Population Balance Modeling: Current Status and Future Prospects

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Annu. Rev. Chem. Biomol. Eng. 2014. 5:123–46

First published online as a Review in Advance on March 3, 2014

The *Annual Review of Chemical and Biomolecular Engineering* is online at chembioeng.annualreviews.org

This article's doi: 10.1146/annurev-chembioeng-060713-040241

Keywords

stochastic internal coordinates, crystal morphology, stem cell differentiation, gene regulatory processes, biofilm growth, personalized medicine

Abstract

Population balance modeling is undergoing phenomenal growth in its applications, and this growth is accompanied by multifarious reviews. This review aims to fortify the model's fundamental base, as well as point to a variety of new applications, including modeling of crystal morphology, cell growth and differentiation, gene regulatory processes, and transfer of drug resistance. This is accomplished by presenting the many faces of population balance equations that arise in the foregoing applications.

INTRODUCTION

Population balance modeling is an area of ever-increasing application. **Figure 1** shows papers published in the area from 1984 to 2013 that clearly represent a steep increase in the application of population balances. Even if the coverage of the literature behind the illustrated survey is incomplete, the message is unmistakable that the impact of population balance modeling has risen steeply in a relative sense. The same increasing trend is seen in the total number of citations in **Figure 2**. In engineering, population balances have been used in the following areas:

1. crystallization and precipitation
2. dissolution
3. deposition (e.g., chemical vapor deposition and electrodeposition)
4. granulation, aggregation, and flocculation
5. milling
6. drying
7. mixing
8. pneumatic conveyance
9. polymerization
10. multiphase flow and reaction (e.g., fluidized bed reactor, flame, and micellar synthesis of nanoparticles)
11. fermentation
12. cell growth, division, differentiation, and death.

Table 1 provides an interesting list of publications in various other fields of application that have appeared over the years, beyond the more conventional ones listed above. The applications are indeed widely dispersed, thus representing unlimited future potential. The first population balance modeling conference was organized in Hawaii in 2000, following which there have been conferences at intervals of approximately three years.

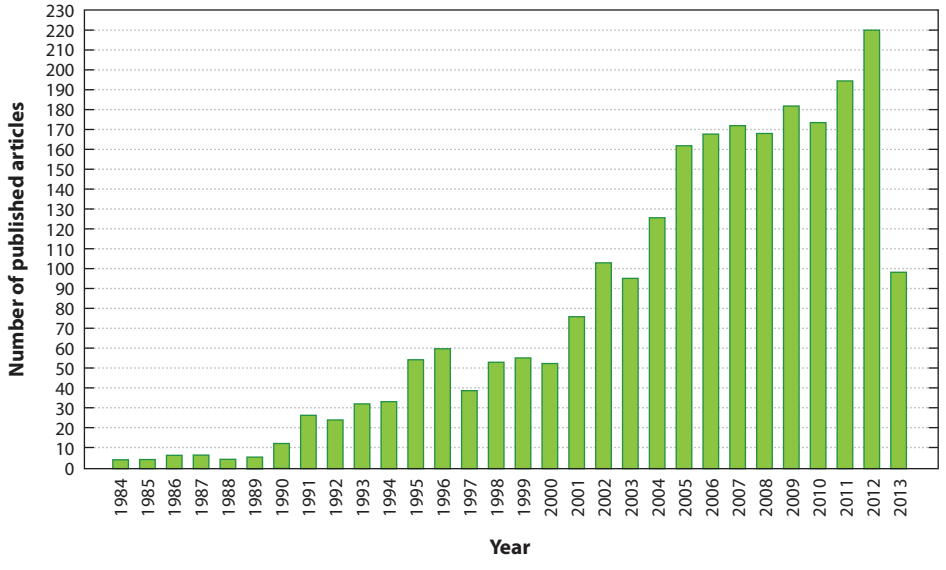

Figure 1

Number of published articles on population balances per year (keyword: "Population Balances"; source: Web of Knowledge, a Thomson Reuters product ©2013 Thomson Reuters. All rights reserved).

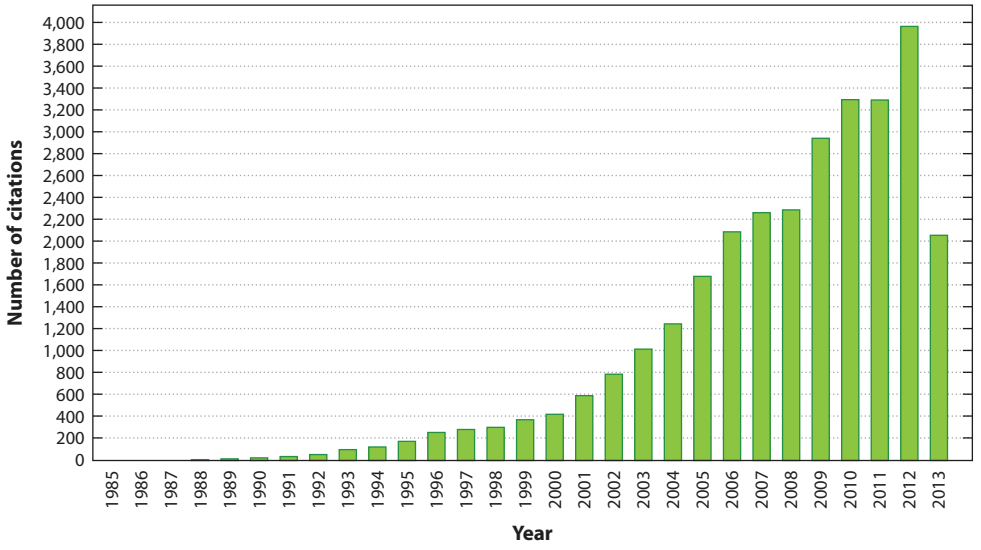

Figure 2

Number of citations per year (keyword: "Population Balances"; source: Web of Knowledge, a Thomson Reuters product ©2013 Thomson Reuters. All rights reserved).

The purpose of this review is to reflect on the current status of this area, critically examine some chosen aspects of its growth, and identify directions for the future. A more comprehensive treatment of this field would far exceed the size limit on articles in this journal. Toward this end, we inquire into the area's genesis to set the background for a general discussion, but only briefly, as several treatments in the past have deliberated on the structure of population balance.

THE GENESIS OF POPULATION BALANCE

That population balance, in one form or another, had a beginning long preceding the appearance of its general version in the publications of Hulburt & Katz (78), Randolph (79), and Fredrickson et al. (80) has been discussed at length by Ramkrishna (81). There have been other extended discussions of the origin of population balance equations [e.g., Jakobsen (82)]. This general formulation has led to the burgeoning growth of population balances for diverse applications in more recent times. Consequently, there have been numerous reviews in the literature (83–86). More recently, several reviews have also appeared of population balances targeting specific application areas (**Table 2**). Besides the early contribution of Randolph (87), which specifically addressed crystallization processes, there have been books on population balance by Ramkrishna (81), who dealt with its generic treatment; Hjortso (88), who focused on applications to biomedical engineering; and Christofides (89), who wrote on the application of population balance to control of crystallization processes.

The population balance framework has been subject to considerable probing of many of its attributes, which makes it incumbent on the authors to clearly define the scope of this review. Consequently, we seek to discuss the following issues: Broadly, we seek to bring to light certain modeling practices that have crept in with the growth of applications that require more deliberation. These have to do with the manner in which the phenomenological implements of population balances have been treated at large. In our view, these modeling issues take precedence over other germane matters, such as solution methods, that have advanced considerably in the past few years.

Table 1 Applications of population balance modeling in different areas

Areas of applications	Specific details	References
Agriculture engineering	Fractionation of ground switchgrass, hydrolysis of cellulose, airborne dust removal	1–4
Astrophysics and astronomy	Population balance equations for levels of a quantum system, calculation of highly excited hydrogen b_n factor	5, 6
Biochemistry and molecular biology	Gene regulatory processes, transcription, translation	7–13
Biomedical engineering	Kidney stone formation, cancer treatment	14, 15
Biotechnology and bioengineering	Cell cycle dynamics, cellulase production in airlift reactor, bioreactor design, cell proliferation, cell morphology, aeration of bread dough, growth of hairy roots, enzymatic lysis of cells	16–27
Cell biology	Cell aggregation dynamics, cryopreservation, stem cell differentiation, mammalian cell culture, neutropenia	28–36
Civil and environment engineering	Water softening, deepwater plumes, dissolved air flotation, struvite crystallization in urine, activated sludge flocculation, drag reduction	37–42
Electrochemistry	Bubble dynamics at gas-evolving electrodes, chemical vapor deposition, electrostatic precipitators	43–45
Energy fuels	Gas-liquid-solid-phase reactor, silicon nanoparticles, oxy-coal jet flames, hydrolysis of cellulose, Fischer-Tropsch synthesis, asphaltene precipitation, reactive extractions, pyrolysis of wood, coal combustion, enhanced oil recovery	3, 46–54
Geography	Electrification of particles in dust storms, flocculation of colloidal montmorillonite, soil respiration	55–57
Hematology	Kinetics of platelet aggregation, leukemic cell proliferation	36, 58
Novel functional particles	Single-walled carbon nanotube formation	59
Ophthalmology	Pterygium formation, corneal epithelial maintenance and graft losses	60, 61
Personalized medicine	Chemotherapy for leukemia	15, 58
Pharmaceutical engineering	Polymorphic transformation, crystal morphology distribution, nucleation, Ostwald ripening, continuous crystallization, dissolution, breakage, aggregation, granulation, tablet manufacturing	62–72
Respiratory systems	Modeling techniques for the deposition of inhaled particles	73
Telecommunications	Impact evaluation of rare metals in waste mobile phone and personal computer	74
Transportation	Soot particle-size distribution emitted from diesel engine, soot formation, CO_2 emission	75–77

The second issue we wish to focus on is new applications with potential for wide impact. The ensuing sections describe the system and the general form of the population balance equation and identify its phenomenological components for further discussion.

The System and Its Description

The population balance equation is concerned with modeling a system composed of a continuous or discrete number of entities interacting with their environment, generally assumed to be a continuous phase. The foregoing entities are usually particles, although, more abstractly, they could be an ensemble of systems of states described by a vector. This vector may contain both so-called internal coordinates, representing properties chosen to represent the entity, and external coordinates, usually meant to describe the physical location of the center of mass of the entity.

Table 2 List of review articles on population balances

Year	Authors	Title	Area
2013	Solsvik & Jakobsen (90)	On the solution of the population balance equation for bubbly flows using the high-order least squares method: implementation issues	Numerics (least squares method)
2012	Sporleder et al. (86)	On the population balance equation	General formulation (directions and critiques)
2012	Sajjadi et al. (91)	Review on gas-liquid mixing analysis in multiscale stirred vessel using CFD	Population balance equation–computational fluid dynamics coupling
2011	Mortier et al. (92)	Mechanistic modelling of fluidized bed drying processes of wet porous granules: a review	Formulation (fluidized bed drying), population balance equation–computational fluid dynamics coupling
2011	Bajcinca et al. (93)	Integration and dynamic inversion of population balance equations with size-dependent growth rate	Formulation and numerics (direct and inverse problem)
2010	Kiparissides et al. (94)	From molecular to plant-scale modeling of polymerization processes: a digital high-pressure low-density polyethylene production paradigm	Formulation and numerics (polymerization)
2010	Sadiku & Sadiku (95)	Numerical simulation for nanoparticle growth in flame reactor and control of nanoparticles	Formulation, numerics, and control (nanoparticle synthesis)
2010	Rigopoulos (96)	Population balance modelling of polydispersed particles in reactive flows	Formulation and numerics (reactive precipitation)
2010	Liao & Lucas (97)	A literature review on mechanisms and models for the coalescence process of fluid particles	Formulation (coalescence)
2010	Yu & Lin (98)	Nanoparticle-laden flows via moment method: a review	Formulation (particle flow)
2009	Liao & Lucas (99)	A literature review of theoretical models for drop and bubble breakup in turbulent dispersions	Formulation (breakage)
2008	Tindall et al. (100)	Overview of mathematical approaches used to model bacterial chemotaxis II: bacterial populations	Formulation (chemotaxis)
2008	Ribeiro & Lage (101)	Modelling of hydrate formation kinetics: state-of-the-art and future directions	Formulation (hydrate formation)
2007	Dukhin et al. (102)	Gravity as a factor of aggregative stability and coagulation	Formulation (coagulation)
2007	Roth (103)	Particle synthesis in flames	Formulation (reactive precipitation)
2006	Maximova & Dahl (104)	Environmental implications of aggregation phenomena: current understanding	Formulation (aggregation)
2005	Taboada-Serrano et al. (105)	Modeling aggregation of colloidal particles	Formulation (aggregation)
2005	Vale & McKenna (106)	Modeling particle size distribution in emulsion polymerization reactors	Formulation (emulsion polymerization)
2005	Cameron et al. (107)	Process systems modelling and applications in granulation: a review	Formulation and numerics (granulation)
2003	Henson (10)	Dynamic modeling of microbial cell populations	Formulation (microbial cells)
2003	Somasundaran & Runkana (108)	Modeling flocculation of colloidal mineral suspensions using population balances	Formulation (flocculation)

(*Continued*)

Table 2 (*Continued*)

Year	Authors	Title	Area
2003	Kodera & McCoy (171)	Distribution kinetics of plastics decomposition	Formulation (depolymerization)
2002	Braatz (109)	Advanced control of crystallization processes	Identification and control
2002	Ramkrishna & Mahoney (84)	Population balance modeling. Promise for the future	Formulation and numerics (status and future outlook)
2000	Mohanty (110)	Modeling of liquid-liquid extraction column: a review	Formulation (liquid-liquid extraction)
1994	Kovscek & Radke (111)	Fundamentals of foam transport in porous media	Formulation (foam transport)
1993	Rawlings et al. (112)	Model identification and control of solution crystallization processes: a review	Identification and control
1991	Tavare (172)	Batch crystallizers	Formulation (crystallization)
1985	Ramkrishna (83)	The status of population balances	Formulation
1979	Ramkrishna (85)	Statistical models of cell populations	Formulation (microbial cells)

In our discussion, we use the terms entity and particle interchangeably. No spatial gradients of any internal coordinate are assumed, although a more elaborate theory could include them. The population is described through a number (or mass or any other quantitative) distribution of the entities in the joint space of internal and external coordinates. Continuous distributions are encountered when the state space, either internal or external, is continuous, so that a (suitably) smooth number density is implied. This number density must be understood to be an expected quantity, in contrast with the actual number density; the relationship between the two may be found in References 81 and 113. In many applications, whether or not there is dependence on external (i.e., spatial) coordinates, the number distribution of entities is a density in physical space even if the internal coordinates are discrete. External coordinates are generally continuous, although discrete versions are of course conceivable. The internal coordinates, however, can be discrete or continuous. The total number of entities in the system at any instant t is obtained by integration over the entire range of continuous coordinates and summed over the range of discrete coordinates. The population balance equation is simply a number conservation of entities, on which depends the behavior of the entire system, including the entities and their environment. The overall description of the system is given by the usual partial differential equations of conservation of mass, momentum, and energy for the continuous phase, coupled with the population balance equation. The continuous phase variables are represented by a vector field, $\mathbf{y}$, depending on $\mathbf{r}$ and t. The population balance describes how existing entities change their states continuously, as well as how they give rise to new entities at their own expense. The continuous change of individual entities may be either deterministic, as described by ordinary differential equations, or stochastic, as determined by stochastic differential equations. The reader is referred to Ramkrishna (81) for a detailed discussion on these matters and for derivation of the equations. In presenting the population balance equations, we distinguish between continuous and discrete internal coordinates.

For the purposes of this review, we denote the state of the distributed entity by vector $\mathbf{z}$, which includes both internal coordinates ($\mathbf{x}$) and external coordinates ($\mathbf{r}$). Thus, this vector includes as its components particle properties, such as size (e.g., mass) and physical space coordinates. We use the notation $f_1(\mathbf{z}, t \mid \mathbf{y})$ to represent the number density, which deserves some explanation, as it deviates from that commonly employed in the literature. First, the subscript 1 allows for distinction from multiparticle densities required when interactions exist among particles (113). Second, the inclusion of $\mathbf{y}$ as a conditional argument in the number density is an expression of its dependence on the environment without it being a density in $\mathbf{y}$-space.

The Population Balance Equation: Deterministic Internal Coordinates

We first consider the case of continuous internal coordinates. As stated earlier, the external coordinates remain continuous in all cases.

Continuous internal coordinates. When particle properties change in a deterministic way, in accord with a velocity field $\dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t)$ that accounts for rate of change of internal coordinates as well as physical motion, the population balance equation is given by

$$\frac{\partial f_1(\mathbf{z}, t \,|\, \mathbf{y})}{\partial t} + \nabla \cdot \dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t) f_1(\mathbf{z}, t \,|\, \mathbf{y}) = h(\mathbf{z}, t \,|\, \mathbf{y}), \quad \mathbf{z} \in \Omega, \ t > 0, \qquad 1.$$

where $\Omega \equiv \Omega_{\mathbf{x}} \times \Omega_{\mathbf{r}}$, with $\Omega_{\mathbf{x}}$ defining the domain of internal coordinates and $\Omega_{\mathbf{r}}$ representing the physical domain in which the entities are present. The right-hand side accounts for various ways in which the number of entities can change with a conditional dependence on $\mathbf{y}$. Its elucidation depends on the processes responsible for change in numbers (e.g., breakage, aggregation, and primary and secondary nucleation). The performance of the model is clearly related to the veracity of both $\dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t)$ and $h(\mathbf{z}, t \,|\, \mathbf{y})$. If we denote $\mathbf{z} = [\mathbf{x}, \mathbf{r}]$, then this notation allows us to write $\dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t) = [\dot{\mathbf{X}}(\mathbf{z}, \mathbf{y}, t), \dot{\mathbf{R}}(\mathbf{z}, \mathbf{y}, t)]$, where $\dot{\mathbf{X}}(\mathbf{z}, \mathbf{y}, t)$ represents the rates of change of internal coordinates and $\dot{\mathbf{R}}(\mathbf{z}, \mathbf{y}, t)$ represents the spatial velocity.

Discrete internal coordinates. For discrete internal coordinates, the population balance equation takes a form slightly different from Equation 1. We consider a denumerable set of states, each designated by a single integer subscript i, which could represent either one or many discrete internal coordinates by suitable ordering. A simple example is that of discrete particle sizes in designated bins. In contrast with continuous changes of internal coordinates implied in Equation 1, we envisage here that the entity undergoes a jump process from one state to another without the creation of more entities. In the current context, these jumps are regarded as deterministic, occurring at average time intervals (although the classical jump process is generally a stochastic process, which is considered below in the section on Continuous Internal Coordinates). For a slightly more complicated second example, consider an entity comprising two types of molecules, A_1 and A_2, and an irreversible reaction that transforms A_1 to A_2 with transition rate k. Suppose the total number of molecules is two in the entity. Denoting the internal coordinate of the entity by $\{a_1, a_2\}$, where a_j is the number of molecules of A_j, we have three discrete states denoted as $i = 1 : \{a_1 = 2, a_2 = 0\}$, $i = 2 : \{a_1 = 1, a_2 = 1\}$, and $i = 3 : \{a_1 = 0, a_2 = 2\}$ for this entity. If at most one A_1 molecule can undergo reaction in an infinitesimal time interval, then the rate of transition from state 1 to state 2 is $2k$ and from state 2 to state 3 is k, with all other transition rates being zero. The foregoing discussion should set the tone for formulating more general discrete states. We now return to the population balance equation for the general discrete case.

Retaining the continuity of spatial coordinates, which could accommodate continuous motion of the entities through physical space, we define the number density $f_{1,i}(\mathbf{r}, t \,|\, \mathbf{y})$. Insofar as this number density is still the expected density, it is a suitably smooth function of both $\mathbf{r}$ and t for each i. The population balance equation can be readily identified as

$$\frac{\partial f_{1,i}(\mathbf{r}, t \,|\, \mathbf{y})}{\partial t} + \sum_{j=1}^{\infty} [\Gamma_{i \to j}(\mathbf{r} \,|\, \mathbf{y}) f_{1,i}(\mathbf{r}, t \,|\, \mathbf{y}) - \Gamma_{j \to i}(\mathbf{r} \,|\, \mathbf{y}) f_{1,j}(\mathbf{r}, t \,|\, \mathbf{y})] + \nabla_{\mathbf{r}} \cdot \dot{\mathbf{R}}_i(\mathbf{r}, \mathbf{y}) f_{1,i}(\mathbf{r}, t \,|\, \mathbf{y}) = h_i(\mathbf{r}, t \,|\, \mathbf{y}), \quad \mathbf{r} \in \Omega_{\mathbf{r}}, \ t > 0, \qquad 2.$$

where $\Gamma_{j \to i}(\mathbf{r} \,|\, \mathbf{y})$ is the (average) rate at which an entity transitions from state j to state i, with no implications as to its symmetry with respect to the subscripts. For the second example above, we have $\Gamma_{1 \to 2} = 2k$, $\Gamma_{2 \to 3} = k$, and $\Gamma_{1 \to 3} = \Gamma_{2 \to 1} = \Gamma_{3 \to 1} = \Gamma_{3 \to 2} = 0$. The summation term

on the left-hand side of Equation 2 is the discrete equivalent of the convective divergence term with respect to internal coordinates on the left-hand side of Equation 1. Thus, it is not meant to describe processes that cause a change in the number of entities. Instead, the term on the right-hand side of Equation 2 is the discrete equivalent of the right-hand side of Equation 1, and it will account for the net source of entities of state i as a result of processes that create new entities at the expense of existing ones. The examples of particle breakage and aggregation are well known to population balance modelers, and the reader is referred to the literature for how $h_i(\mathbf{r}, t \mid \mathbf{y})$ is formulated for these processes (81, 86). Before we close this section, we should reflect on how the discrete state of a specific entity changes with time. The use of transition rates from one discrete state to another is in fact the basic implement of a Markov chain, and in this sense, the state of a given entity changes randomly. However, when there are a large number of entities, the average rate of any given transition is the same as that attributed to that in a single entity. From this point of view, the difference between this class of models and those in the section on Discrete Internal Coordinates, below, is only one of a notable increase in complexity in the latter.

The Population Balance Equation: Random Internal Coordinates

As in the previous section, we first consider the case of continuous internal coordinates.

Continuous internal coordinates. If particle properties change randomly in accord with the Itô stochastic differential equations,

$$d\mathbf{z} = \dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t)dt + \sqrt{2\mathbf{D}(\mathbf{z}, \mathbf{y}, t)}d\mathbf{W}_t, \qquad 3.$$

then, following Reference 81, the population balance may be written as

$$\frac{\partial f_1}{\partial t} + \nabla \cdot \dot{\mathbf{Z}}(\mathbf{z}, \mathbf{y}, t) f_1 = \nabla\nabla : \tilde{\mathbf{D}} f_1 + h(\mathbf{z}, t \mid \mathbf{y}), \quad \mathbf{z} \in \Omega, \ t > 0, \qquad 4.$$

in which we let $\tilde{\mathbf{D}} \equiv \sqrt{\mathbf{D}\mathbf{D}^T}$. In Equation 3, $\mathbf{D}$ represents a matrix coupling the various Wiener processes in the differential vector $d\mathbf{W}_t$ (see Reference 114) and must arise from various considerations.[1] The phenomenology in Equation 4 is represented by the functions $\dot{\mathbf{Z}}$, $\mathbf{D}$, and h. The effectiveness of the population balance model depends on these functions.

The partial differential equation in $\mathbf{y}$ to which the population balance Equation 1 or Equation 4 will be coupled must include in general all the transport equations for multiphase flow. The form of these equations will vary greatly with the application, making it inconvenient to present a general formalism without straying far afield. We therefore focus for the present only on the phenomenological components of the population balance equation, even when it is coupled with the transport equations for environmental variables.

Discrete internal coordinates. When the internal coordinates of the entity are discrete and behave stochastically, the temporal evolution of its state is described by a master equation (114, 115). The internal state of an entity may be described by a discrete vector field $\{\mathbf{x}(t) \in \Re^n\}$, where the components of $\mathbf{x}$ may be integers. Several (e.g., m) processes (see sidebar, Processes with Discrete Internal Coordinates), occurring randomly, are envisaged to create discrete changes in the state vector $\mathbf{x}$. (For example, the entity may be a cell or a microemulsion particle, and $\mathbf{x}$ may

[1] For example, Equation 3 could come about by Fokker-Planck approximations of the master equation for the discrete system in the entity using van Kampen's system size expansion or Moyal's expansion.

PROCESSES WITH DISCRETE INTERNAL COORDINATES

Application of this class of models is imaginable for somewhat disparate situations. For example, it could apply to a machine or a process that functions when all of its components do. The components could fail in the course of time with different time-dependent propensities (transition rates). In this case, the i^{th} component would define two states of its own, one functioning and the other not.

represent the number of molecules of n different chemical species in it undergoing m reactions.) Let the k^{th} process add an integral increment of $\mathbf{v}_k$ to $\mathbf{x}$ at a rate of $\lambda_k(\mathbf{x})$. The master equation for an entity is then given by

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \sum_k [\lambda_k(\mathbf{x} - \mathbf{v}_k) P(\mathbf{x} - \mathbf{v}_k, t) - \lambda_k(\mathbf{x}) P(\mathbf{x}, t)], \quad t > 0, \qquad 5.$$

where $P(\mathbf{x}, t)$ is the probability that the entity has state $\mathbf{x}$ at time t. Equation 5 must of course be subject to an initial condition expressing the initial state of the entity. In formulating Equation 5, we ignored any possible role of the environment of the entity (i.e., the vector $\mathbf{y}$). Through physical transport of environmental species across the boundary of the entity, an environmental dependence could be envisaged so that Equation 5 could be modified to read as

$$\frac{\partial P(\mathbf{x}, t \,|\, \mathbf{y})}{\partial t} = \sum_{k'} [\lambda_{k'}(\mathbf{x} - \mathbf{v}_{k'} \,|\, \mathbf{y}) P(\mathbf{x} - \mathbf{v}_{k'}, t \,|\, \mathbf{y}) - \lambda_{k'}(\mathbf{x} \,|\, \mathbf{y}) P(\mathbf{x}, t \,|\, \mathbf{y})], \quad t > 0. \qquad 6.$$

The index k' in the above equation is different from k appearing in Equation 5 to accommodate new sources and sinks owing to transport across the surface of the entity. Thus, the range of k' subsumes that of k. The conditional dependence on $\mathbf{y}$ holds only for those added processes accounting for transport across the boundary. Thus, when $k' = k$, the transition rates do not involve $\mathbf{y}$, although the notation shows dependence.

The population balance equation of interest is to describe a population of entities, each of which is associated with master Equation 6. We define an expected number density $f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y})$ by $N(\mathbf{r}, t) P(\mathbf{x}, t \,|\, \mathbf{y})$, where $N(\mathbf{r}, t)$ is the total population density of entities at location $\mathbf{r}$ and time t. Note in particular that no explicit spatial dependence is incorporated in Equation 6, although, insofar as there is dependence on $\mathbf{y}$, an implicit spatial dependence is inherited. The population balance equation for this situation can be written as

$$\begin{aligned} &\frac{\partial f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y})}{\partial t} + \sum_{k'} [\lambda_{k'}(\mathbf{x} \,|\, \mathbf{y}) f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y}) - \lambda_{k'}(\mathbf{x} - \mathbf{v}_{k'} \,|\, \mathbf{y}) f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y})] + \\ &\nabla_{\mathbf{r}} \cdot \dot{\mathbf{R}}(\mathbf{x}, \mathbf{r}, \mathbf{y}) f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y}) = \nabla_{\mathbf{r}} \nabla_{\mathbf{r}} : \tilde{\mathbf{D}}_{\mathbf{r}} f_1(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y}) + h(\mathbf{x}, \mathbf{r}, t \,|\, \mathbf{y}). \end{aligned} \qquad 7.$$

The diffusion term on the right-hand side is concerned only with physical space. Equation 7 must of course be coupled with the transport equations for the environmental vector $\mathbf{y}$. For a general discussion of boundary conditions, the reader is referred to Reference 81, which applies to all the cases considered above. Finally, we remark that population balance equations can be formulated for any entity whose dynamics can be described by a master equation by adopting the procedure that has been followed in this article. Thus, the classical jump process, in which continuous stochastic motion is interrupted randomly by jumps, can also be formulated into a population balance equation. However, the solution of population balance equations becomes very complicated if it is left in the form of Equation 7. In fact, even the solution of the master equation is extremely difficult. Consequently, there have been attempts to convert the master equation to a

Fokker-Planck equation (and hence a set of stochastic ordinary differential equations, which can be solved for sample paths using well-established stochastic algorithms). In meeting the first goal of this review, which is a critical examination of the phenomenological implements of population balances, we have laid out the domain of the latter in sufficient generality for a focused discussion of this issue.

Stochastic Analysis of Populations

The previous sections concerned deterministic and stochastic internal coordinates of individual entities. The population of entities was assumed to be sufficiently large that deterministic behavior could be expected of their number. If, however, the number of entities in the system is itself small, then it would also behave randomly owing to randomness in the behavior of individual entities. The modeling of such systems would need stochastic population balances, which have been discussed in Reference 113, as well as in chapter 7 of Reference 81. Some applications of this framework have been considered in the past (116, 117), and its application to cancer treatment is discussed briefly in Personalized Medicine, below.

PHENOMENOLOGICAL ISSUES

Table 3 identifies the main phenomenological quantities of the population balance model under various circumstances. Particularly important to note is that the phenomenology is governed by functions that describe the behavior of individual entities over a broad range of their internal and external coordinates. We review the general features of each quantity shown in the rightmost column in **Table 3**.

Motion in Internal Coordinate Space

We organize our discussion as it appears in categories along the rows in **Table 3** from the top to the bottom.

Continuous internal coordinates (deterministic). In many situations, there is good understanding of the behavior of individual entities in isolation, which may be sufficient for incorporation into a population balance model as long as a satisfactory model exists to account for the joint effect of the entities on the local environment. This is because in such cases the behavior of an individual entity in the presence of others is influenced only by the intervening continuous phase.

Table 3 Phenomenological components of population balance models

	Internal coordinates	Number density	Population balance equation number	Phenomenological quantities
Deterministic continuous	$\mathbf{x} \in \Re^n$	$f_1(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$	Equation 1	$\dot{\mathbf{X}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$, $\dot{\mathbf{R}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$, $b(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$
Discrete deterministic	$i = 1, 2, \ldots, n$	$f_{1,i}(\mathbf{r}, t \mid \mathbf{y})$	Equation 2	$\dot{\mathbf{R}}_i(\mathbf{r}, \mathbf{y})$, $\Gamma_{i \to j}(\mathbf{r} \mid \mathbf{y})$, $b_i(\mathbf{r}, t \mid \mathbf{y})$
Stochastic continuous	$\mathbf{x} \in \Re^n$	$f_1(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$	Equation 4	$\dot{\mathbf{X}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$, $\dot{\mathbf{R}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$, $\tilde{\mathbf{D}}$, $b(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$
Stochastic discrete	$\mathbf{x} \in I \times I \times \cdots \times I$ (n times) $I \equiv \{0, 1, 2, \ldots\}$	$f_1(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$	Equation 7	$\dot{\mathbf{R}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$, $\tilde{\mathbf{D}}_{\mathbf{r}}$, $\lambda_{k'}(\mathbf{x} \mid \mathbf{y})$, $b(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$

The formulation is accomplished by the usual transport equations involving chemical reaction and convective diffusion. For example, in dispersed-phase gas-liquid reaction systems, there already exist transport rates of gaseous components to (or from) the liquid phase that can be readily incorporated into population balance models in which the entities are bubbles (118).

An example of recent activity is the modeling of crystal morphology in crystallization processes. A description of crystal morphology requires the specification of all its faces from the crystal center, which contribute to the entity's (crystal's) internal coordinates, $\mathbf{x}$. In this situation, avenues frequently exist for identifying $\dot{\mathbf{X}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$; thus, dependence on both internal and external coordinates may be dispensed with in favor of including only the local supersaturation, which would be a component of $\mathbf{y}$.

When the behavior of individual entities is uncertain and subject to speculation, satisfactory performance of the population balance model cannot be taken for granted. If mechanistic insight is available, affording expressions with phenomenological parameters, fitting population data to the model to obtain parameter values naturally allows identification of the model. An example of this may be found in Reference 119. However, note that parameter fitting with prescribed forms could risk the loss of details that may reveal themselves in the solution of inverse problems (65).

Discrete and continuous internal coordinates (deterministic). The entry in the second row of **Table 3**, which corresponds to discrete transitions, has interesting applications. Thus, the production of nanoparticles in microemulsion droplets considered by Bandyopadhyaya et al. (120–122) is an example. As another very elementary example, consider a reactor regenerator system (123) in which catalyst particles circulate between a reactor, where reaction deactivates the catalyst, and a regenerator in which catalyst activity is regenerated. The particles have two discrete states: the presence in the reactor unit, or presence in the regenerator unit, and the catalytic activity as a continuous internal coordinate. There is a transition from one unit to the other, which may be described by transition rates (shown in **Table 3**) as a function of the time (age) spent in the unit. The fouling of the catalyst in the reactor is a function of its environment, and the reactivation of the catalyst is a function of its environment in the regenerator. The catalyst activity is a dynamic variable in both units. Although this problem is readily formulated, one may envisage numerous more challenging problems in chemical reactor engineering. Modeling of Fischer-Tropsch synthesis presents a complex scenario with four different phases: solid dispersed-phase catalyst particles; two liquid phases, one an organic dispersed phase and the other an aqueous continuous phase; and a dispersed gas phase as bubbles.

Continuous internal coordinates (stochastic). The earliest example in the application of continuous, stochastic internal coordinates appears to have arisen in crystallization (124). Thus, crystals of a given size seemed to display growth-rate dispersion about a mean value. Ulrich (125) presents a review of the phenomenon. When there is growth-rate dispersion, the population balance equation using a diffusion term along the size coordinate provides an appropriate description of the observed crystal size distribution (126). More generally, the use of Itô stochastic differential equations for continuous internal coordinates naturally leads to the appearance of diffusion terms (81). Of course, this begs the question of how one formulates a physical model that leads to the stochastic differential equation. Usually, it is done by assuming an idealized stochastic process (such as white Gaussian noise) to model a source of fluctuation. A classic example is that of Langevin, who modeled Brownian motion of a particle subject to a random force from the molecular environment (127). Footnote 1 refers to a procedure described in References 114 and 115 that generates Equation 3 from the master equation. The master equation is readily identified for reaction/diffusion systems. This equation, in confluence with the system size expansion or

Moyal's expansion, leads to Equation 3 for applications in which a continuous approximation is available for the discrete random internal coordinates. The solution of Equation 3 must draw on sample path-wise simulation algorithms available in the literature (128, 129).

Discrete internal coordinates (stochastic). When continuous approximation of discrete stochastic coordinates is untenable, it would be necessary to seek the solution of Equation 7. As pointed out earlier, this would be a considerably demanding task, and it would be essential to resort to Monte Carlo simulation techniques. In this connection, the Gillespie algorithm (130)—or equivalently, the method of quiescence intervals by Shah et al. (131), with embellishments such as the tau-leap strategy of Gillespie and coworkers (132)—becomes a viable strategy in such cases.

Motion in Physical Space

The motion of entities in physical space has been denoted in **Table 3** as $\dot{\mathbf{R}}(\mathbf{x}, \mathbf{r}, \mathbf{y})$ or $\dot{\mathbf{R}}_i(\mathbf{r}, \mathbf{y})$. It is basically hindered motion of polydisperse particles, and it represents a problem of considerable complexity. Confrontation of this complexity will depend on advances in multiphase flow; we do not discuss this issue further, as other reviews have addressed it at length (91).

Sources and Sinks

The notation $h(\mathbf{x}, \mathbf{r}, t \mid \mathbf{y})$ or $h_i(\mathbf{r}, t \mid \mathbf{y})$, used to represent sources and sinks of entities, does not display its inherent dependence on the number density. This dependence manifests either as a function or as a functional of the number density. The processes contributing to this term are generally (*a*) nucleation, (*b*) breakage (fission), and (*c*) aggregation. Similar processes occur in other systems, although with different terminologies.

Combination of breakage and aggregation processes. Although the phenomenological description of breakage and aggregation processes is well established, the manner in which they are often put to use deserves more introspection. Breakup processes are generally viewed as linear, although nonlinear breakage models have also been of interest (133). However, aggregation processes are usually nonlinear. In modeling these processes, we are concerned with the state of the particle environment and envision the circumstances leading to breakage or aggregation. These circumstances are generally different for breakage and aggregation. But when both breakage and aggregation occur, the population balance equation features the rates of these processes, ignoring the foregoing differences. Stated another way, events leading to either process could exclude those leading to the other. The source and sink terms for breakage and aggregation are invariably summed together; for such summation to be admissible, the two processes must be independent of each other, which is not always a secure assumption for reasons just articulated. In the real system, these processes are often segregated in different zones to a greater or lesser extent, but this is not always a conscious input to the model. This is particularly true of systems where population balances must be combined with computational fluid dynamics to model the environmental phase.

Aggregation by multiple mechanisms. The first derivation of an aggregation kernel came from the work of von Smoluchowski (134, 135), who was concerned with the aggregation of particles by Brownian motion. The procedure is one of considering a pair of particles; viewing from a frame of reference, mounted on one of the particles, the motion of the other particle; and examining the probability of their intersection. Whereas von Smoluchowski's work was concerned with spheres between which no force existed, Spielman (136) showed how to include viscous interaction between

the particles on their aggregation. Numerous studies have analyzed coalescence frequencies for drops in a stirred dispersion. Of these, the most popular has been that of Coulaloglou & Tavlarides (137), who produced the first interesting synthesis of how coalescence between two droplets in a liquid-liquid dispersion must occur when (random) drainage of the intervening film occurs down to a critical thickness. Subsequent papers (138–141), which have included more mechanistic considerations of film drainage, as well as the effects of surface charge in a dynamic Langevin equation framework, have potential for accommodating more diverse coalescence phenomena.

Consider now aggregation by different mechanisms in the same system. Relative motion of any two particles can be most conveniently analyzed by the Langevin equation, accounting for all forces on the particles by summing them (70, 81). The aggregation kernel can be obtained from the Fokker-Planck equation, which corresponds to the foregoing Langevin equation. Brownian motion and gravitational settling provide an ideal example. Simons et al. (142) analyzed this problem with the Fokker-Planck equation for the combination of the two mechanisms and arrived at an aggregation frequency that exceeds considerably that obtained by simply adding the two frequencies. The addition of aggregation frequencies is therefore a practice that requires circumspection.

Scaling behavior and inverse problems. Numerous instances of scaling behavior have been observed with population balance equations. Many classical references of scaling behavior are provided in chapter 5 of Reference 81. This behavior not only is interesting for its own sake but has several attributes. First, it provides definitive validation of the formulated model. Second, it makes for efficient predictions of dynamic behavior. Third, it allows for the identification of the behavior of single entities, especially when it is influenced notably by its fellows. Fourth, it often facilitates through the solution of inverse problems the identification of breakage and aggregation kernels (41, 143, 144). When scaling behavior exists, it can contain information about aggregation behavior sensitive enough to correctly reproduce even singular behaviors of aggregation kernels obtained by an inverse problem. This is shown in Reference 145. An interesting application to self-similar growth of cell populations is shown in Reference 146. There is currently gradually mounting interest in inverse problems, as evidenced by the sporadic appearance of publications on their applications to population balances (147–150).

Because of inherent sensitivity of inverse problems to errors in input data, the effort calls for judicious choice of regularization strategies so that the information obtained is robust. Investigation of scaling is still felt to be a worthwhile endeavor for its potential benefits. For example, computational data obtained from population balance coupled with computational fluid dynamics could be examined for compression by the local volumetric energy dissipation or other hydrodynamic quantities, as may be appropriate.

MORE RECENT APPLICATIONS OF POPULATION BALANCES

Recently, there have been several new applications of population balances. We briefly review them here.

Population Balances and Computational Fluid Dynamics

The combination of computational fluid dynamics and population balances is but a natural effort to accommodate heterogeneity in process equipment. The thrust in this area has been largely computational, and comparison with experiments, to the extent it has been possible, has shown only qualitative agreement. Although this may be a reflection of system complexity, some of the

issues raised in the section on Sources and Sinks, above, could potentially influence quantitative conformance. Computational methods have relied on the use of the quadrature method of moments (151) in this effort. Although this method has facilitated computation, it cannot make full use of the distribution of internal coordinates, a limitation rightly pointed out by Marchisio et al. (151). Bubble columns have been modeled (152) with discretization methods (153), but not without other compromising simplifying assumptions. Chen et al. (154) showed various features of bubble columns with a detailed population balance model, including discrete bubble sizes. Whereas the model related well to some measurements, other data for validation were unavailable. Vikhansky & Kraft (155) modeled a rotating-disc liquid-liquid contactor with population balance coupled to a $k - \varepsilon$ turbulence model, including breakage and coalescence. They used Monte Carlo simulations for solution, but comparison with data appeared somewhat sketchy.

Numerous other publications could have been cited here but were omitted because of limits placed on the size of this review. It is hoped that the general conclusions from the cited papers are not seriously in conflict with the spirit of those omitted. However, an important outcome of research in this area is the extent to which classical idealizations, such as perfect mixing, can misrepresent the behavior of engineering equipment.

Modeling of Crystal Morphology

Control of the shape or morphology of crystals is an important issue in crystallization processes owing to its high impact in determining the quality of commonly used crystalline materials, such as pharmaceutical drugs, food products, fertilizers, specialty chemicals, cosmetics, electronics, and optical materials. Therefore, there is a need to develop efficient morphological population balance models (MPBMs) for model-based control of morphology distributions in crystallizers. The internal coordinates for morphology distributions are perpendicular distances (known as *h-vector*) of crystallographic families of faces from an appropriately chosen crystal center. The dimensions of MPBMs, and hence the computational efforts required to simulate them, increase with the number of internal coordinates. One of the challenges in developing MPBMs is to account for dynamically varying numbers of internal coordinates owing to appearances and disappearances of crystal faces. Therefore, some of the earlier efforts (156) focused on the study of morphology evolution with no transformations (i.e., the number of internal coordinates remains invariant). Efforts have also been made to reduce the dimension of MPBMs for computability and measurability. At fixed supersaturation, when relative growth rates are constant, the dynamic changes in *h-vector* can be represented by the dynamics of the h of a reference family, hence reducing the dimension of MPBM to one (157). Equivalently, under similar conditions, the dynamics of *h-vector* can be expressed using the age of crystals, which also gives rise to 1D MPBM (158). Briesen (159) transformed the 2D MPBM of parallelepiped-shaped crystals in length-width coordinate systems to volume-shape factor coordinates. Integration over the shape-factor coordinate yielded a 1D MPBM in volume (measurable quantity) space, and the dynamic changes in the shape factor were inferred assuming initial Gaussian distribution of shape factors. Such transformations are convenient under specific situations, but it is worth noting that the solution of MPBMs, not involving crystal breakage or aggregation, but otherwise under fairly general morphologies, can always be readily obtained through the method of characteristics (81). Wang and coworkers (160) applied 3D MPBM to potash alum, in which the internal coordinates are the hs of three families of faces. Subsequently, they performed principal component analysis to reduce the *h-vector* dimension of potash alum, which resulted in 3D MPBM in principal component space (161). In this case, there is no effective reduction in the number of internal coordinates, as it is the same as the dimension of symmetry-reduced *h-vector*. The works cited above are restricted to a single morphology and

CHALLENGES IN MODELING CRYSTAL MORPHOLOGY DISTRIBUTIONS

Application of population balances to predict morphological evolution in crystal populations has greatly advanced in recent years. It has been used successfully for model-based control of 2D crystals in industrial crystallizers (173). The current challenges in this area are (*a*) development of advanced sensors to monitor populations of multifaceted crystals; (*b*) techniques to reduce the dimension of MPBM; and (*c*) formulation, nucleation, breakage, and aggregation of kernels for faceted crystals.

do not consider morphology transformations. Wan et al. (162) introduced an ad hoc way to account for morphology transformations by exchanging the number distribution between different morphologies. They showed transformation of alum crystals with three families to those with one family of faces. Because the crystal state space for alum was not identified, the transition of crystals from three families to two families was missed completely. Ramkrishna and coworkers (64) demonstrated the construction of crystal state space for asymmetric octagonal crystals and developed coupled population balance equations accounting for morphology transformations. Their framework was built for a few morphologies of asymmetric octagonal crystals and requires more generality to be applicable to other crystalline materials (see sidebar, Challenges in Modeling Crystal Morphology Distributions). Recently, they have developed a comprehensive framework for deriving MPBMs solely from the information about crystal structure and F-faces (63). Their framework uses a set-theoretic approach to generate morphology domains and flux maps and subsequently develops MPBMs that are amenable to solution by the method of characteristics.

Population balance analysis of precipitation processes. The use of population balances has been relatively sparse for precipitation processes for which supersaturation is built up by a set of chemical reactions. This application requires treatment of the reaction system before the supersaturation can be calculated. The papers of Bandyopadhyaya et al. (120, 121) provide a proper setting.

New Applications in Biology

The application of population balances to microbial cells dates back to the early 1960s. Although this activity continues unabated, we focus on newer applications, which are of considerable interest to population balance modelers (see sidebar, Population Balances Needed in Tissue Engineering). We discuss three application areas that represent exciting opportunities. The first discusses modeling of growth and differentiation of stem cells in the bone marrow, the second concerns the modeling of gene regulation, and the third considers personalized medicine.

POPULATION BALANCES NEEDED IN TISSUE ENGINEERING

The area of tissue engineering, which involves growth and differentiation of cells on a scaffold, provides an ideal setting for the formulation of population balances. Indeed, the phenomenological elements of such a model would call for more fundamental understanding than may be currently available, but advances in this field occur at an impressive pace. A similar scenario also exists in the growth of solid tumors.

Growth and differentiation of stem cells. The prospect of clinical applications makes this domain of application a very important area of research (163). Quantitative modeling plays an important role in enabling personalized medicine (to be discussed below). Stem cells, generated in the bone marrow, multiply as well as differentiate into other cell types. This transformation of stem cells through a series of different cell types before discharge into the peripheral blood has been subject to population balance modeling (164, 165). The models would ideally fall in the categories of deterministic discrete and continuous internal coordinates, above. Cell age is used as a continuous internal coordinate for transition rates in the above models. However, insofar as signaling is a precursor to differentiation, modeling strategies discussed in Modeling of Gene Regulation, below, would be relevant to the calculation of transition rates from one cell type to another. Despite the fact that cell age is virtually impossible to observe, Sherer et al. (21) have shown that age-dependent transition rates can be estimated from experimental data by exploiting quasi-static behavior of age distributions in a cell cycle.

Although this demonstration was made for cells going through a regular cell cycle, the methodology appears to be extendable to the bone marrow scenario, in which cell differentiation defines transitions to different states. Sherer et al. (58) also demonstrated that such age-structured transition cell-cycle models can be used to strategically administer drugs with phase-specific activity.

Modeling of gene regulation. Gene regulation occurs within the cell in response to the appearance of a signaling molecule in the cell's environment. The associated intracellular reactions satisfy a system of stochastic differential equations, such as Equation 3. The methodology for arriving at this equation was discussed briefly in the section on Continuous Internal Coordinates (Stochastic), above. The reaction system is stochastic because of the small number of molecules involved in it. At high extracellular levels of the signaling molecule, gene regulation will result in the synthesis of a specific intracellular protein, giving rise to an on cell. At low concentrations of the signaling molecule, the intracellular protein will be at a very low level, producing an off cell. For intermediate levels of the signaling molecule, a region of bistability exists in which a cell may eventually be either off or on. This occurrence of bistability in gene regulatory processes usually has been modeled at the level of a single cell (with a proportional piece of the environment) to interpret experiments at the population level. The steady-state Fokker-Planck equation for Equation 3 with the bistable system will display bimodal behavior, implying that the population will comprise a mixture of on and off cells. This dynamic steady state will feature individual cells commuting randomly between off and on states. The single-cell analysis ignores the fact that even cells, identical at the beginning, will subsequently behave differently from each other because of stochasticity, thus creating changes in their shared environment. Clearly, only population balance analysis can deal with this scenario. When population balance of the type in Equation 4 is used, a unimodal distribution is sometimes predicted for the population, because the well-stirred signaling environment maintains a state between off and on (see References 8 and 9 for demonstration). Gene regulation is a vast area of biology, and population balance will be an indispensable tool in its analysis. A significant application lies in the transfer of drug resistance from one bacterial species to another, where gene regulation enables conjugation between the two species, thus providing for exchange of resistance-bearing plasmids. Understanding of this phenomenon is of great importance for the future development of antibiotic drugs.

Growth in biofilms. The modeling of gene regulation in the previous section is of great consequence to modeling of growth of cell populations in planktonic (well-stirred) and biofilm (diffusion-limited) environments. In biofilm growth, the equation for the environment will feature diffusion terms for the extracellular variables that are exchanged with cells. The models are of

the type encountered in the section on Discrete Internal Coordinates (Stochastic). An upcoming publication by Shu et al. (166) discusses results of a stochastic biofilm model.

Personalized medicine. The issue of personalized medicine in the treatment of disease has arisen out of the realization that the action of a drug is specific to the genomic and metabolic profile of a patient. Testing of blood samples focuses on measurement of specific plasma constituents that evolve from processes in the bone marrow. Although a full realization of personalized medicine would entail modeling methodologies beyond population balances, the latter are an essential part of evaluating the effect of drugs on cells that enter the circulating blood from the bone marrow. For example, during a treatment phase called maintenance therapy in the treatment of children with acute lymphoblastic leukemia, children are tested on a regular basis for the mean cell volume (MCV) of their red blood cells. The change in MCV from normal-sized cells to that of cells during maintenance therapy has been shown to have the highest correlation with treatment (167). Sherer (168) has developed population balance models based on cell volume and cell age to relate MCV to different drug levels and addressed the reverse dependence of measured MCV drug levels through the use of Bayes's theorem. This modeling can help diagnose the effectiveness of the dosage administered. It also has the potential to detect noncompliance.

The containment of side effects is an important issue to add to our consideration of medical treatment. Thus, relating side effects to drug dosage is another aspect of modeling in this area. The death rate of cells as a function of drug concentration and cell age can then be used to investigate within a stochastic population balance framework the response of cancer cells to treatment (15). Of particular interest to designing drug dosage would be the probability with which all cancer cells will have been killed over a treatment period, which determines the acceptable level of side effects.

CONCLUDING REMARKS

Population balance modeling is undergoing phenomenal growth in its applications, with virtually unlimited scope for further expansion. Although engineering applications continue to grow, this article has focused more on biological applications of population balances because of (*a*) the opportunities to develop new facets of the methodology and (*b*) the potential for extraordinary impact on specific areas, which were omitted from discussion to contain the length of this article.

We have identified areas for improvement in the phenomenological implements of population balance modeling. Sources and sinks can conspire to provide adequate fits of data under specific sets of conditions without the capacity to extend into predictive domains. Of course, in a system with diverse aspects of complexity, modeling must be viewed more to provide broad guidance on what can be expected than to snugly confront data. However, in the spirit of minimizing empiricism, it is well to explore methods to relate phenomenological implements more closely to the actual scenarios being modeled. Whereas flow cytometry provides strong experimental support for the development of multidimensional population balance models in biology, the situation in engineering particulate systems is less impressive. Understanding single-particle behavior calls for the development of experimental methods, such as the use of improved imaging techniques (169). An example is contained in the use of confocal microscopy in determining crystal shapes (170).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Naimi LJ, Sokhansanj S, Womac AR, Bi X, Lim CJ, et al. 2011. Development of a population balance model to simulate fractionation of ground switchgrass. *Trans. ASABE* 54:219–27
2. Hosseini SA, Shah N. 2011. Modelling enzymatic hydrolysis of cellulose part I: population balance modelling of hydrolysis by endoglucanase. *Biomass Bioenergy* 35:3841–48
3. Hosseini SA, Shah N. 2011. Enzymatic hydrolysis of cellulose part II: population balance modelling of hydrolysis by exoglucanase and universal kinetic model. *Biomass Bioenergy* 35:3830–40
4. Liao CM, Feddes JJR. 1991. Modeling and analysis of airborne dust removal from a ventilated airspace. *Can. Agric. Eng.* 33:355–61
5. Lipovka AA. 1995. Solution of the set of population balance-equations for atomic and molecular quantum levels in some particular cases. *Astron. Zh.* 72:392–96
6. Rovenskaya NI. 2008. The highly excited hydrogen b_n-factors calculated. *Astrophys. Space Sci.* 314:25–33
7. Stamatakis M. 2013. Cell population balance and hybrid modeling of population dynamics for a single gene with feedback. *Comput. Chem. Eng.* 53:25–34
8. Shu CC, Chatterjee A, Dunny G, Hu WS, Ramkrishna D. 2011. Bistability versus bimodal distributions in gene regulatory processes from population balance. *PLoS Comput. Biol.* 7:e1002140
9. Shu CC, Chatterjee A, Hu WS, Ramkrishna D. 2012. Modeling of gene regulatory processes by population-mediated signaling: new applications of population balances. *Chem. Eng. Sci.* 70:188–99
10. Henson MA. 2003. Dynamic modeling of microbial cell populations. *Curr. Opin. Biotechnol.* 14:460–67
11. Kromenaker SJ, Srienc F. 1994. Cell-cycle kinetics of the accumulation of heavy and light chain immunoglobulin proteins in a mouse hybridoma cell line. *Cytotechnology* 14:205–18
12. Mantzaris NV. 2007. From single-cell genetic architecture to cell population dynamics: quantitatively decomposing the effects of different population heterogeneity sources for a genetic network with positive feedback architecture. *Biophys. J.* 92:4271–88
13. Rounseville KJ, Chau PC. 2005. Three-dimensional cell cycle model with distributed transcription and translation. *Med. Biol. Eng. Comput.* 43:155–61
14. Borissova A, Goltz GE, Kavanagh JP, Wilkins TA. 2010. Reverse engineering the kidney: modelling calcium oxalate monohydrate crystallization in the nephron. *Med. Biol. Eng. Comput.* 48:649–59
15. Sherer E, Hannemann RE, Rundell A, Ramkrishna D. 2007. Estimation of likely cancer cure using first- and second-order product densities of population balance models. *Ann. Biomed. Eng.* 35:903–15
16. Fernandes RL, Carlquist M, Lundin L, Heins AL, Dutta A, et al. 2013. Cell mass and cell cycle dynamics of an asynchronous budding yeast population: experimental observations, flow cytometry data analysis, and multi-scale modeling. *Biotechnol. Bioeng.* 110:812–26
17. Bannari R, Bannari A, Vermette P, Proulx P. 2012. A model for cellulase production from *Trichoderma reesei* in an airlift reactor. *Biotechnol. Bioeng.* 109:2025–38
18. Rathore AS, Sharma C, Persad A. 2012. Use of computational fluid dynamics as a tool for establishing process design space for mixing in a bioreactor. *Biotechnol. Prog.* 28:382–91
19. Fadda S, Cincotti A, Cao G. 2012. A novel population balance model to investigate the kinetics of in vitro cell proliferation: part I. Model development. *Biotechnol. Bioeng.* 109:772–81
20. Zhang H, Zhang K, Fan SD. 2009. CFD simulation coupled with population balance equations for aerated stirred bioreactors. *Eng. Life Sci.* 9:421–30
21. Sherer E, Tocce E, Hannemann RE, Rundell AE, Ramkrishna D. 2008. Identification of age-structured models: cell cycle phase transitions. *Biotechnol. Bioeng.* 99:960–74
22. Cipollina C, Vai M, Porro D, Hatzis C. 2007. Towards understanding of the complex structure of growing yeast populations. *J. Biotechnol.* 128:393–402
23. Hatzis C, Porro D. 2006. Morphologically-structured models of growing budding yeast populations. *J. Biotechnol.* 124:420–38
24. Martin PJ, Chin NL, Campbell GM. 2004. Aeration during bread dough mixing II. A population balance model of aeration. *Food Bioprod. Process.* 82:268–81
25. Han BB, Linden JC, Gujarathi NP, Wickramasinghe SR. 2004. Population balance approach to modeling hairy root growth. *Biotechnol. Prog.* 20:872–79

26. Mhaskar P, Hjortso MA, Henson MA. 2002. Cell population modeling and parameter estimation for continuous cultures of *Saccharomyces cerevisiae*. *Biotechnol. Prog.* 18:1010–26
27. Hunter JB, Asenjo JA. 1990. A population balance model of enzymatic lysis of microbial-cells. *Biotechnol. Bioeng.* 35:31–42
28. Fu CL, Tong CF, Dong C, Long M. 2011. Modeling of cell aggregation dynamics governed by receptor-ligand binding under shear flow. *Cell. Mol. Bioeng.* 4:427–41
29. Fadda S, Briesen H, Cincotti A. 2011. The effect of EIF dynamics on the cryopreservation process of a size distributed cell population. *Cryobiology* 62:218–31
30. Luni C, Doyle FJ, Elvassore N. 2011. Cell population modelling describes intrinsic heterogeneity: a case study for hematopoietic stem cells. *IET Syst. Biol.* 5:164–73
31. Ma YP, Wang JK, Liang SL, Dong C, Du Q. 2010. Application of population dynamics to study heterotypic cell aggregations in the near-wall region of a shear flow. *Cell. Mol. Bioeng.* 3:3–19
32. Mancuso L, Liuzzo MI, Fadda S, Pisu M, Cincotti A, et al. 2009. Experimental analysis and modelling of in vitro proliferation of mesenchymal stem cells. *Cell Prolif.* 42:602–16
33. Pisu M, Concas A, Fadda S, Cincotti A, Cao G. 2008. A simulation model for stem cells differentiation into specialized cells of non-connective tissues. *Comput. Biol. Chem.* 32:338–44
34. Sidoli FR, Mantalaris A, Asprey SP. 2004. Modelling of mammalian cells and cell culture processes. *Cytotechnology* 44:27–46
35. Nielsen LK, Bender JG, Miller WM, Papoutsakis ET. 1998. Population balance model of *in vivo* neutrophil formation following bone marrow rescue therapy. *Cytotechnology* 28:157–62
36. Huang PY, Hellums JD. 1993. Aggregation and disaggregation kinetics of human blood platelets: part 1. Development and validation of a population balance method. *Biophys. J.* 65:334–43
37. Nason JA, Lawler DF. 2010. Modeling particle-size distribution dynamics during precipitative softening. *J. Environ. Eng.* 136:12–21
38. Bandara UC, Yapa PD. 2011. Bubble sizes, breakup, and coalescence in deepwater gas/oil plumes. *J. Hydraul. Eng.* 137:729–38
39. Matsui Y, Fukushi K, Tambo N. 1998. Modeling, simulation and operational parameters of dissolved air flotation. *Aqua* 47:9–20
40. Hanhoun M, Montastruc L, Azzaro-Pantel C, Biscans B, Frèche M, Pibouleau L. 2013. Simultaneous determination of nucleation and crystal growth kinetics of struvite using a thermodynamic modeling approach. *Chem. Eng. J.* 215:903–12
41. Nopens I, Nere N, Vanrolleghem PA, Ramkrishna D. 2007. Solving the inverse problem for aggregation in activated sludge flocculation using a population balance framework. *Water Sci. Technol.* 56:95–103
42. Mohanarangam K, Cheung SCP, Tu JY, Chen L. 2009. Numerical simulation of micro-bubble drag reduction using population balance model. *Ocean Eng.* 36:863–72
43. Bryson AW, Hofman DL. 1989. A population balance approach to the study of bubble behavior at gas-evolving electrodes. *J. Appl. Electrochem.* 19:116–19
44. White CM, Zeininger G, Ege P, Ydstie BE. 2007. Multi-scale modeling and constrained sensitivity analysis of particulate CVD systems. *Chem. Vapor Depos.* 13:507–12
45. Zhao HB, Zheng CG. 2008. A stochastic simulation for the collection process of fly ashes in single-stage electrostatic precipitators. *Fuel* 87:2082–89
46. Qi NN, Zhang K, Xu G, Yang YP, Zhang H. 2013. CFD-PBE simulation of gas-phase hydrodynamics in a gas-liquid-solid combined loop reactor. *Pet. Sci.* 10:251–61
47. Balaji S, Du J, White CM, Ydstie BE. 2010. Multi-scale modeling and control of fluidized beds for the production of solar grade silicon. *Powder Technol.* 199:23–31
48. Pedel J, Thornock JN, Smith PJ. 2013. Ignition of co-axial turbulent diffusion oxy-coal jet flames: experiments and simulations collaboration. *Combust. Flame* 160:1112–28
49. Fan W, Hao X, Xu YY, Li YW. 2011. Simulation of catalyst on-line replacement for Fischer-Tropsch synthesis in slurry bubble column reactor. *Chem. Technol. Fuels Oils* 47:116–33
50. Khoshandam A, Alamdari A. 2010. Kinetics of asphaltene precipitation in a heptane-toluene mixture. *Energy Fuels* 24:1917–24
51. Barta HJ, Drumm C, Attarakih MM. 2008. Process intensification with reactive extraction columns. *Chem. Eng. Process.* 47:745–54

52. Klose W, Schinkel A. 2002. Measurement and modelling of the development of pore size distribution of wood during pyrolysis. *Fuel Process. Technol.* 77:459–66
53. Junk KW, Brown RC. 1993. A model of coal combustion dynamics in a fluidized-bed combustor. *Combust. Flame* 95:219–28
54. Zitha PLJ, Du DX. 2010. A new stochastic bubble population model for foam flow in porous media. *Transp. Porous Media* 83:603–21
55. Sow M, Crase E, Rajot JL, Sankaran RM, Lacks DJ. 2011. Electrification of particles in dust storms: field measurements during the monsoon period in Niger. *Atmos. Res.* 102:343–50
56. Furukawa Y, Watkins JL. 2012. Effect of organic matter on the flocculation of colloidal montmorillonite: a modeling approach. *J. Coast. Res.* 28:726–37
57. Vokou D, Chalkos D, Karamanlidou G, Yiangou M. 2002. Activation of soil respiration and shift of the microbial population balance in soil as a response to *Lavandula stoechas* essential oil. *J. Chem. Ecol.* 28:755–68
58. Sherer E, Hannemann RE, Rundell A, Ramkrishna D. 2006. Analysis of resonance chemotherapy in leukemia treatment via multi-staged population balance models. *J. Theor. Biol.* 240:648–61
59. Wen JZ, Celnik M, Richter H, Treska M, Vander Sande JB, Kraft M. 2008. Modelling study of single walled carbon nanotube formation in a premixed flame. *J. Mater. Chem.* 18:1582–91
60. Kwok LS, Coroneo MT. 1994. A model for pterygium formation. *Cornea* 13:219–24
61. Sharma A, Coles WH. 1989. Kinetics of corneal epithelial maintenance and graft loss—a population balance model. *Investig. Ophthalmol. Vis. Sci.* 30:1962–71
62. Flood AE, Wantha L. 2013. Population balance modeling of the solution mediated transformation of polymorphs: limitations and future trends. *J. Cryst. Growth* 373:7–12
63. Singh MR, Ramkrishna D. 2013. A comprehensive approach to predicting crystal morphology distributions with population balances. *Cryst. Growth Des.* 13:1397–411
64. Chakraborty J, Singh MR, Ramkrishna D, Borchert C, Sundmacher K. 2010. Modeling of crystal morphology distributions. Towards crystals with preferred asymmetry. *Chem. Eng. Sci.* 65:5676–86
65. Mahoney AW, Doyle FJ, Ramkrishna D. 2002. Inverse problems in population balances: growth and nucleation from dynamic data. *AIChE J.* 48:981–90
66. Iggland M, Mazzotti M. 2012. Population balance modeling with size-dependent solubility: Ostwald ripening. *Cryst. Growth Des.* 12:1489–500
67. Zhang HT, Quon J, Alvarez AJ, Evans J, Myerson AS, Trout B. 2012. Development of continuous anti-solvent/cooling crystallization process using cascaded mixed suspension, mixed product removal crystallizers. *Org. Process Res. Dev.* 16:915–24
68. Mangin D, Garcia E, Gerard S, Hoff C, Klein JP, Veesler S. 2006. Modeling of the dissolution of a pharmaceutical compound. *J. Cryst. Growth* 286:121–25
69. Chakraborty J, Ramkrishna D. 2011. Population balance modeling of environment dependent breakage: role of granular viscosity, density and compaction. Model formulation and similarity analysis. *Ind. Eng. Chem. Res.* 50:13116–28
70. Ramkrishna D. 2004. On aggregating populations. *Ind. Eng. Chem. Res.* 43:441–48
71. Kayrak-Talay D, Dale S, Wassgren C, Litster J. 2013. Quality by design for wet granulation in pharmaceutical processing: assessing models for a priori design and scaling. *Powder Technol.* 240:7–18
72. Boukouvala F, Niotis V, Ramachandran R, Muzzio FJ, Ierapetritou MG. 2012. An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. *Comput. Chem. Eng.* 42:30–47
73. Gradon L, Podgórski A. 1996. Deposition of inhaled particles: discussion of present modeling techniques. *J. Aerosol Med.* 9:343–55
74. Yamasue E, Numata T, Okumura H, Ishihara KN. 2009. Impact evaluation of rare metals in waste mobile phone and personal computer. *J. Jpn. Inst. Met.* 73:198–204
75. Lee J, Sung NW, Huh KY. 2011. Prediction of soot particle size distribution for turbulent reacting flow in a diesel engine. *Int. J. Eng. Res.* 12:181–89
76. Mosbach S, Celnik MS, Raj A, Kraft M, Zhang HR, et al. 2009. Towards a detailed soot model for internal combustion engines. *Combust. Flame* 156:1156–65

77. Kakudate K, Kajikawa Y, Adachi Y, Suzuki T. 2002. Calculation model of CO_2 emissions for Japanese passenger cars. *Int. J. Life Cycle Assess.* 7:85–93
78. Hulburt H, Katz S. 1964. Some problems in particle technology: a statistical mechanical formulation. *Chem. Eng. Sci.* 19:555–74
79. Randolph AD. 1964. A population balance for countable entities. *Can. J. Chem. Eng.* 42:280–81
80. Fredrickson A, Ramkrishna D, Tsuchiya H. 1967. Statistics and dynamics of procaryotic cell populations. *Math. Biosci.* 1:327–74
81. Ramkrishna D. 2000. *Population Balances: Theory and Applications to Particulate Systems in Engineering*. New York: Academic
82. Jakobsen HA. 2008. *Chemical Reactor Modeling: Multiphase Reactive Flows*. Berlin: Springer-Verlag
83. Ramkrishna D. 1985. The status of population balances. *Rev. Chem. Eng.* 3:49–95
84. Ramkrishna D, Mahoney AW. 2002. Population balance modeling. Promise for the future. *Chem. Eng. Sci.* 57:595–606
85. Ramkrishna D. 1979. Statistical models of cell populations. *Adv. Biochem. Eng.* 11:1–47
86. Sporleder F, Borka Z, Solsvik J, Jakobsen HA. 2012. On the population balance equation. *Rev. Chem. Eng.* 28:149–69
87. Randolph A. 1971. *Theory of Particulate Processes: Analysis and Techniques of Continuous Crystallization*. New York: Academic
88. Hjortso M. 2005. *Population Balances in Biomedical Engineering*. New York: McGraw Hill Prof.
89. Christofides PD. 2002. *Model-Based Control of Particulate Processes*. Dordrecht, Neth.: Kluwer Acad. Publ.
90. Solsvik J, Jakobsen HA. 2013. On the solution of the population balance equation for bubbly flows using the high-order least squares method: implementation issues. *Rev. Chem. Eng.* 29:63–98
91. Sajjadi B, Raman AAA, Ibrahim S, Shah R. 2012. Review on gas-liquid mixing analysis in multiscale stirred vessel using CFD. *Rev. Chem. Eng.* 28:171–89
92. Mortier S, De Beer T, Gernaey KV, Remon JP, Vervaet C, Nopens I. 2011. Mechanistic modelling of fluidized bed drying processes of wet porous granules: a review. *Eur. J. Pharm. Biopharm.* 79:205–25
93. Bajcinca N, Qamar S, Flockerzi D, Sundmacher K. 2011. Integration and dynamic inversion of population balance equations with size-dependent growth rate. *Chem. Eng. Sci.* 66:3711–20
94. Kiparissides C, Krallis A, Meimaroglou D, Pladis P, Baltsas A. 2010. From molecular to plant-scale modeling of polymerization processes: a digital high-pressure low-density polyethylene production paradigm. *Chem. Eng. Technol.* 33:1754–66
95. Sadiku O, Sadiku ER. 2010. Numerical simulation for nanoparticle growth in flame reactor and control of nanoparticles. *J. Comput. Theor. Nanosci.* 7:2262–70
96. Rigopoulos S. 2010. Population balance modelling of polydispersed particles in reactive flows. *Prog. Energy Combust. Sci.* 36:412–43
97. Liao YX, Lucas D. 2010. A literature review on mechanisms and models for the coalescence process of fluid particles. *Chem. Eng. Sci.* 65:2851–64
98. Yu MZ, Lin JZ. 2010. Nanoparticle-laden flows via moment method: a review. *Int. J. Multiph. Flow* 36:144–51
99. Liao YX, Lucas D. 2009. A literature review of theoretical models for drop and bubble breakup in turbulent dispersions. *Chem. Eng. Sci.* 64:3389–406
100. Tindall MJ, Maini PK, Porter SL, Armitage JP. 2008. Overview of mathematical approaches used to model bacterial chemotaxis II: bacterial populations. *Bull. Math. Biol.* 70:1570–607
101. Ribeiro CP, Lage PLC. 2008. Modelling of hydrate formation kinetics: state-of-the-art and future directions. *Chem. Eng. Sci.* 63:2007–34
102. Dukhin AS, Dukhin SS, Goetz PJ. 2007. Gravity as a factor of aggregative stability and coagulation. *Adv. Colloid Interface Sci.* 134–35:35–71
103. Roth P. 2007. Particle synthesis in flames. *Proc. Combust. Inst.* 31:1773–88
104. Maximova N, Dahl O. 2006. Environmental implications of aggregation phenomena: current understanding. *Curr. Opin. Colloid Interface Sci.* 11:246–66
105. Taboada-Serrano P, Chin CJ, Yiacoumi S, Tsouris C. 2005. Modeling aggregation of colloidal particles. *Curr. Opin. Colloid Interface Sci.* 10:123–32

106. Vale HM, McKenna TF. 2005. Modeling particle size distribution in emulsion polymerization reactors. *Prog. Polym. Sci.* 30:1019–48
107. Cameron IT, Wang FY, Immanuel CD, Stepanek F. 2005. Process systems modelling and applications in granulation: a review. *Chem. Eng. Sci.* 60:3723–50
108. Somasundaran P, Runkana V. 2003. Modeling flocculation of colloidal mineral suspensions using population balances. *Int. J. Miner. Process.* 72:33–55
109. Braatz RD. 2002. Advanced control of crystallization processes. *Annu. Rev. Control* 26:87–99
110. Mohanty S. 2000. Modeling of liquid-liquid extraction column: a review. *Rev. Chem. Eng.* 16:199–248
111. Kovscek AR, Radke CJ. 1994. Fundamentals of foam transport in porous media. *Foams Fundam. Appl. Pet. Ind.* 242:115–63
112. Rawlings JB, Miller SM, Witkowski WR. 1993. Model identification and control of solution crystallization processes: a review. *Ind. Eng. Chem. Res.* 32:1275–96
113. Ramkrishna D, Borwanker J. 1973. A puristic analysis of population balance—I. *Chem. Eng. Sci.* 28:1423–35
114. Gardiner CW. 1985. *Handbook of Stochastic Methods*. Berlin: Springer
115. van Kampen NG. 1992. *Stochastic Processes in Physics and Chemistry*. Amsterdam: Elsevier
116. Sherer E, Ramkrishna D. 2008. Stochastic analysis of multistate systems. *Ind. Eng. Chem. Res.* 47:3430–37
117. Sherer E, Hannemann RE, Rundell AE, Ramkrishna D. 2009. Application of stochastic equations of population balances to sterilization processes. *Chem. Eng. Sci.* 64:764–74
118. Froment GF, Bischoff KB, De Wilde J. 1990. *Chemical Reactor Analysis and Design*. New York: Wiley
119. Gunawan R, Ma DL, Fujiwara M, Braatz RD. 2002. Identification of kinetic parameters in multidimensional crystallization processes. *Int. J. Mod. Phys. B* 16:367–74
120. Bandyopadhyaya R, Kumar R, Gandhi K, Ramkrishna D. 1997. Modeling of precipitation in reverse micellar systems. *Langmuir* 13:3610–20
121. Bandyopadhyaya R, Kumar R, Gandhi K. 2000. Simulation of precipitation reactions in reverse micelles. *Langmuir* 16:7139–49
122. Bandyopadhyaya R, Kumar R, Gandhi K. 2001. Modelling of $CaCO_3$ nanoparticle formation during overbasing of lubricating oil additives. *Langmuir* 17:1015–29
123. Levenspiel O. 1972. *Chemical Reaction Engineering*. New York: Wiley
124. White E, Wright P. 1971. Magnitude of size dispersion effects in crystallization. *AIChE Symp. Ser.* 67:81–87
125. Ulrich J. 1989. Growth rate dispersion—a review. *Cryst. Res. Technol.* 24:249–57
126. Larson M, White E, Ramanarayanan K, Berglund K. 1985. Growth rate dispersion in MSMPR crystallizers. *AIChE J.* 31:90–94
127. Langevin P. 1908. On the theory of Brownian motion. *C. R. Acad. Sci.* 146:530–33
128. Rao N, Borwanker J, Ramkrishna D. 1974. Numerical solution of Ito integral equations. *SIAM J. Control* 12:124–39
129. Talay D. 1995. Simulation of stochastic differential systems. In *Probabilistic Methods in Applied Physics*, ed. P Krée, W Wedig, pp. 54–96. Berlin: Springer
130. Gillespie DT. 1977. Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* 81:2340–61
131. Shah B, Ramkrishna D, Borwanker J. 1977. Simulation of particulate systems using the concept of the interval of quiescence. *AIChE J.* 23:897–904
132. Cao Y, Gillespie DT, Petzold LR. 2006. Efficient step size selection for the tau-leaping simulation method. *J. Chem. Phys.* 124:044109
133. Bilgili E, Scarlett B. 2005. Population balance modeling of non-linear effects in milling processes. *Powder Technol.* 153:59–71
134. von Smoluchowski M. 1917. Versuch einer mathematischen Theorie der Koagulationskinetik kolloider Lösungen. *Z. Phys. Chem.* 92:129–68
135. Chandrasekhar S. 1943. Stochastic problems in physics and astronomy. *Rev. Mod. Phys.* 15:1
136. Spielman LA. 1970. Viscous interactions in Brownian coagulation. *J. Colloid Interface Sci.* 33:562–71
137. Coulaloglou C, Tavlarides L. 1977. Description of interaction processes in agitated liquid-liquid dispersions. *Chem. Eng. Sci.* 32:1289–97

138. Muralidhar R, Ramkrishna D. 1986. Analysis of droplet coalescence in turbulent liquid-liquid dispersions. *Ind. Eng. Chem. Fundam.* 25:554–60
139. Tobin T, Muralidhar R, Wright H, Ramkrishna D. 1990. Determination of coalescence frequencies in liquid-liquid dispersions: effect of drop size dependence. *Chem. Eng. Sci.* 45:3491–504
140. Tobin T, Ramkrishna D. 1992. Coalescence of charged droplets in agitated liquid-liquid dispersions. *AIChE J.* 38:1199–205
141. Tobin T, Ramkrishna D. 1999. Modeling the effect of drop charge on coalescence in turbulent liquid-liquid dispersions. *Can. J. Chem. Eng.* 77:1090–104
142. Simons S, Williams MMR, Cassell JS. 1986. A kernel for combined Brownian and gravitational coagulation. *J. Aerosol Sci.* 17:789–93
143. Sathyagal A, Ramkrishna D, Narsimhan G. 1995. Solution of inverse problems in population balances—II. Particle break-up. *Comput. Chem. Eng.* 19:437–51
144. Wright H, Ramkrishna D. 1992. Solutions of inverse problems in population balances—I. Aggregation kinetics. *Comput. Chem. Eng.* 16:1019–38
145. Wright H, Muralidhar R, Ramkrishna D. 1992. Aggregation frequencies of fractal aggregates. *Phys. Rev. A* 46:5072
146. Ramkrishna D. 1994. Toward a self-similar theory of microbial populations. *Biotechnol. Bioeng.* 43:138–48
147. Williams M, Meloy T, Tarshan M. 1994. Assessment of numerical solution approaches to the inverse problem for grinding systems: dynamic population balance model problems. *Powder Technol.* 78:257–61
148. Raikar NB, Bhatia SR, Malone MF, Henson MA. 2006. Self-similar inverse population balance modeling for turbulently prepared batch emulsions: sensitivity to measurement errors. *Chem. Eng. Sci.* 61:7421–35
149. Braumann A, Man PL, Kraft M. 2011. The inverse problem in granulation modeling—two different statistical approaches. *AIChE J.* 57:3105–21
150. Kostoglou M, Karabelas A. 2005. On the self-similar solution of fragmentation equation: numerical evaluation with implications for the inverse problem. *J. Colloid Interface Sci.* 284:571–81
151. Marchisio DL, Fox RO. 2005. Solution of population balance equations using the direct quadrature method of moments. *J. Aerosol Sci.* 36:43–73
152. Bhole M, Joshi J, Ramkrishna D. 2008. CFD simulation of bubble columns incorporating population balance modeling. *Chem. Eng. Sci.* 63:2267–82
153. Kumar S, Ramkrishna D. 1996. On the solution of population balance equations by discretization—I. A fixed pivot technique. *Chem. Eng. Sci.* 51:1311–32
154. Chen P, Sanyal J, Dudukovic M. 2004. CFD modeling of bubble columns flows: implementation of population balance. *Chem. Eng. Sci.* 59:5201–7
155. Vikhansky A, Kraft M. 2004. Modelling of a RDC using a combined CFD-population balance approach. *Chem. Eng. Sci.* 59:2597–606
156. Cardew P. 1985. The growth shape of crystals. *J. Cryst. Growth* 73:385–91
157. Zhang Y, Doherty MF. 2004. Simultaneous prediction of crystal shape and size for solution crystallization. *AIChE J.* 50:2101–12
158. Borchert C, Nere N, Ramkrishna D, Voigt A, Sundmacher K. 2009. On the prediction of crystal shape distributions in a steady-state continuous crystallizer. *Chem. Eng. Sci.* 64:686–96
159. Briesen H. 2006. Simulation of crystal size and shape by means of a reduced two-dimensional population balance model. *Chem. Eng. Sci.* 61:104–12
160. Ma CY, Wang XZ, Roberts KJ. 2008. Morphological population balance for modeling crystal growth in face directions. *AIChE J.* 54:209–22
161. Wang XZ, Ma CY. 2009. Morphological population balance model in principal component space. *AIChE J.* 55:2370–81
162. Wan J, Wang XZ, Ma CY. 2009. Particle shape manipulation and optimization in cooling crystallization involving multiple crystal morphological forms. *AIChE J.* 55:2049–61
163. Wilson A, Trumpp A. 2006. Bone-marrow haematopoietic-stem-cell niches. *Nat. Rev. Immunol.* 6:93–106
164. Adimy M, Crauste F, Ruan S. 2005. A mathematical study of the hematopoiesis process with applications to chronic myelogenous leukemia. *SIAM J. Appl. Math.* 65:1328–52

165. Foley C, Mackey MC. 2009. Dynamic hematological disease: a review. *J. Math. Biol.* 58:285–322
166. Shu C-C, Ramkrishna D, Chatterjee A, Hu W-S. 2013. Role of intracellular stochasticity in biofilm growth. Insights from population balance modeling. *PLoS ONE.* In press. doi: 10.1371/journal.pone.0079196.
167. Witte AS, Cornblath DR, Schatz NJ, Lisak RP. 1986. Monitoring azathioprine therapy in myasthenia gravis. *Neurology* 36:1533–34
168. Sherer EA. 2007. *Age-structured cell models in the treatment of leukemia: identification, inversion, and stochastic methods for the evaluation and design of chemotherapy protocols*. PhD Thesis, Purdue Univ., West Lafayette, Indiana. 274 pp.
169. Nagy ZK, Fevotte G, Kramer H, Simon LL. 2013. Recent advances in the monitoring, modelling and control of crystallization systems. *Chem. Eng. Res. Des.* 91:1903–22
170. Singh MR, Chakraborty J, Nere N, Tung H-H, Bordawekar S, Ramkrishna D. 2012. Image-analysis-based method for 3D crystal morphology measurement and polymorph identification using confocal microscopy. *Cryst. Growth Des.* 12:3735–48
171. Kodera Y, McCoy BJ. 2003. Distribution kinetics of plastics decomposition. *J. Jpn. Pet. Inst.* 46:155–65
172. Tavare NS. 1991. Batch crystallizers. *Rev. Chem. Eng.* 7:211–355
173. Ma CY, Wang XZ. 2012. Model identification of crystal facet growth kinetics in morphological population balance modeling of L-glutamic acid crystallization and experimental validation. *Chem. Eng. Sci.* 70:22–30