Using Ordinary and Stochastic Differential Equations to Simulate Cell Activities through an Agent-based Model

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Background

Agent-based models are used for simulating cellular and subcellular processes because they are straightforward to visualize and use and easily extensible. BioLogic is an agent-based simulator of cells which (1) addresses the complexity of cells by being able to deal with hundreds of molecules, (2) interacts with a hierarchical structure , which is easy to specify using XML, (3) adapts to the high variability of experimental data by simple logical variables such as high, low, or none, and (4) bypasses the lack of knowledge about reaction rates by using relative, discrete - valued variables such as fast or slow.

Although logical variables are sufficient for developing and verifying qualitative models of chemical reactions, an extension which uses ordinary and stochastic differential equations to define the rates, at least for some variables which are more easily measurable, could yield very specific results about the system such as end concentration of products and average speeds of formations.

The regulation of apoptosis in cells is an example of a complex biological process to which BioLogic has been applied. Figure 1 shows the complex interactions that have been included in the description, and figure 2 shows examples of reactions occurring in apoptosis.

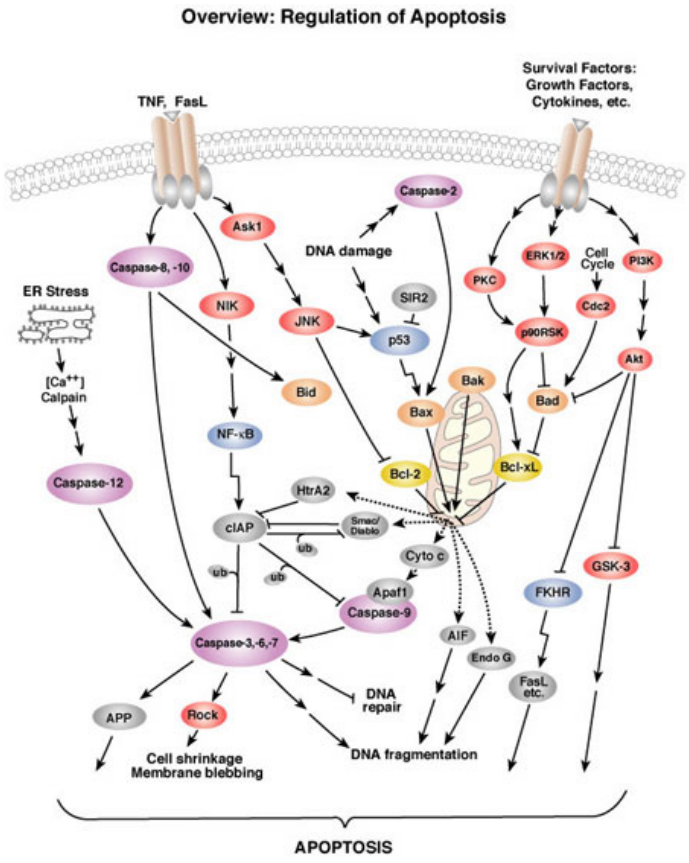

Figure 1. Model for apoptosis

```
#########  Fas_pathway #############
Fas + FasL ->>> Fas:FasL
Fas:FasL + FADD ->>> Fas:FasL:FADD
Fas:FasL:FADD ->> Caspase8
Fas:FasL:FADD -> 0
Fas:FasL:FADD ->> Fas:FasL:FADD + JNK

#####  Inhibitors_of_Apoptosis  ##########
Flips + Caspase8 -> Flips:Caspase8
Bcl-xL + SigMitoApoptosisOUT -> Bcl-xL
Bcl-2 + SigMitoApoptosisOUT -> Bcl-2
Bcl-xL + Apaf1 -> Bcl-xL:Apaf1
IAP + Caspase3 -> IAP:Caspase3
IAP + Caspase8 -> IAP:Caspase8
IAP + Caspase9 ->> IAP:Caspase9
STATs + Bcl ->>> Bcl + Bcl-2 + Bcl-xL
HSP70 + CytoC:Apaf1 ->>> HSP70
HSP27 + CytoC ->> HSP27
14-3-3 + Bad ->> 14-3-3:Bad
```

Figure 2. Reactions relevant for apoptosis

These descriptions of reactions are written intuitively and add no abstraction barrier between the user and the modeling part of the program.

Methods

The differential equations would replace the discrete rates in the evolution part of the program, transforming the entire simulation into a precise stochastic process as opposed to one where the true rates are not known. Figure 3 shows examples of such replacements to be made in BioLogic.

1. Supposing there is a reaction where A and B react to form C:

   $A + B \rightarrow^{k} C$

   the rate law for this reaction is:

   R = k [A] [B]

   An ordinary differential equation modeling the rate of change of A with respect to time would be

   $\frac{dA}{dt} = -R = -k[A][B]$

   and b with respect to time

   $\frac{dB}{dt} = -R = -k[A][B]$

   The rate of change in C with respect to time would be

   $\frac{dC}{dt} = R = k[A][B]$

2. Supposing there is another reaction in which C forms D and goes out of the system,

   $C \rightarrow^{k_1} D$

   the rate law for this reaction is

   $R_1 = k_1[C]$

   and the rate of change of C with respect to time according to this equation would be

   $\frac{dC_1}{dt} = -R_1 = -k_1C$

   Therefore, the net equation for change in C is

   $\frac{dC_{net}}{dt} = -k_1C + k[A][B]$

If the rates and concentrations are known, it is simple to implement continuous rates instead of a parameter that takes values: fast, medium, slow, etc. Noting that many rate constants are not known, it would be useful

to implement a scaling method in the program , which sets a scale of rates based on the available differential equations. After the scaling is implemented, one could use the logical variables like ‘faster than’ or ‘much slower than’ to describe the unknown reaction rates relative to the precise ones.

Applications

This system has many applications in the biological sciences as it allows an experimenter to easily simulate all of the activities in a cell simultaneously knowing only reaction rates and to decide the best experimental design. The program can be modified also to address host pathogen interactions and their effects.