Models of Cellular Networks[1]

August 5, 2018

[1] HMS, 2018, v1.0

Download the Software First

To download the software go to the web site:

`http://tellurium.analogmachine.org/`

Pick the download that is appropriate for your computer.

Do this now......

Scientific Models

A model is something that helps us understand more clearly the patterns we see in the observations we make.

Examples:

1. Observations of the sun, moon etc led to the development of the Copernican model with the sun at the center.
2. Germ theory of disease, i.e disease is the result of infectious living agents

Scientific Models

Models can be:

- Verbal/Text
- Pictures
- Mathematical equations
- Computer algorithms

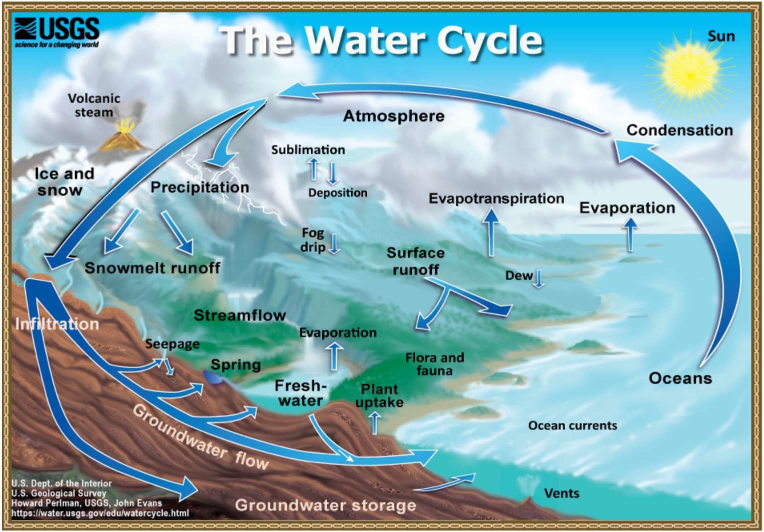
Why are Models Useful?

- They help organize our data and thoughts.
- They help transmit out ideas to our colleagues.
- They enable us to predict the future.
- They help engineers design and build new devices, processes, etc.

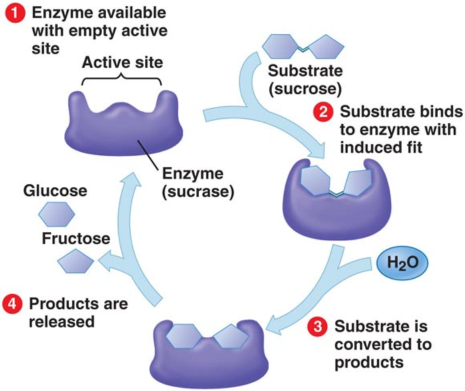
Models in the form of Text

1. Substrate binds to the enzymes active site on the enzyme to form an enzyme-substrate complex.
2. Enzyme-substrate complex undergoes internal rearrangements to form products.
3. The enzyme releases the product of the reaction.
4. The enzyme is not changed and returns to normal shape, ready to catalyze another reaction.

Models as Pictures



Models as Pictures



Why Mathematical Models?

1. Mathematics is a precise language. This helps us formulate ideas and identify underlying assumptions.
2. Mathematics has well-defined rules for manipulation, thus is it a good reasoning tool.
3. Computers can be used to perform numerical calculations using mathematical models.

Characteristics of Mathematical Models

1. Models are abstractions of reality
2. Models are a representation of a particular thing, idea, or condition.
3. Mathematical Models are simplified representations of some real-world entity
   3.1 can be in equations or computer code
   3.2 are intended to mimic essential features while leaving out distracting inessentials
4. Mathematical models are characterized by assumptions about:
   4.1 Variables (the things which change)
   4.2 Parameters (the things which do not change)
   4.3 Mathematical equations (the relationship between the two)

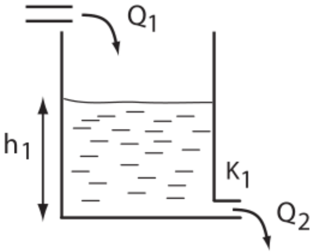
Types of mathematical model

Many types:

- Statistical (machine learning)
- Boolean
- Automata
- ODE
- Algebraic
- Stochastic
- Machine learning

Water Tank Model

Water tank model



Water Tank Model: quantities

Write out the Equations

Write out the Equations

Q_i Units are volume per minute

$\frac{dV}{dt} = Q_1 - Q_2$

$V = hA$

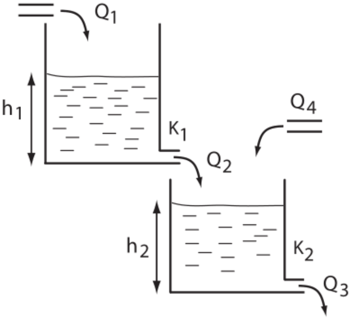
$\frac{dV}{dt} = h\frac{dA}{dt}$

Let $Q_2 = Kh$ (very approximate). The final model is:

$$\frac{dh}{dt} = \frac{Q_1}{A} - \frac{hK}{A}$$

Water Tank Model

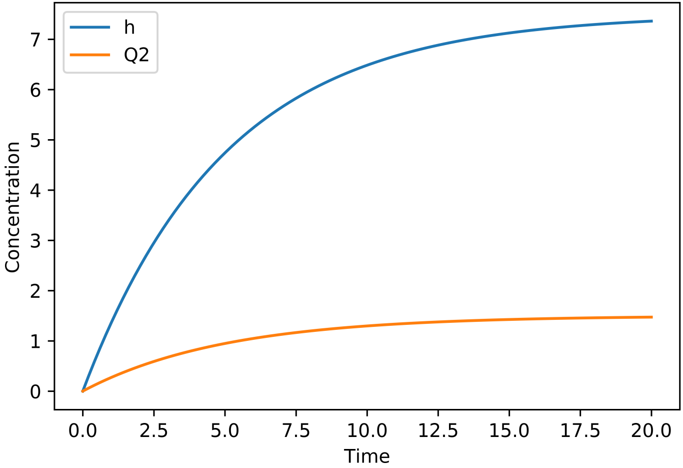
Two water tank model



$$\frac{dV_1}{dt} = Q_1 - Q_2$$

$$\frac{dV_2}{dt} = Q_2 + Q_4 - Q_3$$

Use a Simulation



Use a Simulation

```
import pylab
import tellurium as te

r = te.loada('''
     inflow: -> h; Q1/A;
        Q2: h ->; k1*h/A

     k1 = 0.2; Q1 = 1.5; A = 1.0
''')

m = r.simulate (0, 20, 100, ['time', 'h', 'Q2'])

pylab.plot (m['time'], m["h"], label='h')
pylab.plot (m['time'], m["Q2"], label='Q2')
pylab.xlabel ('Time')
pylab.ylabel ('Concentration')
pylab.legend()
pylab.savefig('tankSimulation.png', dpi=1000)
```

Models of Reaction Networks

$$aA + bB + \ldots \rightarrow pP + qQ + \ldots$$

Rate of reaction:

$$v = k_1 A^a B_b \ldots + k_2 P^p Q^q \ldots$$

Example:

$$A \rightarrow B$$

$$v = k_1 A$$

Reversible:

$$v = k_1 A - k_2 B$$

Models of Reaction Networks

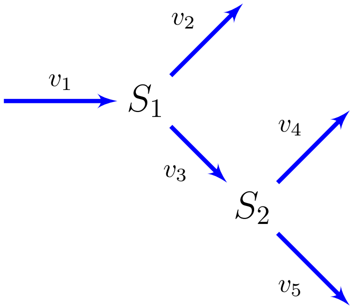
Mass-Balance Equation:

$$\xrightarrow{v_1} S \xrightarrow{v_1}$$

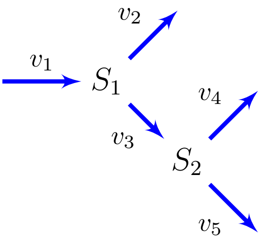
$$\frac{dS}{dt} = v_1 - v_2$$

$$\frac{dS_i}{dt} = \sum \textit{Inflows} - \sum \textit{Outflows} \tag{1}$$

Models of Reaction Networks



Models of Reaction Networks



$$\frac{dS_1}{dt} = v_1 - v_2 - v_3$$

$$\frac{dS_2}{dt} = v_3 - v_4 - v_5$$

Models of Reaction Networks

$$
\begin{aligned}
A + X &\xrightarrow{v_1} 2X \\
X + Y &\xrightarrow{v_2} Z \\
Z &\xrightarrow{v_3} Y + B
\end{aligned}
$$

Models of Reaction Networks

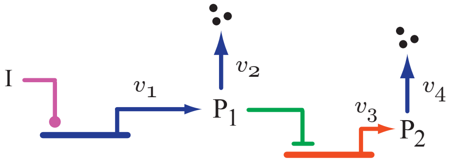
$$\begin{aligned} A + X &\xrightarrow{v_1} 2X \\ X + Y &\xrightarrow{v_2} Z \\ Z &\xrightarrow{v_3} Y + B \end{aligned}$$

$$\frac{dA}{dt} = -v_1 \qquad \frac{dX}{dt} = v_1 - v_2$$

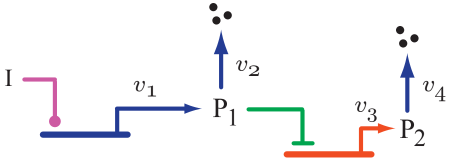
$$\frac{dY}{dt} = v_3 - v_2 \qquad \frac{dZ}{dt} = v_2 - v_3$$

$$\frac{dB}{dt} = v_3$$

Models of Gene Regulator Networks



Models of Gene Regulator Networks



$$\frac{dP_1}{dt} = v_1 - v_2$$

$$\frac{dP_2}{dt} = v_3 - v_4$$

Stoichiometry Matrix

When describing multiple reactions in a network, it is convenient to represent the stoichiometries in a compact form called the **stoichiometry matrix**.

$$\mathbf{N} = \mathbf{m} \times \mathbf{n} \text{ matrix}$$

The columns of the stoichiometry matrix correspond to the individual chemical reactions in the network. The rows correspond to the molecular species, with one row per species.

The stoichiometric matrix is not concerned with describing reaction rates. Reaction rates are given by rate laws in a separate vector

$$\mathbf{N} = \begin{array}{cc} & \longleftarrow \quad v_j \quad \longrightarrow \\ \begin{array}{c} \uparrow \\ S_i \\ \downarrow \end{array} & \begin{bmatrix} c_{ij} & \cdots & \cdots \\ \vdots & & \\ \vdots & & \end{bmatrix} \end{array}$$

Models of Gene Regulator Networks

$$S_1 \xrightarrow{v_1} S_2 \xrightarrow{v_2} S_3 \xrightarrow{v_3} S_4 \xrightarrow{v_4} S_5$$

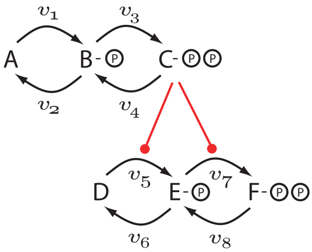
Example Stoichiometry Matrix

$$S_1 \xrightarrow{v_1} S_2 \xrightarrow{v_2} S_3 \xrightarrow{v_3} S_4 \xrightarrow{v_4} S_5$$

$$\mathbf{N} = \begin{array}{c} \\ \\ \\ \\ \\ \end{array}\begin{array}{cccc} v_1 & v_2 & v_3 & v_4 \end{array}$$

$$\mathbf{N} = \left[\begin{array}{rrrr} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{array}\right] \begin{array}{l} S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array}$$

Signalling Networks



$$
\mathbf{N} = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array}
\begin{array}{c}
\begin{array}{cccccccc} v_1 & v_2 & v_3 & v_4 & v_5 & v_6 & v_7 & v_8 \end{array} \\
\left[\begin{array}{cccccccc}
-1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1
\end{array}\right]
\end{array}
$$

System Equation

$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v}$$

$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix}$$

System Equation

```
A -> B; k1*A - k2*B;
B -> C; k3*B - k4*C;
```

The system equation for this model is:

$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v} = \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} k_1 A - k_2 B \\ k_3 B - k_4 C \end{bmatrix}$$

System Equation

```
import tellurium as te

r = te.loada ('''
   J1: A -> B; k1*A - k2*B;
   J2: B -> C; k3*B - k4*C;

   k1 = 0.1; k2 = 0.02;
   k3 = 0.3; k4 = 0.04;
   A  = 10;  B  = 0; C = 0;
''')

print r.getFullStoichiometryMatrix()
```

Exercises

Derive a set of differential equations for the following model in terms of the rate of reaction, v_1, v_2, and v_3:

$$A \xrightarrow{v_1} 2B$$
$$B \xrightarrow{v_2} 2C$$
$$C \xrightarrow{v_3} \emptyset$$

Write out the stoichiometry matrix for this system.

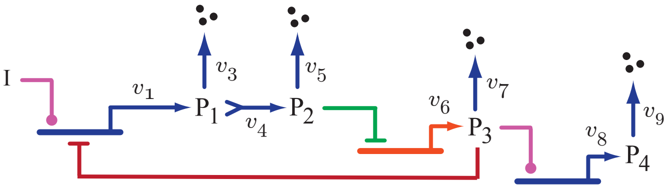
Exercises

Given the following stoichiometry matrix, write out the corresponding network diagram.

$$
\begin{array}{c c}
 & \begin{array}{ccccc} v_1 & v_2 & v_3 & v_4 & v_5 \end{array} \\
\begin{array}{c} A \\ B \\ C \\ D \\ E \\ F \\ G \end{array} &
\begin{bmatrix}
-1 & 0 & -1 & 0 & 0 \\
1 & -1 & 0 & 0 & 3 \\
0 & 2 & -1 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 \\
0 & 0 & 0 & 1 & -1 \\
0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & -1 & 0
\end{bmatrix}
\end{array}
$$

Exercises

Derive the mass-balance equations for the following gene regulatory network:



Boundary and Floating Species

Molecular species that are not dependent on the action of the model are sometimes called **boundary species.**

Often boundary species are fixed by the modeler but it is possible for the modeler to impose a particular change in a boundary species to simulate, for example the adminstration of a drug as a bolus or as a continuous infusion.

Molecular species that change in time as a result of the action of the model are sometimes called **floating species**.

Common Rate Laws

Mass-action: $v = kA$

Michaelis-Menten:

$$\text{Irreversible: } v = \frac{V_m S}{K_m + S}$$

$$\text{Reversible: } v = \frac{V_m/K_1(S - P/K_{eq})}{1 + S/K_1 + P/K_2}$$

Gene regulatory rate laws:

$$\text{Activatory: } \quad v = \frac{V_m S^n}{K + S^n}$$

$$\text{Inhibitory: } \quad v = \frac{V_m}{K + S^n}$$

$V_m =$ Maximal velocity, $\quad K_m, K_1, K_2, K =$ Michaelis Constants

$n =$ Hill coefficient (1 to 8)