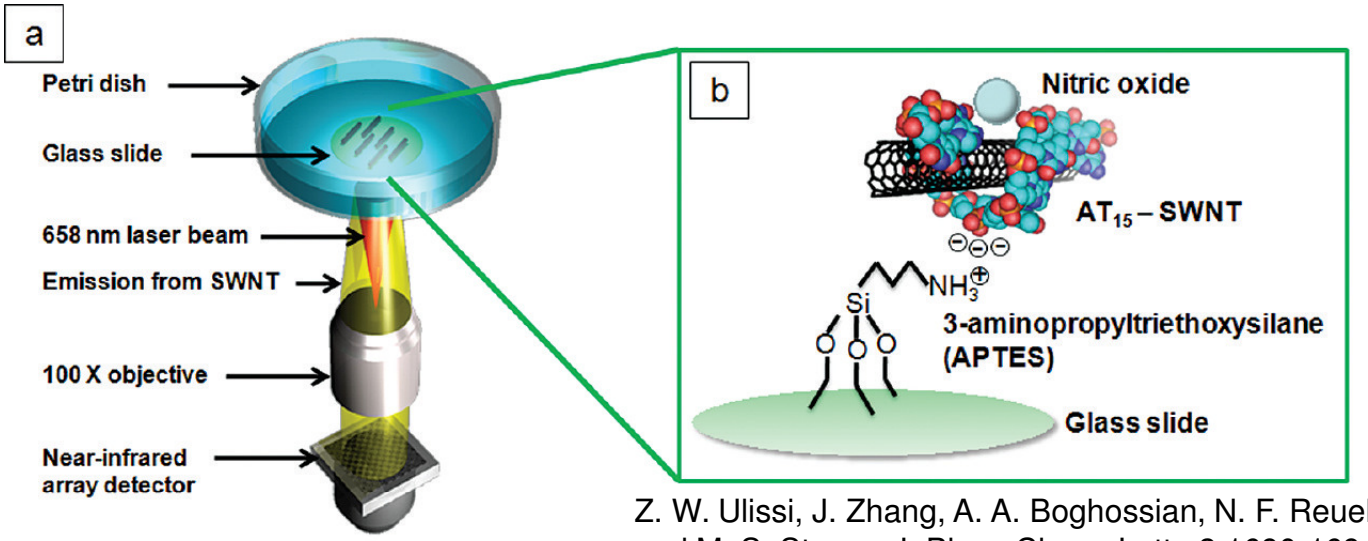

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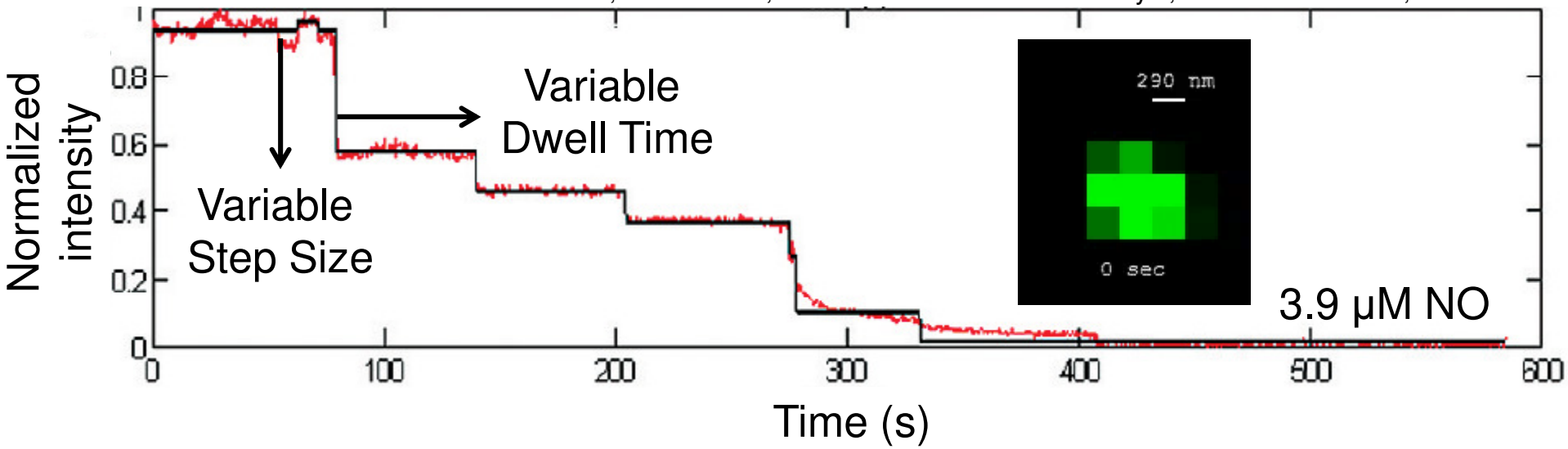
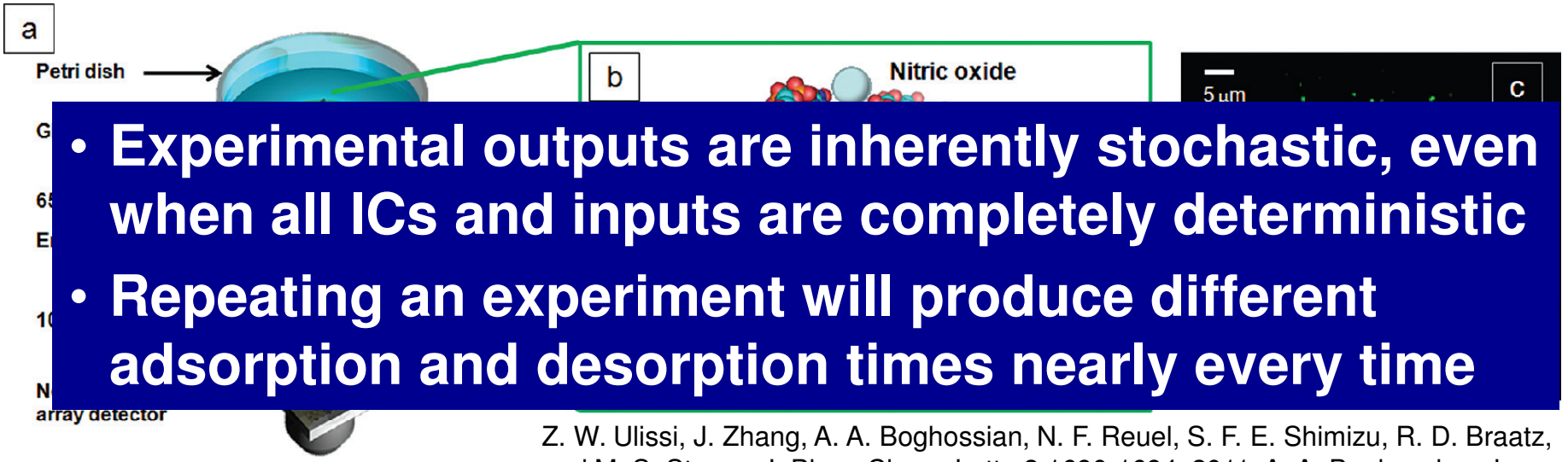


Example: Single-molecule carbon nanotube sensor arrays

- **Experimental outputs are inherently stochastic, even when all ICs and inputs are completely deterministic**
- **Repeating an experiment will produce different adsorption and desorption times nearly every time**



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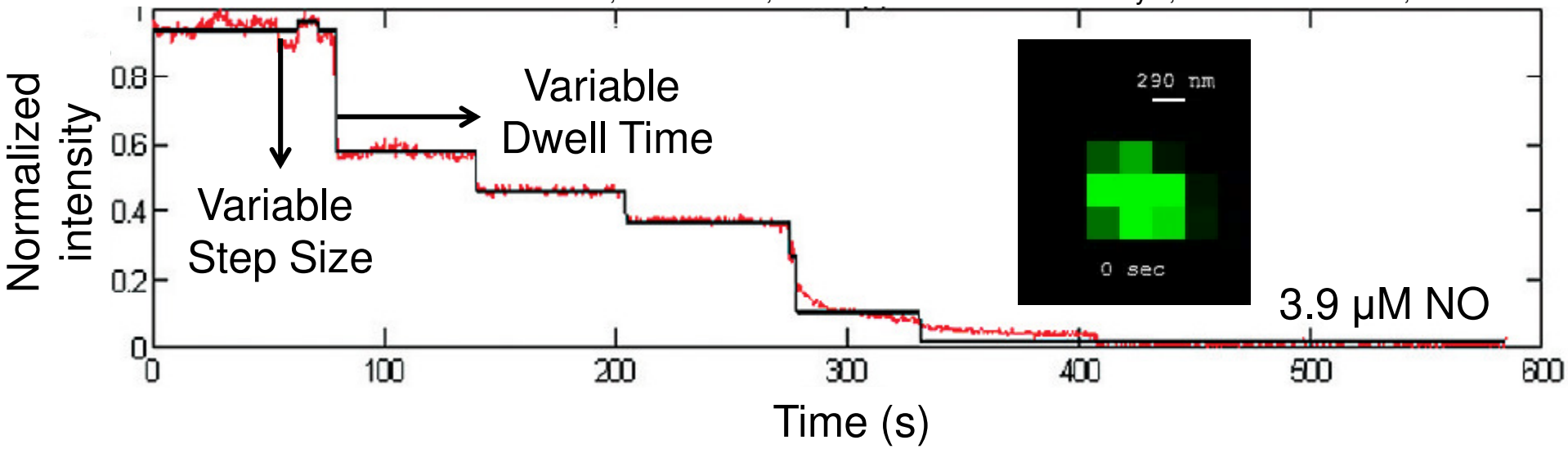


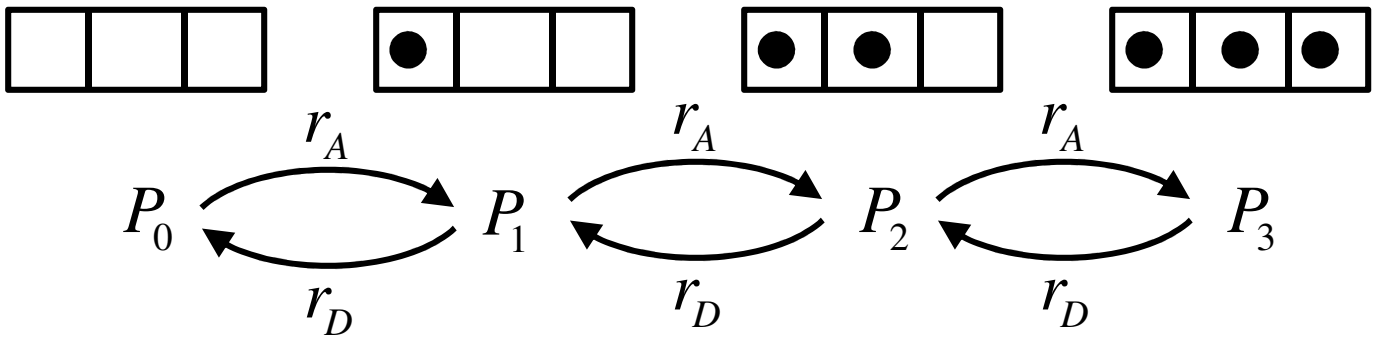
Example: Single-molecule carbon nanotube sensor arrays

Such phenomena are described by a Chemical Master equation

$$\frac{\partial P(\sigma,t)}{\partial t} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t)$$

E.g., consider adsorption/desorption on one carbon nanotube

Four configurations (simplified diagram)



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Chemical Master equation $\frac{\partial P(\sigma,t)}{\partial t} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t)$

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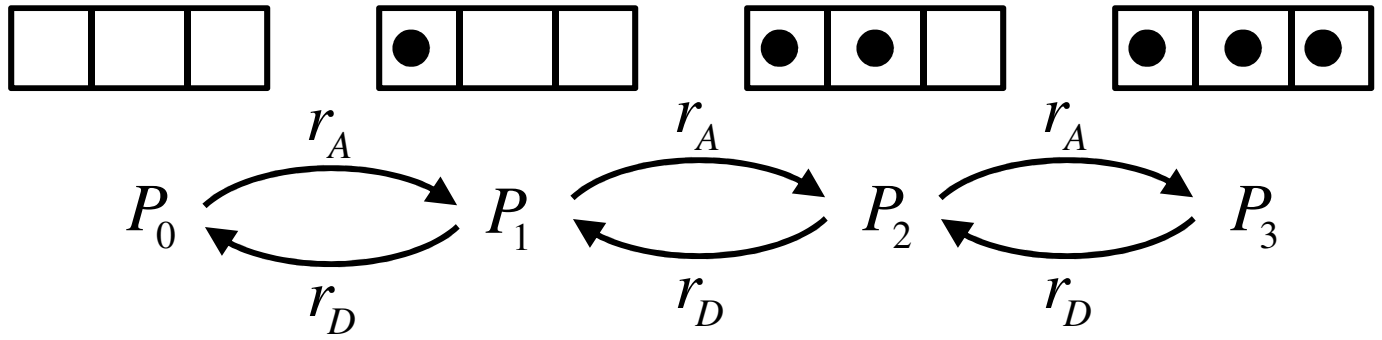

- **Simulation outputs are inherently stochastic, even when all ICs and inputs are completely deterministic**
- **Often a huge number of configurations (>>10^9)**
  → usually kinetic Monte Carlo (KMC) simulation is used to simulate a possible future state trajectory instead
- **Just as in experiments, repeating a KMC simulation will produce different trajectories nearly every time**

Example: Crystal nucleation within nL droplets

- **Nucleation in nL droplets applied to proteins & drugs**

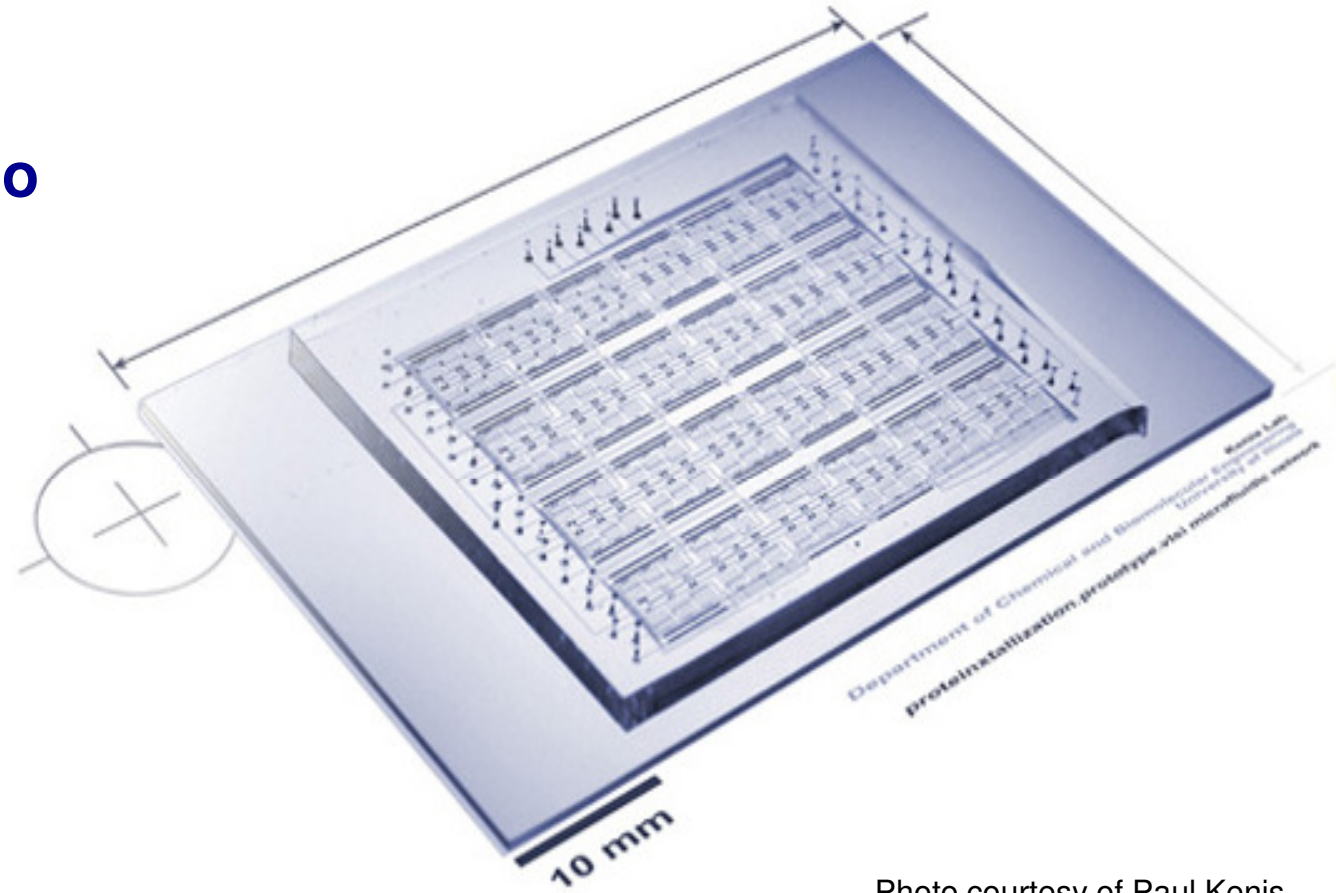

Photo courtesy of Paul Kenis

L. M. Goh, K. J. Chen, V. Bhamidi, G. He, N. C. S. Kee, P. J. A. Kenis, C. F. Zukoski, and R. D. Braatz. Crystal Growth & Design, 10:2515-2521, 2010; K. Chen, L. M. Goh, G. W. He, V. Bhamidi, P. J. A. Kenis, C.F. Zukoski, and R. D. Braatz. Chem. Eng. Sci., 77:235-241, 2012

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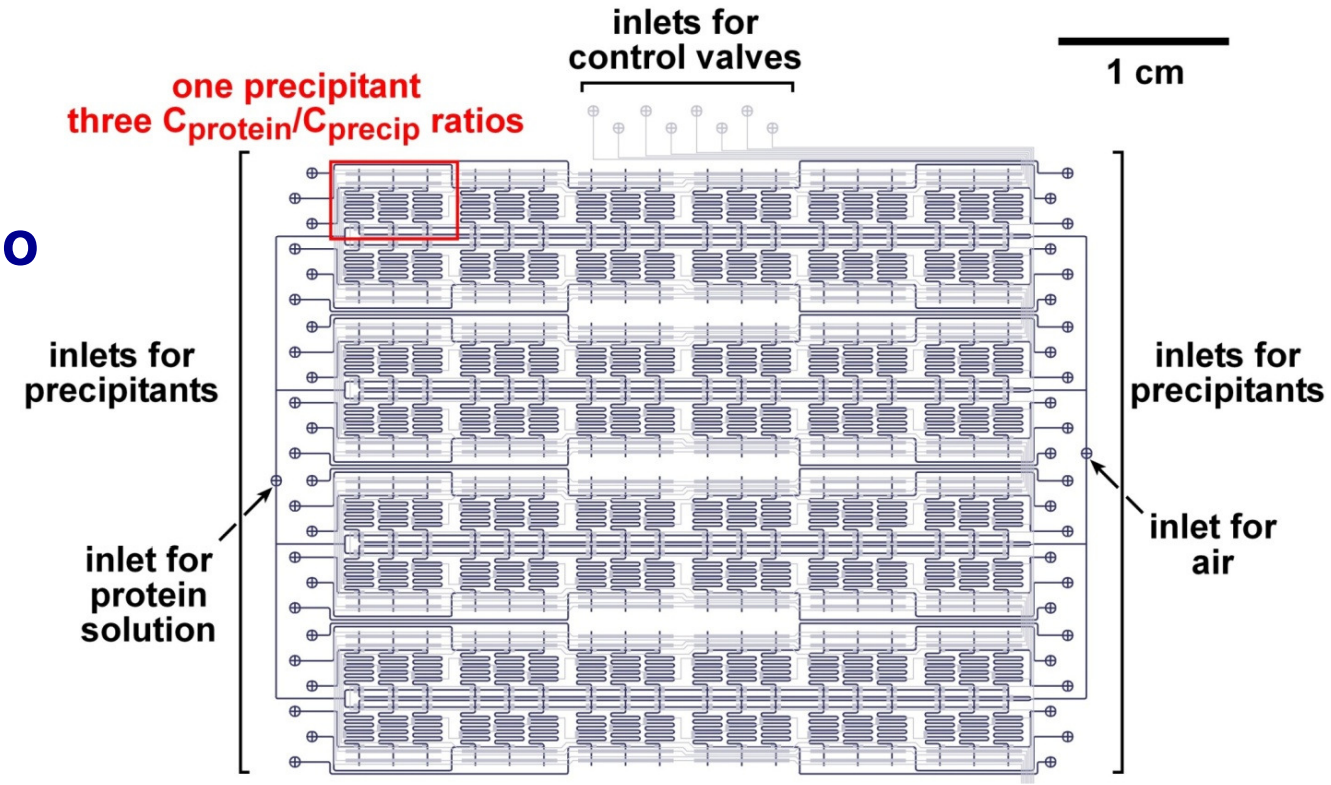

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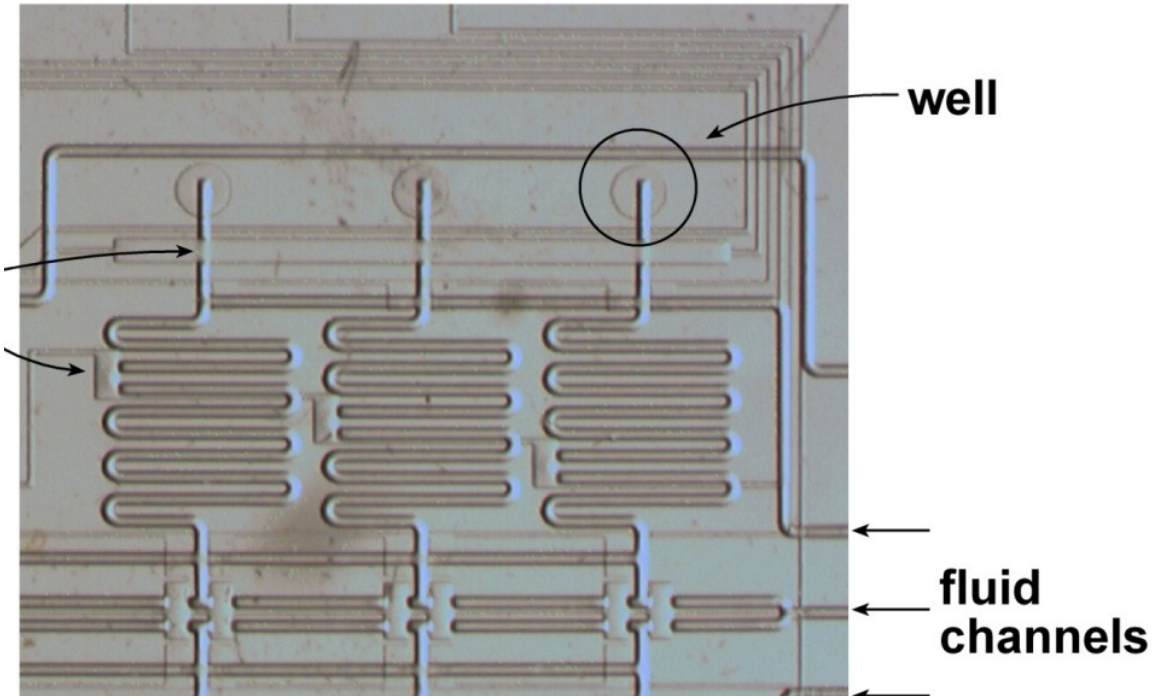
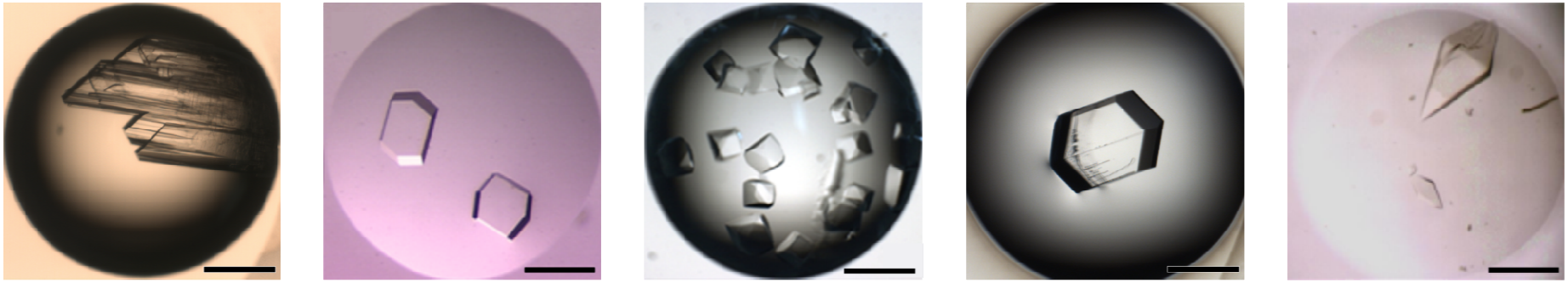


Scale bar is 500 µm



L-histidine | lysozyme | ribonuclease A | succinic acid | thaumatin

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Crystal Growth & Design, 10:2515-2521, 2010

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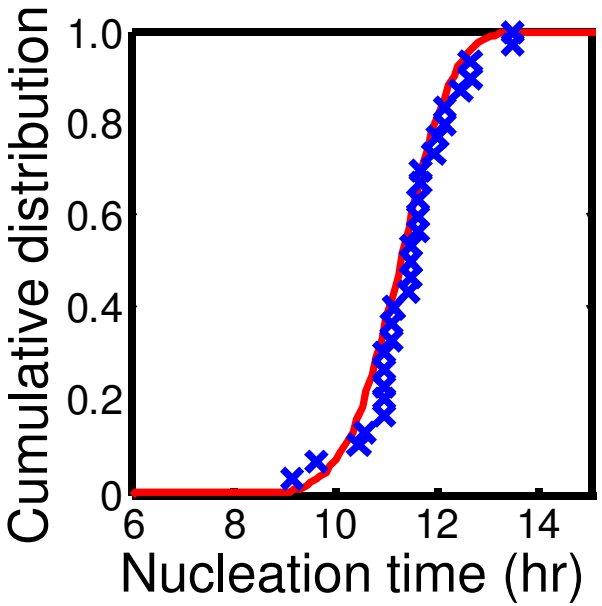
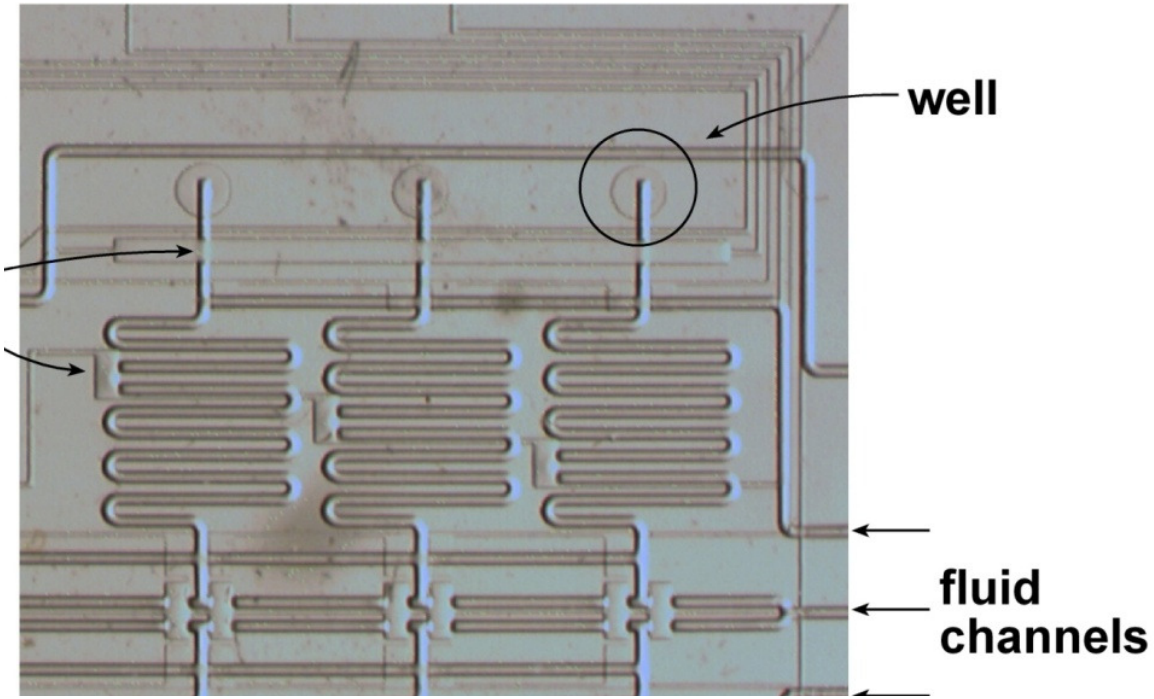
- **Nucleation in nL droplets applied to proteins & drugs**
- **Nucleation time = time to nucleate at least one crystal**





- **Measure a distribution of induction times, even when the exact same experimental conditions are repeated**
- **Nucleation results from a few molecules coming together**

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Typical Challenges, and Some Questions

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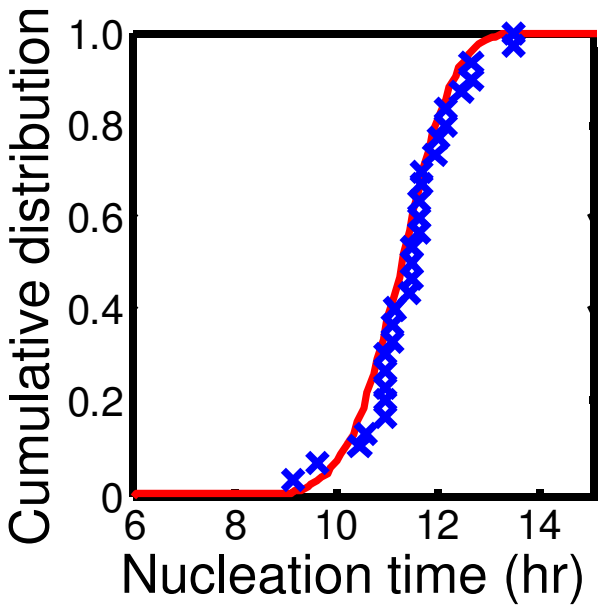
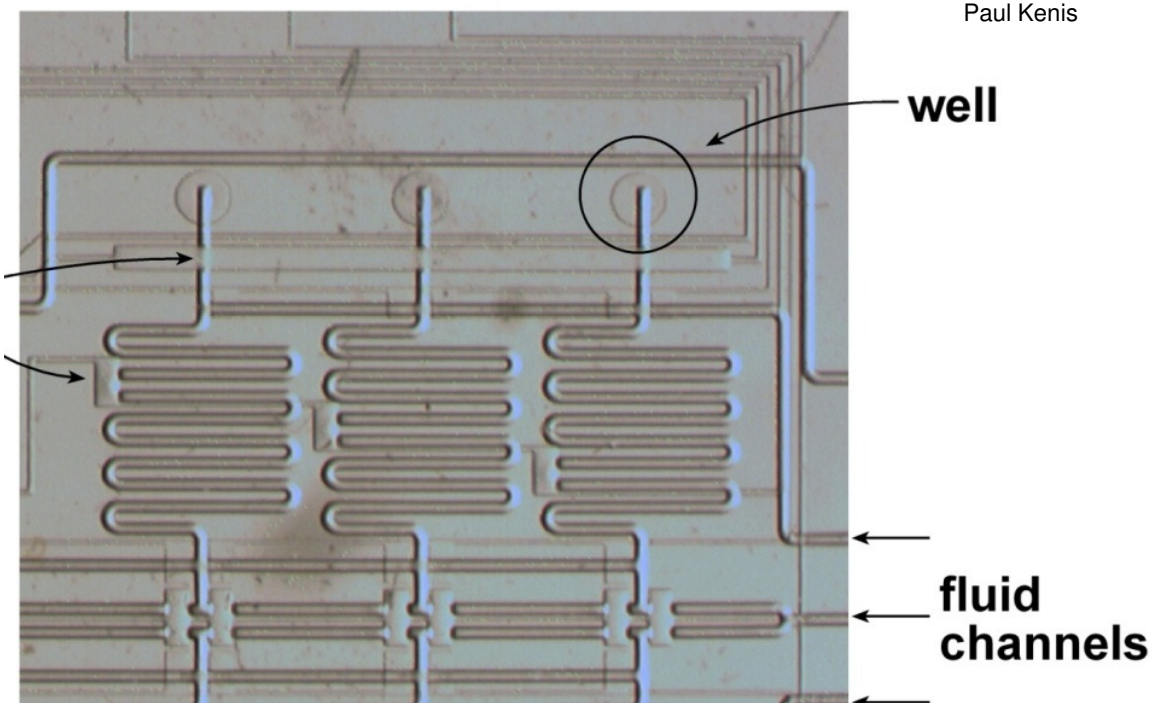
2. **Sparsity of on-line measurements available for process identification**

2. Sparsity of on-line measurements available for process identification: Example

- **Can detect when crystals form in nL drops by x-ray crystallography**
- ***Only 1 data point per experiment***



Courtesy of Paul Kenis



- **No real-time sensors are available for measurement *during* nucleation**
- **In particular, no real-time measurement of solution concentrations in nL droplets**

L. M. Goh, K. J. Chen, V. Bhamidi, G. He, N. C. S. Kee, P. J. A. Kenis, C. F. Zukoski, and R. D. Braatz. Crystal Growth & Design, 10:2515-2521, 2010

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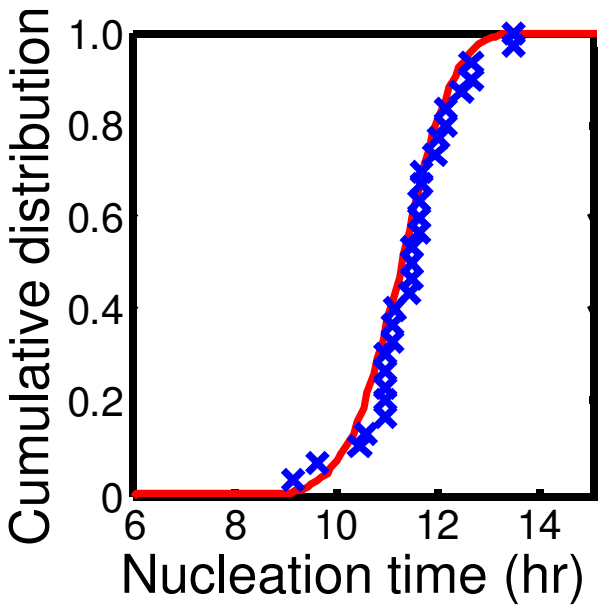

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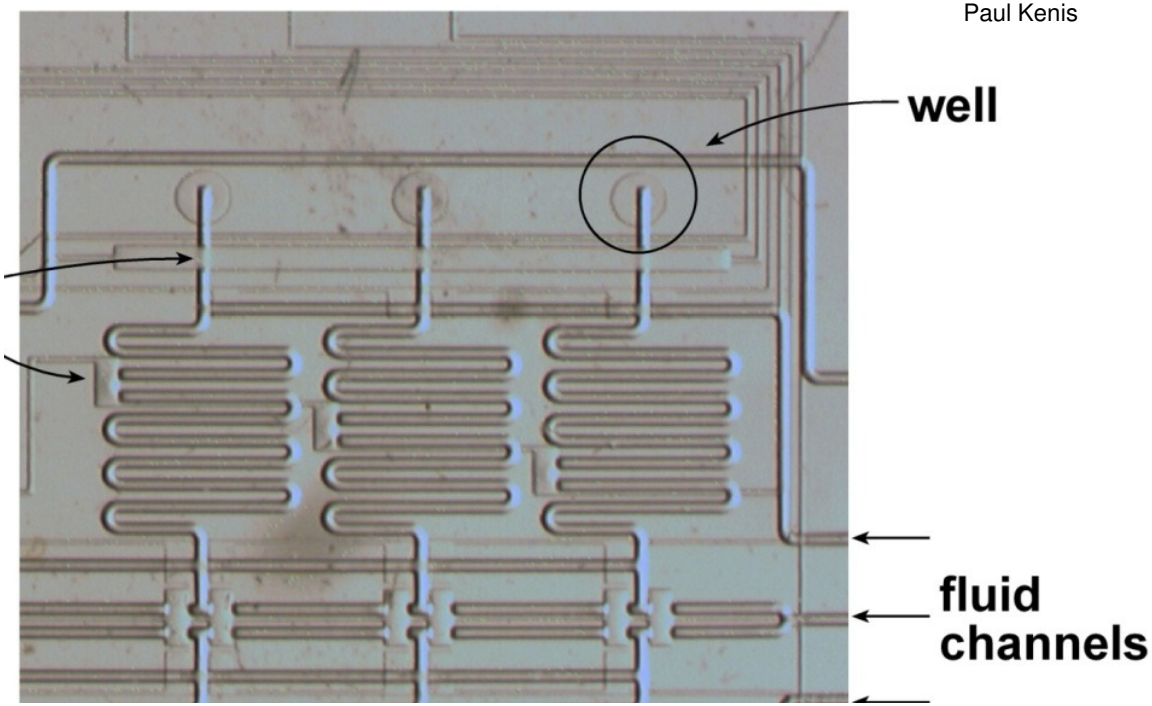

- **The only real-time manipulated variable is typically the temperature, but most proteins and many drugs are too thermally sensitive for T to be used as a manipulated variable**

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Some approaches:

- → **Run lots of KMC simulations, fit low-order models, and use to estimate parameters and for design (Kevrekidis, Vlachos)**
- → **Accelerate KMC by exploiting scale separation inherent in many systems (Rao, Rawlings, Kevrekidis, Vlachos, …)**
- → **Numerically solve Chemical Master equation (Paul Barton, George Stephanopoulos, Mustafa Khammash)**
- → **Analytically solve Chemical Master equation by exploiting the structure of interactions between events**

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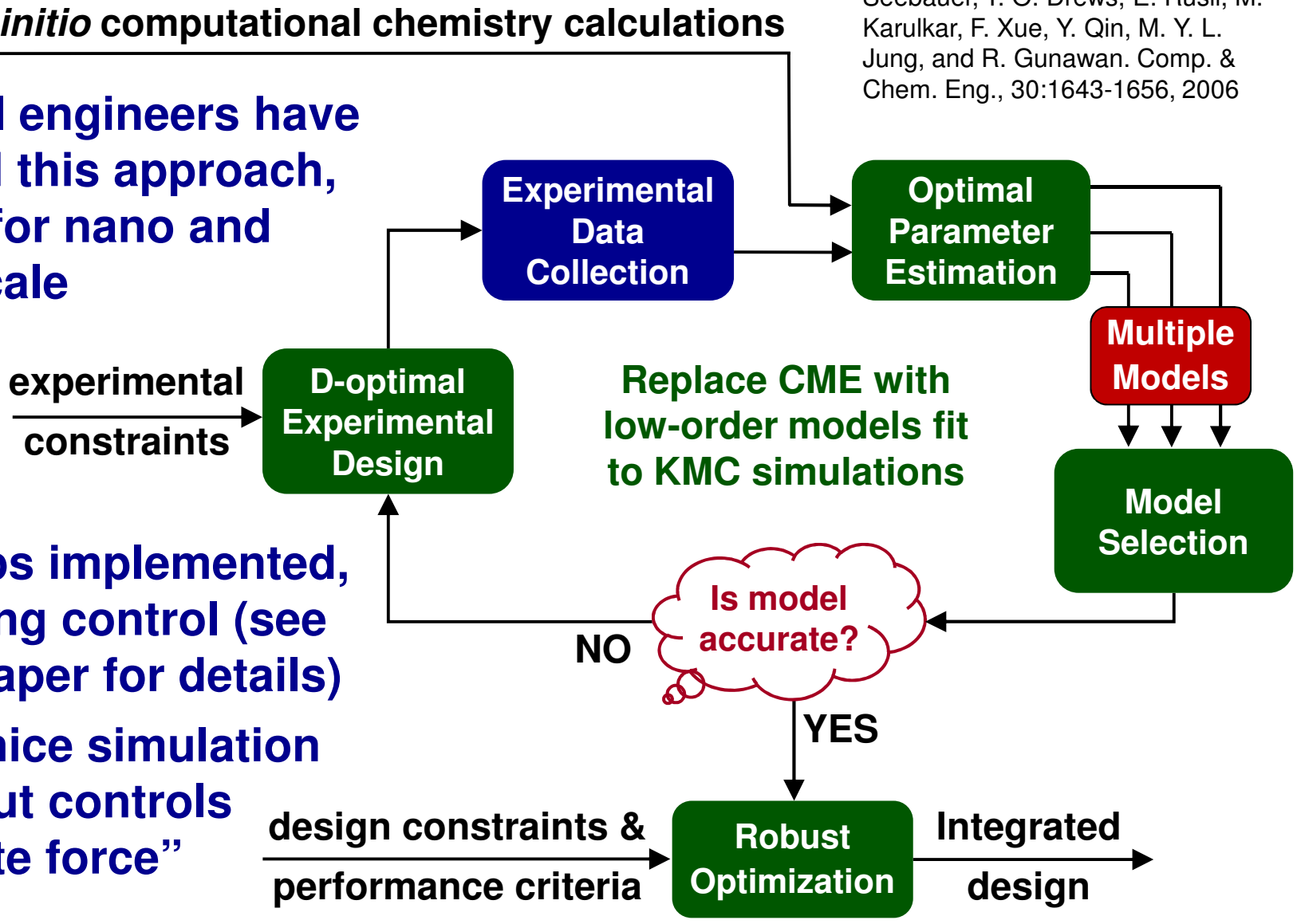
PSE Tools Based on KMC Simulations

R. D. Braatz, R. C. Alkire, E. G. Seebauer, T. O. Drews, E. Rusli, M. Karulkar, F. Xue, Y. Qin, M. Y. L. Jung, and R. Gunawan. Comp. & Chem. Eng., 30:1643-1656, 2006

- **Several engineers have applied this approach, works for nano and multiscale**
- **All steps implemented, including control (see cited paper for details)**
- **Some nice simulation work but controls is "brute force"**



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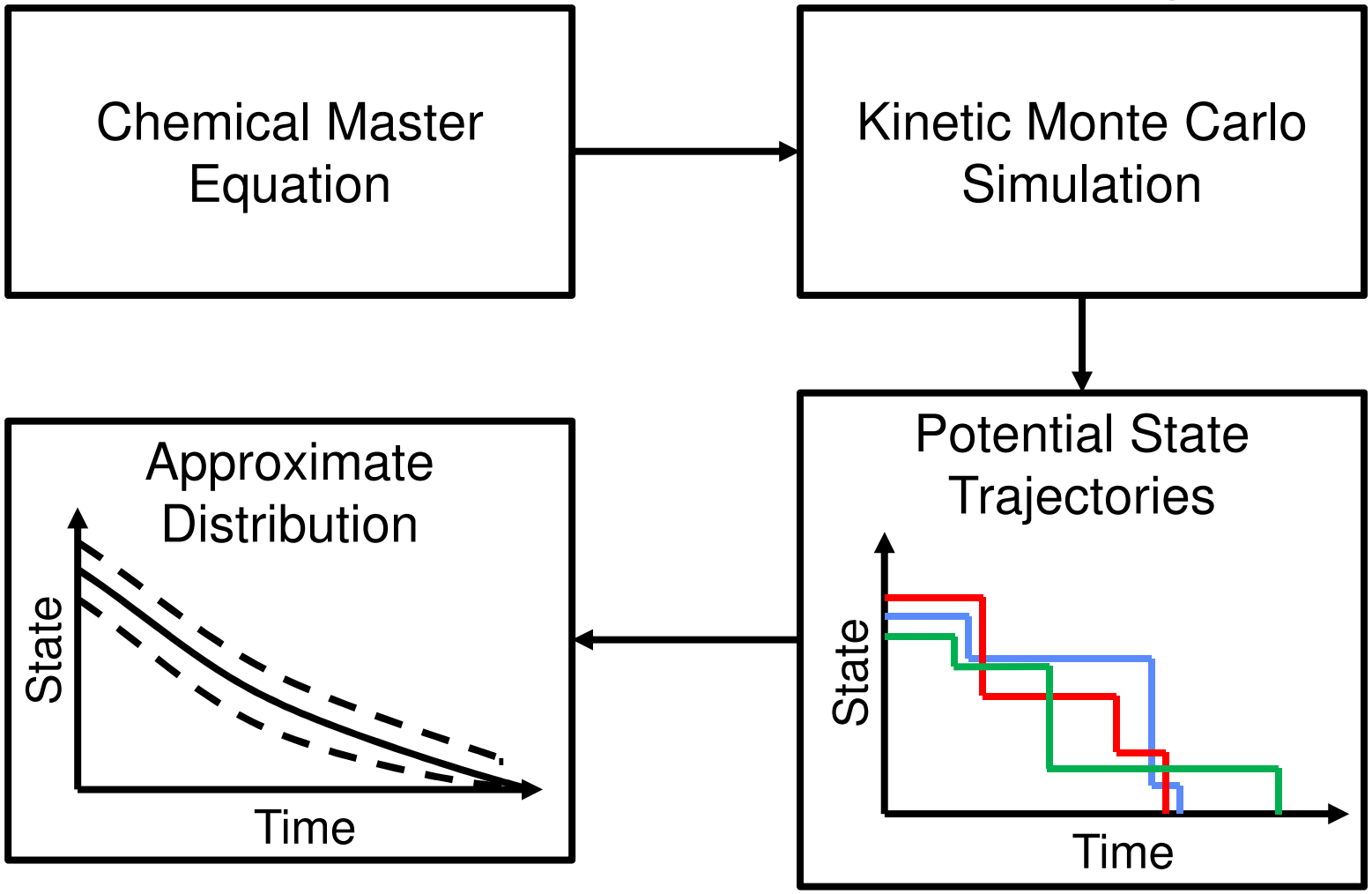
Standard Approach is to use KMC Simulations to Construct Distributions of State Trajectories



→ **High computational cost and inconvenient for analysis/control**

Q: Could there be a better way, at least for some nanosystems?

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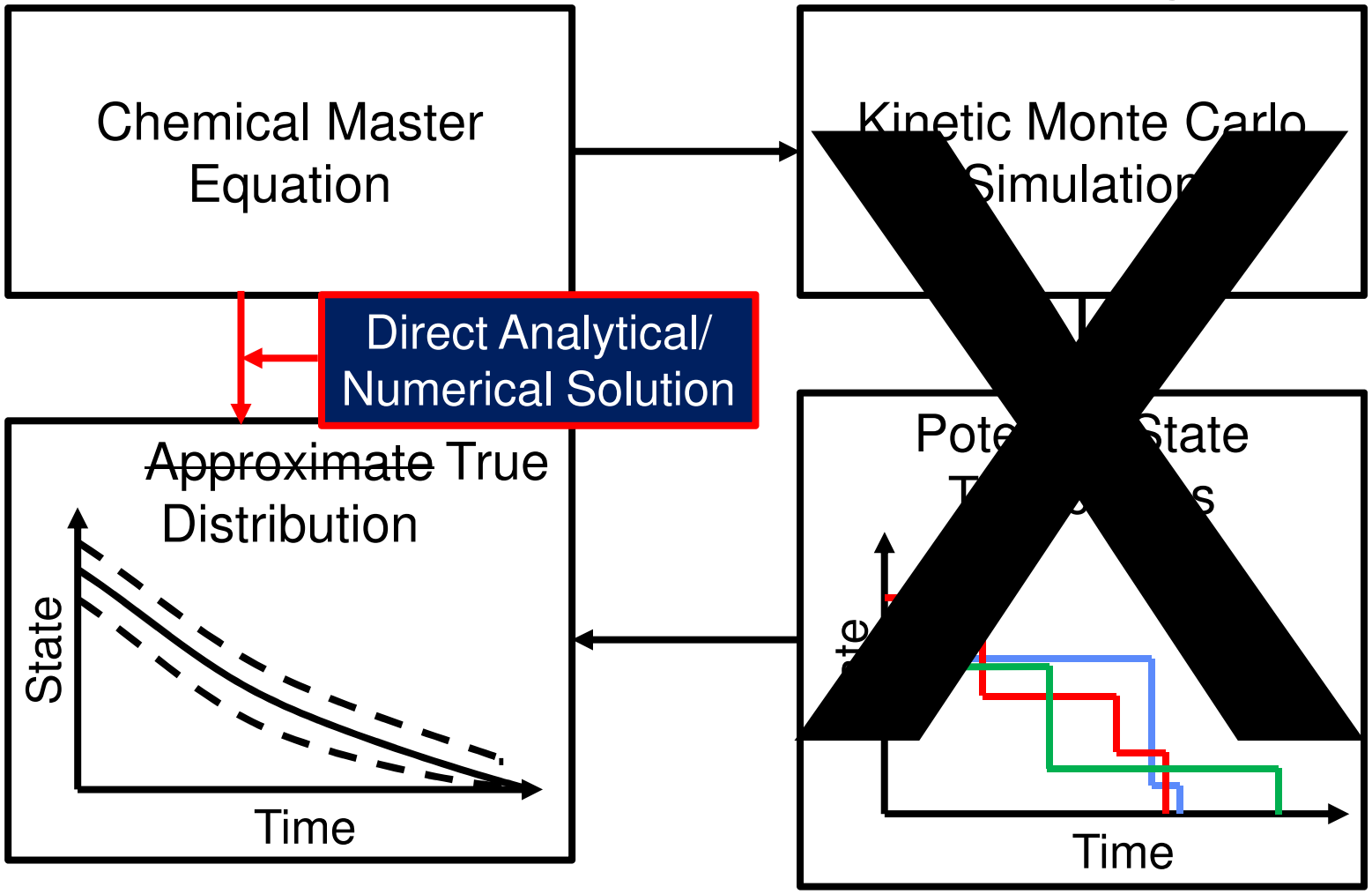

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Structure of Chemical Master Equation

- **Chemical Master equation:**

$$\frac{dP(\sigma,t)}{dt} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t)$$

- **Linear time-varying system:**
  - **Probabilities stacked into a single state vector *x*(*t*)**

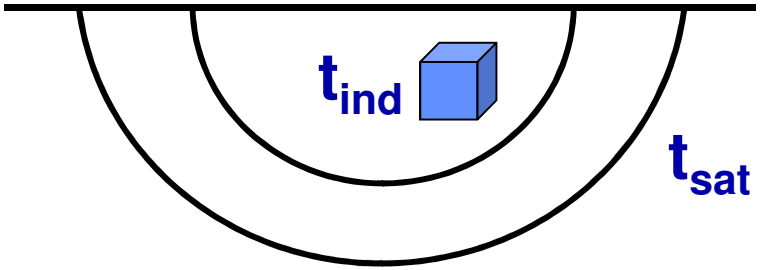
$$\frac{d}{dt}x(t) = A(t;\theta)x(t)$$

  - **The chemical kinetic, adsorption and desorption constants, diffusion coefficients, and equilibrium constants collected into the vector θ**
  - **Transition rates collected into the matrix *A*(*t*;θ) that depends on temperature, external species concentrations, etc.**
  - ***A*(*t*;θ) is highly structured for most nanoscale systems**

Example: Crystal nucleation within nL droplets

- **Chemical Master equation for nucleation in a nanodroplet:**

$$\frac{dP_n(t)}{dt} = \kappa(t)\left[P_{n-1}(t) - P_n(t)\right],\ n = 0,1,2,...$$



where

$P_n(t)$ = probability that population size $N(t)$ has the value n at time t

$\kappa(t)$ = time-varying probability of nucleation = f(nucleation rate, $V(t)$)

- **Use probability generating function* to generate analytical solution**

$$P_n(t) = \frac{1}{n!}\left[\int_0^t \kappa(s)ds\right]^n e^{-\int_0^t \kappa(s)ds}, \quad n = 0,1,2,...$$

- **Have applied analytical model to identify nucleation kinetics under operating conditions very difficult to achieve in other systems**
- **Also used to quantify uncertainties and gain insights into mechanisms**

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* D. G. Kendall, J. Roy. Stat. Soc. Ser. B, 11:211-229, 1949

Solution via a probability generating function

Chemical Master equation:

$$\frac{dP_n(t)}{dt} = \kappa(t)\left[P_{n\text{-}1}(t) - P_n(t)\right],\ n = 0,1,2,...$$

Equation must satisfy the PDE (match each term):

$$\frac{\partial \varphi(z,t)}{\partial t} = (z-1)\kappa(t)\varphi(z,t) \quad \text{where} \quad \varphi(z,t) = \sum_{n=0}^{\infty} z^n P_n(t)$$

Define $\kappa(t)\partial t = \partial s$ and integrate analytically to obtain

$$\varphi(z,t) = e^{(z-1)\int_0^t \kappa(s)ds} = e^{z\int_0^t \kappa(s)ds} e^{-\int_0^t \kappa(s)ds}$$

Expand first term in a Taylor series to obtain

$$\varphi(z,t) = \left[1 + z\int_0^t \kappa(s)ds + \frac{z^2}{2!}\left(\int_0^t \kappa(s)ds\right)^2 + \cdots\right] e^{-\int_0^t \kappa(s)ds}$$

Solution via a probability generating function

Chemical Master equation:

$$\frac{dP_n(t)}{dt} = \kappa(t)\left[P_{n\text{-}1}(t) - P_n(t)\right],\ n = 0,1,2,...$$

Equation must satisfy the PDE (match each term):

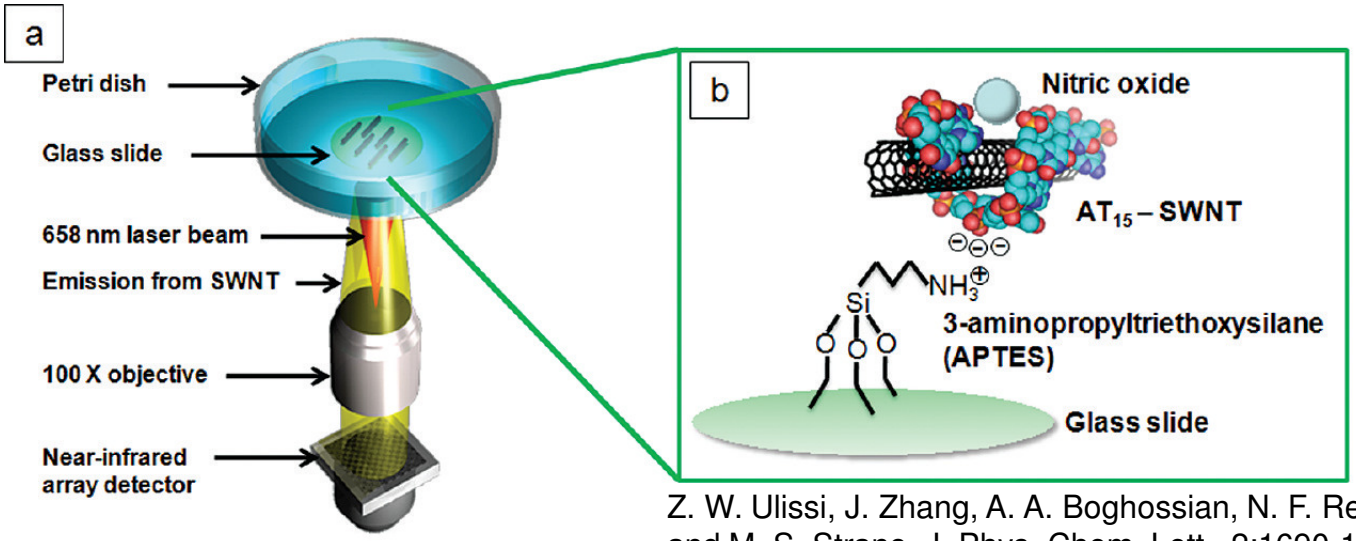
$$\frac{\partial \varphi(z,t)}{\partial t} = (z-1)\kappa(t)\varphi(z,t) \quad \text{where} \quad \varphi(z,t) = \sum_{n=0}^{\infty} z^n P_n(t)$$

This CME is easy to solve by other methods; PGFs also applies to systems with two-way interactions

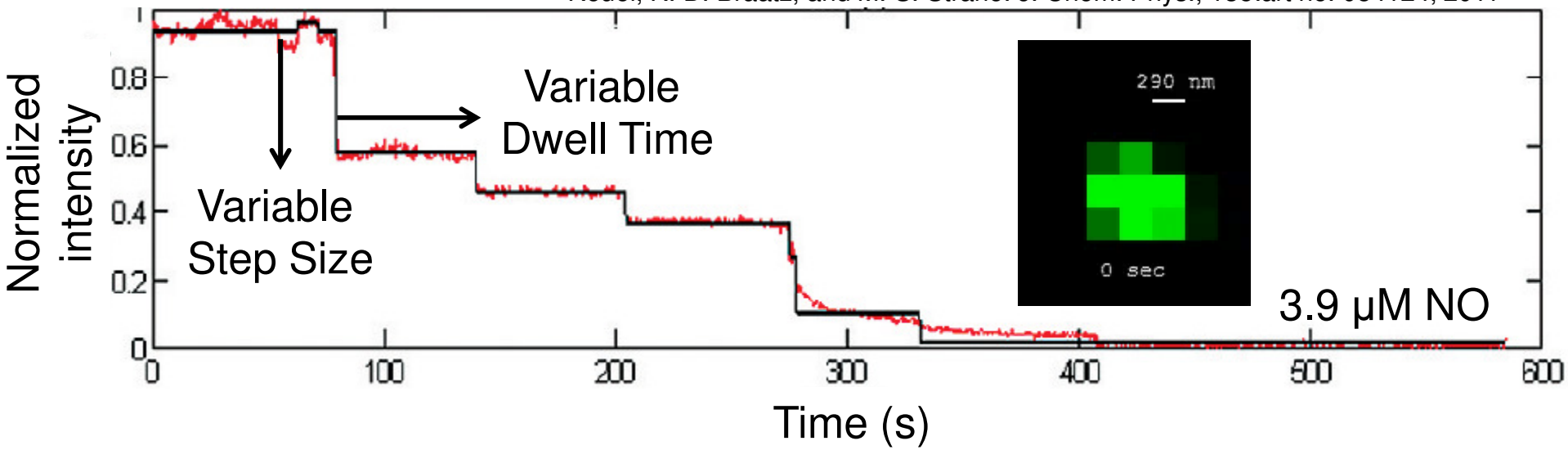
Expand first term in a Taylor series to obtain

$$\varphi(z,t) = \left[1 + z\int_0^t \kappa(s)ds + \frac{z^2}{2!}\left(\int_0^t \kappa(s)ds\right)^2 + \cdots\right] e^{-\int_0^t \kappa(s)ds}$$

Example: Single-molecule carbon nanotube sensor arrays

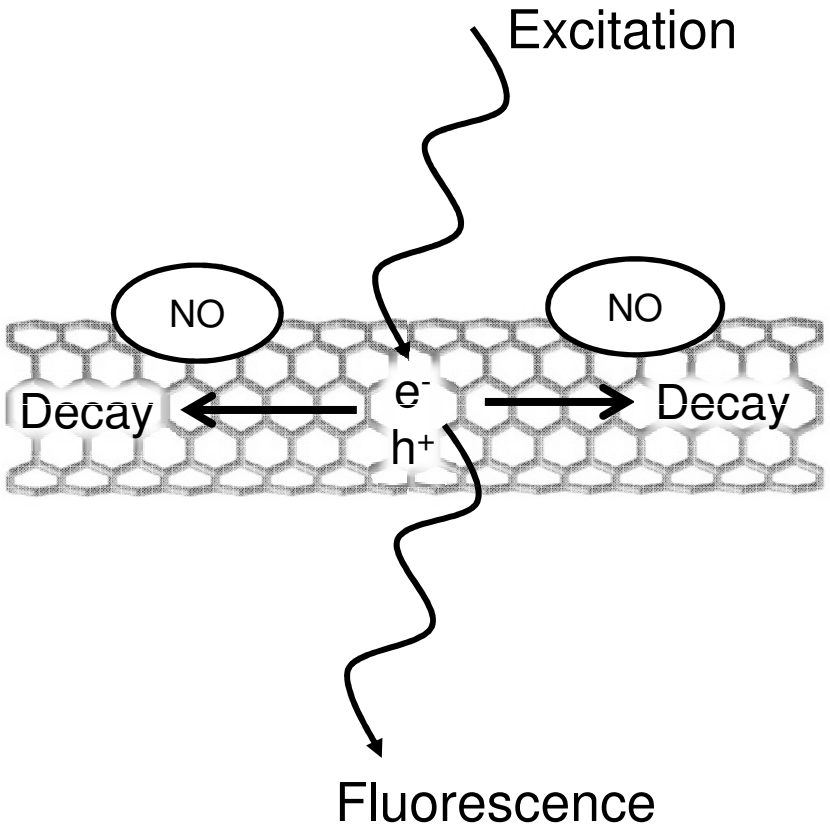


Z. W. Ulissi, J. Zhang, A. A. Boghossian, N. F. Reuel, S. F. E. Shimizu, R. D. Braatz, and M. S. Strano. J. Phys. Chem. Lett., 2:1690-1694, 2011; A. A. Boghossian, J. Zhang, F. T. Le Floch, Z. W. Ulissi, P. Bojo, J.-H. Han, J.-H. Kim, J. R. Arkalgud, N. F. Reuel, R. D. Braatz, and M. S. Strano. J. Chem. Phys., 135:art no. 084124, 2011



Example: Single-molecule sensor model

Full Model

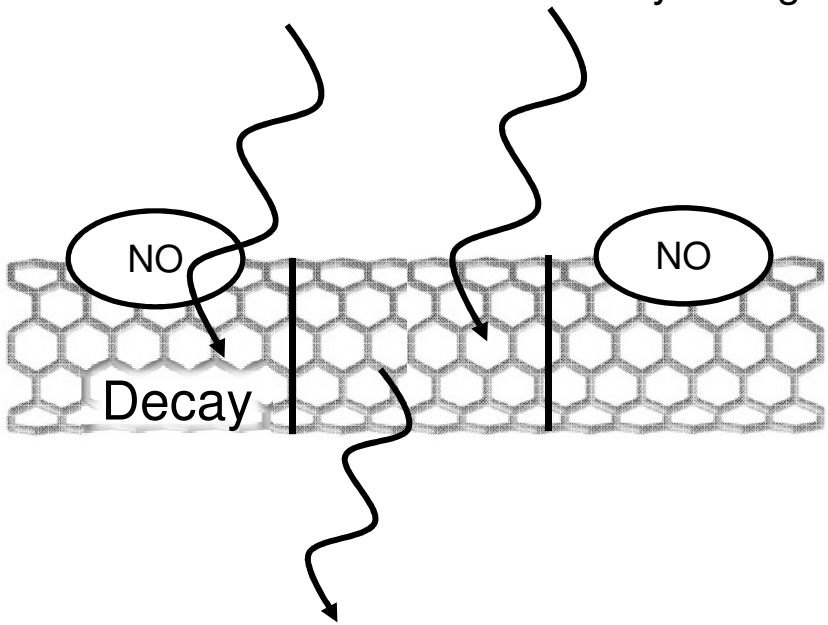


(DNA not shown to simplify figures)

D. M. Harrah and A. K. Swan. ACS nano, 5:647-655, 2011

Simplified Model

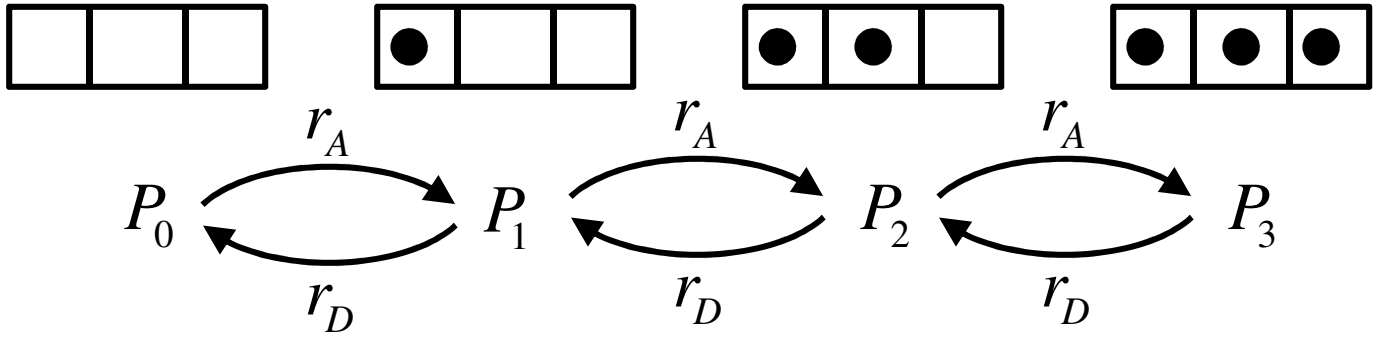
- Finite constant number of uniform segments
- Each segment is independent
- A segment with NO does not fluoresce
- A segment without NO fluoresces
- Only one NO can bind to each site
- Don't consider size of the intensity change



Quenching depends on the action of single molecules

Example: Single-molecule sensor arrays

- **Chemical Master equation with use of equivalent classes (good)**

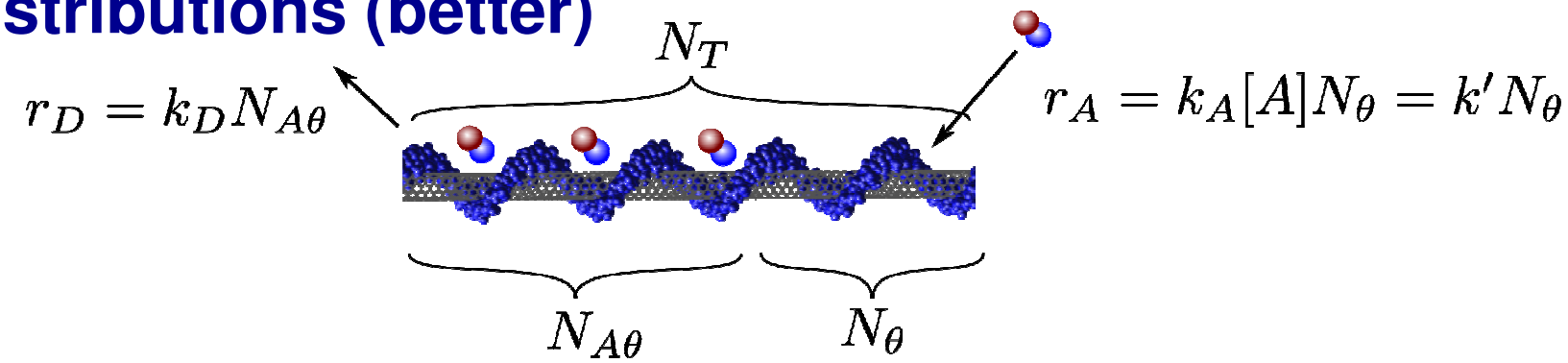


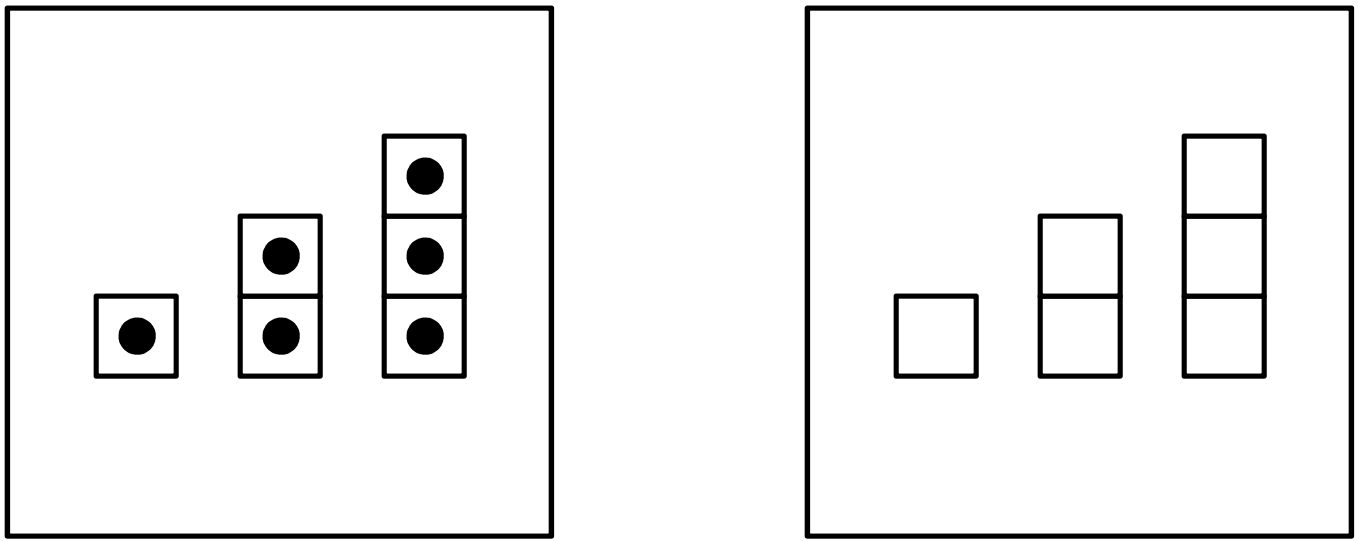
$$\frac{dP(\sigma,t)}{dt} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t)$$

Z. W. Ulissi, J. Zhang, A. A. Boghossian, N. F. Reuel, S. F. E. Shimizu, R. D. Braatz, and M. S. Strano. J. Phys. Chem. Lett., 2:1690-1694, 2011; A. A. Boghossian, J. Zhang, F. T. Le Floch, Z. W. Ulissi, P. Bojo, J.-H. Han, J.-H. Kim, J. R. Arkalgud, N. F. Reuel, R. D. Braatz, and M. S. Strano. J. Chem. Phys., 135:art no. 084124, 2011

Example: Single-molecule sensor arrays

- **Reformulate in terms of discrete population distributions (better)**





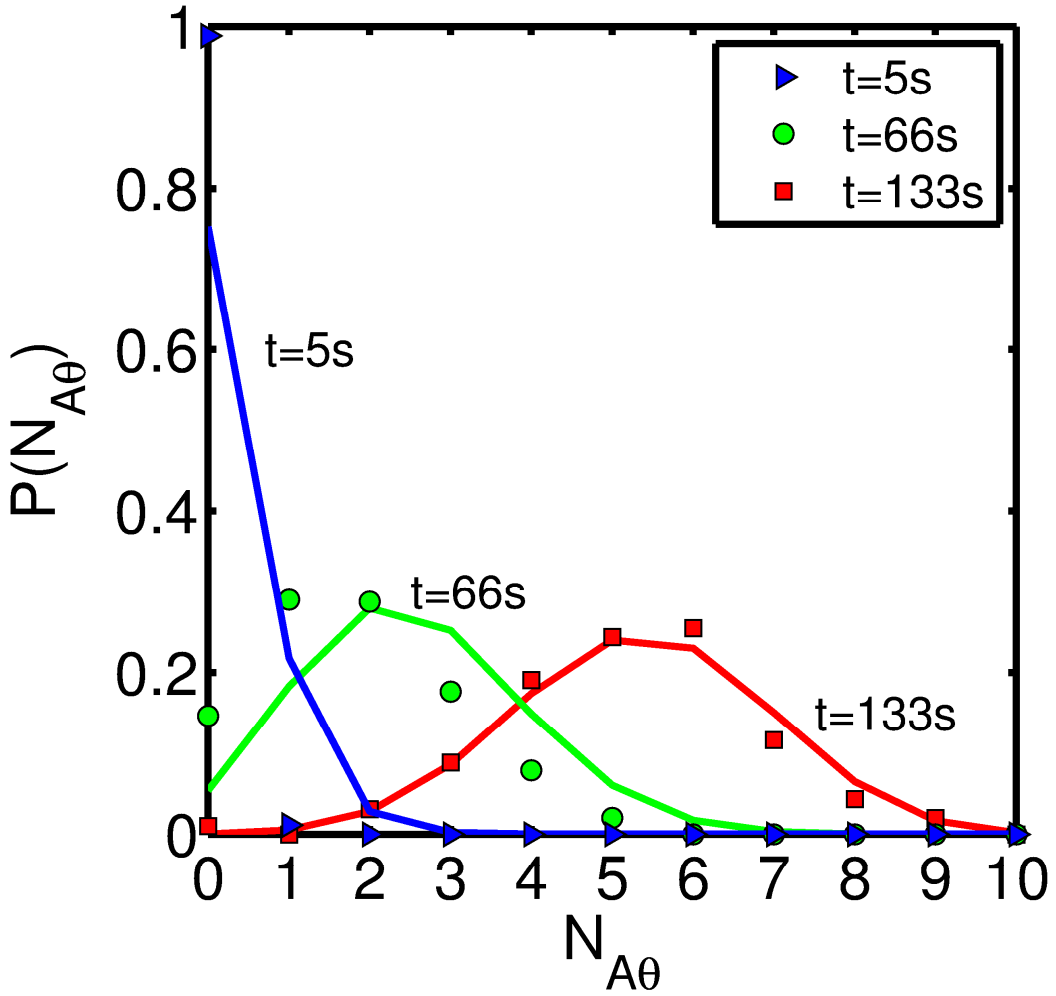
- **Solution still conforms to the Chemical Master eqn.**

Example: Single-molecule sensor arrays

- **First parts of the solution in Siegert, 1949 (possibly earlier in the Markov Chain literature)**
- **The solution is a discrete convolution of time-varying binomial distributions (from solving ODEs)**
- **Relevant literature:**
  - A. J. F. Siegert. On the approach to statistical equilibrium. Physical Review, 76:1708-1714, 1949
  - I. M. Krieger and P. G. Gans. First-order stochastic processes. J. Chem. Phys., 32:247-250, 1960
  - D. T. Gillespie. The Chemical Langevin and Fokker-Planck equations for the reversible isomerization reaction. J. Phys. Chem. A, 106:5063-5071, 2002
  - T. Jahnke and W. Huisinga. Solving the chemical master equation for mono-molecular reaction systems analytically. J. Math. Biology, 54:1-26, 2007

Example: Single-molecule NO sensor arrays

- **Comparison to experimental data:**



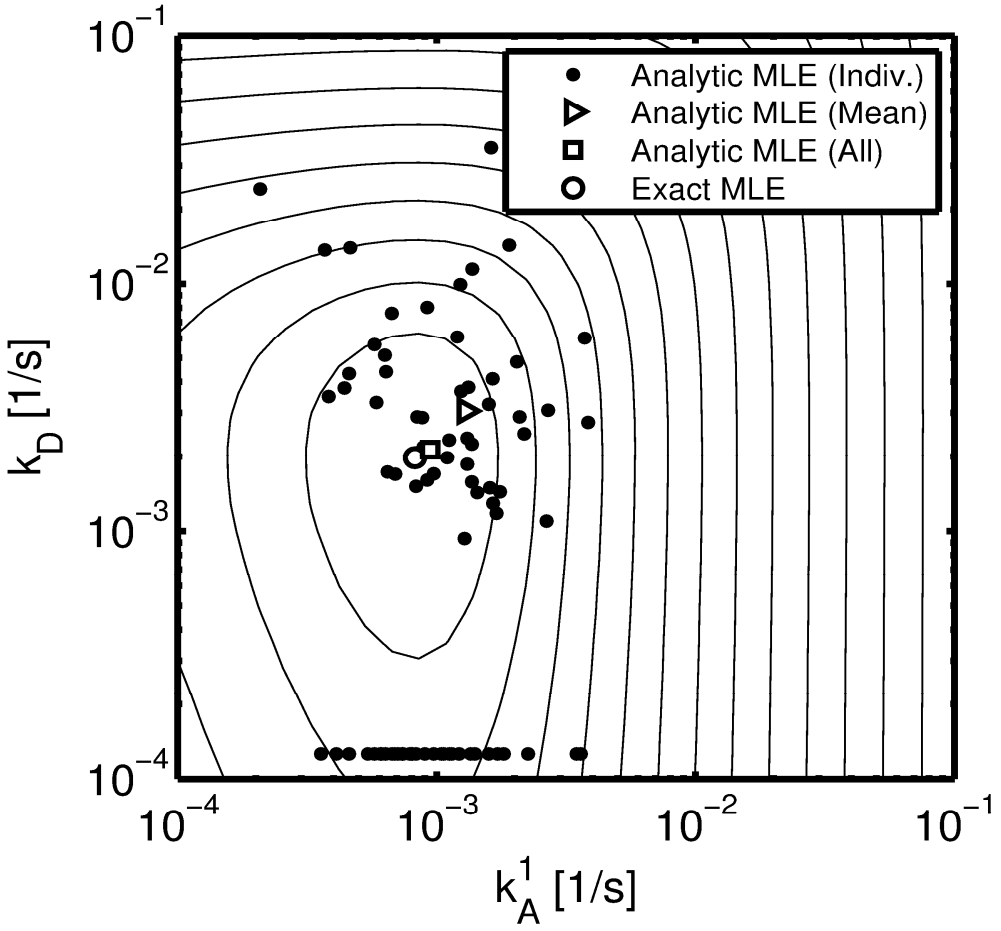
Z. W. Ulissi, J. Zhang, A. A. Boghossian, N. F. Reuel, S. F. E. Shimizu, R. D. Braatz, and M. S. Strano. J. Phys. Chem. Lett., 2:1690-1694, 2011

Analytical solution enables the answering of many fundamental and practical systems questions

- How to optimally estimate adsorption rate constants (and local NO concentrations) for 2D carbon nanotube sensor arrays?
- What is the uncertainty in the parameter estimates?
- How much of the variance in sensor data is intrinsic vs. other sources?
- What is the best achievable state estimation and feedback control performance?

Maximum Likelihood Estimation (MLE)

→ **Analytical solution makes it possible to derive an analytical expression for the maximum likelihood estimates**



- **Ignoring the specific stochastic nature can give wrong results**
- **Estimate obtained by averaging results of KMCs was off by a factor of 8**
- **Analytical expressions for uncertainty in the parameters, intrinsic variation vs. other sources**
- **Enables 2D estimation & control (w/Jay H. Lee)***

Z. W. Ulissi, J. Zhang, A. A. Boghossian, N. F. Reuel, S. F. E. Shimizu, R. D. Braatz, and M. S. Strano. J. Phys. Chem. Lett., 2:1690-1694, 2011

* H. Jang, K.-K. K. Kim, J. H. Lee, and R. D. Braatz. Fast moving horizon estimation for a distributed parameter system. *12th International Conference on Control, Automation and Systems*, Jeju Island, Korea, Paper TA01-2, October 17-21, 2012.

Addressing Systems & Control Challenges

1. High state dimensionality and inherent stochasticity of molecular events

→ **Analytically solve Chemical Master equation by exploiting structure of interactions between events**

(i) **Probability-generating functions**

(ii) **Reformulation as discrete population balance equations**

(iii) **Exploiting of symmetries** (Z. W. Ulissi, M. C. Molaro, M. S. Strano, and R. D. Braatz. Proceedings of the American Control Conference, Montreal, Quebec, pp. 1-8, 2012; J. G. VanAntwerp, A. P. Featherstone, B. A. Ogunnaike, and R. D. Braatz. Automatica, 43:191-211, 2007)

(iv) **Linear time-varying dynamical systems theory**

→ **Greatly facilitates dynamic analysis, experimental design, parameter & state estimation, optimal control, …**

→ **Still need more theoretical approaches**

Typical Challenges, and Some Questions

1. **High state dimensionality and inherent stochasticity of molecular events**

   Q: How do we formulate tractable approaches to address systems with these characteristics?

2. **Sparsity of on-line measurements available for process identification**

   Q: How do we abstract the most information from the data, and redesign systems to obtain more data?

Some Approaches:

→ Employ high-throughput NEMS/MEMS devices

→ Instead of filtering away the noise, exploit it

2. Employ high-throughput NEMS/MEMS devices to resolve sparsity of on-line measurements

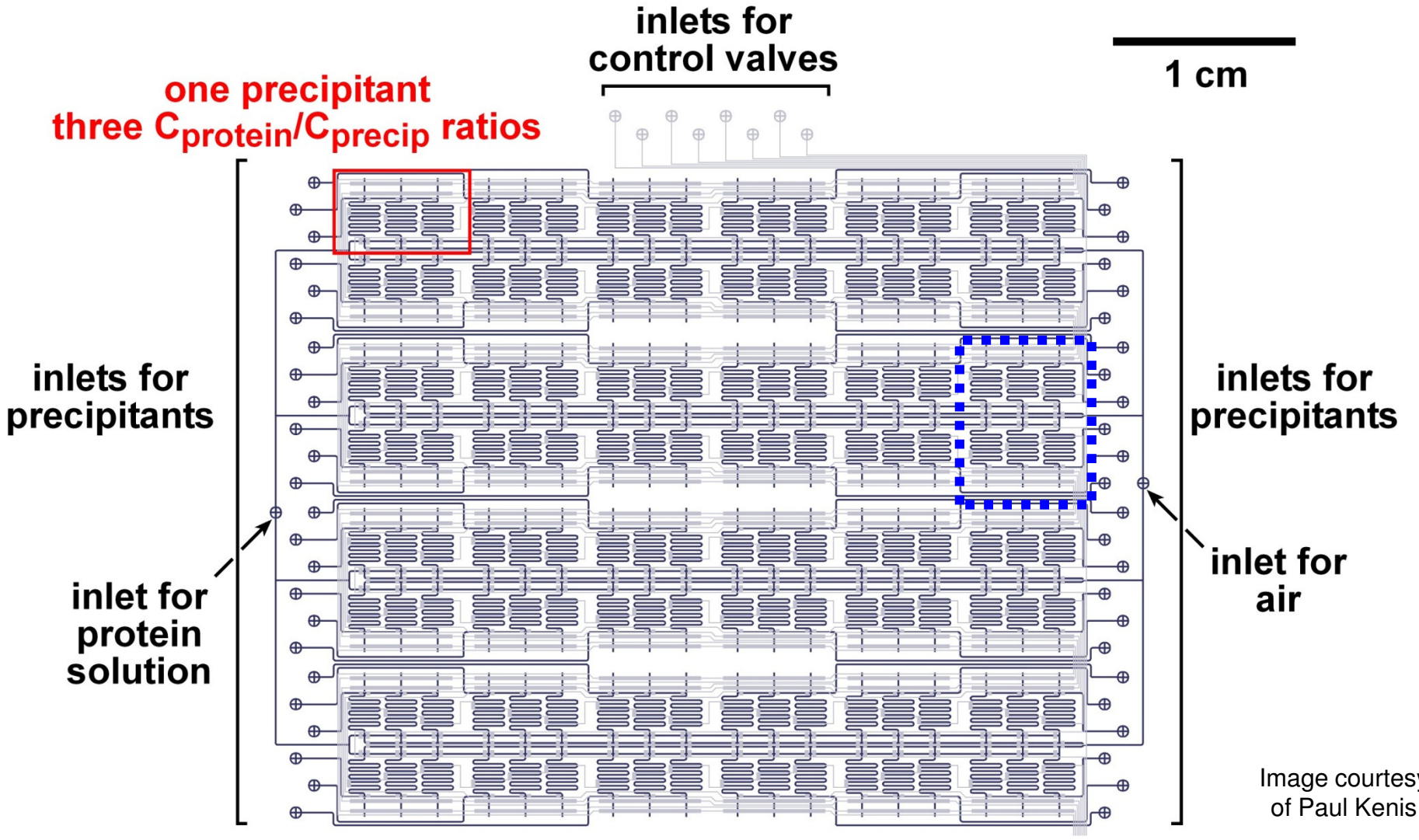
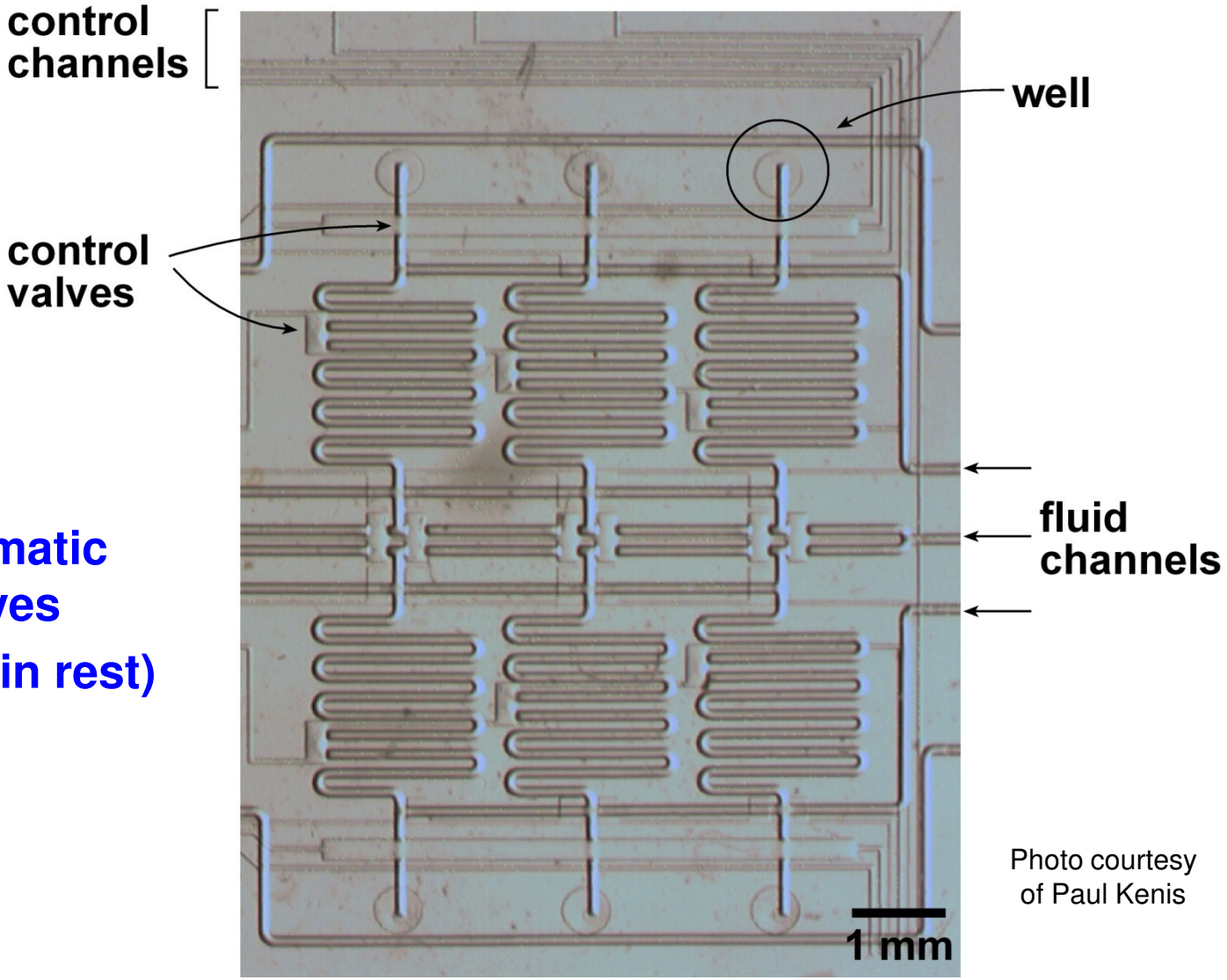


Image courtesy of Paul Kenis

144 measurements for each chip: optical + x-ray

2. Employ high-throughput NEMS/MEMS devices to resolve sparsity of on-line measurements

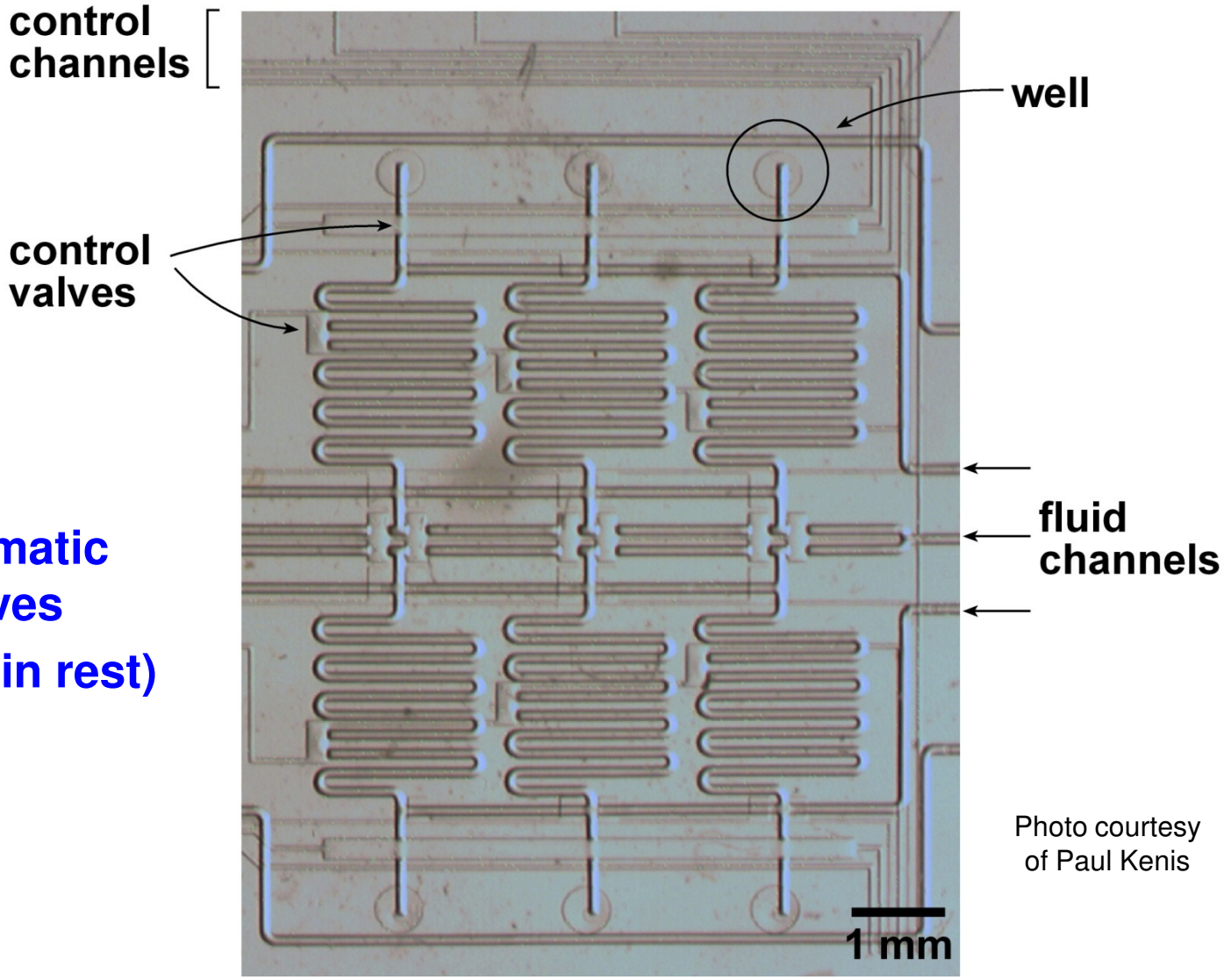


Pneumatic valves (closed in rest)

Photo courtesy of Paul Kenis

L. M. Goh, K. J. Chen, V. Bhamidi, G. He, N. C. S. Kee, P. J. A. Kenis, C. F. Zukoski, and R. D. Braatz. Crystal Growth & Design, 10:2515-2521, 2010

Mixing Array for 6 Wells



Pneumatic Valves (closed in rest)

Photo courtesy of Paul Kenis

Introducing Precipitant A

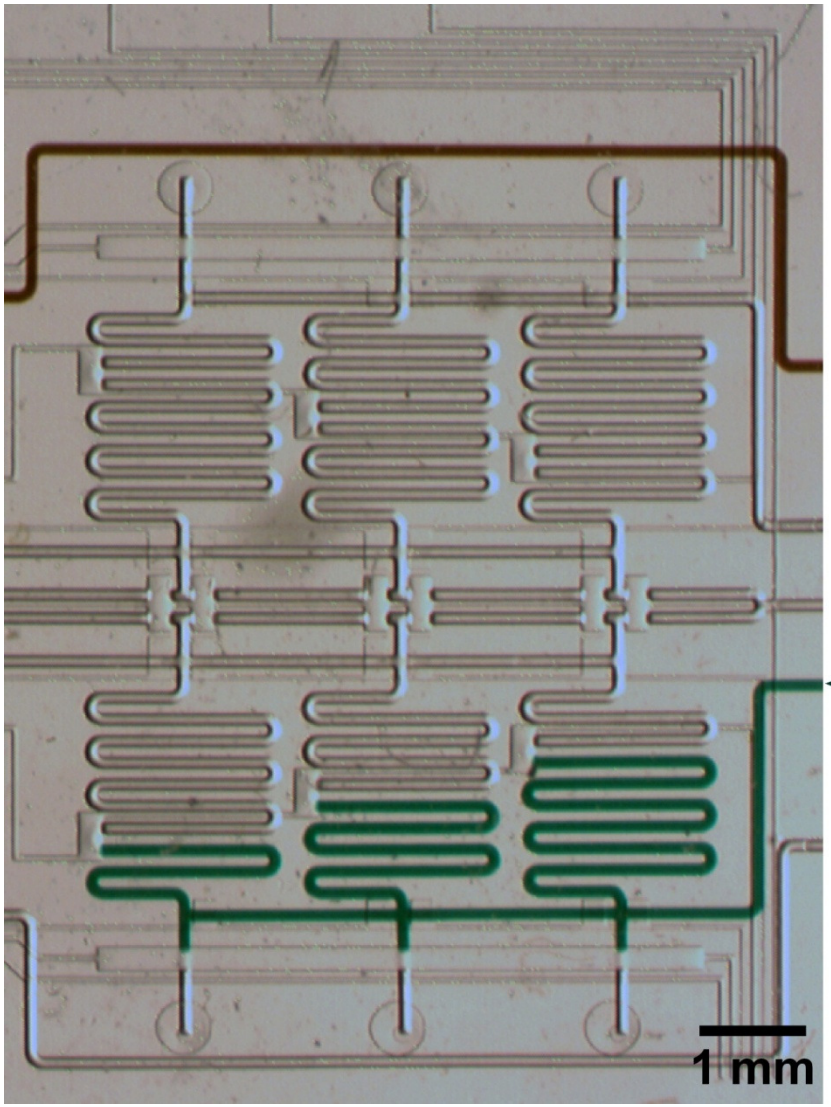


Photo courtesy
of Paul Kenis

Introducing Precipitant B

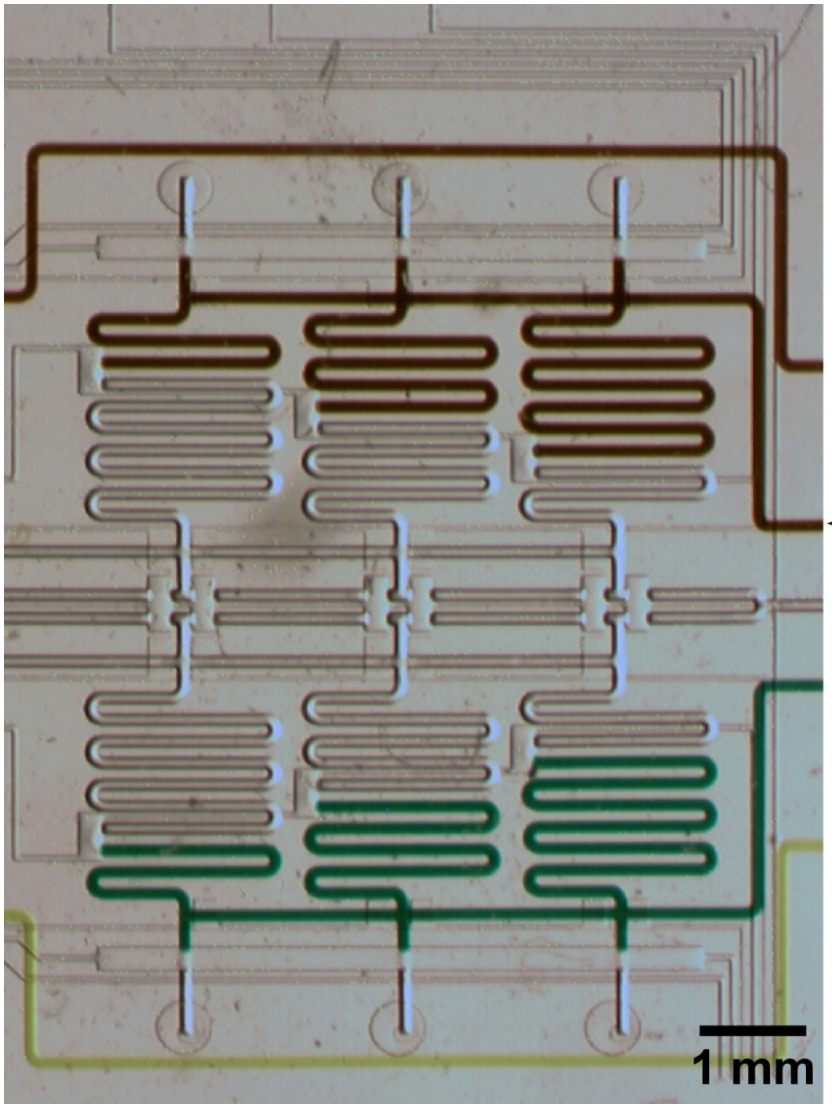


Photo courtesy
of Paul Kenis

Introducing Protein

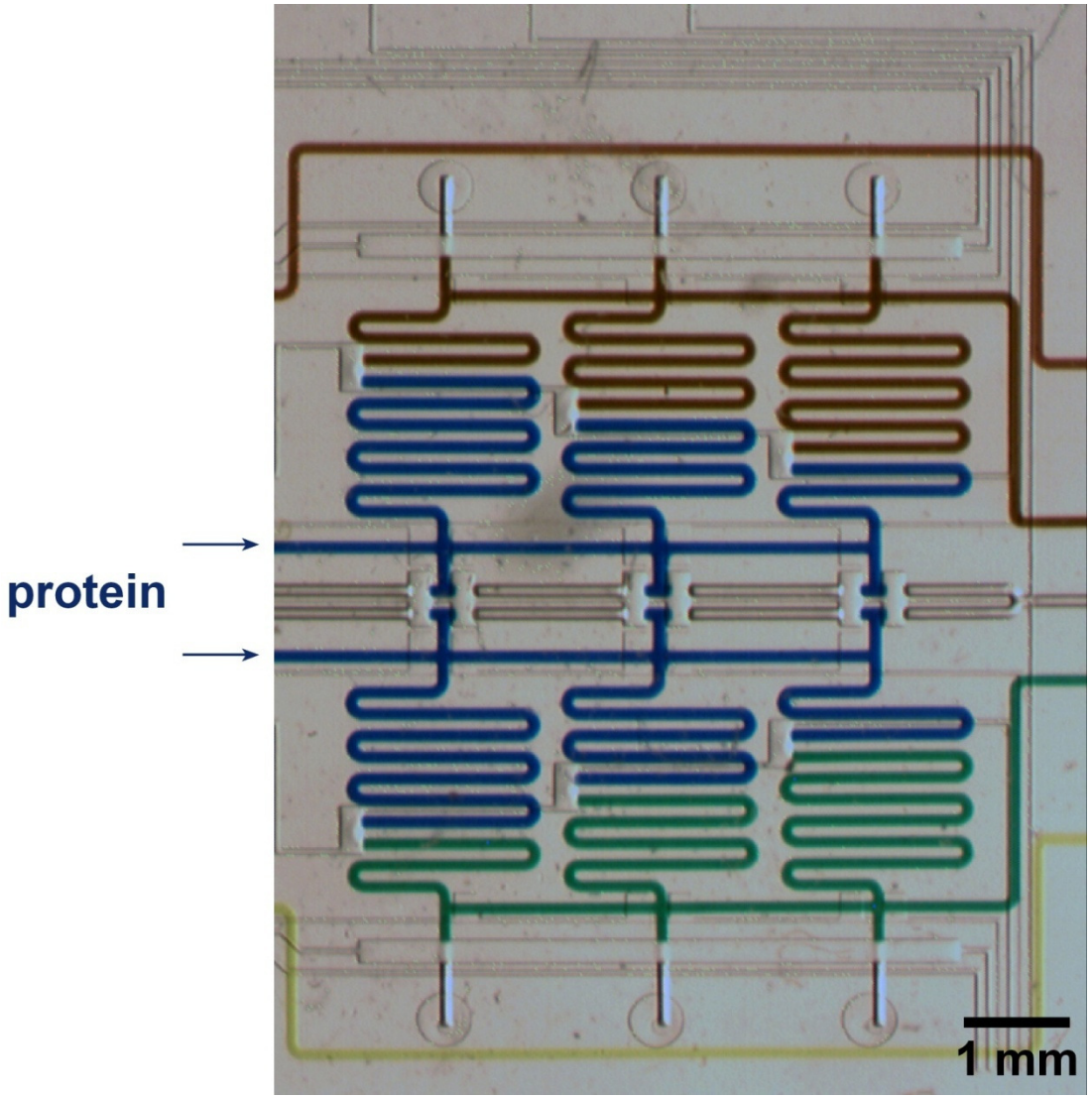


Photo courtesy
of Paul Kenis

Empty Mixtures into Wells

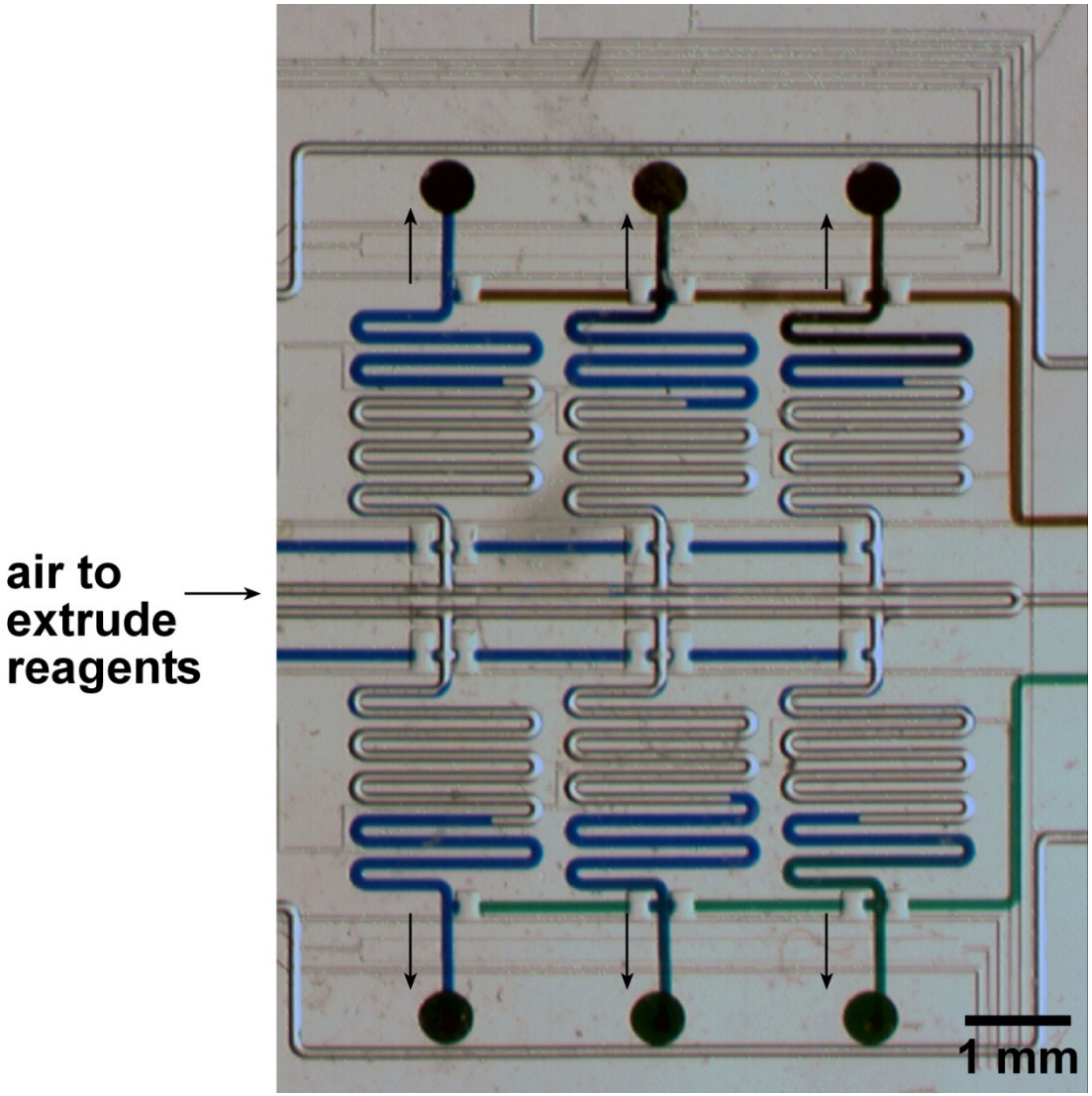
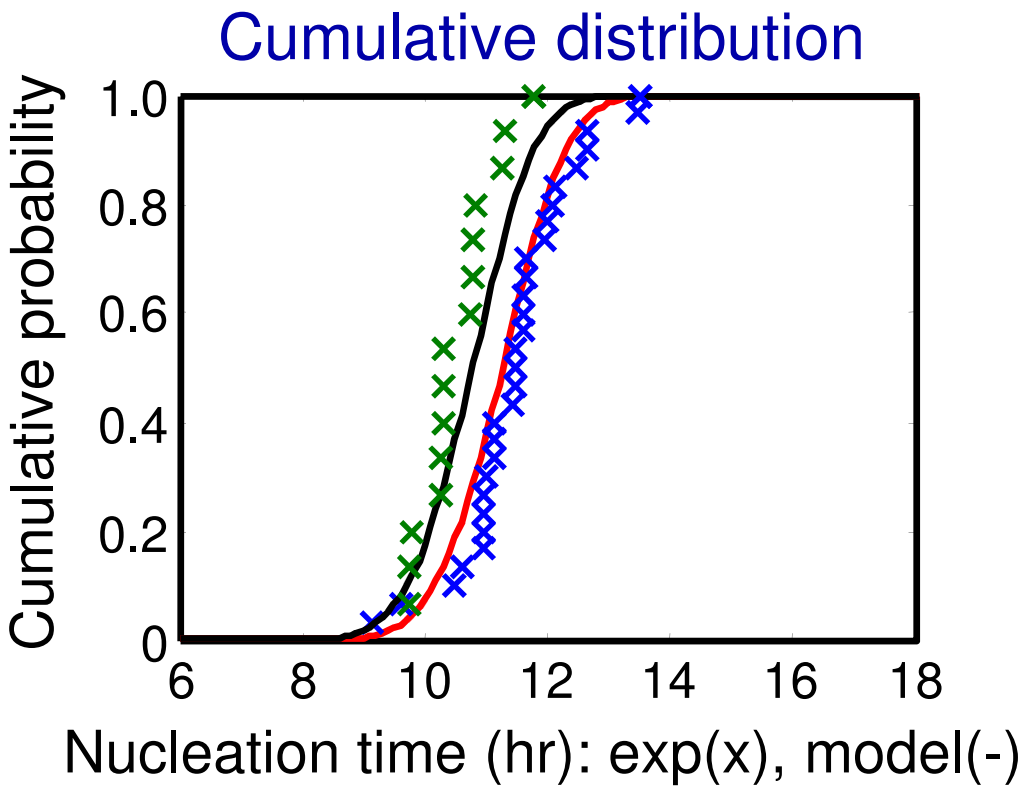


Photo courtesy
of Paul Kenis

Example Application: Lysozyme-NaCl-H2O System

Estimate nucleation kinetics from fitting CDF for a single experiment condition (exps. repeated in parallel)
→ used the "noise" to identify model parameters!



$$J(S) = AC\exp\left(-\frac{B}{(\ln S)^2}\right)$$

Parameter estimates:

$A = 2.2\times10^5$, $B = 9.1$

See references for many more applications:

- L. M. Goh, K. J. Chen, V. Bhamidi, G. He, N. C. S. Kee, P. J. A. Kenis, C. F. Zukoski, and R. D. Braatz. Crystal Growth & Design, 10:2515-2521, 2010
- K. Chen, L. M. Goh, G. W. He, V. Bhamidi, P. J. A. Kenis, C.F. Zukoski, and R. D. Braatz. Chem. Eng. Sci., 77:235-241, 2012

Typical Challenges, and Some Questions

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2. **Sparsity of on-line measurements available for process identification**

   Q: How do we abstract the most information from the data, and redesign systems to obtain more data?

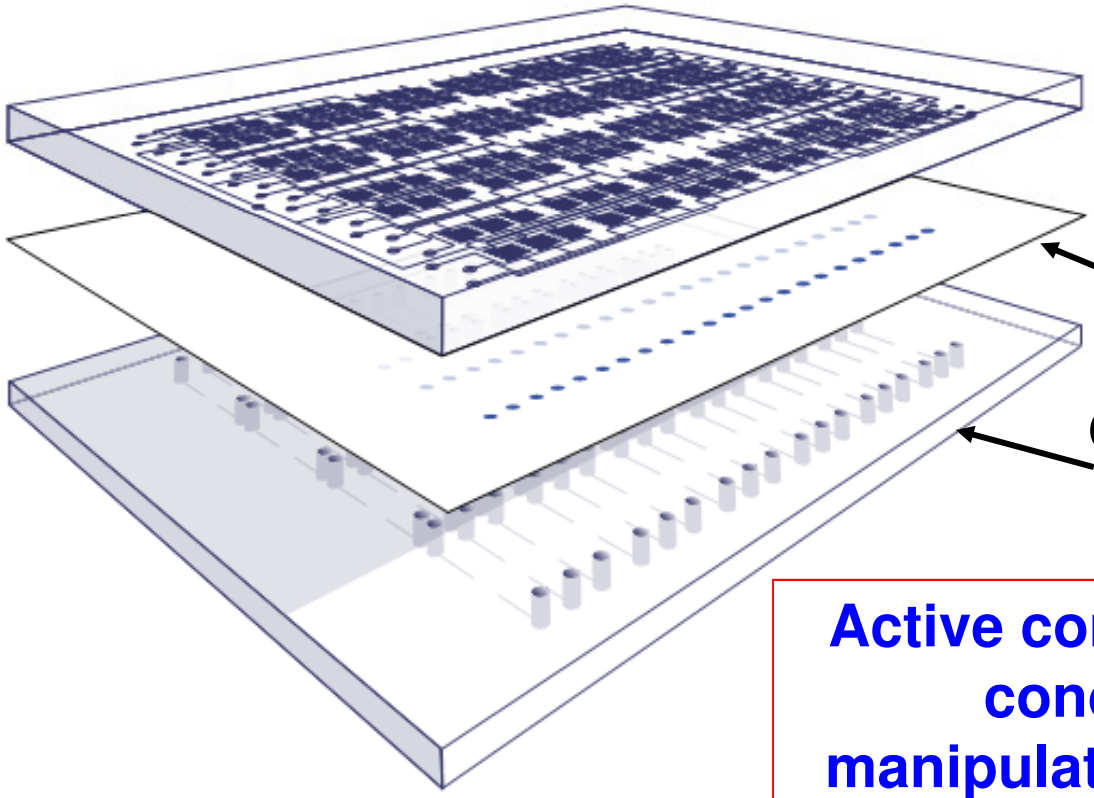
3. **Sparsity of manipulated variables available for process identification and control**

   Q: How do we redesign systems to have more manipulated variables, and formulate tractable approaches to dealing with some of these new modes of manipulation?

3. Create new dof to resolve sparsity of manipulated variables – actuate via surfaces

Nano/Microfluidics Chip:

144 crystallization wells, 5-30 nL each



4 Layers:

Control layer on

Metering + Mixing layer

Layer with through-holes

Crystallization wells and evaporation channels

Active control of evaporation and condensation rates by manipulation of external humidity

S. Talreja, S. L. Perry, S. Guha, V. Bhamidi, C. F. Zukoski, and P. J. A. Kenis. J. Phys. Chem. B, 114:4432-4441, 2010

3. Create new dof to resolve sparsity of manipulated variables – actuate via surfaces

Maximize crystal size for xrd by controlled redissolution & growth

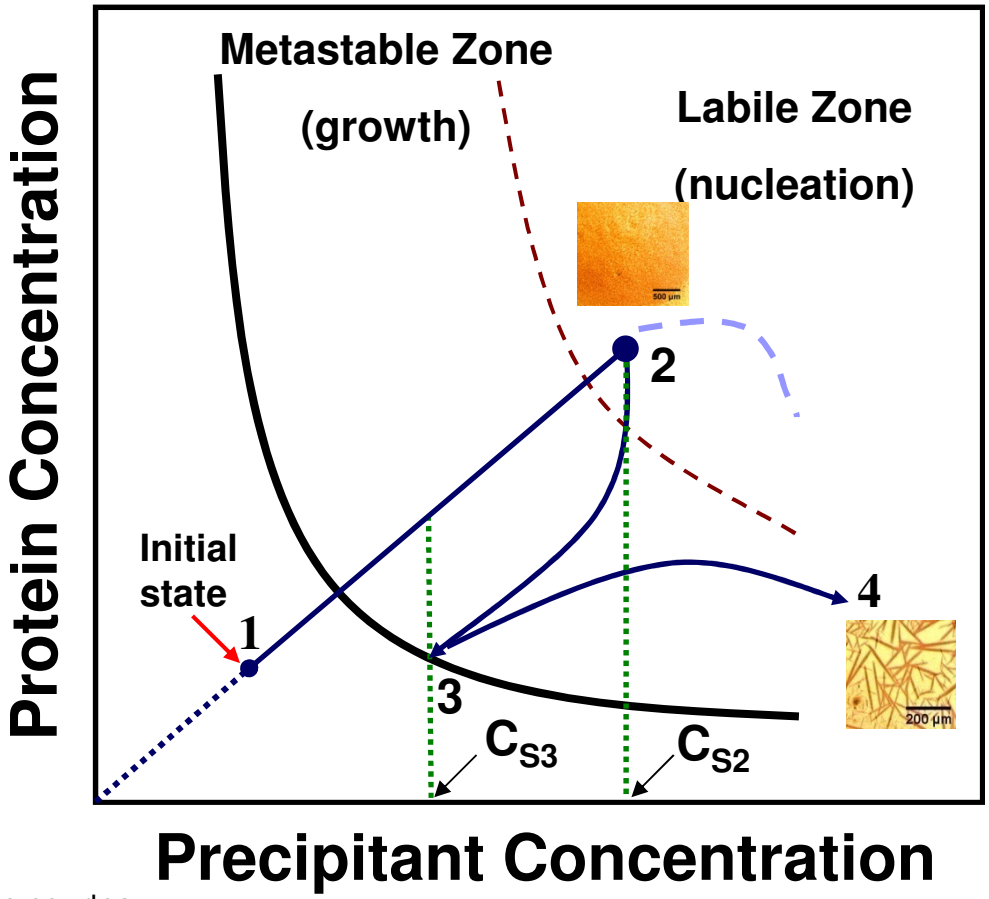
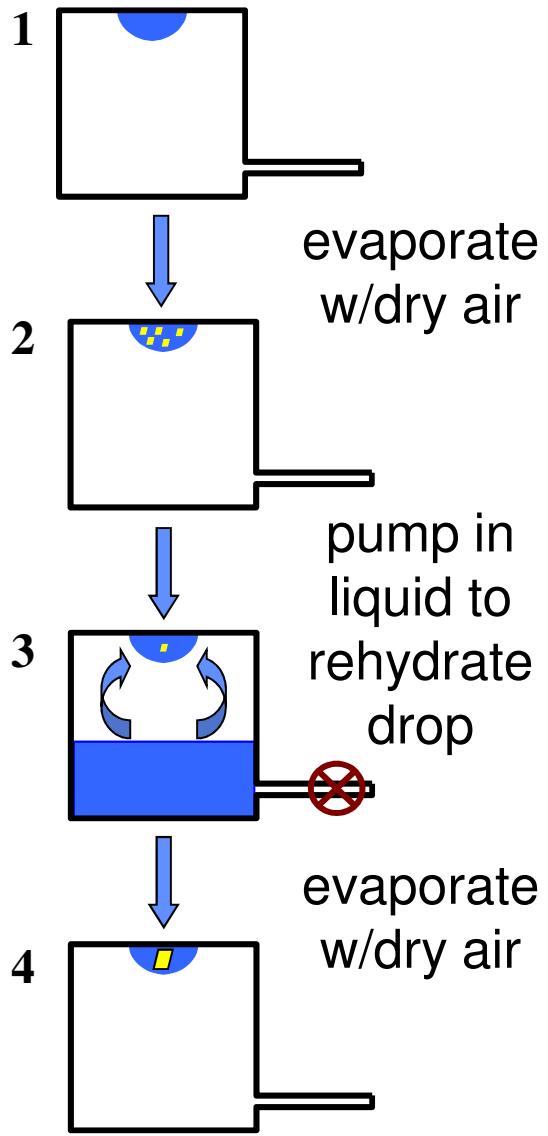


Photo courtesy of Paul Kenis



S. Talreja, S. L. Perry, S. Guha, V. Bhamidi, C. F. Zukoski, and P. J. A. Kenis. J. Phys. Chem. B, 114:4432-4441, 2010

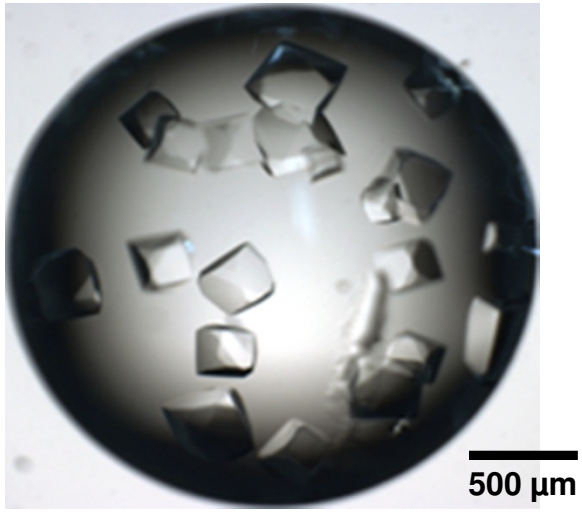
3. Create new dof to resolve sparsity of manipulated variables – actuate via surfaces

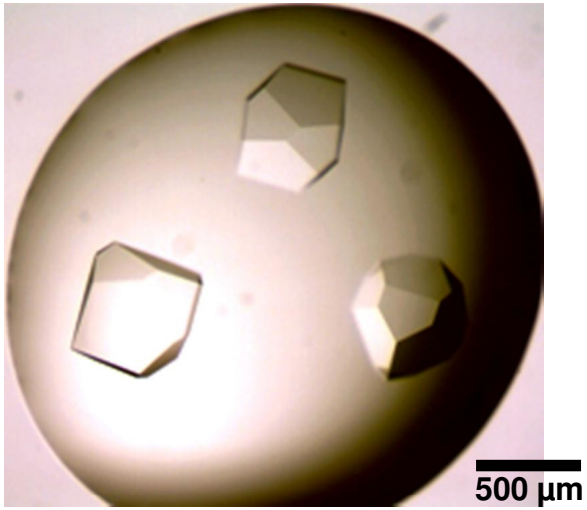
RNase A

C_P/C_S = 10 mg/(mL-M)

C_{P0} = 20 mg/mL

C_{S0} = 2 M



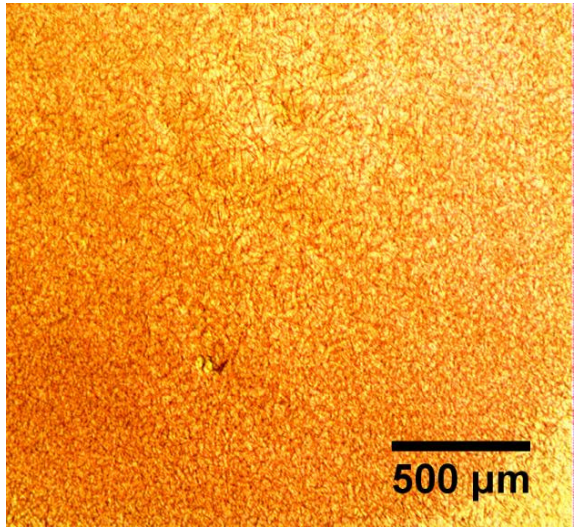


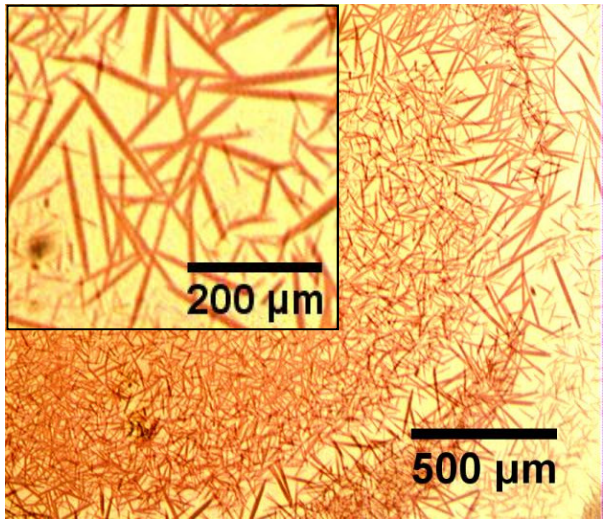
Without Control

With Control

Bacteriorhodopsin (a membrane protein; very difficult!)

C_{P0} = 5 mg/mL

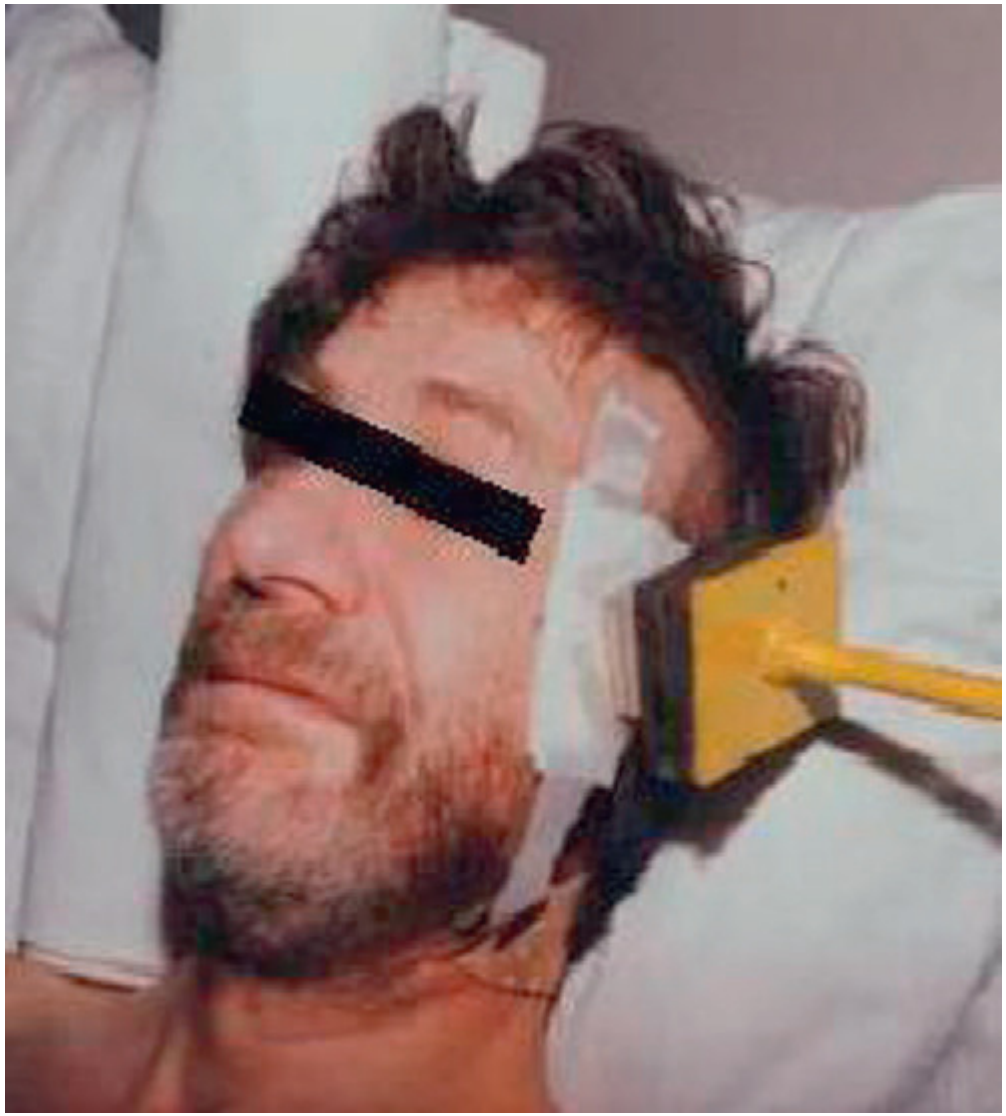




Photos courtesy of Paul Kenis

S. Talreja, S. L. Perry, S. Guha, V. Bhamidi, C. F. Zukoski, and P. J. A. Kenis. J. Phys. Chem. B, 114:4432-4441, 2010

3. Create new dof to resolve sparsity of manipulated variables – actuate via external fields



- **Approach: actuate through external fields**
- **Photograph shows the use of an external magnetic to focus nanoparticles to a tumor**
- **A lot of research is focused on precise control of the motion of particles and the formation of nanostructured materials (e.g., Paul Barton, George Stephanopoulos, Ben Shapiro)**

Photo courtesy of A.S. Lübbe et al., Cancer Research, 56:4686-4693, 1996; A. Sarwar, A. Nemirovski, and B. Shapiro, Journal of Magnetism and Magnetic Materials, 324:742-754, 2012

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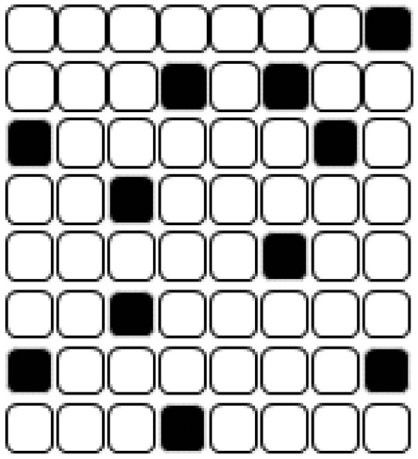
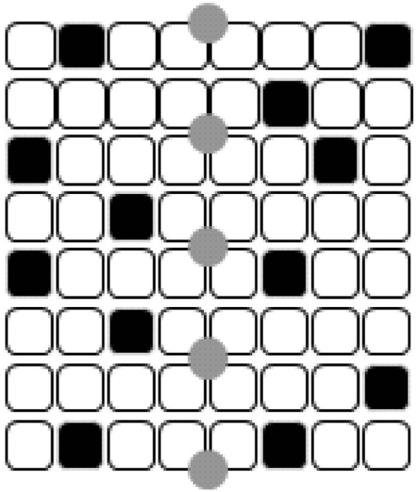
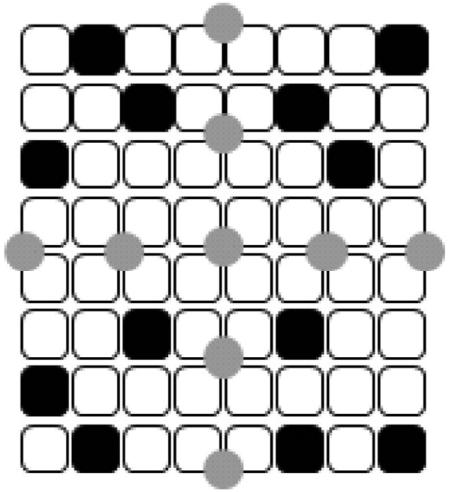


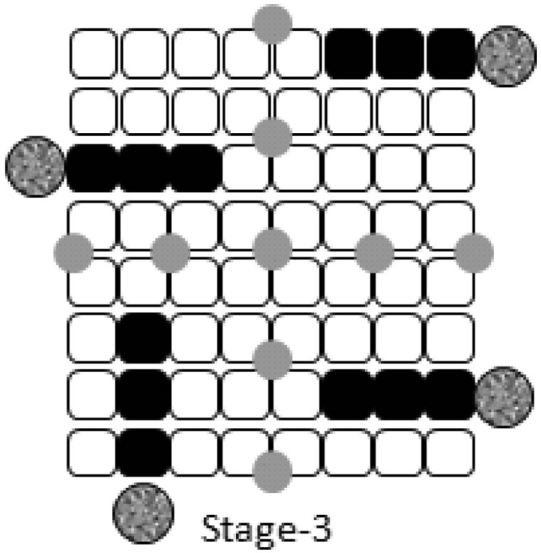
Random Initial Configuration



Stage-1



Stage-2



Stage-3

- **Use of charges above or below a surface to control of the motion of particles to form nanostructured materials**
- **Evolution of control points to construct a 2D nanostructure**

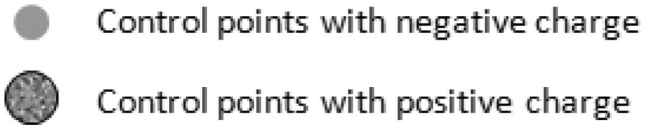
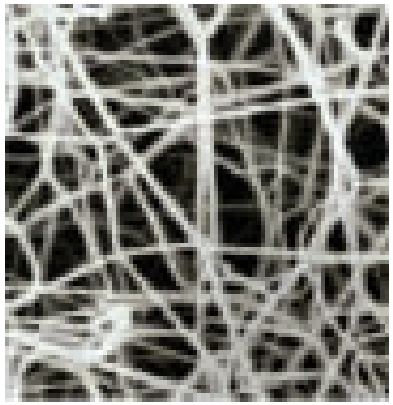
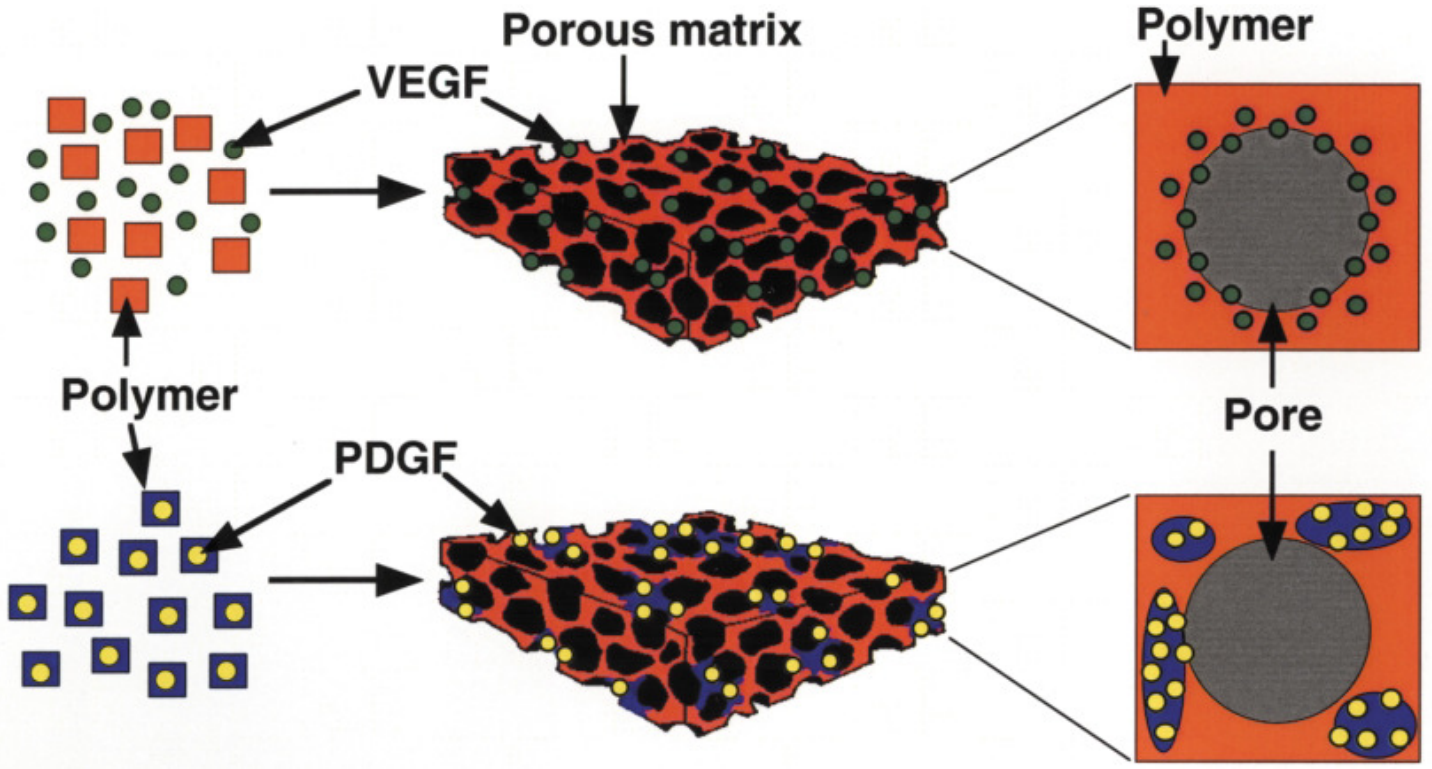


Image from E. O. P. Solis, P. I. Barton, and G. Stephanopoulos. Ind. Eng. Chem. Res., 49:7746-7757, 2010

3. Create new dof to resolve sparsity of manipulated variables – embedded actuation

- **Approach: embed control *into* the system**
- **Release molecules in response to local pH, light, pressure, chemical concentration, temperature, …**

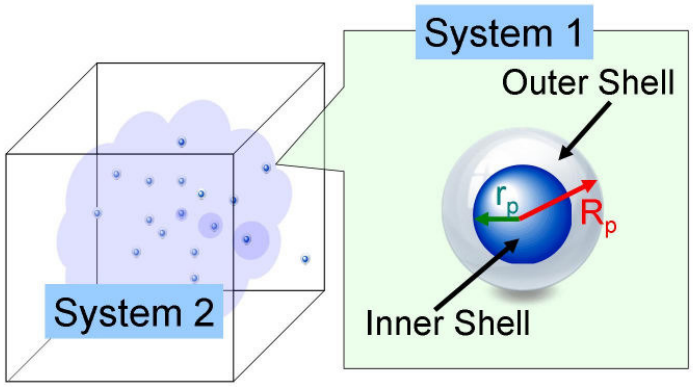


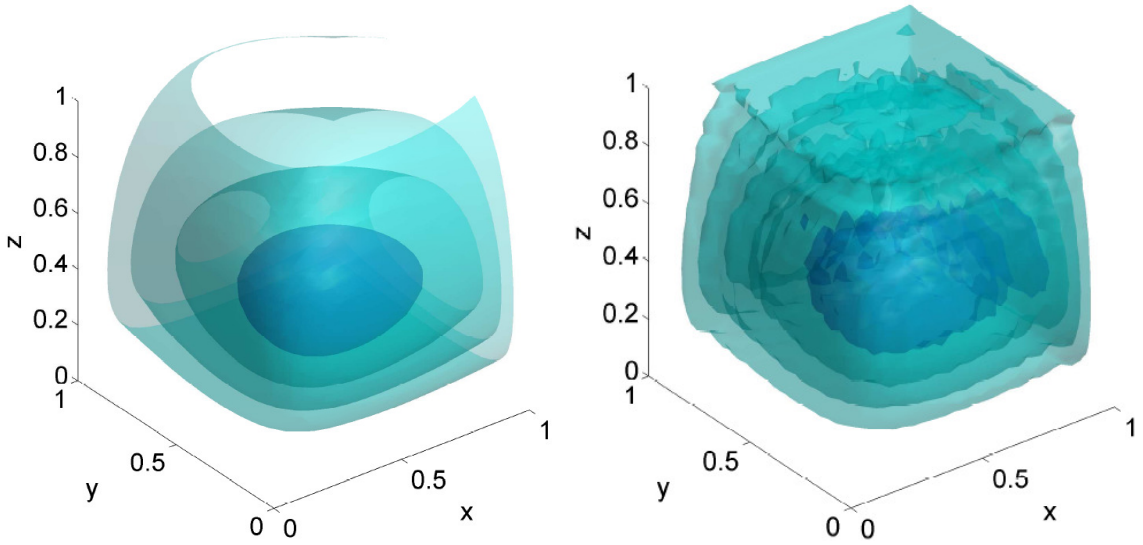


Images from W. M. Saltzman and W. L. Olbricht. Nat. Rev. Drug Disc., 1:177-186, 2002

3. Create new dof to resolve sparsity of manipulated variables – embedded actuation

- **Example of design of embedded particles to release molecules in response to local concentration**
- **Comparison of reference and achieved 3D isosurfaces for the concentration of a signaling molecule released from polymer spheres within a tissue construct**





M. Kishida, D. W. Pack, and R. D. Braatz, *Proceedings of the American Control Conference*, pp. 4361-4366, 2010

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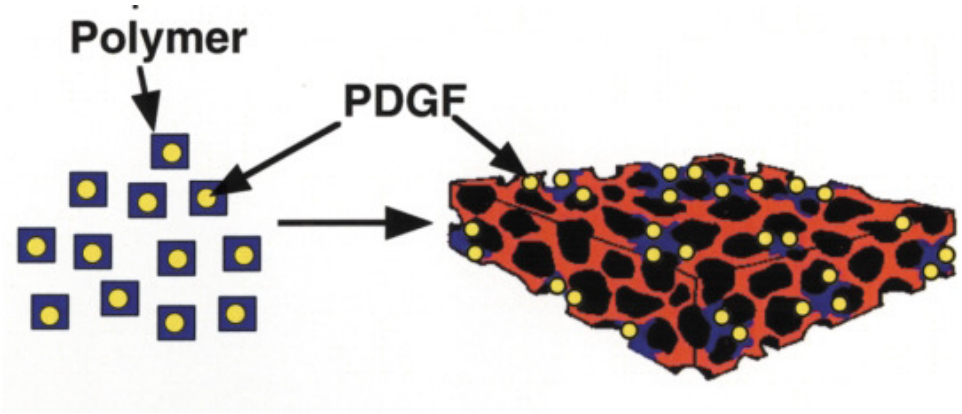
3. **Sparsity of manipulated variables available for process identification and control**

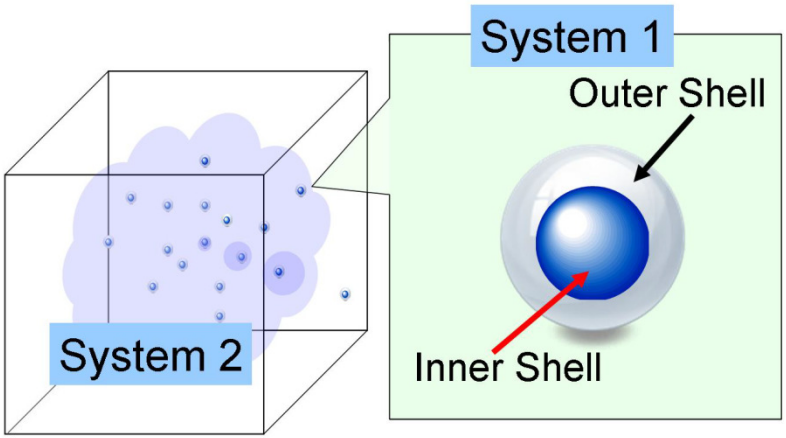
   Q: How do we redesign systems to have more manipulated variables, and formulate tractable approaches to dealing with some of these new modes of manipulation?

Some more questions

- **Approach: embed control *into* the system**
- **Release molecules in response to local pH, light, pressure, chemical concentration, temperature, …**
- **Q: How to handle the large number of dofs?**

→ E.g., a discretization approach for the design and placement of nanoparticles in a tissue construct would require $100\times100\times100\times100\times10 = 10^9$ design variables





$$\frac{\partial c_i}{\partial t} + v \cdot \nabla c_i = \nabla \cdot (D_{eff,i} \nabla c_i) + R_{gen,i} - R_{con,i}$$

Typical Challenges, and Some Questions

1. **High state dimensionality and inherent stochasticity of molecular events**
   - Q: How do we formulate tractable approaches to address systems with these characteristics?
2. **Sparsity of on-line measurements available for process identification**
   - Q: How do we abstract the most information from the data, and redesign systems to obtain more data?
3. **Sparsity of manipulated variables available for process identification and control**
   - Q: How do we redesign systems to have more manipulated variables, and formulate tractable approaches to dealing with some of these new modes of manipulation?

Summary

- Discussed control of systems in which key phenomena occur at the nanoscale
- Discussed some approaches to address the challenges:
  - Fast KMC+ or direct analytical or numerical solution of the Chemical Master equation (by exploiting model structure)
  - Employ high-throughput NEMS/MEMS (to generate data)
  - Exploit information from the intrinsic process noise
  - Create new degrees of freedom for control (surfaces, external fields, and embedded actuation)
- Illustrated approaches on a variety of applications
- Model identification, estimation, and control designs have been validated in experiments

Outline

- Introduction
- Challenges and questions
- Some approaches
- Some more questions

Structure of Chemical Master Equation

- **Chemical Master equation:**

$$\frac{dP(\sigma,t)}{dt} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t)$$

- **Linear time-varying system:**
  - **Probabilities stacked into a single state vector *x*(*t*)**

$$\frac{d}{dt}x(t) = A(t;\theta)x(t)$$

  - **The chemical kinetic, adsorption and desorption constants, diffusion coefficients, and equilibrium constants collected into the vector θ**
  - **Transition rates collected into the matrix *A*(*t*;θ) that depends on temperature, external species concentrations, etc.**
  - ***A*(*t*;θ) is highly structured for most nanoscale systems**

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Some more questions

Q: How to develop theory and algorithms for the identification, estimation, and control of

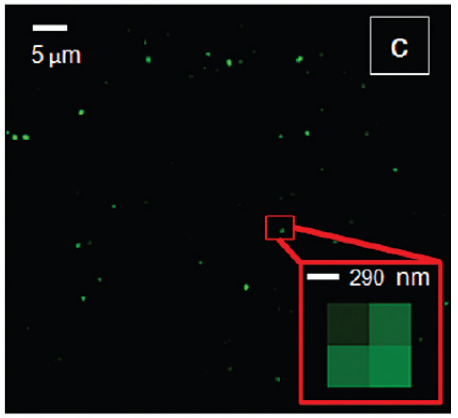
- **Nanoscale systems**

$$\frac{d}{dt}x(t) = A(t;\theta)x(t); \qquad \frac{d}{dt}x(t) = A(u(t);\theta)x(t)$$

- **Multiscale systems, e.g.,**

$$\frac{d}{dt}x(t) = A(y(t);\theta)x(t)$$

$$L(y(t),u(t);\varphi) = 0 \quad \text{(IPDAE system)}$$



Probabilities are computed in the CME model, but usually measure result of a single realization; w/different stochasticity

→ Would increase theoretical confidence (by directly analyzing the CME instead of low-order fit), & provide real-time solutions

Some more questions

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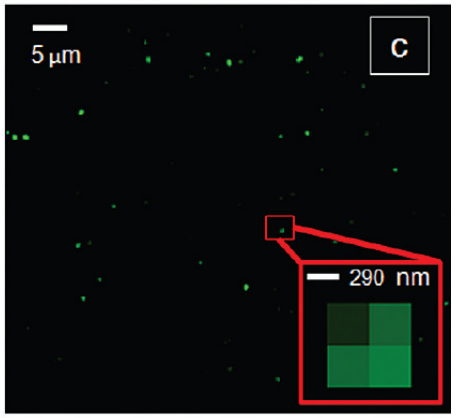

Q: How to best deal with uncertainties vs. inherent stochasticity (largely non-Gaussian)? Direct application of Markov Chain Monte Carlo & Polynomial Chaos Expansions or something better able to exploit the model structure?

Some more questions

- **Q: How do we educate our nanoscale collaborators to transition our systems engineering methods into practice?**
- **Partial solution: serve on nano PhD committees**
- **Partial solution: jointly supervise graduate students and postdocs to solve their nanosystems problems**
- **Partial solution: Courses; MIT graduate students take**
  - **Numerical methods (probability, statistics, Chemical Master Eqns., KMC simulation, population balance models, IPDAEs) – ALL**
  - **Systems engineering (structural analysis, dynamic modeling, steady-state and dynamic simulation and simulators, optimization, DAEs, SPC, process control) – most graduate students take this**

  → Students gain understanding and learn the same language as process systems engineers

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