Improving Information Quality of Ordinary Differential Equation Algorithm with Importance Splitting

***Abstract*—Genetic circuits become an important modeling mechanism in gene and protein regulation and differentiation. Ordinary Differential Equations (ODE) is a generally used model for genetic simulation. A new model, called ODEIS, is provided in this report which combines both ODE analysis with importance splitting in order to trigger the reaction of rare events. In this project, we made a software tool to help analyze concentration changes of different species. This software tool can be used to visualize data, select samples, build Bayesian network, edit Bayesian network, simulate the changes of concentration with ODE and ODEIS on the Bayesian network. The comparison of ODE and ODEIS performance on data simulation was also provided in this software tool.**

Keywords—importance sampling, importance splitting, ordinary differentiation equations.

INTRODUCTION

Ordinary Differential Equations (Weisstein (2011) algorithm can be used to show the states of species at different time intervals during a period of time. However, since the rare events barely occur, it is hard to draw a general conclusion based on the simulation results. Importance splitting (Arpino et al., 2011) starts with the rare events and derives the path it is generated. In this way, we can have a big picture of rare events and how they are derived.

In this project, we will provide a method to systematically determine the relative function and update the states so that the simulation will be in favor of rare events. Also, it can remove irrelevant events periodically. In this way, we can better present the effect of important reactions.

I. RELATED WORK

Information quality has been investigated by many relating to the use of importance splitting for rare-event simulation. Simulation for rare-event simulation was investigated by L'Ecuyer, Demersand Tuffins (2006), Haraszti and Townsend (1999) for packet switching networks.

Importance splitting in statistical model checking was investigated by Jegourel, Legay and Sedwards (2014). An overview of importance splitting for rare event simulation was discussed by Morio, Pastel and Le Gladn (2010). Rare event estimation was also investigated by Cerou and Guyader (2007) for adaptive particle techniques.

Garvels and Kroese (1998) investigated and compared both the theoretical and empirical different implementations of the RESTART (REpetitive Simulation Trials after Reaching Thresholds) method that is a widely applicable simulation technique for the estimation of rare event probabilities. RESTART was also studied for its efficiency and application guidelines by Villen-Altamirano and Altamirano (2011) and by Villen-Altamirano (2009) for network of queues with Erlang service times, and by Villen-Altamirano for general Jackson networks.

Monte Carlo simulation was used in studies by Cancela, Murry and Rubina (2016) for simulation of Markovian systems, by Botev and Kroses (2010) for the generalized splitting method, and by Demers, L'Ecuyer and Tuffin (2005 for splitting for rare-event simulation.

Smart sampling for lightweight verification of Markov decision processes was studied by D'Argenio et al. (2015). Modularity and deteminisism in computational Markov models was studied by Crouzen (2014).

Previous studies for genetic applications of rare-event simulation, importance splitting, circuit and network design were investigated by Cardinale et al. (2013), Arpino et al. (2013), Brophy and Voigt (2014), Abdol et al. (2017), Gibson and Mjoisness (2001), Huynh et al. (2012), and Kushwaha and Salis (2015), MacDonald et al. (2011), Ingram et al. (2006), Hancock et al. (2015), Huang et al. (2007)

Other related work was performed by Wolovick (2012) and Hartmanns and Timmer (2015).

DEFINITIONS

Importance Sampling

Importance sampling (Wu et al., 2011) allows the rare event of interest to be weighted so that the event occurs more frequently during the simulation.

Importance Splitting

Importance splitting starts with the rare events; a breadth first search is conducted to update all of the states and to decide the importance function; and the joint probability are estimated with Monte Carlo simulation and also can be used to decide the threshold.

Input: system model $\mathcal{M}$
Input: goal state set $G \neq \varnothing$
$g(G) \leftarrow 0$
queue.push(G)
repeat
  $s \leftarrow$ queue.pop()
  for all $s' \in \mathcal{M}$.predecessors(s) **do**
    if s' not visited **then**
      $g(s') \leftarrow g(s) + 1$
      queue.push(s')
    end if
  end for
until queue empties **or** s_0 visited
$g(s) \leftarrow g(s_0)$ for every non visited state s
$f(s) \leftarrow g(s_0) - g(s)$ for every state s
return f

Figure 1. Relative Function Algorithm

ODE Algorithm

ODE algorithm considers the probability of each reaction occurs is the same. It divides the time into several equal intervals and computes the change of the concentration in each time interval. The total concentration of the species can be updated after each time interval.

Improving ODE Algorithm with Importance Splitting

Starting with the rare events, we want to discover the path they are derived. By using the graph search of the rare event, we can assign relative importance weights to reactions and updates of the states at each stage. Each time we check the capacity of the concentrations, if the capacity of the concentrations is greater than the threshold, we will drop some reactions with the change ratio less than average.

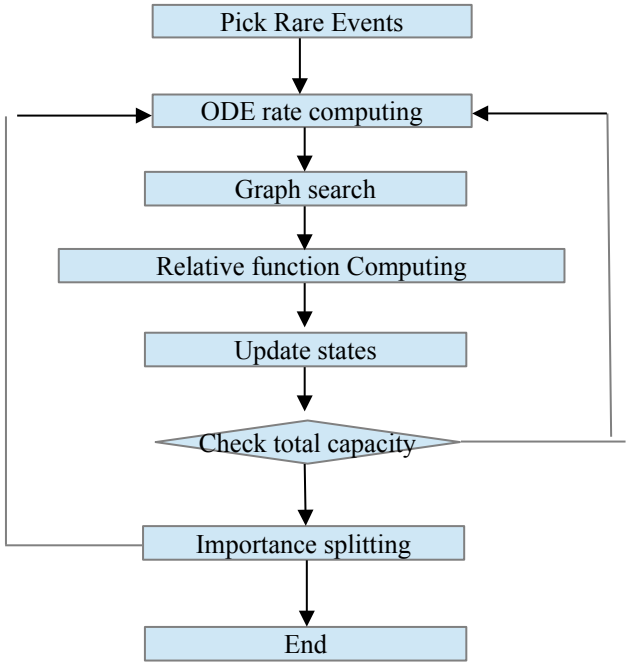


Figure 2. Flow Chart of the ODEIS Algorithm.

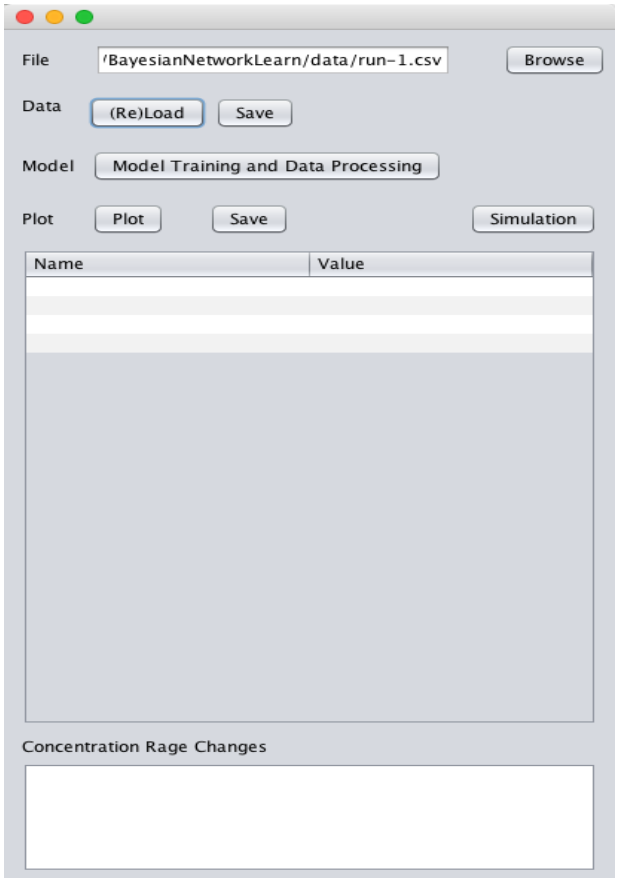


Figure 3. ODEIS User Interface.

Experiments

After the text edit has been completed, the paper is ready for the template. Duplicate the template file by using the Save As command, and use the naming convention prescribed by your conference for the name of your paper. In this newly created file, highlight all of the contents and import your prepared text file. You are now ready to style your paper; use the scroll down window on the left of the MS Word Formatting toolbar.

We implemented a software tool to present the experimental results of both ODE and ODEIS. This software tool can be used to finish the entire data cleaning, data modeling and model simulation. In figure 3, we can click browse to choose data set which is a csv file.

After clicking "(Re)Load" button, we can see data visualization window as shown in figure 4. in this windows, the first row lists data in each attribute. When we click on a particular attribute windows, we can see a big picture of the attribute. In the big window, we can click on outliers and they will be removed from the dataset. We include this functionality to the software tool just because, only if we see the data set, we can figure out what is going on in the data set , which is convenient for us to do data cleaning there. We also compute the average, and standard deviation of each attribute. The mean line represents the average of the corresponding attribute. Three lines are above the mean line, which represents mean + std,

mean + std * 2, mean + std * 3, respectively. Three lines are below the mean line, which represents mean – std, mean – std *2, and mean – std * 3. According to six-sigma theory, the majority of the data is within mean plus or minors three std. Outside of this range are outlier. These lines can help us to decide if the data are belong to the distribution or not.

Data selection can be done in the big window. After data selection, we need to click "save" button to save the cleaned data set. The cleaned data set will be used to do data modeling and network building. If the data set is cleaned wrong, we can start over load the dataset again and process the data set again.

After data selection, as shown in figure 5, we can click "Model Training and Data Processing" button to make Bayesian network model. After the model is built, we can see the information box saying the model was built.

Most of people also want to see what the model look like, that is why we also visualize the bayesian network. On the bayesian network window, as shown in figure 6, we can also edit the network based on the domain knowledge. For bayesian network, this is possibly the most important step, because, bayesian network was built with the training data, it may represent the real world associations. But, possibly, some of the connections do not make sense based on the domain knowledge.

The way we edit the bayesian network is that we can click the node we are interested, drag the mouse to another node, if there is a connection between the two nodes, the connection will be deleted, if there is no connection between them the connection will be added. In this way, we can add and delete edges between any nodes.

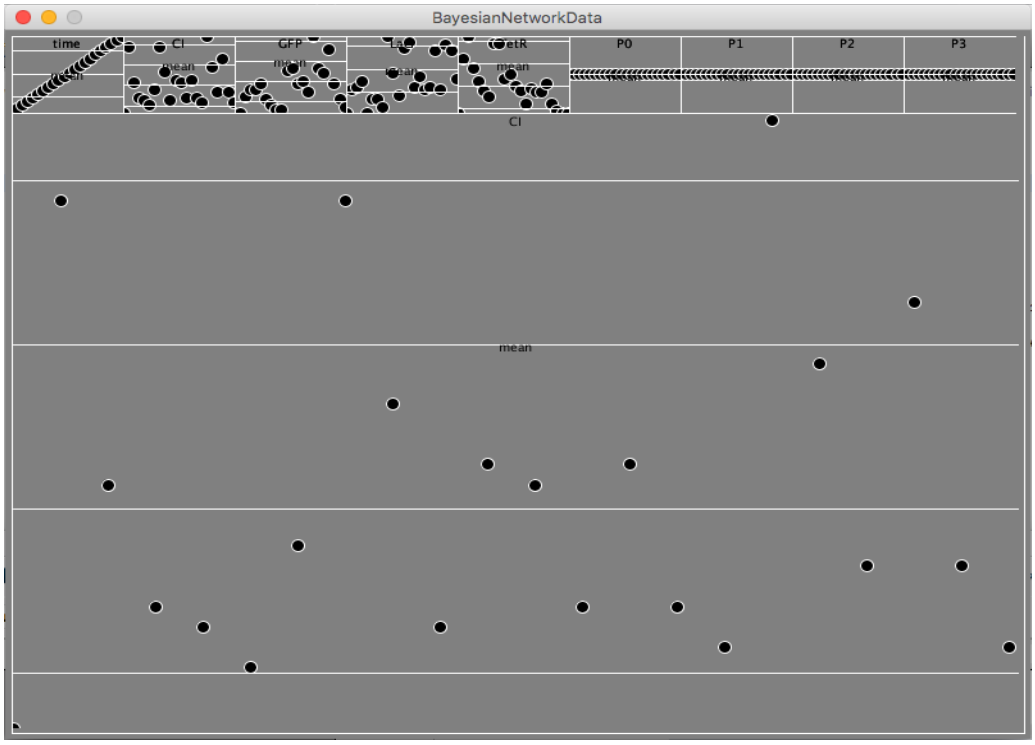


Figure 4. Data Visualization

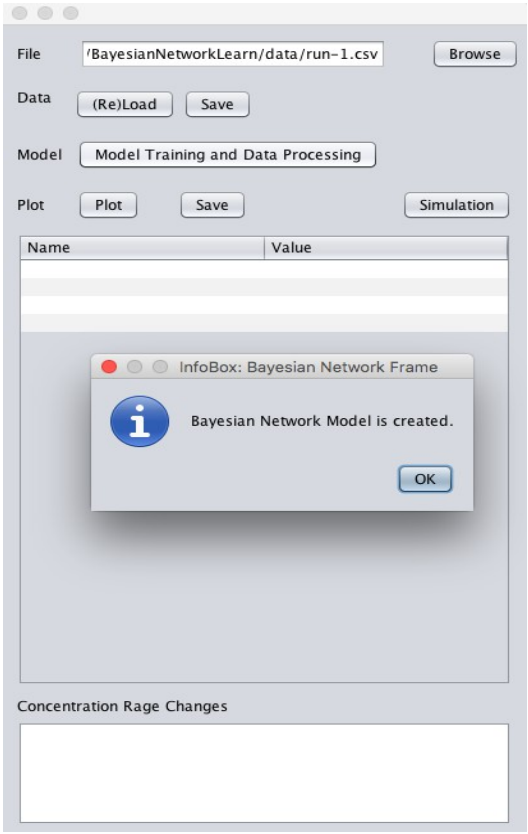


Figure 5. Bayesian Network Training and Model Building

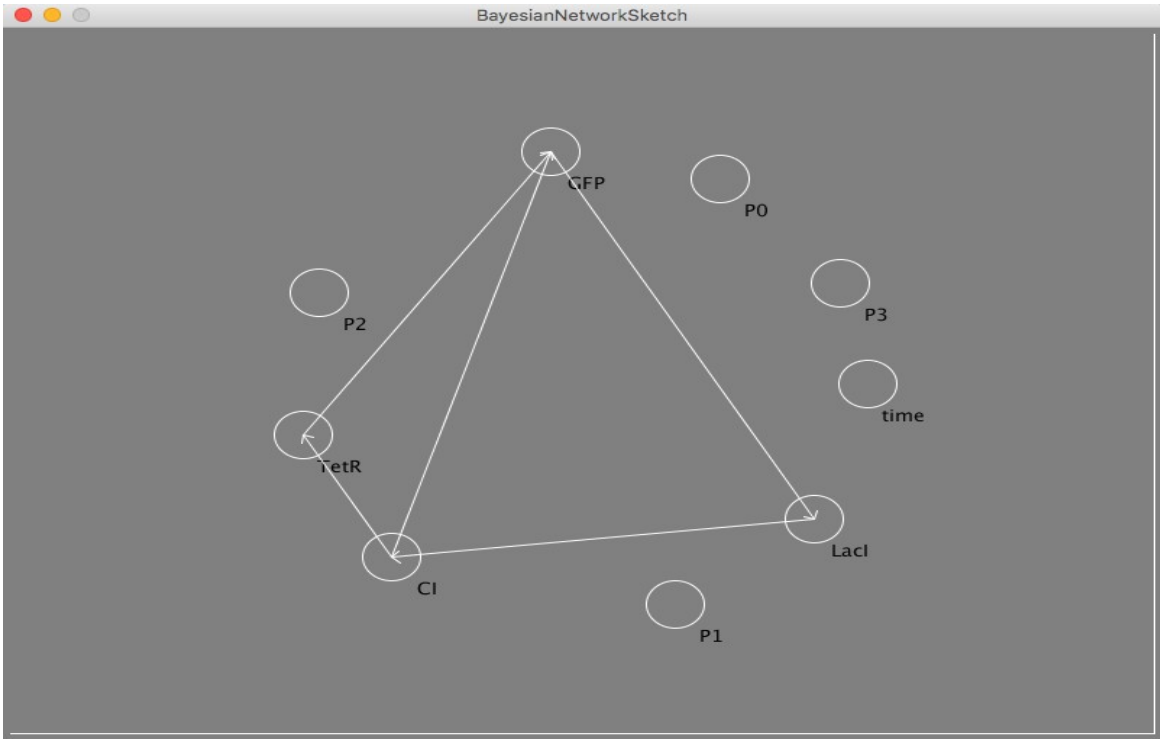
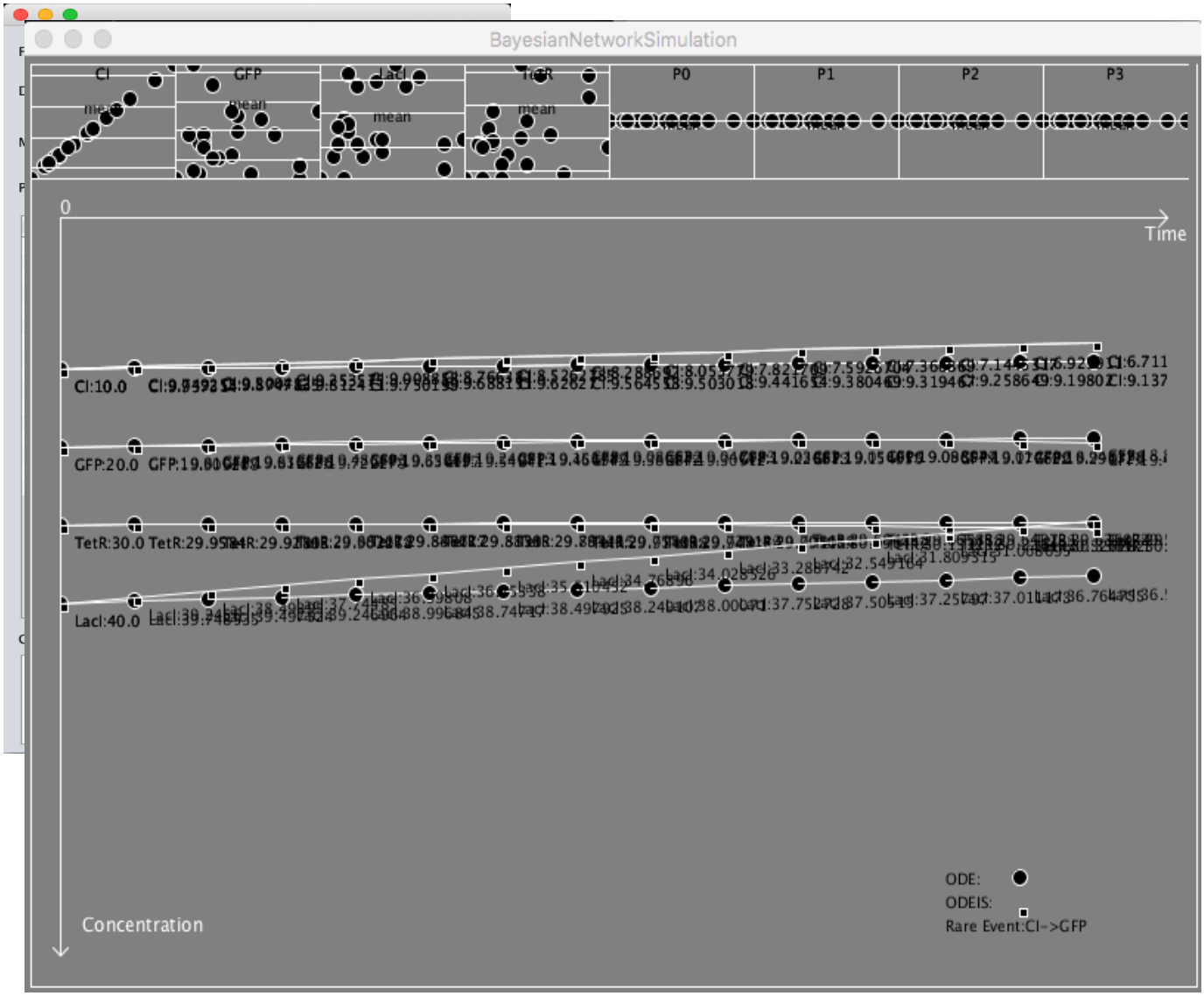
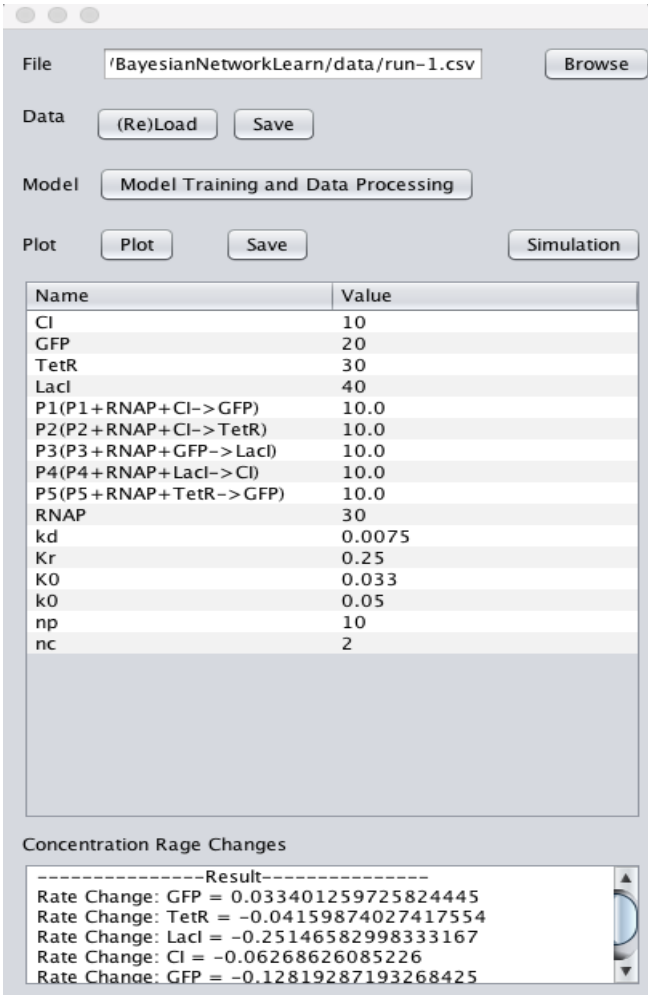


Figure 6. Bayesian Network

Figure 7. Initial Values for ODE Simulation



(a) Comparison of ODE and ODEIS Analysis.
The rare event, CI → GFP occurs more often in ODEIS since CI was consumed faster in ODEIS.
(b) The Rate Change of ODE Analysis.



The rate change of GFP is the smallest in CI → GFP, so that CI → GFP was chosen as the rare event

Figure 8. ODE and ODEIS Experimental Results.

After model editing, as shown in figure 7, we click on save and the initial values of the model will also listed in the control window. Right now, we are ready for simulation.

We click on "Simulation" button, the experimental results will show both in a data plot window and the bottom of the control window. In the data plot window, as shown in figure 8 (a), we can see the two sets of curves for both ODE and ODEIS and the rare event is also indicated in the window. In the control window, as shown in figure 8 (b), we can see the change rate of each species is listed on the bottom of the window.

In this simulation, as shown in figure 8 (b), since the concentration change rate of GFP is the smallest in ODE, the reaction, CI → GFP, is chosen as the rare event. As shown in 8(a), CI was consumed faster with ODEIS since, the ODEIS algorithm can pick CI → GFP reaction more often since it is defined as rare event in the first place.

Conclusion

In this project, we use importance splitting to improve ODE algorithm. We explained the definitions, ODEIS algorithm and showed the experimental results. ODEIS algorithm can efficiently improve ODE algorithm by add relevant importance weights to rare events so that the effects of the rare events can be presented.

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APPENDIX A

ODE Experimental results
The mean of given vector is=2.5

pass test=org.rosuda.REngine.REXPGenericVector

Rate Change: GFP = 0.033401259725824445

Rate Change: TetR = -0.04159874027417554

Rate Change: LacI = -0.25146582998333167

Rate Change: CI = -0.06268626085226

Rate Change: GFP = -0.12819287193268425

ODEIS Experimental results
Total Concentration = 110.0

Rate Change: d[GFP]/dt = 0.033401259725824445, from CI, rate=10.0

Rate Change: d[TetR]/dt = -0.04159874027417554, from CI, rate=10.0

Rate Change: d[LacI]/dt = -0.25146582998333167, from GFP, rate=20.0

Rate Change: d[CI]/dt = -0.06268626085226, from LacI, rate=40.0

Rate Change: d[GFP]/dt = -0.12819287193268425, from TetR, rate=30.0

f[CI]=0.018340125972582444

f[CI]=0.018340125972582444

f[GFP]=0.004853417001666831

f[LacI]=0.0012313739147739996

f[TetR]=0.0021807128067315744

Total Concentration = 108.51292991638184

Rate Change: d[GFP]/dt = 0.042218123867402396, from CI, rate=9.749255

Rate Change: d[TetR]/dt = -0.03278187613259759, from CI, rate=9.749255

Rate Change: d[LacI]/dt = -0.25055101017591763, from GFP, rate=19.810417

Rate Change: d[CI]/dt = -0.062210766719135446, from LacI, rate=39.2456

Rate Change: d[GFP]/dt = -0.12813280129760082, from TetR, rate=29.9584

f[CI]=0.01922181238674024

f[CI]=0.01922181238674024

f[GFP]=0.004944898982408234

f[LacI]=0.001278923328086455

f[TetR]=0.0021867198702399167

Total Concentration = 107.05898094177246

Rate Change: d[GFP]/dt = 0.05159272932007142, from CI, rate=9.500412

Rate Change: d[TetR]/dt = -0.023407270679928566, from CI, rate=9.500412

Rate Change: d[LacI]/dt = -0.24969948449027668, from GFP, rate=19.638588

Rate Change: d[CI]/dt = -0.06170912745256496, from LacI, rate=38.49395

Rate Change: d[GFP]/dt = -0.12808528913361888, from TetR, rate=29.92562

f[CI]=0.02015927293200714

f[CI]=0.02015927293200714

f[GFP]=0.005030051550972329

f[LacI]=0.001329087254743504

f[TetR]=0.0021914710866381124

Total Concentration = 105.63981628417969

Rate Change: d[GFP]/dt = 0.06156410171597976, from CI, rate=9.253575

Rate Change: d[TetR]/dt = -0.013435898284020226, from CI, rate=9.253575

Rate Change: d[LacI]/dt = -0.24892283116574432, from GFP, rate=19.485603

Rate Change: d[CI]/dt = -0.061179300533421764, from LacI, rate=37.74485

Rate Change: d[GFP]/dt = -0.12805126957704857, from TetR, rate=29.902212

f[CI]=0.021156410171597976

f[CI]=0.021156410171597976

f[GFP]=0.005107716883425566

f[LacI]=0.0013820699466578232

f[TetR]=0.0021948730422951435

Total Concentration = 104.25720405578613

Rate Change: d[GFP]/dt = 0.07217355462821182, from CI, rate=9.008858

Rate Change: d[TetR]/dt = -0.0028264453717881666, from CI, rate=9.008858

Rate Change: d[LacI]/dt = -0.2482331708967132, from GFP, rate=19.35263

Rate Change: d[CI]/dt = -0.060619014413845915, from LacI, rate=36.99808

Rate Change: d[GFP]/dt = -0.1280317070168007, from TetR, rate=29.888777

f[CI]=0.022217355462821182

f[CI]=0.022217355462821182

f[GFP]=0.005176682910328679

f[LacI]=0.0014380985586154086

f[TetR]=0.0021968292983199304

Total Concentration = 102.91300582885742

Rate Change: d[GFP]/dt = 0.083464575315473, from CI, rate=8.766381

Rate Change: d[TetR]/dt = 0.00846457531547301, from CI, rate=8.766381

Rate Change: d[LacI]/dt = -0.2476429750736802, from GFP, rate=19.240913

Rate Change: d[CI]/dt = -0.06002572340792097, from LacI, rate=36.25338

Rate Change: d[GFP]/dt = -0.1280275878939576, from TetR, rate=29.88595

f[CI]=0.0233464575315473

f[CI]=0.0233464575315473

f[GFP]=0.0052357024926319795

f[LacI]=0.0014974276592079024

f[TetR]=0.0021972412106042397

Total Concentration = 101.60921096801758

Rate Change: d[GFP]/dt = 0.09548266948775003, from CI, rate=8.5262785

Rate Change: d[TetR]/dt = 0.020482669487750044, from CI, rate=8.5262785

Rate Change: d[LacI]/dt = -0.24716490873490357, from GFP, rate=19.151787

Rate Change: d[CI]/dt = -0.059396575630810876, from LacI, rate=35.510452

Rate Change: d[GFP]/dt = -0.1280399195787261, from TetR, rate=29.894415

f[CI]=0.024548266948775002

f[CI]=0.024548266948775002

f[GFP]=0.005283509126509641

f[LacI]=0.001560342436918912

f[TetR]=0.0021960080421273907

Total Concentration = 100.34791374206543

Rate Change: d[GFP]/dt = 0.10827516587744027, from CI, rate=8.288692

Rate Change: d[TetR]/dt = 0.03327516587744028, from CI, rate=8.288692

Rate Change: d[LacI]/dt = -0.24681151721023292, from GFP, rate=19.086672

Rate Change: d[CI]/dt = -0.058728352411989496, from LacI, rate=34.76896

Rate Change: d[GFP]/dt = -0.1280697167963929, from TetR, rate=29.914898

f[CI]=0.02582751658774403

f[CI]=0.02582751658774403

f[GFP]=0.005318848278976706

f[LacI]=0.0016271647588010506

f[TetR]=0.0021930283203607107

Total Concentration = 99.13134002685547

Rate Change: d[GFP]/dt = 0.12189081330947174, from CI, rate=8.053779

Rate Change: d[TetR]/dt = 0.04689081330947176, from CI, rate=8.053779

Rate Change: d[LacI]/dt = -0.24659493730742799, from GFP, rate=19.047083

Rate Change: d[CI]/dt = -0.05801742021885895, from LacI, rate=34.028526

Rate Change: d[GFP]/dt = -0.12811799500078666, from TetR, rate=29.948174

f[CI]=0.027189081330947173

f[CI]=0.027189081330947173

f[GFP]=0.005340506269257201

f[LacI]=0.0016982579781141044

f[TetR]=0.0021882004999213343

Total Concentration = 97.96185398101807

Rate Change: d[GFP]/dt = 0.1363790565437172, from CI, rate=7.821709

Rate Change: d[TetR]/dt = 0.061379056543717225, from CI, rate=7.821709

Rate Change: d[LacI]/dt = -0.2465265384635611, from GFP, rate=19.03463

Rate Change: d[CI]/dt = -0.05725965968904005, from LacI, rate=33.288742

Rate Change: d[GFP]/dt = -0.12818575679500294, from TetR, rate=29.995064

f[CI]=0.02863790565437172

f[CI]=0.02863790565437172

f[GFP]=0.005347346153643888

f[LacI]=0.0017740340310959946

f[TetR]=0.0021814243204997057

Total Concentration = 96.84196281433105

Rate Change: d[GFP]/dt = 0.1517895000701823, from CI, rate=7.5926704

Rate Change: d[TetR]/dt = 0.07678950007018231, from CI, rate=7.5926704

Rate Change: d[LacI]/dt = -0.24661651208025137, from GFP, rate=19.051016

Rate Change: d[CI]/dt = -0.05645039311192568, from LacI, rate=32.549164

Rate Change: d[GFP]/dt = -0.12827398249470792, from TetR, rate=30.056442

f[CI]=0.03017895000701823

f[CI]=0.03017895000701823

f[GFP]=0.005338348791974863

f[LacI]=0.0018549606888074322

f[TetR]=0.002172601750529208

Total Concentration = 95.77433204650879

Rate Change: d[GFP]/dt = 0.16817063602179608, from CI, rate=7.366869

Rate Change: d[TetR]/dt = 0.0931706360217961, from CI, rate=7.366869

Rate Change: d[LacI]/dt = -0.24687350710174671, from GFP, rate=19.098047

Rate Change: d[CI]/dt = -0.05558428559438007, from LacI, rate=31.809315

Rate Change: d[GFP]/dt = -0.12838361110948276, from TetR, rate=30.133232

f[CI]=0.031817063602179604

f[CI]=0.031817063602179604

f[GFP]=0.005312649289825328

f[LacI]=0.001941571440561993

f[TetR]=0.002161638889051724

Total Concentration = 94.7617826461792

Rate Change: d[GFP]/dt = 0.18556857256693396, from CI, rate=7.1445317

Rate Change: d[TetR]/dt = 0.11056857256693398, from CI, rate=7.1445317

Rate Change: d[LacI]/dt = -0.24730415221796795, from GFP, rate=19.177622

Rate Change: d[CI]/dt = -0.054655245041872386, from LacI, rate=31.068695

Rate Change: d[GFP]/dt = -0.1285155176465108, from TetR, rate=30.226402

f[CI]=0.0335568572566934

f[CI]=0.0335568572566934

f[GFP]=0.005269584778203203

f[LacI]=0.0020344754958127615

f[TetR]=0.0021484482353489173

Total Concentration = 93.80730438232422

Rate Change: d[GFP]/dt = 0.2040250707131057, from CI, rate=6.925911

Rate Change: d[TetR]/dt = 0.1290250707131057, from CI, rate=6.925911

Rate Change: d[LacI]/dt = -0.2479126667802028, from GFP, rate=19.291729

Rate Change: d[CI]/dt = -0.05365628876997722, from LacI, rate=30.326782

Rate Change: d[GFP]/dt = -0.1286705005558133, from TetR, rate=30.336971

f[CI]=0.03540250707131057

f[CI]=0.03540250707131057

f[GFP]=0.005208733321979721

f[LacI]=0.002134371123002278

f[TetR]=0.0021329499444186703

Total Concentration = 92.91404914855957

Rate Change: d[GFP]/dt = 0.22357535985380164, from CI, rate=6.7112856

Rate Change: d[TetR]/dt = 0.14857535985380166, from CI, rate=6.7112856

Rate Change: d[LacI]/dt = -0.24870046359691067, from GFP, rate=19.442438

Rate Change: d[CI]/dt = -0.05257940192108179, from LacI, rate=29.583044

Rate Change: d[GFP]/dt = -0.12884924735590042, from TetR, rate=30.465996

f[CI]=0.037357535985380164

f[CI]=0.037357535985380164

f[GFP]=0.005129953640308931

f[LacI]=0.00224205980789182

f[TetR]=0.0021150752644099585