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Computational Modelling of Biological Systems

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Your Thoughts

With the people around you discuss what you understand by the term *model*?

In this Context

An abstract process where a process of interest is represented on a computer in a very precise manner using mathematics.

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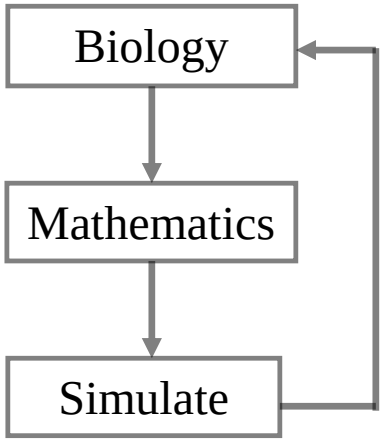
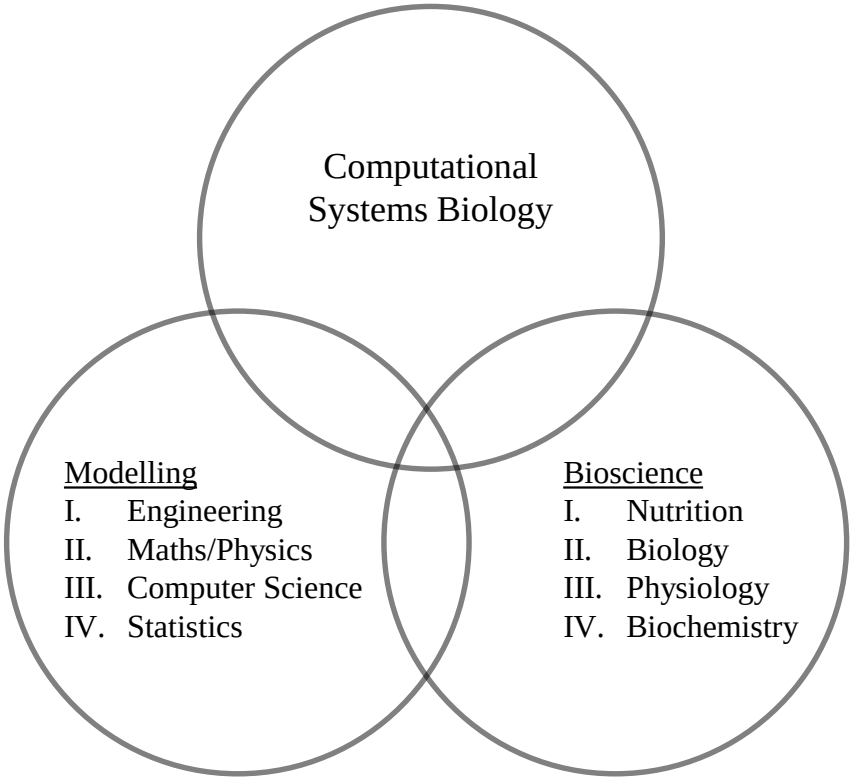
The Process



Not a New Technique

- 1952- Hodgkin & Huxley developed a physiological model of nerve excitation.
- 1960 a cardiac cell model developed by Nobel (Noble 1960).
- The field of mathematical/computational biology is vast.

Overview


Computational
Systems Biology
Modelling
I. Engineering
II. Maths/Physics
III. Computer Science
IV. Statistics
Bioscience
I. Nutrition
II. Biology
III. Physiology
IV. Biochemistry

Learning Outcomes

1. To know what a computer model is.

2. To know the steps involved in building a computer model.

3. To begin to think about biological systems you could model.

Activity

Consider why Computational Models are used in Biology Research?

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The Reasons

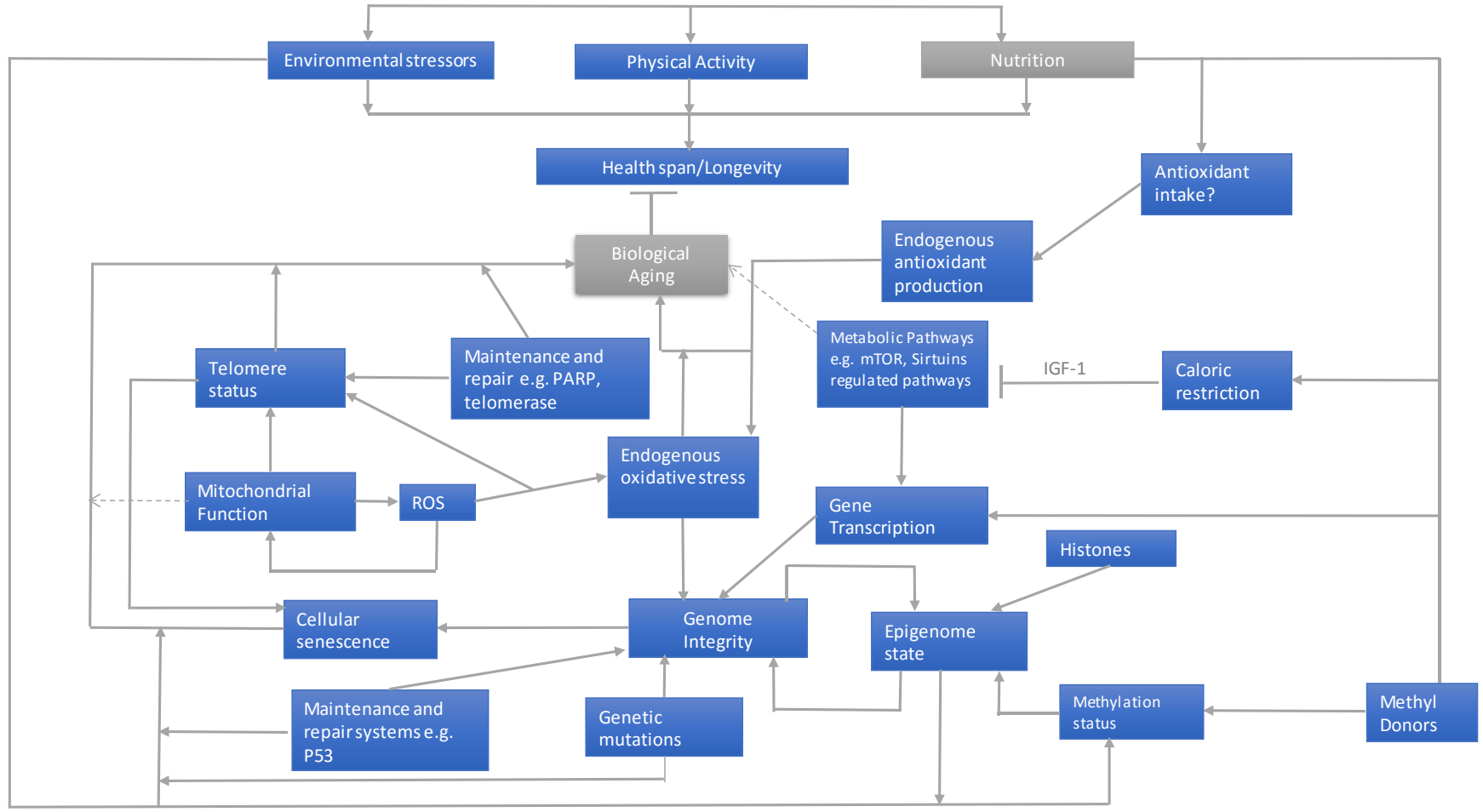
1. Analysing how biological components interact.

2. Biological components give rise to overlapping metabolic networks, comprising of many interactions.

3. Interactions- non-linear & involve complex feedback & feed-forward loops.

4. Challenging to reason about biological systems by human intuition alone.

Examine the Picture



Mc Auley. In Conn's Handbook of Models for Human Aging (2018)

Is it possible to fully analyse what is happening?

Reasons continued

5. Model offers an alternative means of handling complexity.
6. Beginning to facilitate the representation of biological systems on a multi-scale manner.
7. Contrasts with reductionism.

Systems Biology

- It has been recognized that to appreciate the interactions involved in cells, tissues & organ systems, integrative approaches needed.

- Integrative approaches build on data from diverse sources:

  - Metabolomics
  - Proteomics
  - Genomics

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Systems Biology

Can a biologist fix a radio?—Or, what I learned while studying apoptosis

As a freshly minted Assistant Professor, I feared that everything in my field would be discovered before I even had a chance to set up my laboratory. Indeed, the field of apoptosis, which I had recently joined, was developing at a mind-boggling speed. Components of the previously mysterious process were being discovered almost weekly, frequent scientific meetings had little overlap in their contents, and it seemed that every issue of *Cell*, *Nature*, or *Science* had to have at least one paper on apoptosis. My fear led me to seek advice from David Papermaster (currently at the University of Connecticut), who I knew to be a person with pronounced common sense and extensive experience. David listened to my outpouring of primal fear and explained why I should not worry.

David said that every field he witnessed during his decades in biological research developed quite similarly. At the first stage, a small number of scientists would somewhat leisurely discuss a problem that would appear esoteric to others, such as whether cell cycle is controlled by an oscillator or whether cells can commit suicide. At this stage the understanding of the problem increases slowly, and scientists are generally nice to each other, a few personal antipathies notwithstanding. Then, an unexpected observation, such as the discovery of cyclins or the finding that apoptosis failure can contribute to cancer, makes many realize that the previously mysterious process can be dissected with available tools and, importantly, that this effort may result in a miracle drug. At once, the field is converted into a Klondike gold rush with all the characteristic dynamics, mentality, and morals. A major driving force becomes the desire to find the nugget that will secure a place in textbooks, guarantee an unrelenting envy of peers, and, at last, solve all financial problems. The assumed proximity of this imaginary nugget easily attracts both financial and human resources, which results in a rapid expansion of the field. The understanding of the biological process increases accordingly and results in crystal clear models that often explain everything and point at targets for future miracle drugs. People at this stage are not necessarily nice, though, as anyone who has read about a gold rush can expect. This description fit the then current state of the apoptosis field rather well, which made me wonder why David was smiling so reassuringly. He took his time to explain.

At some point, David said, the field reaches a stage at which models, that seemed so complete, fall apart, predictions that were considered so obvious are found to be wrong, and attempts to develop wonder drugs largely fail. This stage is characterized by a sense of frustration at the complexity of the process, and by a sinking feeling that despite all that intense digging the promised cure-all may not materialize. In other words, the field hits the wall, even though the intensity of research remains unabated for a while, resulting in thousands of publications, many of which are contradictory or largely descriptive. The flood of publications is explained, in part, by the sheer amount of accumulated information (about 10,000 papers on apoptosis were published yearly over the last few years), which makes reviewers of the manuscripts as confused and overwhelmed as their authors. This stage can be summarized by the paradox that the more facts we learn the less we understand the process we study.

It becomes slowly apparent that even if the anticipated gold deposits exist, finding them is not guaranteed. At this stage, the Chinese saying that it is difficult to find a black cat in a dark room, especially if there is no cat, comes to mind too often. If you want to continue meaningful research at this time of widespread desperation, David said, learn how to make good tools and how to keep your mind clear under adverse circumstances. I am grateful to David for his advice, which gave me hope and, eventually, helped me to enjoy my research even after my field did reach the state he predicted.

At some point I began to realize that David's paradox has a meaning that is deeper than a survival advice. Indeed, it was puzzling to me why this paradox manifested itself not only in studies of fundamental processes, such as apoptosis or cell cycle, but even in studies of individual proteins. For example, the mystery of what the tumor suppressor p53 actually does seems only to deepen as the number of publications about this protein rises above 23,000.

The notion that your work will create more confusion is not particularly stimulating, which made me look for guidance again. Joe Gall at the Carnegie Institution, who started to publish before I was born, and is an author of an excellent series of essays on the history of biology (Gall, 1996), relieved my mental suffering by pointing out that a period of stagnation is eventually interrupted by a new development. As an example, he referred to the studies of cell death that took place in the nineteenth century (Gall, 1996, chapter 29), faded into oblivion, and reemerged a century later with about 60,000 studies on the subject published during a single decade. Even though a prospect of a possible surge in activity in my field was relieving, I started to wonder whether anything could be done to expedite this event, which brought me to think about the nature of David's paradox. The generality of the paradox suggested some common fundamental flaw of how biologists approach problems.

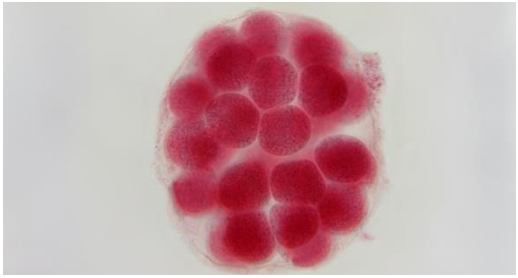
To understand what this flaw is, I decided to follow the advice of my high school mathematics teacher, who recommended testing an approach by applying it to a problem that has a known solution. To abstract from peculiarities of biological experimental systems, I looked for a problem that would involve a reasonably complex but well understood system. Eventually, I thought of the old broken transistor radio that my wife brought

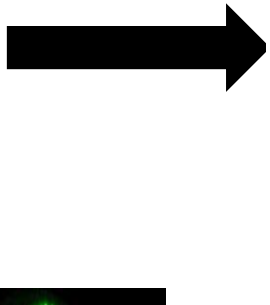
Figure 1. The radio that has been used in this study

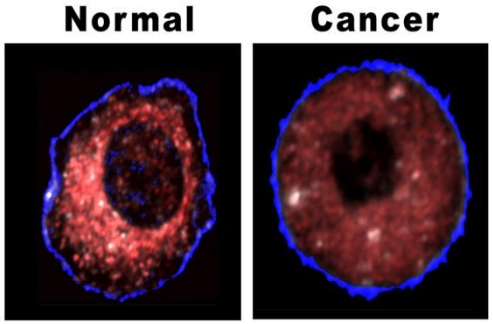
https://www.cell.com/cancer-cell/pdf/S1535-6108(02)00133-2.pdf

Systems Biology

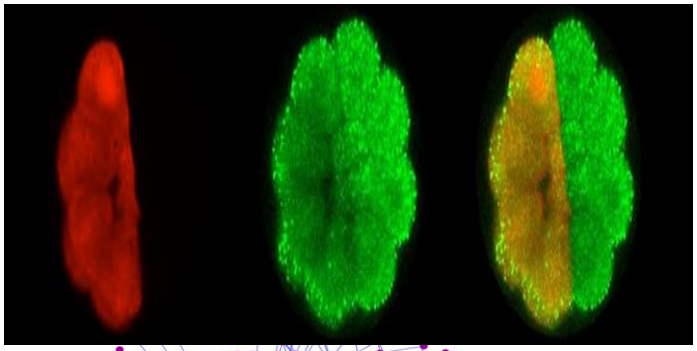
Multi Cell physiology



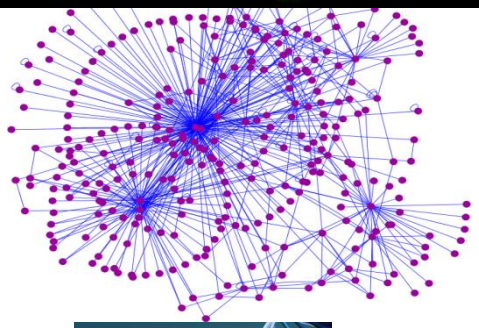




Cellular Physiology



Molecular Network



Genome

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Advantages

In vivo or *in vitro* techniques limited:

- Resource-intensive
- Expensive
- Time consuming
- Impractical
- Can be unethical

Your thoughts

Can you think of some examples of when a study might be:

1. Impractical
2. Unethical

Studying Ageing

OXFORD

doi: 10.1093/bib/bbw116
Paper

Computational modelling folate metabolism and DNA methylation: implications for understanding health and ageing

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Answer-Ethics

Studies examining nutrient/drug toxicity /deficiency often depend on animals.

Recent guidelines suggest reducing the number of animals used in such experiments.

Modelling proposed as an alternative.

Investigating cholesterol metabolism and ageing using a systems biology approach

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Systems Biology and Synthetic Biology: A New Epoch for Toxicology Research

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The Model Building Process

The Challenges

Spend five minutes making a list of what you consider to be the challenges of building a model?

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My Experience

- Can be difficulty to assemble diverse data into a form a computer can use.
- Time consuming.
- Difficult to represent the complexity of biological systems- gaps in understanding are commonplace.
- Difficult to get appropriate data to build the models as a lot of data is unsuitable.
- Once complete, biologists can be sceptical.

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The Up side!

A rewarding & Enjoyable Experience

You don’t have to be a computing/mathematical genius.

You develop a much deeper understanding of Biology.

You think about biological systems in a different way & sometimes see things wet lab scientists miss.

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Why Build Models?

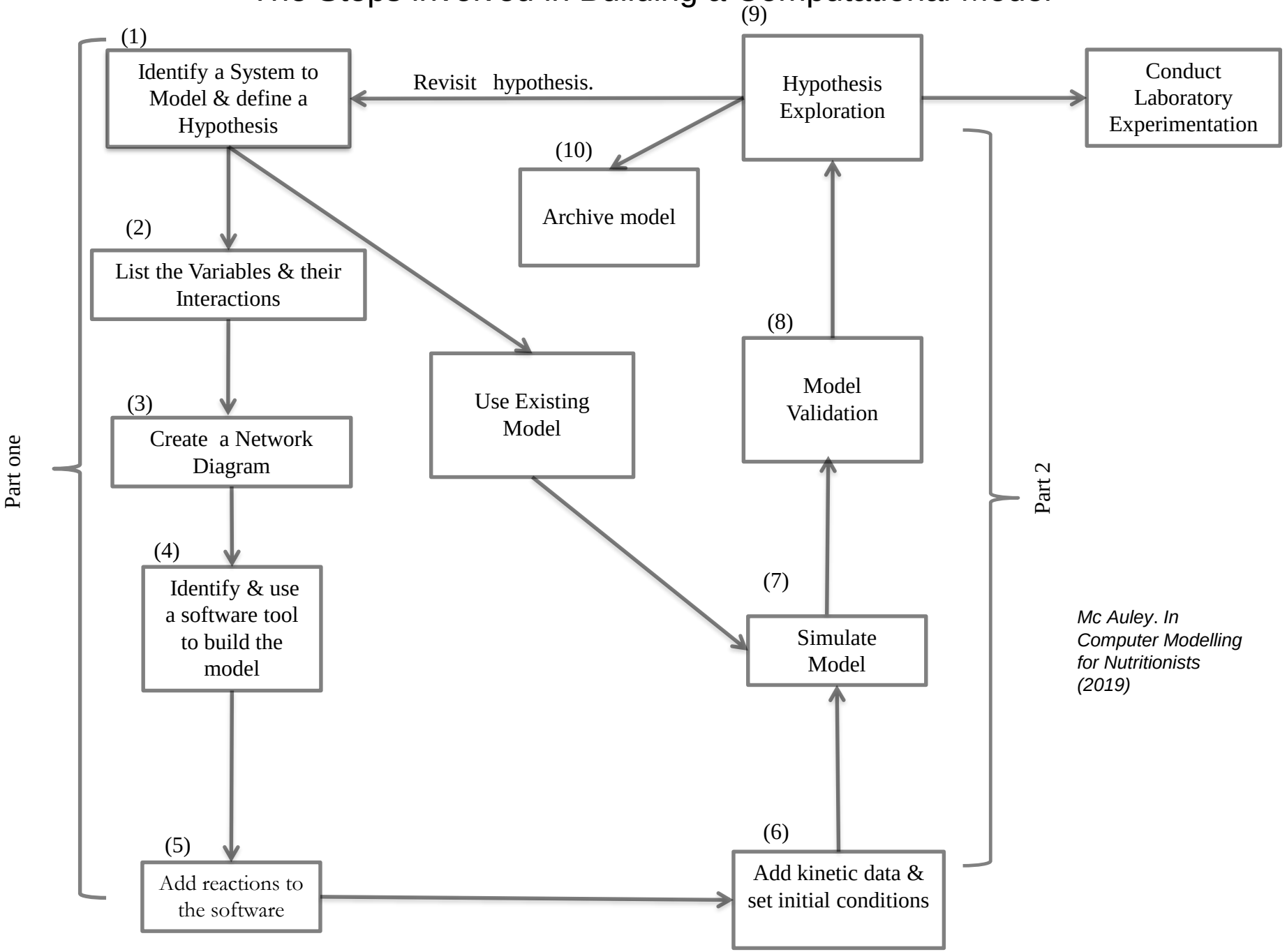
Despite the challenges- computational models of biological systems are becoming increasingly popular:

- Convenient, cheap, ethical and effective way of dealing with biological complexity.
- Allows hypotheses/experiments to be tested that are difficult to do *in vivo* or *in vitro*.
- Relevant to the study of ageing.
- Vital part of systems biology.

Advantages

Advantages of Modelling Adapted from Leloup and Goldbeter (2000)	
1	Can improve our understanding of the biology and generate new insights.
2	Can highlight gaps in current knowledge.
3	Can be used as a predictive tool e.g. to test a particular hypothesis.
4	Can improve our understanding of the biological process.
5	Can develop the capacity to make clear, testable predictions.
6	Can provide a framework to ask questions that may be difficult to pose in reality, or may be difficult to answer using conventional means.
7	May lead to counterintuitive explanations and unusual predictions.
8	Provide a means to analyse complex situations involving multiple variables, which are impossible to handle using human intuition alone.
9	Can provide a rapid way to analyse a biological system under a wide range of conditions.
10	The availability of huge amounts of high-throughput biological data.

The Steps involved in Building a Computational Model



Mc Auley. In Computer Modelling for Nutritionists (2019)

Steps 1 and 2

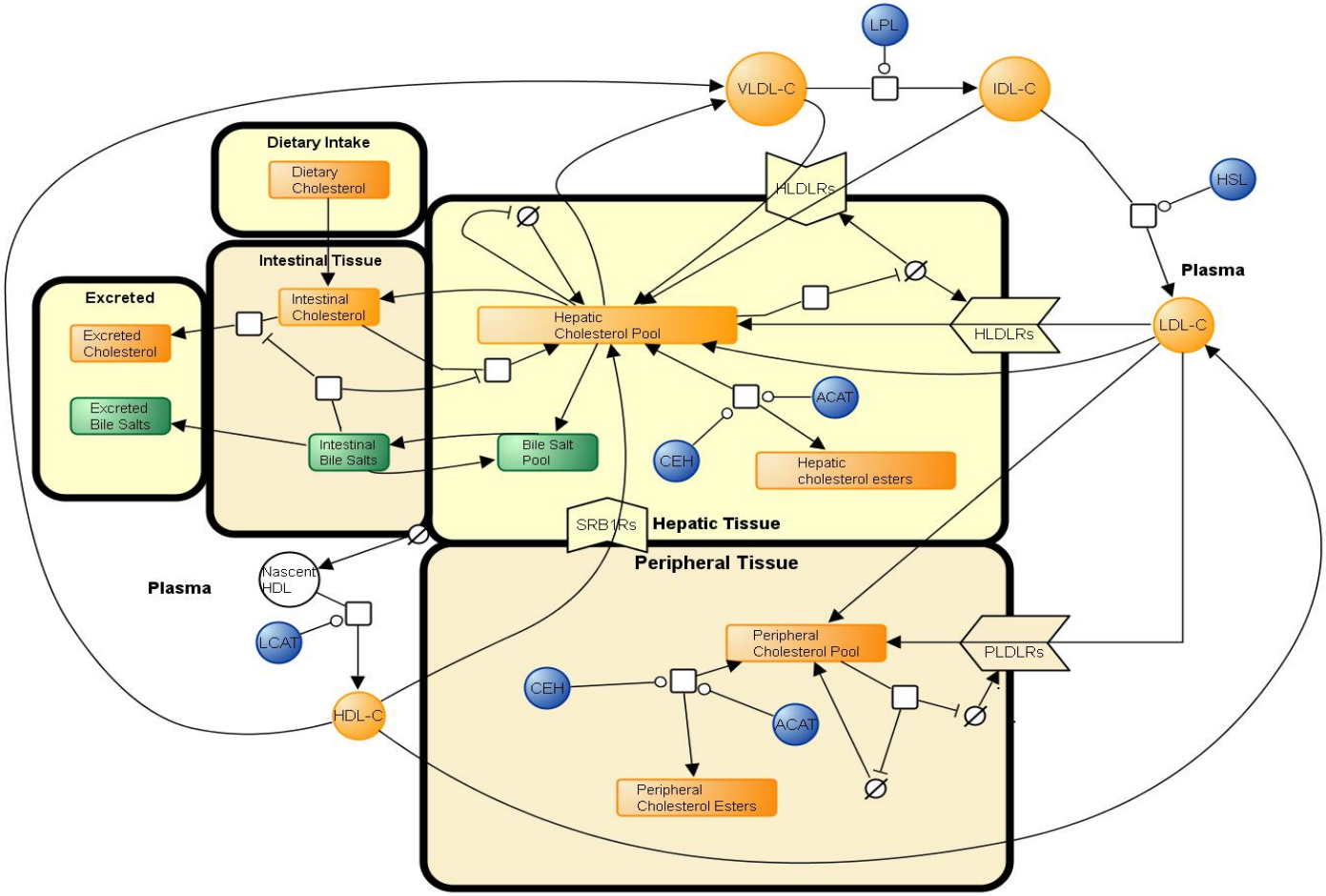
Cholesterol metabolism is is an area that offers a degree of familiarity.

Hypothesis to be tested. Dietary cholesterol has no effect on LDL-C.

Create reactions.

R1:Dietary Cholesterol -> Intestinal Cholesterol
R2: Intestinal Cholesterol Synthesis -> Intestinal Cholesterol
R3: Hepatic Bile Salts -> Intestinal Bile Salts

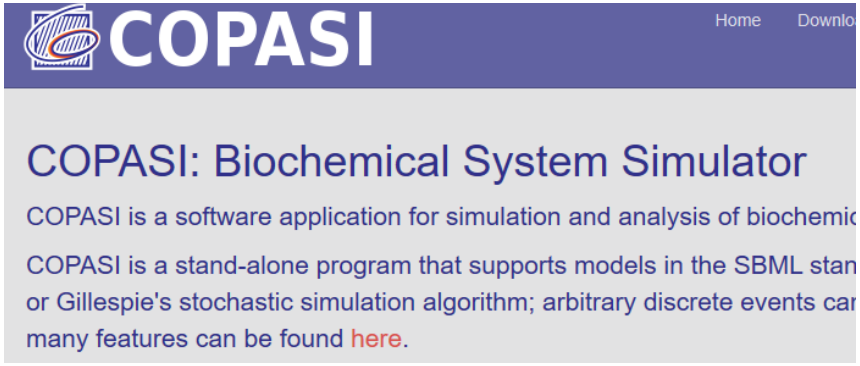
Steps 3: Network Diagram



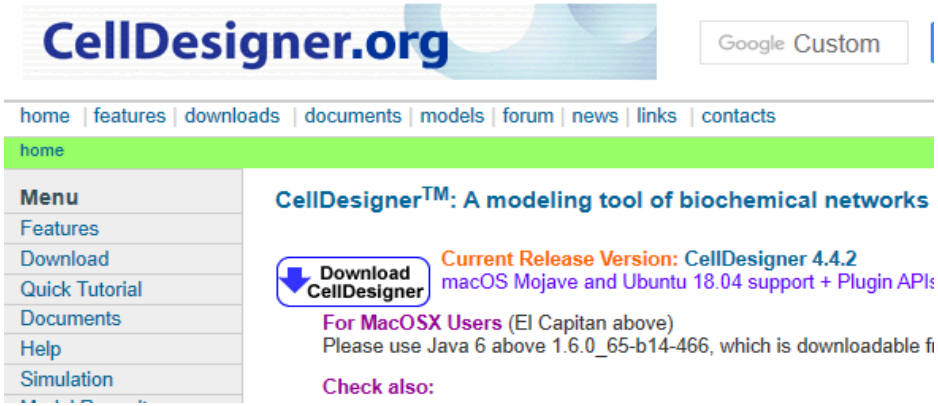
Mc Auley et al. In BMC Systems Biology (2012)

Steps 4: Software tools

COPASI & Cell Designer



http://copasi.org/



http://www.celldesigner.org/

Steps 5: Adding Biochemical Reactions

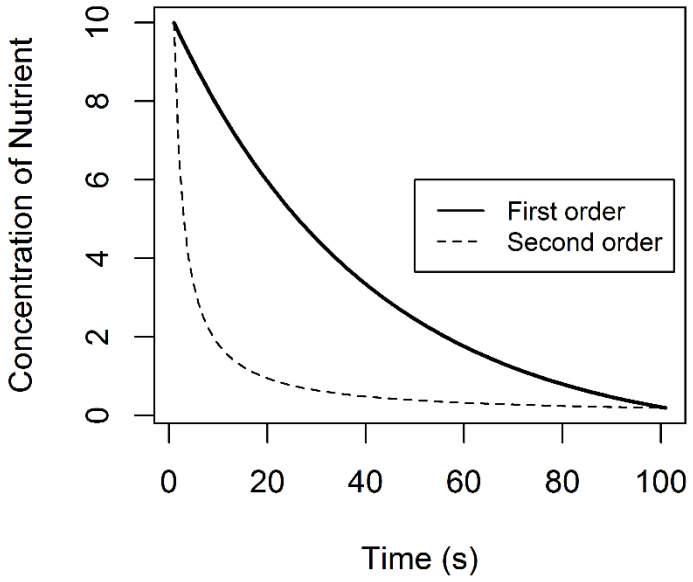
Adding Reactions using COPASI

1. Download, install and open COPASI.
2. Go to the side panel, click Model, a Model window will appear.
3. Beside '**Model**' enter a name e.g. 'Model of Cholesterol Metabolism.'
4. Change the time unit to days (this model is in days).
5. Click File → Save As, give the file a name.
6. Go to the side panel and click Model → Biochemical → Reactions.
7. The 'Reactions' window will appear.
8. Double click to the left of 'New Reaction', this will allow a new reaction to be entered.
9. A new window will appear.
10. Where 'Reaction' is in bold at the top of the window delete 'reaction_1' and enter 'R1'
11. Below '**Reaction**' is a row for adding the word equation.

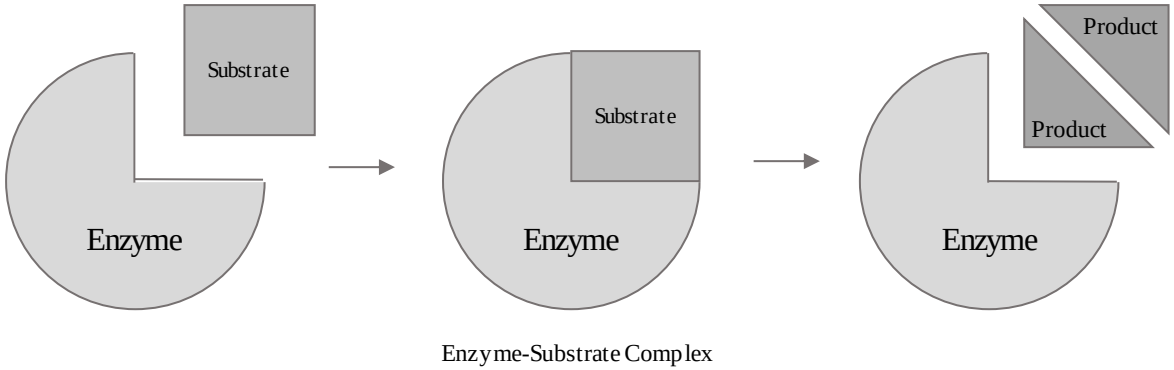
Enter reaction R1 by typing, DC -> IC. The row will turn blue when the data

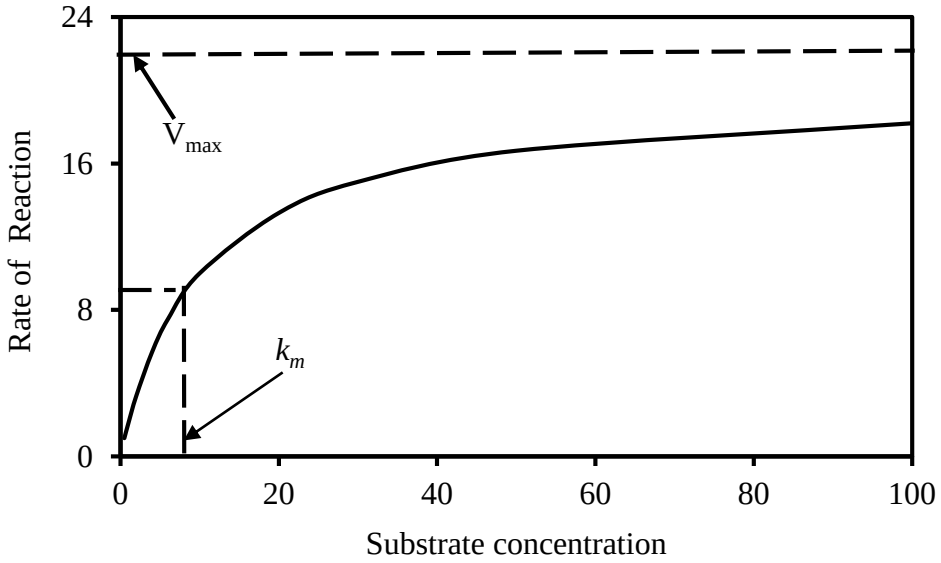
Steps 6: Parameters

Types of Reactions	
Order	Reaction
Zero order	$N \rightarrow \theta$
1st order	$N \rightarrow P$
2nd Order	$N1+N2 \rightarrow P$



Steps 6: Parameters





Michaelis-Menten Kinetics

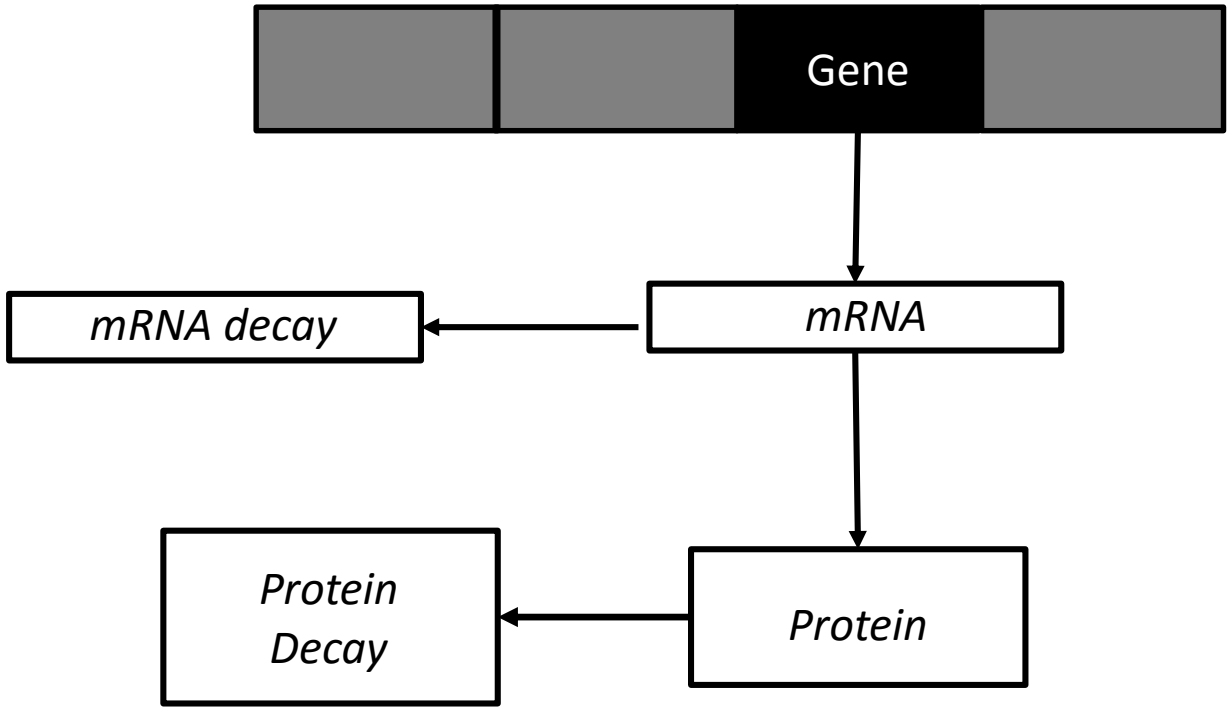
$$v = \frac{V_{max}[S]}{k_m + [S]}$$

Steps 6: Parameters

https://www.brenda-enzymes.org/

Your First Model

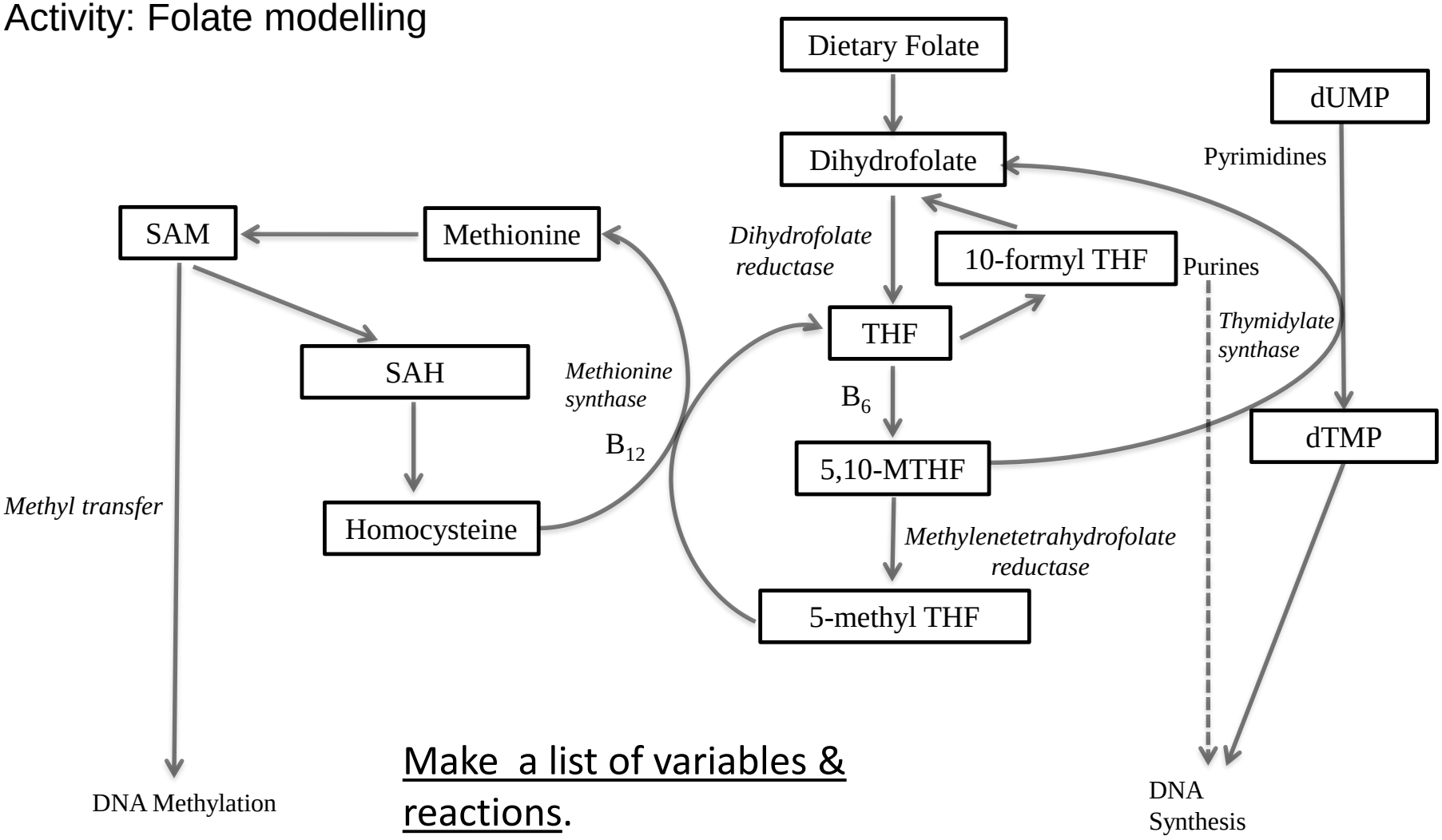
Make a list of variables & reactions.



Your Model Summary

Table. 1 Summary of Simple Gene Model		
Variables	Abbreviation	Reactions

Activity: Folate modelling



Make a list of variables & reactions.

Folate metabolism:
Abbreviations:dUMP,deoxyuridinemonophosphate;dTMP,deoxythymidinemonophosphate;10frormyl THF, 10-formyltetrahydrofolate SAH, S-Adenosyl-L-homocysteine; SAM, S-Adenosyl methionine; THF, Tetrahydrofolate; 5, 10 MTHF, 5, 10 methylene THF.
Diuagram adapted from Lamprecht and Lipkin (2003)

Your Model Summary

Table 2. Summary of Folate Model		
Variables	Abbreviation	Reactions

Steps 7,8,9:Simulate/Validate

A list of Cellular Reactions

Biologist do not need to know how to Code- Let the computer do the work!

Abbreviations

F=Folate
THF=Tetrahydrfolate
5MTHF=5- methyltetrahyrofolate
510MTHF= 5,10 methylenetetrahydrofolate
Met=Methionine
SAM=S-adenosylmethionine
SAH=S adenslyhomocyteine
Hcy=Homocysteine
DHF=Dihydrofolate
10Form= 10,formyl THF

Reactions

$F \xrightarrow{k_1} DHF$

$DHF \xrightarrow{k_2} THF$

$THF \xrightarrow{k_3} 510MTHF$

$510MTHF \xrightarrow{k_4} 5MTHF$

$510MTHF \xrightarrow{k_5} DHF$

$5MTHF + Hcy \xrightarrow{k_6} THF + Met$

$Met \xrightarrow{k_7} SAM$

$THF \xrightarrow{k_8} 10FORM$

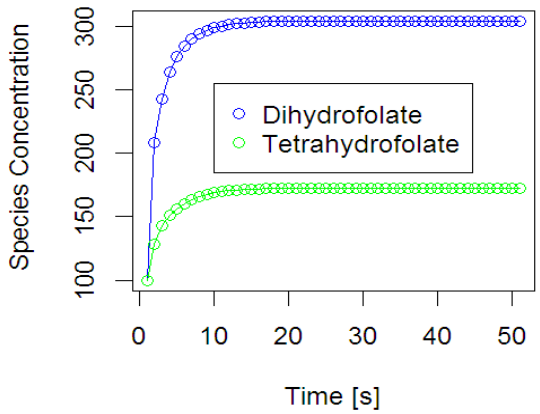
$10FORM \xrightarrow{k_9} DHF$

$SAM \xrightarrow{k_{10}} DNA\_CH_3 + SAH$

$SAH \xrightarrow{k_{11}} Hcy$

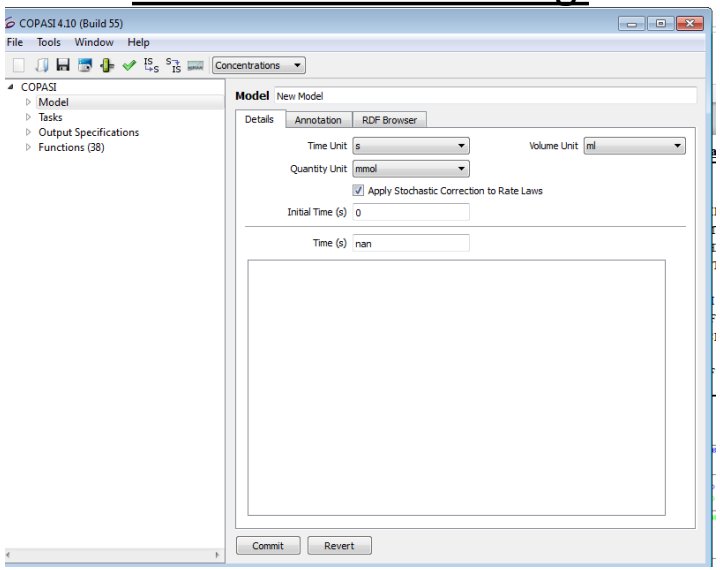
$10FORM + 510MTHF \xrightarrow{k_{12}} DNA$

Enter your reactions into a computer programme which has a friendly & intuitive user interface!



Run simulations

COPASI Model Building



Steps 7,8,9:Simulate/Validate

Reactions

$F \xrightarrow{k_1} DHF$

$DHF \xrightarrow{k_2} THF$

$THF \xrightarrow{k_3} 510MTHF$

$510MTHF \xrightarrow{k_4} 5MTHF$

$510MTHF \xrightarrow{k_5} DHF$

$5MTHF + Hcy \xrightarrow{k_6} THF + Met$

$Met \xrightarrow{k_7} SAM$

$THF \xrightarrow{k_8} 10FORM$

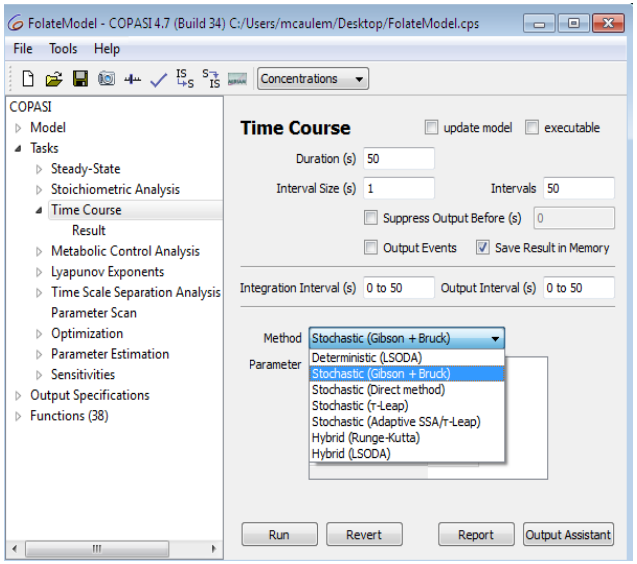
$10FORM \xrightarrow{k_9} DHF$

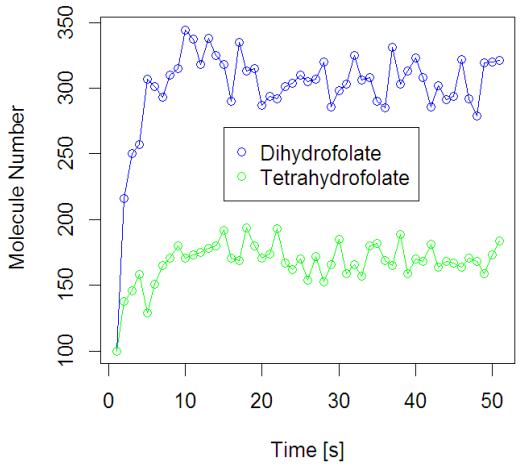
$SAM \xrightarrow{k_{10}} DNA\_CH_3 + SAH$

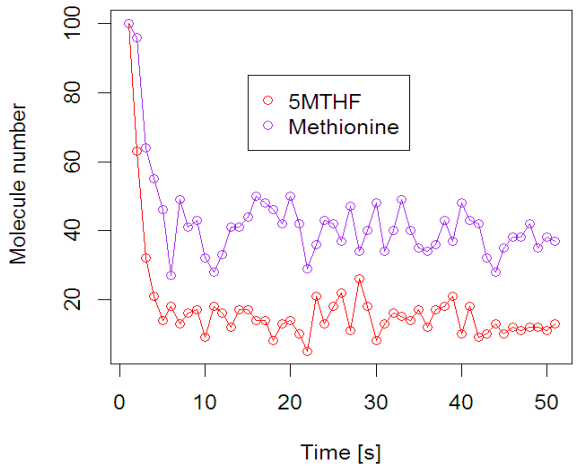
$SAH \xrightarrow{k_{11}} Hcy$

$10FORM + 510MTHF \xrightarrow{k_{12}} DNA$

Stochastic Framework

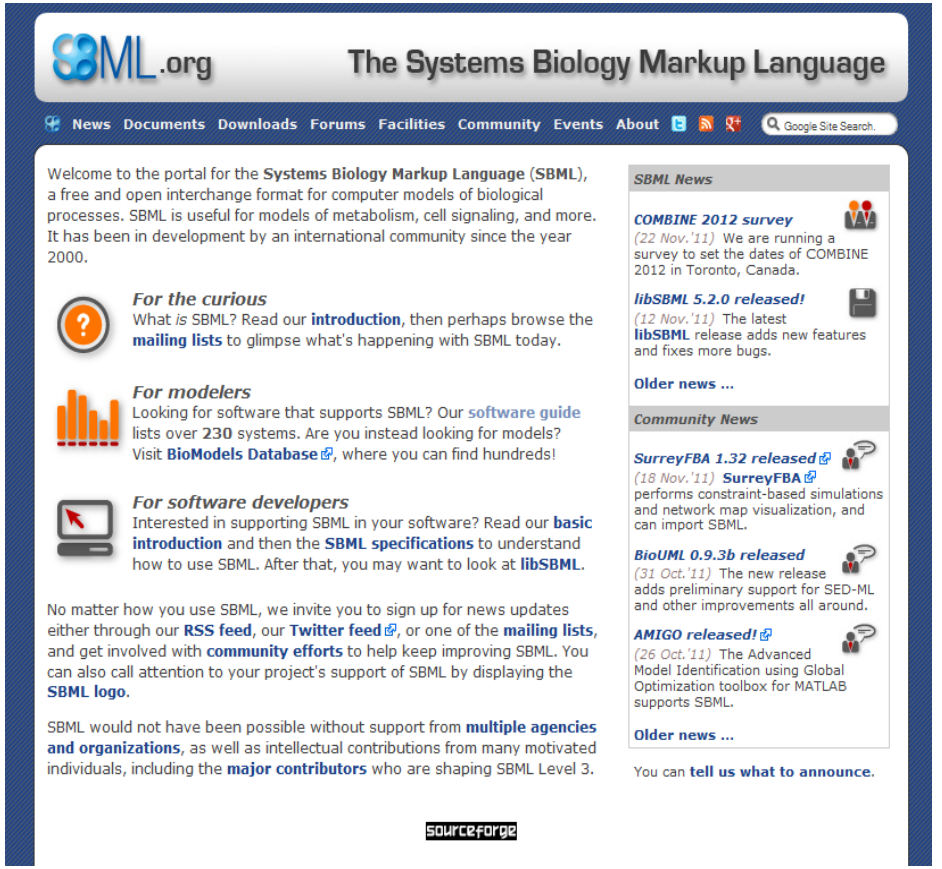






Step 10:Archive

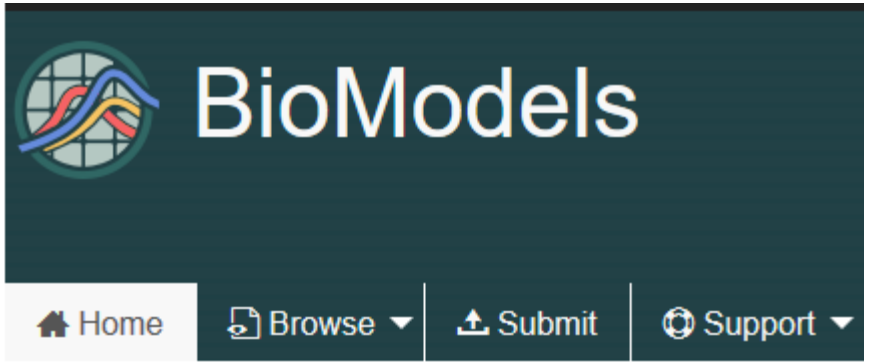
- Historically models constructed with a variety of software tools.
- Gave rise to difficulties in sharing, enhancing & modifying.
- Understanding of biology changes quickly.
- In response a group of software engineers developed SBML.



The Systems Biology Markup Language (SBML)

Step 10:BioModels Database

- A repository for storing SBML based models, published in peer reviewed journals.
- Consists of both a curated & non-curated section.
- Excellent resource for exploring biological models.



https://www.ebi.ac.uk/biomodels/

Learning Check

List the steps in building a mathematical model.

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Activity

How could you create a model of Glycolysis?

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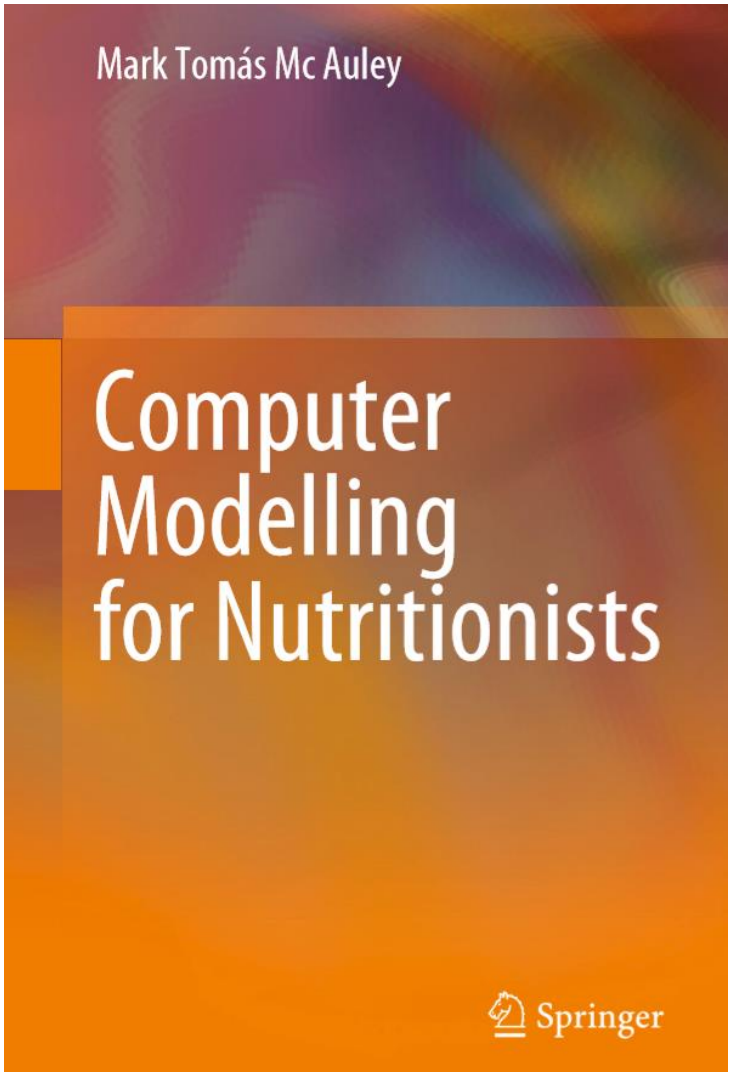
References



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