PHYS 597A: Graphs and Networks in Systems Biology

Optimization based Network Modeling and Analysis of Stochastic Processes

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Course Project Presentation
Presentation Overview

Motivation for the Project
Network Evolution
Concepts in the Project
Literature Review - Stochastic Simulator by DT Gillespie

Research Interests
Optimization of Network Processes
Chemical Reaction Networks
Complex Supply Chain Networks
Motivation

How are the real networks modeled?

What is the process governing the specific connectivity of the real-world networks?

Can the network be modeled in an optimization based approach?

What are the procedures to model the network using optimization of processes?

How can such a network compare with the real world network?
Network Evolution - Theory

Random Network Models - Erdos / Renyi
   - Connection probability dependence on the connectivity

Real World Network modeling
   - Growth
   - Preferential Attachment
   - Aging
   - Network Re-wiring
   - Node Removal (random, preferential)
Network Evolution - Theory

Algorithm Based modeling of evolution
1. Connection probability
2. Number of nodes entering the network
3. Time-based process

Mathematically incorporates all that is required for a real-network

Can the network evolved based on algorithm represent a particular network?

How can a network represent a particular real world network to a high degree of similarity?
Network Evolution - Theory

Relative dependence of network statistics in large networks:

1. Connection Probability vs. Degree Distribution

\[ p(N) = cN^{-k/l} \]

For a Random Graph

2. Growth:

\[ n_t = f(<k>/l_{ij}) \]

No. of nodes entering the system:
1. Directly proportional to average degree in the network
2. Inversely proportional to distance between a selected node pair
Network Evolution - Theory

Aging:

1. Based on distance (from key nodes) and time step
2. End of a sequence of optimization - nodes that have distances greater than critical values are found
3. If the node has
   \[ \frac{k_i}{<k>} > k_{critical} \]
   the node will be eliminated
Network Evolution - Theory

Connection Probability:

1. Distance Dependent Probability:
   \[ P_\alpha(i, j) = \beta e^{-\alpha d(i, j)} \]

2. Degree Dependent Probability:
   \[ P_c(i, j) = \frac{k_i^{-\gamma}}{\sum_{M} k_m^{-\gamma}} \]

3. Dependent Probability (to incorporate large distance connectivity):
   \[ P_d(i, j) = \frac{\beta}{[d(i, j)]^{-\alpha}} \]
Network Evolution - Theory

Clustering:

Selected nodes constrained to have clustering co-efficient above critical values

Goal Programming approach

Other Constraints:

1. Pathlengths
2. Upper limit on the degree of selected nodes.
Network Evolution - Optimization Model

Minimize
\[ Z = \sum_{i} d_i^- + d_i^+ \]

Sub to:
\[ p(N) > cN^{-n/e} \]
\[ p(N) = \lambda_1 P_\alpha(a,b) + \lambda_2 P_\gamma(a,b) + \lambda_3 P_d(a,b) \]
\[ \lambda_1 + \lambda_2 + \lambda_3 = 1 \]
\[ P_\alpha(i,j) = \beta e^{-\alpha d(i,j)} \]
\[ P_c(i,j) = \frac{k_i^{-\gamma}}{\sum_k k_m^{-\gamma}} \]
\[ P_d(i,j) = \frac{\beta}{[d(i,j)]^{-\alpha}} \]
Network Evolution - Optimization Model

In between sequential optimization:

\[ \frac{k_i}{\langle k \rangle} \geq k_{\text{critical}} \]

\[ K_i > k_{\text{critical}} \times \langle k \rangle \times \partial_i \]

\[ \partial_i = 0, 1; \]
Literature Review - Exact Stochastic Simulation

Summary:

Chemical Reaction Network - Spatially Homogenous system
If a fixed volume V contains a uniform mixture of:
   N - Chemical metabolites
   M - Chemical reaction pathways
   $X_1, X_2, ..., X_n$ - number of molecules of metabolite 1, 2, .., N

Can we predict the number of molecules in the system for each metabolite after any time t in the system?

Treat the system as a network of “discrete” variable values changing through “stochastic” processes.
Literature Review - Exact Stochastic Simulation

Conventional Methods:
Deterministic approach:
Assumptions - interaction is continuous and predictable

Consider the set of Chemical Reactions:

\[ A + 2C \rightarrow B; \]
\[ B \rightarrow C; \]
\[ A + 2B \rightarrow F + D; \]
\[ F \rightarrow G \]
\[ B \rightarrow D; \]
\[ D + G \rightarrow F; \]
\[ E \rightarrow D \]
Literature Review - Exact Stochastic Simulation

A + 2C ----> B; B ----> C;
Literature Review - Exact Stochastic Simulation

A + 2C ----> B; B ----> C; A + 2B ----> F + D; F ----> G; B ----> D
Literature Review - Exact Stochastic Simulation

A + 2C ----> D; B ----> C; A + 2B ----> F + D; F ----> G; B ----> D; D + G ----> F; E ----> D
The number of molecules of each metabolite can be expressed as an ordinary differential equation.

\[
\frac{dX_A}{dt} = f_A(X_A, X_B, \ldots, X_N)
\]
\[
\frac{dX_B}{dt} = f_B(X_A, X_B, \ldots, X_N)
\]
\[
\vdots
\]
\[
\frac{dX_N}{dt} = f_N(X_A, X_B, \ldots, X_N)
\]

\(f\) = function of the connectivity and stoichiometric constants

(eg). \[
\frac{dX_B}{dt} = k_1[A][B]^2 - k_2[C][D][F]^2
\]
Literature Review - Exact Stochastic Simulation

Assumptions in deterministic approach to networks:

1. Change in the concentration levels is continuous
   - Mathematically, the time evolution of the system is a continuous function.
   - The reaction rate equations are governed by continuous ordinary differential equations

2. The reactions in the network are deterministic in nature
   - The temporal nature of the participation of the metabolites in different reactions are deterministic in nature
Assumptions in stochastic approach to networks:

1. The time evolution of the system is not continuous
   - Molecular population levels can change in integer levels

2. The interaction process is stochastic / probabilistic in nature
   - because it is impossible to predict the exact levels of concentration of the metabolites at any instant of time
   - take into account to the exact levels of reaction rates and positions of the nodes in the network
Literature Review - Exact Stochastic Simulation

Questioning the Assumptions:

1. What is the acceptability of the assumption of discrete nature of the system?
Literature Review - Exact Stochastic Simulation

Physical Basis of the Stochastic Formulation of Chemical Kinetics

Stochasticity - The collisions of molecules in itself is a random process.

Molecular Collision:

Consider two molecules $S_1$ and $S_2$ in the system
Let $r_1$ and $r_2$ be the molecular radii
$v_1$ and $v_2$ be the velocities of the molecules in the system
Then, $r_{12} = r_1 + r_2$ and $v_{12} = v_1 + v_2$

In interval $dt$, volume swept $dV_{coll} = \pi r_{12}^2 v_{12} \, dt$
Collision occurs in time interval $(t, t+dt)$
Literature Review - Exact Stochastic Simulation

Estimate the number of molecules in the volume space $dV_{\text{coll}}$
Divide the number by $dt$ and limit $dt \to 0$

Limitation: In an infinitesimally small volume $dV_{\text{coll}}$, we may find either 1 or 0 molecules of $S_2$.

How to overcome the limitation?
- The system is homogenous.
- $dv_{\text{coll}}/V$ can be considered
  - $dv_{\text{coll}}/V = V^{-1} \pi r_{12}^2 v_{12} \ dt = \text{average probability of collision}$

$X_1, X_2$ molecules in the system
Collision Probability $= X_1 \ X_2 \ V^{-1} \pi r_{12}^2 \ v_{12} \ dt$
Literature Review - Exact Stochastic Simulation

Stochastic Reaction Constant $C_u$:
Reaction Probability per unit time (analogous with reaction rate)

$$R_1: S_1+S_2 \longrightarrow 2S_1$$

c_1 \, dt = \text{average prob that a 1-2 pair will react according to the reaction } R_1$

$X_1, X_2 \text{molecules in the system } \Rightarrow X_1X_2 \, c_1 \, dt \text{ is the probability that reaction } R_1 \text{ will occur in the system in infinitesimal time interval } dt$
Literature Review - Exact Stochastic Simulation

Calculating the Stochastic time evolution:

\[ C_u \, dt = \text{Probability that the reaction } R_u \text{ will occur in the system in infinitesimal time interval } dt \]
- fundamental hypothesis in the model

Questions: given \((X_1, X_2, \ldots, X_N)\)
1. When will the next reaction occur?
2. What reaction will it be?

Reaction Probability Density function:
\[ P(\tau, u, \Delta d\tau) = \text{Probability that, given the state } (X_1, X_2, \ldots, X_N) \text{ at time } t, \text{ the next reaction in } V \text{ will occur in the infinitesimal time interval } (t+\tau, t+\tau+d\tau) \text{ and the reaction will be } R_u \]
Literature Review - Exact Stochastic Simulation

\( h_u c_u \, dt = \) Probability that reaction \( R_u \) will occur in infinitesimal time interval \((t, t+dt)\), given that the system is in the state \((X_1, X_2, .., X_{N+})\) at time \(t\) for \(u = 1, 2, .. M\)

\[
P_0(\tau) = \exp\left[-\sum_{v=1}^{M} a_v \, d\tau' \right]
\]

\[
P(\tau, \mu) = a_v \exp(-a_0 \tau)
\]

\( = 0, \text{ otherwise} \)
Thank you!

• Questions?