Differential Equation Models for Systems Biology: A Survey

DI ZHAO*

dzh002@latech.edu

Computational Analysis and Modeling, Louisiana Tech University

Ruston, LA 71272

Abstract

In this paper, we will review the current progress of modeling systems biology by differential equations including ordinary differential equation (ODE), partial differential equation (PDE) and stochastic differential equation (SDE). Also, we will discuss related issues including model selection, parameter estimation, model checking and software.

Key words: differential equation, modeling, systems biology

1 INTRODUCTION

Systems biology studies the interactions among the components of biological networks [32], and these networks include gene regulatory network (GRNs), metabolic network, signal transduction network, electrophysiology, *etc.* There are several reviews for systems biology. Ideker *et al.* reviewed systems biology in [37], Kitano reviewed in [59], and Fontana reviewed in [25]. Because of computational intensiveness of many systems biology projects, computational challenges of systems biology are discussed in [24] [30].

Systems biology modeling studies systems biology by mathematical or statistical models and computer programming. Klipp *et al.* published a book of systems biology models in 2009 [58], and Alfieri *et al.* discussed cell modeling in [2].

A GRN governs the rates at which genes in the network are transcribed into mRNA [33], and understanding and modeling GRNs are an important theme in post-genomic research [29]. Bolouri published a book of GRNs modeling [8] in 2008. Review papers of GRNs modeling provide us the overview of this area. Jong reviewed GRNs modeling in [42] [44] [50], and Karlebach *et al.* reviewed in [57]. Schlitt devided GRN models into four classes: part lists, topology models, control logic models and dynamic models in [79], and Ropers *et al.* reviewed three methods of the modeling of GRNs: graph theory, differential equation and stochastic master equation in [54].

Metabolic network modeling and signal transduction network modeling are parts of systems biology modeling. Coombes *et al.* reviewed differential equation models for network architecture, biophysical dynamics and signal

transduction of neuro systems in [13], Rodríguez *et al.* reviewed models for metabolism in [75], and Cho *et al.* reviewed signal transduction modeling in [87].

Cell electrophysiology or cellular electrophysiology studies of the electrical properties of biological cells. Cronin published a book of mathematics for cell electrophysiology in 1981 [14], Doi published a book of computational electrophysiology in 2010 [21], and Pásek reviewed computer modeling in cardiac cell electrophysiology in [71].

All biological systems are concisely controlled, and control theory is an important tool for systems biology modeling. The first book of systems biology and control theory is published in 2009 [38]. Papers of systems biology and control theory are published in recent years. Sontag *et al.* discussed molecular systems biology and control in [83], and Wolkenhauer *et al.* discussed the relationship between systems biology and control theory in [88] [89].

In this paper, we will review the current progress of modeling systems biology by differential equations including ODE in section 2, PDE in section 3 and SDE in section 4. Since the number of papers in differential equation modeling of systems biology is large, we will emphasize on the main works of this area. Additionally, each paper cited in this paper is Internet available as the author's searching, and books cited in this paper are related to differential equation models for systems biology.

2 ORDINARY DIFFERENTIAL EQUATION

ODE is the current mainstream method for systems biology modeling. ODE models for systems biology has the general form:

$$\frac{\partial X}{\partial t} = f(X), \tag{1}$$

where X is a property of components of the biological system such as the concentration of mRNA in GRNs, X is usually a vector, and f is a function for X. There are two kinds of ODE models for systems biology: linear ODE models and nonlinear ODE models.

2.1 Linear ordinary differential equation

When f in Eq. (1) is a linear function, we will obtain linear ODE with the form:

$$\frac{\partial X}{\partial t} = AX, \tag{2}$$

where A is the constant matrix. In linear ODE models, matrix A consists of all information of the biological systems.

The advantage of linear ODE is the possibility of realizing large-scale network models because of its simpliness and uniform format. By Eq. (2), linear ODE models transform a biological problem to a numerical linear algebra problem. Data mining techniques such as PCA and ICA can be useful to extract meaningful information from matrix A. However, the disadvantage of linear ODE also comes from its simpliness: the relationship among variables is limited to be linear, which is usually different from biological mechanism

in cells.

2.1.1 GRNs models

Linear ODE has wide application to GRNs modeling. In [16], based on the mass action law and the mass conservation laws, Alves *et al.* developed a ODE model to describe the regulation of gene expression in prokaryotes. Zak *et al.* developed a coupled system of ODEs with 54 variables for a in silico GRNs in [92]:

$$\frac{\partial X_{P_{IJ}}}{\partial t} = k_{P_{IJ}} X_{P_{IJ}} X_{J_2} + k_{UP_{IJ}} X_{J_2 P_{IJ}}, \tag{3.1}$$

$$\frac{\partial X_I}{\partial t} = k_{TI} X_{MI} - 2k_{I_2} X_I^2 + 2k_{UI_2} X_{I_2} - k_{dI} X_I, \tag{3.2}$$

$$\frac{\partial X_{I_2}}{\partial t} = k_{I_2} X_I^2 - k_{UI_2} X_{I_2} - k_{dI_2} X_{I_2} - \sum PB + \sum PU, \tag{3.3}$$

$$\frac{\partial X_{MI}}{\partial t} = k_{RP_{IJ}} X_{P_{IJ}} + k_{RJP_{IJ}} X_{J_2 P_{IJ}} - k_{dMI} X_{MI}, \tag{3.4}$$

$$\frac{\partial X_{MI}}{\partial t} = k_{R1} X_{P_{I1}} + k_{R2} X_{P_{I2}} + \cdots + k_{RN} X_{P_{RN}} + k_{dMI} X_{MI}, \tag{3.5}$$

where Eq. (3.1) describes binding and unbinding of transcription factors to promoters, Eqs. (3.2) and (3.3) describes translation, and Eqs. (3.4) and (3.5) describe the transcription rate in two different cases.

Software is helpful to simplify the process of building linear ODE models. Dilão *et al.* developed a software tool, GeneticNetworks, to model GRNs by linear ODE in [19].

A kind of linear differential equation, with the name of piecewise-linear differential equation (PLDE), has successful application to GRNs modeling.

Grognard *et al.* provide a review of PLDE based modeling for GRNs in [49]. PLDE has the general form

$$\frac{\partial X_i}{\partial t} = g_i\left(X_i\right) - \gamma_i X_i, 1 \leq i \leq I,$$

where X_i is the celluar concentration of the product of gene i, I is the total number of genes, and $\gamma_i > 0$ is the degration rate of X_i. In the most general form, the function g_i is defined as

$$g_i\left(X_i\right) = \sum_{l \in L} k_{il} b_{il}\left(X_i\right) \geq 0,$$

where $k_{il} > 0$ is a rate parameter, b_{il} is a function defined in terms of sums or multiplications of step functions s^+ and s^-:

$$\begin{aligned} s^+\left(X_i, \theta_i\right) &= 1, X_i > \theta_i, \\ s^-\left(X_i, \theta_i\right) &= 0, X_i < \theta_i, \\ s^-\left(X_i, \theta_i\right) &= 1 - s^+\left(X_i, \theta_i\right). \end{aligned}$$

The biological significance of steps functions is to express the conditions under which the gene i at location l is expressed at the rate k_{il}.

Since 1999, researchers in the bioinformatics group at INRIA Rhône-Alpes developed series of PLDE based algorithms. In [40], Jong *et al.* presented an implemented method for the qualitative simulation of large and complex GRNs. Jong *et al.* described a method that is able to deal with large and complex systems, and discussed its performance in simulation experiments

with random regulatory networks in [41]. In [45], Jong *et al.* present a PLDE based method for the hybrid modeling and simulation of GRNs. Batt *et al.* developed a PLDE based model and simulation method for GRNs in [46]. In [47], Jong *et al.* present a method based on a class of PLDE for the qualitative simulation of GRNs. Ropersa *et al.* modeled the carbon starvation response network and simulate the response of *Escherichia coli* cells to carbon deprivation by PLDE in [48]. In [51], Porreca *et al.* present a PLDE model for the structural identification of GRNs. Jong *et al.* developed a method of finding all steady states of GRNs described by PLDE models in [52].

2.1.2 Metabolic network models

Linear ODE is applied to metabolic network modeling of systems biology. Current review in this area comes from Terzer *et al.* those who surveyed genome-scale metabolic networks in [84].

Ao *et al.* developed ODE models of the central metabolism of *Methylobacterium extorquens* AM1, a methylotrophic and environmental important bacterium, in [4], and the models include 80 variables for different metabolite concentrations. Dräger *et al.* modeled metabolic networks in *Corynebacterium glutamicum* in [23]:

$$\frac{\partial X}{\partial t} = N f\left(X, t, p\right), \tag{4}$$

where X is the concentration of the metalolites, and N is the stoichiometric matrix. Gilbert *et al.* developed an combination approach of petri nets

and differential equations to model the influence of the raf kinase inhibitor protein (RKIP) on the extracellular signal regulated kinase (ERK) signalling pathway in [28]. Kaplan *et al.* developed ODE based simulation framework to model the evolving structure of the cell metabolism in [56], and the ODE models is similar to Eq. (4). Yang *et al.* developed the arachidonic acid metabolic network in [91]:

$$\frac{\partial X_s}{\partial t} = \frac{K_{cat} X_{E_t} X_S}{K_m + X_S},$$

where X_s is the concentration of the enzyme substrate, X_{E_t} is the concentration of the enzyme, and K_{cat} and K_m are constants.

2.1.3 Signal transduction models

Linear ODE has application to signal transduction network modeling of systems biology. Beirer *et al.* developed linear ODE models for the control of signal transduction cycles in [7]. Asthagiri *et al.* studied feedback effects on signal dynamics in a Mitogen-Activated Protein Kinase (MAPK) pathway model with ODE format in [60]. Mitrophanov *et al.* developed delay ODE

models for the CovR/S signal transduction system in [65]:

$$
\begin{aligned}
\frac{\partial X_1}{\partial t} &= k_{-1}X_{ADP}X_2 + k_2X_2X_3 + k_5X_2 + k_{10}X_6^{(d_6)} \\
&\quad -k_1X_{ATP}X_1 - k_{-2}X_1X_4 - k_{11}X_1, \\
\frac{\partial X_2}{\partial t} &= kX_{ATP}X_1 + k_{-2}X_1X_4 - k_{-1}X_{ADP}X_2 - k_2X_2X_3 - k_9X_3, \\
\frac{\partial X_3}{\partial t} &= k_{-2}X_1X_4 + k_4X_4 + k_8X_5^{(d_5)} \\
&\quad -k_2X_2X_3 - k_3X_{X-P}X_3 - k_9X_3, \\
\frac{\partial X_4}{\partial t} &= k_2X_2X_3 - k_{-2}X_1X_4 - k_3X_{X-P}X_3 - k_4X_4, \\
\frac{\partial X_5}{\partial t} &= \frac{k_6}{(1+K_6X_4)} - k_7X_5, \\
\frac{\partial X_6}{\partial t} &= \frac{k_6}{\left(1+K_6X_4^{(d_4)}\right)} - k_7X_6, \\
\frac{\partial X_7}{\partial t} &= \frac{k_{12}}{(1+K_{12}X_4)^5} - k_7X_5, \\
\frac{\partial X_8}{\partial t} &= k_{14}X_7^{(d_7)} - k_{15}X_8,
\end{aligned}
$$

where $X_1, \cdots, X_8, X_{ADP}, X_{ATP}$ and X_{X-P} are the concentrations of the reactants.

2.2 Nonlinear ordinary differential equation

When f in Eq. (1) is a nonlinear function, we will obtain nonlinear ODE. The number of existing papers of nonlinear ODE is less than that of linear ODE. Binder *et al.* developed nonlinear ODE and pathway dynamics for the interrelations between dynamics and structure of signal transduction

pathways in [7]:

$$\frac{\partial X_i}{\partial t} = \left(\rho_i R\left(t\right) + \sum_{k\neq i}^{n} \alpha_{ik} X_k\right)\left(1 - \frac{X_i}{C_i}\right) - \beta_i X_i,$$

where β_i is the dephosphorylation of the kinases by phosphatases and $R\left(t\right)$ denotes the time dependent concentration of the stimulated receptor. Rauch *et al.* developed nonlinear ODE models for trans-membrane signal transduction in turing-type cellular pattern formation in [74]:

$$\begin{aligned}
\frac{\partial X}{\partial t} &= c_X - \lambda_X X + \frac{V_1 X}{K_1 + X} - \frac{V_3 XY}{K_3 + X} - \alpha_X X + \beta_X M_X\left(x, y\right), \\
\frac{\partial Y}{\partial t} &= c_Y - \lambda_Y Y + \frac{V_2 X}{K_2} - \alpha_Y Y + \beta_Y M_Y\left(x, y\right),
\end{aligned}$$

where X is the concentration of the activator and Y is the concentration of inactivator, M_X and M_Y are extracellular matrix. Singh *et al.* modeled regulatory mechanisms in IL-6 signal transduction in hepatocytes by a nonlinear ODE system with 68 variables, and the details can be found in APPENDIX-II of [81].

In [27], Gentilini defined S-system differential equations:

$$\frac{\partial X_i}{\partial t} = \alpha_i \prod_{j=1}^{M+N} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{M+N} X_j^{h_{ij}}, i = 1, \cdots, M, j = 1, \cdots, N,$$

where $X_1, \cdots, X_M$ are dependent variables, $X_{M+1}, \cdots, X_N$ are independent variables, α_i are production rate constants, β_i are degradation rate constants, and the author developed automatic procedures for transform GRNs to S-systems differential equations with examples. DNA microarray mea-

surements of mRNA concentrations are a tool to obtain the whole-genome information of transcriptional activity, and Rosenfeld studied characteristics of transcriptional activity of GRNs by nonlinear ODE in [76]:

$$\frac{\partial X_i}{\partial t} = \alpha_i \prod_{k=N+1}^{2N} Y_k^{P_{ik}} \prod_{k=1}^{N} X_k^{P_{ik}} - \beta_i \prod_{k=N+1}^{2N} Y_k^{P_{ik}} \prod_{k=1}^{N} X_k^{P_{ik}}, i = 1, \cdots, N, \quad (5.1)$$

$$\frac{\partial Y_i}{\partial t} = \gamma_i \prod_{k=1}^{N} X_k^{P_{ik}} \prod_{k=N+1}^{2N} Y_k^{P_{ik}} - \delta_i \prod_{k=1}^{N} X_k^{P_{ik}} \prod_{k=N+1}^{2N} Y_k^{P_{ik}}, i = N+1, \cdots, 2N, \quad (5.2)$$

where X_i is the protein copy numbers and Y_i is the mRNA copy numbers. The first term of left-hand-side of Eq. (5.1) describes production of proteins by ribosomes, and the second term of left-hand-side of Eq. (5.1) describes disappearance of the i-th protein; the first term of left-hand-side of Eq. (5.2) describes transcription, and the second term of left-hand-side of Eq. (5.2) describes decay of mRNAs in the process of templating by ribosome and subsequent dissolution in the cytoplasmic environment.

3 PARTIAL DIFFERENTIAL EQUATION

While one variable such as time can be considered in ODE models, PDE models are built to simulate the systems with multi variables such as both time and space. For example, if a biological system of multiple cells is considered, the dimentional PDE models are used for modeling.

PDE has wide applications to GRNs modeling. Dilão *et al.* developed PDE models for GRNs in [15] [17] [18] [20]. In [15], Dilão *et al.* developed a PDE framework for the regulation of gene expression in prokaryotes, and this

is the first paper of the author's effort of PDE modeling of GRNs. In [17], Dilão *et al.* fit the parameters of a PDE model describing the production of gap gene proteins Hunchback and Knirps of *Drosophila*. In [18], Dilão *et al.* developed the PDE model of bicoid mRNA concentration and caudal mRNA concentration during the first stage of development of *Drosophila*. Recently, Dilão *et al.* developed a mRNA diffusion model [20]:

$$\begin{aligned} \frac{\partial X}{\partial t} &= -dX + D\frac{\partial^2 X}{\partial x^2}, \\ \frac{\partial X}{\partial t} &= aX, \end{aligned}$$

where X is the concentration of bicoid protein, a is the rate of production of bicoid mRNA, d is the degration rate of bicoid mRNA, and D is the degration rate of bicoid mRNA in the cytoplasm.

In [6], Benítez *et al.* developed activator-inhibitor models of GRNs in root and loof epidermal cell patterning in *Arabidopsis thaliana*:

$$\frac{\partial X}{\partial t} = D_X \Delta X - k_1 X + k_2 \frac{X^2}{Y}, X \in N, \tag{6.1}$$

$$\frac{\partial X}{\partial t} = D_X \Delta X - k_1 X, X \notin N, \tag{6.2}$$

$$\frac{\partial Y}{\partial t} = D_Y \Delta Y - k_3 Y + k_4 X^2, X \in N, \tag{6.3}$$

$$\frac{\partial Y}{\partial t} = D_Y \Delta Y - k_3 Y, X \notin N, \tag{6.4}$$

where Eqs. (6.1) and (6.2) are for the changing rate of activator and Eqs. (6.3) and (6.4) are for the changing rate of inhibitor, N is a discrete small area and D_X and D_Y are constants. In [10], Chen *et al.* developed a dynamic

system of gene expression:

$$\frac{\partial X}{\partial t} = f(Y) - VX, \tag{7.1}$$

$$\frac{\partial Y}{\partial t} = f(X) - VY, \tag{7.2}$$

where X is the concentration of mRNA, Y is the concentration of protein and f is transcription functions, and three transcription functions are developed in this paper. Li *et al.* developed a two-dimensional spatio-temporal dynamic PDE model for gene-protein interaction network in early *Drosophila* development in [61]:

$$\begin{aligned}
\frac{\partial X_i(t,x,y)}{\partial t} &= k_i(x,y) - \alpha_i(x,y) X_i(t,x,y) \\
&\quad + \sum_{j=1}^{14} \beta_{ij}(x,y) f(Y_j(t-\tau_j,x,y)) + v_i(t,x,y), \\
\frac{\partial Y_j(t,x,y)}{\partial t} &= \varpi_j(x,y) + \alpha_j(x,y) X_j(t,x,y) \\
&\quad - \lambda_j(x,y) Y_j(t,x,y) + \gamma_j(x,y) \Delta Y_j(t,x,y) + \xi_i(t,x,y),
\end{aligned}$$

where the total number of mRNA i and protein j is 14, X_i is the concentration of mRNA, Y_j is the concentration of transcription factors and (x, y) is the position.

PDE is also applied to metabolic network and signal transduction network. Velázquez *et al.* reviewed PDE models for chemotaxis in [85], and the

earliest model of chemotactic aggregation is Keller-Segel model:

$$\begin{aligned} \frac{\partial X}{\partial t} + \nabla \cdot j_X &= 0, \\ \frac{\partial Y}{\partial t} + \nabla \cdot j_Y &= f(X, Y), \end{aligned}$$

where X is the concentration of the cells, Y is the concentration of the chemicals, j_X is the cell fluxes and j_Y is the chemical fluxes. The author discussed singularity formation of the model and continuation of the solutions beyond the blow-up time in the paper [85].

4 STOCHASTIC DIFFERENTIAL EQUATION

The development of deterministic models meets difficulties of large uncertainties from chemical reactions, network structure and parameter values [53], and stochastic models can be applied to model the uncertainties from the biological systems.

SDE has general form [70]:

$$\frac{\partial X}{\partial t} = f(t, X) + g(t, X) \frac{\partial W_t}{\partial t},$$

where f and g are given functions, and W_t is white noise. SDE modeling of systems biology is a relatively new area, and there are books, papers and dissertations of SDE modeling of systems biology. Wilkinson offers a book of SDE modeling of systems biology [86]. Ullah *et al.* reviewed stochastic

process for SDE in [90]. Climescu-Haulica *et al.* developed a SDE model for transcriptional regulatory networks in [12]:

$$\frac{1}{X}\frac{\partial X}{\partial t} = [f(t, X) - \lambda] + g(t, X)\frac{\partial W_t}{\partial t},$$

where X is the concentration of mRNA of the target gene, f denotes the function that models the transcription rate of the targe gene at time t and, g is a positive scaling parameter.

Some dissertations located in ProQuest select SDE models for systems biology as the topic. For example, Mistry developed stochastic models for the *Arabidopsis* circadian clock in [64]. In [66], Munsky developed the finite state projection approach for the solution of the chemical master equation, and applied this technique to GRNs models. Singh developed SDE to investigate the noise suppression properties of gene network motifs in [82].

SDE models are applied to metabolic network and signal transduction modeling of systems biology. Ao developed SDE models for metabolic network modeling in [3]:

$$(S + T)\frac{\partial X}{\partial t} = -f(t, X) + \frac{\partial W_t}{\partial t},$$

where S is the semi-positive definite symmetric matrix and T is the anti-positive matrix. Manninen *et al.* developed an approach to model neuronal signal transduction using SDE in [62]:

$$\frac{\partial X}{\partial t} = Sf(t, X) + \beta\frac{\partial W_t}{\partial t},$$

where S is the stoichiometric matrix and β is a parameter. In [77], Saarinen *et al.* developed SDE models for cell excitability of cerebellar granule:

$$\frac{\partial X}{\partial t} = f(t, X) + \sigma \frac{\partial W_t}{\partial t},$$

where σ is a parameter.

5 RELATED ISSUES

Which model is the best? Bolouri disscussed model selection in [8]. The selection of differential equation models depend on the problem and the research needs.

After differential equation models is developed, we need to theoretically make sure there is a solution and a unique solution of the model. Numerical methods are needed to be developed to solve these models. Also, there are some related issues such as parameter estimation, model checking, software, *etc.*

Parameter estimation means to determine the value of unknown parameter in differential equations. Methods such as bayesian inference and machine learning can be applied to learn model parameters. There are papers discussing new methods of parameter estimation in systems biology models. Alfieri *et al.* developed a method of parameter estimation for cell cycle ODE models in [2]. Donzé *et al.* developed a method for parameter synthesis in nonlinear dynamical systems of systems biology in [22]. Kahng *et al.* proposed a parameter determination method for nonlinear differential equations

of dynamics of biological systems in [55].

The definition of model checking is to check a model of a system by automatically test whether this model meets given specifications [35]. Algorithmic algebraic model checking is discussed in [67] [68] [69] [72].

Integrated development environment (IDE) software helps to increase the efficiency of systems biology model development. There are two kind of IDE softwares for systems biology: script-based and GUI-based. Script-based systems biology IDE softwares include Jarnac, Matlab systems biology toolbox [80], *etc*, and GUI-based systems biology IDE softwares include Gepasi [63], JDesigner, CellDesigner [26], KinCyte, Dizzy [73], *etc*.

To exchange models developed by different softwares, markup languages are developed, for example Systems Biology Markup Language (SBML) [34], CellML, BioPAX. SBML is a machine-readable language, based on XML, for representing models of biological processes, and SBML can represent metabolic networks, cell-signaling pathways, regulatory networks, and other kinds of systems [31] [35]. The Systems Biology Graphical Notation (SBGN) is a standard graphical representation crafted by a community of biochemists, modelers and computer scientists. To avoid capability duplicate of different tools, software developers build a software framework named System Biology Workbench [78] and BioSPICE.

6 CONCLUSIONS

Differential equation is a powerful tool for systems biology modeling, and we reviewed existing literatures of differential equations for systems biology in

this paper, and IDE software will increase the efficiency of model development for systems biology. We are interested in developing novel differential equation models for systems biology.

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7 DISCLOSURE STATEMENT

No competing financial interests exist.

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