CONTROL OF NANO AND MICROCHEMICAL SYSTEMS

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Abstract

Many advances in the development of nano and microchemical systems have occurred in the last decade. These systems have significant associated identification and control challenges, including high state dimensionality, limitations in real-time measurements and manipulated variables, and significant uncertainties described by non-Gaussian distributions. Some strategies for addressing these challenges are summarized, which include exploiting structure within the stochastic Master equations that describe molecular interactions, manipulating molecular bonds at system boundaries, and manipulating molecules and nanoscale objects through magnetic and electric fields. The strategies are illustrated in a variety of applications that include the estimation of nucleation kinetics of protein and pharmaceutical crystals within fluidic devices, the estimation of two-dimensional concentration fields using DNA-wrapped single-walled carbon nanotube-based sensor arrays, the simultaneous control of nanoscale geometry and electrical activation during thermal annealing in a semiconductor material, and the control of nanostructure formation on surfaces. Promising directions for research and technology development are identified for the next decade.

Keywords

Nanotechnology, Microchemical systems, Molecular nanotechnology

Introduction

Remarkable advances have been made in the last decade on technologies for *nano and microchemical systems*, which are systems in which chemistry is carried out at nano- to microliter volumes (Squires & Quake, 2005; Marre & Jensen, 2010). The objective of using these technologies to manufacture high quality products has motivated a growing literature on the identification and control of these systems. The focus of this article is on the control of chemical systems that have key components with dimensions at the nano or microscale. Atomic force microscopy, thin film deposition, and multiscale systems are minimally covered, as these topics are already described in past reviews (e.g., see Siettos et al., 2006; Vlachos et al., 2006; Christofides & Armaou, 2006; Braatz et al., 2006ab; 2008; Moheimani, 2008; and citations therein). Also, this paper is primarily focused on aspects of microscale systems beyond those covered in a previous review (Kothare, 2006). A summary of challenges that arise when solving control systems tasks for nano and microchemical systems is followed by a description of promising directions for addressing those challenges.

Challenges and Requirements

In a macroscopic system, the measured outputs are stochastic due to measurement noise and unknown disturbances arising from fluctuations in the environment in variables such as temperature and pressure. If the measurement noise and unknown disturbances for a macroscopic system could be completely removed, the measured outputs would be deterministic. This underlying deterministic character of the relationships between process inputs to states and outputs enables macroscopic systems to be described by deterministic models with isolated stochastic terms to account for measurement noise and unknown disturbances (Beck & Arnold, 1977; Ljung, 1999). Much of the phenomena that occur at the nano and microscale are stochastic in a way that is very different from the fluctuations typically observed in a macroscopic system. In particular, ***phenomena at the molecular scale are inherently stochastic***, so that a repeated experiment can produce vastly different outputs even if the overall system has no measurement noise and no unknown disturbances.

As an example of such a phenomenon, consider the nucleation of crystals in droplets of solution, for which a large number of high-throughput microfluidic platforms have been developed over the past decade for the crystallization of organic compounds including amino acids, proteins, and active pharmaceutical ingredients (e.g., see Figure 1 and Hansen et al., 2002; Zheng et al., 2003; Squires & Quake, 2005; Talreja et al., 2005; Anderson et al., 2006; Li & Ismagilov, 2010). These microseparation systems enable the efficient high-throughput search for solvents, molecular additives, and dynamic operating conditions that nucleate and grow high quality protein and pharmaceutical crystals for subsequent analysis via X-ray or neutron crystallography, and enable the investigation of crystallization kinetics for a much wider range of conditions than achievable at the macroscale (ten Wolde & Frenkel, 1997; Vekilov, 2004; Goh et al., 2010). Such applications have the potential to impact structure-function analysis, pharmaceuticals design, bioseparations, controlled drug delivery, treatment of protein condensation diseases, and study of human degenerative conditions (Bucciantini et al., 2002; Vekilov, 2004; Pan et al., 2005). The measured output for a single droplet is the *induction time*, which is the time in which the first crystal nucleates. The measured induction time can vary by a factor of two or more, even when the experiment is designed to have negligible disturbances and measurement biases and noise, due to the very small volume of each droplet and that the very small number of crystals in a droplet (e.g., ten Wolde & Frenkel, 1997; Izmailov et al., 1999). In such a system, treating the measured output as "*the* induction time" is not appropriate, and the true measured output is represented in terms of an induction time distribution or a cumulative induction time distribution (see Figure 2). Quantities derived from such distributions, such as the measured mean induction time or the standard deviation of the induction time, contain much less information than the entire distribution. For nano and microscale systems, the distributions of process outputs are typically not Gaussian, so that the assumption of an underlying Gaussian distribution parameterized by a mean and a variance is not appropriate.

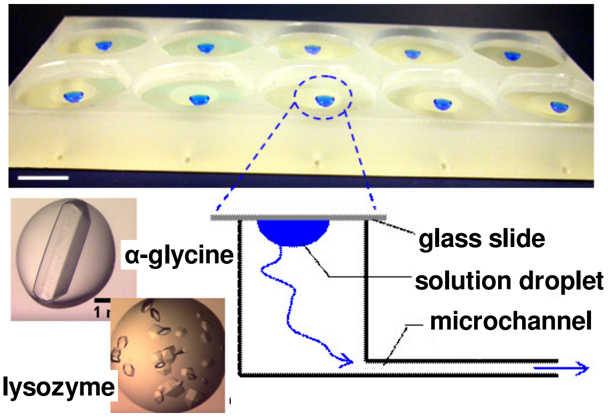

Figure 1. A microfluidic platform that uses evaporation to induce nucleation in microliter droplets (Kee et al., 2008ab). The evaporation rate in each droplet is specified by the partial pressure of water at the droplet surface, the area and length of each channel that connects the droplet to external air, and the humidity of the external air.

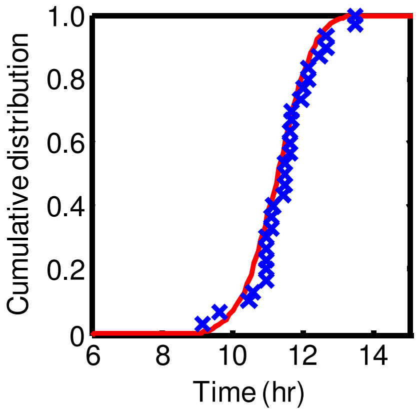

Figure 2. Cumulative induction time distributions for droplets containing lysozyme and sodium chloride in aqueous solution: experimental data (×), and model (line) in Eq. 3 fit to the data (Kee et al., 2008ab). The measured induction times range from about 9 to 14 hr for the same experimental conditions.

As phenomena at the molecular scale are inherently stochastic, the measured outputs of nano and microscale systems that are a direct consequence of those molecular scale dynamics are also inherently stochastic. Stochastic dynamics with continuous states are typically described by Langevin dynamics or the Fokker-Planck equation (Fokker 1914, Planck 1917). However, when there are only a discrete number of states, stochastic dynamics are described by Master equations (Kendall, 1949; Fichthorn and Weinberg, 1991):

$$\frac{dP(\sigma,t)}{dt} = \sum_{\sigma'} W(\sigma',\sigma)P(\sigma',t) - \sum_{\sigma'} W(\sigma,\sigma')P(\sigma,t) \quad (1)$$

where $P(\sigma,t)$ is the probability that the system is in configuration σ at time t, and $W(\sigma',\sigma)$ is the rate of transitions between configuration σ' and σ (in units of inverse time). Each Master equation is the conservation equation for the probability of a configuration (accumulation = in – out), with the overall system described by writing Eq. 1 for every possible configuration in the system. For example, for the nucleation of crystals in droplets, one configuration is the droplet containing no crystals, another configuration is the droplet containing one crystal, etc. The structure of Eq. 1 is relatively simple, being linear in the probabilities $P(\sigma,t)$, each of which lie in the interval between 0 and 1. The probabilities can be stacked into a single state vector $x(t)$ and the transition rates collected into a matrix $A(t;\theta)$ that enables Eq. 1 to be written in state-space form:

$$\frac{d}{dt}x(t) = A(t;\theta)x(t) \quad (2)$$

where $A(t;\theta)$ depends on additional variables such as temperature or concentrations of species external to the system that can vary with time, and on a vector of first-principles model parameters θ such as chemical kinetic, adsorption, or desorption rate constants; surface diffusion coefficients; and equilibrium constants. As an example, the nucleation of crystals in droplets for the microfluidic platform in Figure 1 can be modeled by the Master equations

$$\begin{aligned} \frac{dP_0(t)}{dt} &= -\kappa(t)P_0(t), \\ \frac{dP_n(t)}{dt} &= \kappa(t)(P_{n-1}(t) - P_n(t)), \quad n = 1,2,\ldots, \end{aligned} \quad (3)$$

where $P_n(t)$ is the probability that the number of crystals is equal to n at time t and $\kappa(t) > 0$ is the transition probability of nucleation in units of inverse time, which depends on the solubility, crystallization kinetics, evaporation rate, and initial droplet volume and solution concentrations (Goh et al., 2010; Jiang et al., 2011). In most applications, the initial number of crystals in a droplet is equal to zero, which is described by the initial conditions $P_0(0) = 1$ and $P_n(0) = 0$ for $n > 0$. The number of possible configurations in the above model, as well as the number of states in Eq. 2, is infinite.

As another example, consider the Master equation for adsorption and desorption of molecules on a DNA-wrapped single-walled carbon nanotube used for single-molecule sensing (see Figure 3). A standard approach for reducing the number of configurations is by defining equivalence classes (e.g., Oguz & Gallivan, 2008), which for this application involves ignoring which sites on the nanotube contain the adsorbed molecules. This representation produces the simplified Master equations (Ulissi et al., 2011)

$$\begin{aligned} \frac{dP_0(t)}{dt} &= -k_A' N_T P_0(t) + k_D P_1(t), \\ \frac{dP_i(t)}{dt} &= k_A'\left(N_T - (i-1)\right)P_{i-1}(t) \\ &\quad -\left(k_D i + k_A'(N_T - i)\right)P_i(t) \\ &\quad + k_D(i+1)P_{i+1}(t), \quad i = 1,\ldots,N_T - 1, \\ \frac{dP_{N_T}(t)}{dt} &= k_A' P_{N_T-1}(t) - k_D N_T P_{N_T}(t), \end{aligned} \quad (4)$$

where N_T is the number of potential sites for adsorbed molecules on the nanotube, P_i is the probability that the nanotube has i molecules adsorbed somewhere on its surface, k_D is the desorption rate constant, and k_A' is the adsorption rate constant, which is proportional to the concentration of the adsorbing species in the surrounding solution. Both rate constants can vary with time, due to time-varying temperature during sensing. The nanotube-based sensor computes the latter concentration by real-time estimation of the adsorption rate constant k_A' from the measured adsorption and desorption events (Boghossian et al., 2011). The matrix A in the state equation (Eq. 2) has row and column dimensions equal to the number of potential adsorption sites plus one, which is high for long nanotubes (carbon nanotubes have been grown that are longer than 10 centimeters, Zhang et al., 2011).

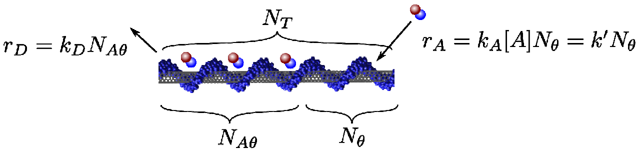

Figure 3. Schematic of adsorption and desorption on a DNA-wrapped single-walled carbon nanotube (Ulissi et al., 2011). The arrow points to an open adsorption site.

The main challenge with implementing control systems tasks for process models described by Master equations ***is that the number of states is usually very large***, often higher than 10^{10}. For this reason, few chemists and chemical engineers have attempted to solve Eq. 1 directly, but instead employ kinetic Monte Carlo (KMC) simulation, which follows a single realization of the Master equation by calling a random number generator to select among the possible transitions with probabilities defined by the kinetic rate laws for each allowed kinetic event. At most one kinetic step can be taken during each time step of the KMC algorithm, with the time step (typically on the order of 1 ns) selected so that the time simulated in the KMC algorithm corresponds to real time (Fichthorn & Weinberg, 1991). Although a KMC simulation is usually much faster than exactly solving the Master Eq. 1 for each possible configuration, a KMC simulation for a process of practical importance is typically on the order of a day using a personal computer of 2011. Further, if an entire state or output distribution is of interest, a large number of KMC simulations are needed to generate even an approximation for the distributions. If the control objective only depends on some statistic of the output distribution, then a feedback controller can be designed based on a low-order "equation-free" model fit to the results of one or more KMC simulations (e.g., Kevrekidis et al., 2004; Siettos et al. 2003). Alternatively, black-box models can be used to replace a full model with a simplified one (Oguz et al. 2008). In both equation-free and black-box models, the physicochemical relationships between the states and controlled variables on the manipulated variables are no longer transparent.

Another challenge is that nanoscale systems typically have ***few variables at the nanoscale available for real-time manipulation by a digital control system***. For example, multilayered polyelectrolyte nanofilms for the spatially localized release of molecules to kill tumor or bacteria cells or promote tissue regeneration are surgically implanted into the macroorganism so that no real-time variables are available for manipulation (e.g., Macdonald et al., 2011; Poon et al., 2011). The only parameters available for optimization to produce a desired time profile of molecular release are specified during the manufacture of the polyelectrolyte nanofilm. As another example, the only variable that typically can be manipulated in real-time during the rapid thermal annealing of a nano or microstructure is the time-varying power to heating lamps. A sparsity of variables for real-time manipulation limits the degrees of freedom available for control.

Reduced availability of manipulated variables tends to be less of an issue for microscale systems than for nanoscale systems. For example, consider that the variables available for real-time manipulation in the microfluidic platform in Figure 1 are the temperature and evaporation rate, which can be implemented by enclosing the entire microfluidic system within a box instrumented with feedback control of temperature and humidity. These manipulated variables, although specified at the macroscale, have a direct effect on the solution concentrations within each droplet. Although it is difficult to specify a different temperature in each droplet in a single device due to the high surface area-to-volume ratio, the evaporation rate can be specified to be different in each droplet by selecting different areas and/or lengths for the channel connecting each droplet to the exterior air (see Figure 1). The selection of temperature, channel areas and lengths, and controlled time-varying evaporation rate enables the direct specification of dynamic conditions within each droplet.

Another control challenge is that ***limited real-time measurements are available for most nanoscale systems***. Sensors require a certain quantity of material to be able to produce useful information. For example, no real-time sensors are available for measuring the solution concentrations in nanoliter droplets. As another example, no real-time sensors are available for measuring the interior pH or concentrations within multilayered polyelectrolyte nanofilms used for the release of growth factors, hormones, or pharmaceutical compounds (Macdonald et al., 2011; Poon et al., 2011). The limited real-time sensors make both identification and control challenging.

Models for nano and microscale systems have significant uncertainties. The distributions of measured outputs for nano and microscale systems are often non-Gaussian, as will be seen in the next section, which is incompatible with the most common parameter estimation and stochastic control systems techniques (Beck & Arnold, 1977, Chen et al., 1995). The non-Gaussian distributions of the measured outputs as well as nonlinearities in the models imply that the probability distributions on the model parameters computed from a rigorous parameter estimation procedure will typically be non-Gaussian.

Promising Research Directions

This section describes some promising approaches for addressing the aforementioned challenges to the control of nano and microscale systems. While any sufficiently general set of systems engineering methods developed for multiscale systems automatically applies to molecular, nanoscale, and microscale systems, which has been discussed in detail in past reviews (Braatz et al., 2006ab), general approaches for multiscale systems can fail to take advantage of the underlying structure of specific classes of nano- and microscale systems that can be exploited to greatly facilitate control systems tasks such as parameter estimation, experimental design, and feedback control.

A significant effort has been directed in the last decade on ***exploiting time-scale separation inherent in many physicochemical systems to accelerate KMC simulations*** (e.g., see Rao & Arkin, 2003; Rico-Martinez et al., 2004; Cao et al., 2005, Chatterjee & Vlachos, 2007; Zheng et al., 2008; Rishi et al., 2011, and citations therein). Rather than basing the completion of control systems tasks on running large numbers of KMC simulations to approximate the dynamics of Master equations, some recent efforts have been towards direct solution of the Master equations that explicitly exploit their sparse and highly structured character. One approach is the direct numerical solution of Eq. 1 using sparse ordinary differential equation solvers (Lakerveld et al., 2011), which is applicable for systems with up to tens of millions of configurations. Further reductions in computational cost can be obtained using methods that project the state vector in the Master equation to a lower dimensional space or employ other model reduction algorithms design for direct application to the Master equations (e.g., see Peles et al., 2006; Engblom, 2009; Engblom et al., 2009; Drawert et al., 2010; and citations therein). Although there is a limit to the complexity of the Master equations that can be solved using these numerical methods, this approach is feasible for many nanoscale systems of practical importance, and numerical algorithms are expected to continue to improve over the next decade.

Another approach for addressing specific classes of systems described by Master equations is by the derivation of analytical or semi-analytical solutions of Eq. 1 by exploiting the structure of the equations. While this approach is not applicable to all nano/microsystems, analytical solutions can be derived for many applications. For example, while the number of states for the nucleation in droplets is infinite, with the matrix A in Eq. 2 having infinite row and column dimensions, the matrix A is highly structured, being both bidiagonal and Toeplitz. For this microfluidic system, a probability-generating function (Kendall, 1949) can be used to derive a semi-analytical solution to Eq. 3 that describes the dynamics of crystal nucleation in droplets as

$$P_n(t) = \frac{1}{n!}\left[\int_0^t \kappa(s)ds\right]^n e^{-\int_0^t \kappa(s)ds}, \tag{5}$$

for all positive integers n (Goh et al., 2010). Numerical evaluation of Eq. 5 only requires a small number of algebraic operations and the computation of an integral whose computational cost at time t can be reduced by incorporating the integral computed at the last previous time instance for which the integral was computed:

$$\int_0^t \kappa(s)ds = \int_0^{t-\Delta t} \kappa(s)ds + \int_{t-\Delta t}^t \kappa(s)ds. \tag{6}$$

The function $\kappa(t)$ and its derivative vary by more than six orders-of-magnitude in a typical induction time experiment, whose dynamics can be efficiently handled by employing an ordinary differential equation solver with adaptive time-stepping,

$$I(t) := \int_0^t \kappa(s)ds \quad \Rightarrow \quad \frac{dI}{dt} = \kappa(t). \tag{7}$$

The above analytical solutions have been applied to the solution of systems engineering problems, such as the identification of parameters in nucleation rate expressions (Goh et al., 2010) and the determination of upper and low bounds on nucleation rates (basically, a state estimation problem, Chen et al., 2011a).

As an example of a different approach in exploiting structure, the state matrix A in Eq. 2 corresponding to Eq. 4 for modeling the adsorption of molecules on a nanotube is tridiagonal and highly structured. Equations 4 can be equivalently formulated in terms of two discrete population balances, with one population being the number of adsorbed molecules and the other population being the number of open sites (Jahnke & Huisinga, 2007). This reformulation facilitates the derivation of an analytical solution that is the convolution of binomial distributions with parameters N_T and $\bar{N}_{A\theta}$, the latter of which is described by

$$\frac{d\bar{N}_{A\theta}}{dt} = k'_A(N_T - \bar{N}_{A\theta}) - k_D\bar{N}_{A\theta} \tag{8}$$

for suitably defined initial conditions (Ulissi et al., 2011). As in Eq. 5, the computational cost of computing the semi-analytical solution of Eq. 8 only requires a small number of algebraic operations and the numerical determination of an integral. This approach has been applied to the (*i*) maximum likelihood estimation of adsorption rates, which have been used to estimate nitric oxide concentration near the carbon nanotube, (*ii*) the quantification of uncertainties in these estimates, and (*iii*) the reconstruction of two-dimensional nitric oxide concentration fields from arrays of carbon nanotubes (Ulissi et al., 2011).

Many methods are available for exploiting the structure of linear ordinary differential equations to derive numerical, analytical, or semi-analytical solutions that can be applied to the Master equations that arise in nano- and microscale systems. For example, the Master equations for some nanoscale systems have an A matrix that is symmetric circulant, in which case the real Fourier matrix can be used to diagonalize the equations, which can be exploited for carrying out systems tasks including robust optimal control design (e.g., see VanAntwerp et al., 2001, and citations therein). Research is expected to continue on fast methods for the analysis of Master equations, both in terms of general methodology and in addressing specific classes of applications, as these methods enable facile application of systems engineering.

Many methods have been developed in recent years for addressing the sparsity of real-time manipulating variables available in most nanoscale systems. ***One approach is to modify the system boundaries at the molecular scale to create desirable feedback interactions during manufacturing*** (Seebauer et al., 2006; 2010). This approach of embedded feedback is the application at the molecular scale of the autoregulatory feedback paradigm developed for macroscale processes many decades ago and investigated more recently in tissue engineering and other biomedical systems (e.g., see Braatz et al., 1994; Kishida et al., 2010; and citations therein). ***Another interesting recent approach is to employ action-at-a-distance magnetic or electric fields for real-time manipulation of molecular motion or nanoparticles*** (Solis et al., 2010ab; Lakerveld et al., 2011; Probst and Shapiro, 2011). This approach provides many more degrees of freedom than relying solely on the selection of initial conditions and self-assembly to attempt to produce a desired positioning or structural arrangement of molecules (e.g., such as in Drews et a., 2006; 2007; Liu et al., 2009; and citations therein). One of the applications of localized feedback or action-at-a-distance fields of high interest has been in combining drug targeting with surface-modified nanoparticles with light to cause the nanoparticles to release their payloads or greatly increase their temperature, often for the purpose of detecting or killing tumor cells (Otsuka et al., 2003; Paciotti et al., 2004; Pissuwan et al., 2006; Ghosh et al., 2008; Liong et al., 2008; Qian et al., 2008). Methods have been developed for the robust optimal control of spatial fields (Kishida & Braatz, 2009ab; 2010ab), for which the manipulated variable is a spatial field, that may be potential for the real-time manipulation of molecular motion or nanoparticles, either by action at a distance (Solis et al., 2010ab; Lakerveld et al., 2011; Probst and Shapiro, 2011) or by fluid flow fields (e.g., Tanyeri et al., 2010; Mathai et al., 2011). Finally, passive control of microscale systems can be achieved by appropriate design of the active volume (Marre & Jensen, 2010).

Sensor technologies are being developed that greatly expand the number and quality of real-time measurements in nanoscale and microscale systems. For example, DNA-wrapped single-walled carbon nanotube-based sensors have been developed that are able to measure the adsorption and desorption of single molecules (Boghossian et al., 2011). These sensors can be arranged into a two-dimensional (2D) array, to enable the real-time measurement of the 2D spatial variation of molecules in nano- and microscale systems. The nanotubes can be chemically modified or coupled with strong-binding enzymes or fluorescent dyes to measure in real-time the spatial concentration fields of different molecules (e.g., see Ahn et al., 2011; Heller et al., 2011; Ulissi et al., 2011; and citations therein).

A strategy for improved estimation of model parameters from limited sensors in nanoscale systems is to abstract additional information from the noise statistics. For example, the estimation of two model parameters from repeating the exact same experiment with only one datum per experiment has been demonstrated for the high-throughput device in Figure 1 (Goh et al., 2010). The two model parameters were associated with a nucleation rate described by classical nucleation theory and the single datum per experiment was the measured induction time. In a macroscale system, it is usually impossible to estimate two model parameters from repeated experiments in which only one datum is measured during each experiment, as the measurement noise and unmeasured disturbances characterize the differences in the measured value in each experiment, and their effects on the measured value are stochastically different in each experiment. In such systems, extra experiments improve the accuracy of the stochastic model for the measurement noise and disturbances but do not provide information on the nominal model.

The situation is very different at the molecular scale, in which phenomena are inherently stochastic. For these systems, stochastic variations in experimental measurements can be separated into two types of sources: (1) intrinsic variability, which arises simply as a consequence of the stochastic nature of molecular events, and (2) extrinsic variability, which is a consequence of variability in the external environment. ***Characterization of the intrinsic variability through numerical or analytical solutions of the Master Eqs. 1 makes it is possible to distinguish between the two types of sources of variability.*** Our group has applied such an approach to separate the variability due to imperfections in our experimental setups from variability associated with molecular events for the detection of single-molecule adsorption and desorption of nitric oxide on DNA-wrapped carbon nanotubes (Ulissi et al., 2011). Such an approach is expected to be useful in many systems in nanoscale science and technology.

For these systems, the intrinsic stochastic variations in the measured values are direct functions of the physicochemical parameters, and ***hence contain information on the parameters***. In the crystallization experiments, the analytical solution for the stochastic variation as a function of the nucleation model parameters can be derived from the Master Eq. 3, so that the model parameters can be estimated accurately by fitting the distribution of induction times obtained by repeating the exact same experiment multiple times (Figure 2). In principle this approach of improving the estimation of physicochemical parameters from the stochastic fluctuations in the measurements can be applied to any molecular system described by Master equations, regardless of whether the Master equations are solved analytically, such as for the micro-crystallization process and the single-molecule sensing system in Figure 3 described by Eq. 4, or solved numerically either by direct solution of the Master equations or by indirect solution via kinetic Monte Carlo simulation. Parameter estimates in the process model are estimated from the distribution of measurements rather than mean values. In some sense, instead of trying to filter away the noise as in a macroscale system, ***the model parameters in many nanoscale systems can be estimated from the noise***. The potential improvement in the accuracy of the parameter estimates obtained by exploiting the additional information in the "noise" will depend on the details of the particular system.

Many high-value applications of carbon nanotubes such as in nanoelectronics require the separation of nanotubes in terms of their chirality, as this molecular structure is directly related to their electronic structure, adsorption kinetics, and chemical reactivity (e.g., see Nair et al., 2006; 2007; Doyle et al., 2008; Sumpter et al., 2008; Sgobba & Guldi, 2009; Chen et al., 2010; 2011b; Liu & Zhang, 2010; and citations therein). Typically the nanotubes are separated by the addition of surfactants followed by centrifugation, which produces a gel with each position along the gel corresponding to a different mixture of chiralities. Various spectroscopic methods are applied to each position, with the objective of estimating the concentrations of nanotubes with each chirality. The amount of peak overlap in the spectra is very high and while advances have been made in the deconvolution of the spectra (e.g., see Nair et al., 2008, and citations therein), more advances are needed to reduce the large uncertainty in some of the estimated concentrations. Advanced control of many nanosystems will require significant advances in sensor calibration that exploit all aspects of the sensor physics, such as the effect of defects in carbon nanotubes on their spectra, while carefully quantifying uncertainties in the estimates.

Polynomial Chaos Expansions (PCEs) is an approach for uncertainty analysis that is applicable to dynamical systems described by continuum models with model parameters that belong to non-Gaussian distributions (Wiener, 1938; Phenix et al., 1998). In recent years PCE-based systems and control methods have been developed (see Nagy & Braatz, 2007; 2010; Fisher & Bhattacharya, 2009; Templeton et al., 2010; and citations therein), that extend techniques such as robust nonlinear control and model predictive control to handling non-Gaussian distributions. Alternative approaches for addressing systems with non-Gaussian distributions such as particle filters (e.g., Lang et al., 2007 and citations therein) have also become popular. As such distributions also appear in nano and microscale chemical systems, it seems likely that some of the PCE-based methods will be useful for addressing their associated systems and control problems.

Conclusions

Challenges in the control of nano and microchemical systems are high model state dimensionality, limitations in real-time measurements and manipulated variables, and significant uncertainties described by non-Gaussian distributions. Promising directions for dealing with these challenges include exploiting model structure of the stochastic model equations, employing molecular modification at system boundaries to create desirable feedback interactions within the material, and manipulation via magnetic and electric fields. These approaches included the numerical or analytical solution of Master Eqs. 1 for

(*i*) distinguishing between fundamental intrinsic variability and extrinsic variability, and

(*ii*) abstracting information on fundamental model parameters from the intrinsic variability or "noise."

Methods were reviewed for the numerical and analytical solution of the Master Equation that commonly arises when modeling nano- and microscale chemical systems, with the analytical methods being (*i*) matrix exponentials, (*ii*) probability generating functions, (*iii*) reformulation as discrete population balance equations, and (*iv*) exploiting symmetries. While these approaches will not apply to all nano- and microscale systems, our experiences is that the methods apply to a surprisingly large number of chemical systems, with some examples of such systems given in this paper. All of the approaches used for directly solving Master equations can be directly applied to any systems problem, such as parameter estimation, quantification of uncertainties in model parameters, state and output estimation, optimal design, and optimal state feedback control. This paper described some of these applications of systems engineering to nano- and microscale chemical systems, including to carbon nanotube-based devices and microfluidic systems. Many more applications of systems engineering to nano- and microscale chemical systems by direct solution of Master equations are expected in the near future.

One of the messages of this paper is to embrace the non-Gaussian stochastic phenomena that occur in nano- and microchemical systems; that stochasticity if understood fundamentally can be more an asset than a hindrance. A way to develop this fundamental understanding of intrinsic variability is to direct numerical or analytical solution of the stochastic equations (Eq. 1) that describe the kinetic phenomena at these length scales. For problems in which such direct methods are not applicable, polynomial chaos expansions was suggested as a potential approach for addressing non-Gaussian distributions during state and output estimation and optimal feedback control design.

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