BioNessie: A Software Tool for the Simulation and Analysis of Biochemical Networks

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Lecture outline

● Modelling strategies, overview

● BioNessie - Xuan Liu
  – Design
  – Functionality
  – Example uses

● Model checking with MC2 using Probalistic Linear Temporal Logic - Robin Donaldson

● Practical session on BioNessie & MC2
How to model

- Analysis
- Validation
- Identification
- Definition
- Simulation

Yes → Validation
No → Definition

Yes → Analysis
No → Simulation
How to model... 1: Identification

- Identify the biological pathway to model (what)
  - RKIP
  - EGF and NGF activated MAPK

- Or, more importantly, identify the biological question to answer (why)
  - What influence does the Raf Kinase Inhibitor Protein (RKIP) have on the Extracellular signal Regulated Kinase (ERK) signalling pathway?
  - How do EGF and NGF cause differing responses in ERK activation, transient and sustained, respectively?
How to model...2: Definition

• This is the key step and is not trivial

• Draw a detailed picture of the pathway to model
  – Define all the proteins/molecules involved
  – Define the reactions they are involved in
  – Where do you draw the model boundary line?

• Check the literature
  – What is known about the pathway and proteins?
  – What evidence is there that protein A binds directly to protein B?
  – Protein C also binds directly to protein B: does it compete with protein A or do they bind to protein B at different sites?
  – Trust & Conflicts: it is important to recognize which evidence to trust and which to discard (talk to the people in the wet lab)

• Simplifying assumptions
  – Many biological processes are very complex and not fully understood
  – Therefore, developing a model often involves making simplifying assumptions
  – For example, the activation of Raf by Ras is very complicated and not fully understood but it is often modelled as:
    • Raf + Ras-GTP = Raf/Ras-GTP -> Raf-x + Ras-GTP
  – Although this is a simplification, it is able to explain the observed data
How to model...2: Definition

- Define the kinetic types
  - Each reaction has a specific kinetic type
  - All the reactions in the RKIP model are mass action (plain, uncatalysed kinetic type):
    - \[ V = k_1[m_1][m_2] - k_2[m_3] \]
  - Another common kinetic type is Michaelis Menten (enzyme catalysis):
    - \[ V = V_{\text{max}}[S] / (K_m+[S]) \]
- Define the rate constants (k’s, km’s, Vmax’s etc)
- Define the initial concentrations
- Check the literature
  - What values have been previously reported?
  - What values are used in similar models?
  - Do you trust them? Are there any conflicts?
  - Measure them yourself in the wet lab
  - Parameter estimation techniques: estimate some parameters based on others and observed data
How to model…3: Simulation

- Once the model has been constructed and parameter data has been assigned you can simulate (run) the model.
- This is a relatively straightforward step as there are many software tools available to simulate differential equation based models.
- For example:
  - BioNessie
  - MatLab
  - Copsai / Gepasi
  - CellDesigner
  - Jarnac
  - WinScamp
  - Many many more
- Runtime options include setting the time to run the model for and the number of data points to take.
How to model…4: Validation

- Simulating the model typically returns a table of data which shows how each specie’s concentration varies over time

- This table can then be used to generate graphs of specie concentrations

- Do the model results match the experimental data?
  - Yes: validation
  - No: back to definition and check for errors
    - Simple typos
    - Wrong kinetics
    - Over simplifications of processes
    - Missing components from the model
    - Incorrect parameter data

- The model can then be validated further by checking the system behaves correctly when things are varied:
  - It might be known how the system behaves when you over-express or knockout a component
  - The model should be able to recreate this behaviour

- If the model’s results do not match known biology, we cannot rely on predictions about unknown biology
How to model…5: Analysis

- After the model has been validated we can then analyse and interpret the results
  - What do the results imply or suggest?
  - What do they tell us that is new and that we did not know/understand before?
  - What predictions can we make?

- Sensitivity analysis can be used to identify the key steps and components in the pathway as well as monitoring how robust the system is:
  - Vary an initial concentration or rate by a small amount and see what affect it has on the system as a whole: small changes in a key value are likely to have a large affect
  - How robust is the system to changes?

- Knockout experiments are easy to do in a model: for example, simply set the initial concentration of the desired component to 0
  - Knockout experiments can be used to identify which components are essential and which are redundant
  - Can also knockout reactions (set rate to 0) to identify essential and redundant reactions in the system
The Design of BioNessie

• **SBML** (Systems Biology Markup Language) enabled.

• **Intuitive easy-to-use interface** for biochemists & modellers. Input biochemical equations.

• **File storage** in XML, SBML, text & graphics

• **Platform Independent** – Java

• **Parallel processing** - Efficient exploitation of available compute resources – multiple core and multiple CPUs, as well as Grid computing (see below)

• **Editor, simulator, and analyser**

• **Model version control**

• **Kinetic law** library creation & management

• **Fast efficient ODE solver** (stiff & non-stiff)

• **Parameter scanning**

• **Sensitivity analysis**

• **Parameter estimation** using a genetic algorithm

• **Advanced model checking** (MC2 using PLTL)
Systems Biology Markup Language

• Machine-readable format for representing computational models in SB
  – Expressed in XML using an XML Schema
  – Intended for software tools—not for humans

• Tool-neutral exchange language for software applications in SB
  – Simply an enabling technology

• Used quite widely in biological modelling

• It is supported by over 40 software systems including Gepasi

• Good documentation, user community and publicly available tools

• www.sbml.org

• Also www.ebi.ac.uk/biomodels
SBML - XML Based Language

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    </listOfReactions>
  </model>
</sbml>
SBML Example Reaction

\[
A \rightarrow^ {k_1} B
\]

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      - `<species id="B" compartment="compartment" initialConcentration="1"/>
    - `/listOfSpecies`
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              - `<ci>` A </ci>
            - `/apply`
          - `/math`
        - `/kineticLaw`
      - `/reaction`
    - `/listOfReactions`
  - `/model>`
Creating a mass action based model by using BioNessie
Creating a new BioProject
Giving a project name
Creating a SBML file in the SIMAP project
Giving a name to the new SBML file and click “Finish”
Done!
Creating a compartment
Created!
Creating a species

![Image of a scientific software interface with a focus on creating a species in a model.]
Creating other species
Creating two parameters: K1 and K2
Creating a reaction $A=B$ with $K_1$ and $K_2$. 

Step 1. Input new reaction name and textual form:
- Name: reaction $A=B$

Step 2. Check the following lists:
- Reactants: $A$
- Products: $B$

This reaction is reversible reaction.

Step 3. Set reaction kinetic type:
- $K_1 = K_2$

Step 4. Add new species and parameters to the model:
- The species will be added: 
- The parameter will be added:

Double click to edit values. Double click to end value.
Simulation
Add another reaction $A+B \rightarrow C$ with $K_1$
Simulation
In this pathway, eleven different kinds of molecules are participated and there are eleven operations altogether.
Model retrieval
Saving models
Model Simulation

The image shows a software interface for model simulation, likely used for scientific or engineering applications. The interface includes graphs and data visualization, indicating the simulation of a system over time. The graph appears to depict various variables and their interactions, possibly related to biochemical or physical processes. The interface allows for adjusting parameters such as time steps and simulation details.
### Results viewer

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</table>

**Simulation Parameters:**
- Total time: 5.0
- Time step: 0.1
- Enable true time simulation: False

**Options:**
- Start
- Stop
- Close
How to save a text file for MC2?
BioNessie is not only an editor and simulator, but also an analyser!

- Parameter Scans
- Sensitivity Analysis
- Model VCS Support
- Model Optimisation
- Advanced Model Checking (by Robin Donaldson)
Parameter Scans
Single/Multi-threaded/Grid-enabled Parameter Scan

- Parameter Scan
  - To explore the behavior of the model over a wide range of parameter values using a parameter scan that runs one simulation for each parameter combination.

- But

  - So, having more than one thread running is beneficial
Single-threaded Parameter Scan

Scanning

- SBML + Parameter Combination 1
- SBML + Parameter Combination 2
- SBML + Parameter Combination 3
- SBML + Parameter Combination 4
- SBML + Parameter Combination 5

Single-threaded process scanning

Thread

Scanning Results
Multithreaded Parameter Scan

Scanning

- SBML + Parameter Combination 1
- SBML + Parameter Combination 2
- SBML + Parameter Combination 3
- SBML + Parameter Combination 4
- SBML + Parameter Combination 5

Single-threaded process scanning

- Thread 1
- Thread 2
- Thread 3
- Thread 4
- Thread 5

Scanning Results
Grid enabled BioNessie Architecture

End User Machines

Send Job Requests

Final results response

Authorization

Job Scheduling across various resources based on Resources Assignment rules

ScotGrid

NGS Clusters

Condor Pool

Results Collecting from various resources
Parameter Scanning in BioNessie
This plot shows the whole trace of selected species - ERKPP for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 4.5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.
This plot shows the min. max and final values of monitoring function Raf1+RKIP for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.
Sensitivity Analyser in BioNessie
Introduction to Sensitivity Analysis

- Sensitivity analysis investigates the changes in the system outputs or behavior with respect to the parameter variations. It is a general technique for establishing the contribution of individual parameter values to the overall performance of a complex system.

- Sensitivity analysis is an important tool in the studies of the dependence of a system on external parameters, and sensitivity considerations often play an important role in the design of control systems.
This creates a plot of the sensitivity of species Raf1, RKIP, Raf1RKIP, ERKPP, Raf1RKIPERKPP, ERK, RKIPPP, MEKPP, MEKPPERK, RP and RKIPPRP to the values of the parameter K6 for the timecourse of 200 timesteps of 200 time units.
Model Version Control System
Introduction to Version Control System

- VCS uses client-server architecture: a server stores the current version(s) of the project and its history, and clients connect to the server in order to check-out a complete copy of the project, work on this copy and then later check-in their changes.

- Client and server connect over a LAN or over the Internet, but client and server may both run on the same machine if VCS has the task of keeping track of the version history of a project with only local developers.

- BioNessie VCS system keeps track of all work and all changes in a set of SBML models and various results for simulation, scanning, sensitivity analysis and fitting. All those changes can be saved either in server side or user’s own machine.
• BioNessie can perform data fitting and for optimisation of model parameters.

• Uses Genetic Algorithm to search different rate constant sets in a predefined range to minimise the difference between the time-course data (obtained from wet lab) and simulation results of the model.
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Results:

\[ k_1 = 0.25190257413867045 \]
\[ k_2 = 0.00547984481485533 \]
How to obtain and install BioNessie

- In order to obtain a copy of BioNessie, you may send an email to Xuan Liu (xliu@brc.dcs.gla.ac.uk) for registration. Please provide your Name, Institute, Address and a valid "email address", to which an email will be sent with the login/password required to download BioNessie. Please read the terms of the "Evaluation License Agreement", under which BioNessie is distributed.

- Go to “Download” tag:

- Input the Login/Password
How to obtain and install BioNessie

- Please use the "Save Link As..." (Netscape/Firefox) or "Save Target As..." (IE) or "Download Linked File" (Safari) option of your web browser to download the file.

- By downloading the BioNessie below you are consenting to be bound by and are becoming a party to the "Evaluation Licence Agreement". If you do not agree to all of the terms of this agreement, DO NOT download the software, or click "Cancel" button.

  - Windows (2000 and above)
  - Mac (Intel)
  - Linux (coming soon ...)
How to obtain and install BioNessie

• Installation is easy. Please follow the instructions which will be shown on installation process.
Advanced Model Checking