Models of Cellular Networks[1]

July 19, 2021

[1] HMS, 2021, v1.1

Scientific Models

A model is something that helps us understand more clearly the observations we make around us.

Examples:

1. Observations of the sun, mood 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 infection living agents

Scientific Models

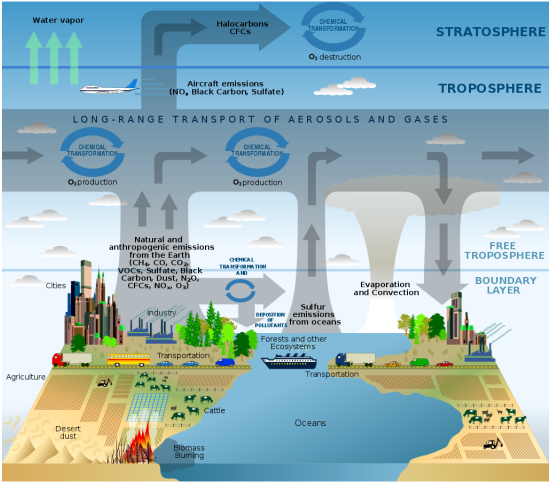
Models can be:

- Verbal/Text
- As pictures
- As mathematical equations
- As computer algorithms

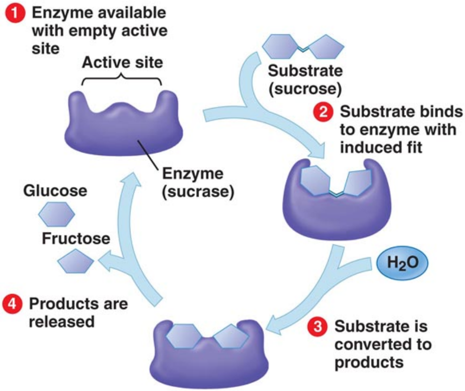
Why are Models Useful?

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

Models as Pictures



Models as Pictures



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-substreate 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.

Why Mathematical Models?

1. Mathematics is a precise language. This helps us to 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.

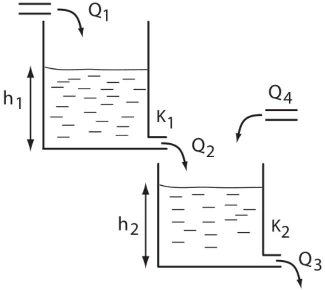
Types of mathematical model

Many types:

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

Water Tank Model

Water tank model



Our aim it to make quantitative predictions on the height of water.

We cannot easily do this with just the picture diagram.

We must convert the picture into a mathematical model.

Water Tank Model: Assumptions

In building the mathematical model we will make some assumptions, most notably:

- Mass is conserved as water moves from one tank to another.
- External environment is constant, for example the temperature.
- We assume Torrielli's Law for the flow of water out of a tank:

  $\text{flow} = K\sqrt{\text{height of water in tank}}$

Water Tank Model: quantities

Different kinds of quantities:

Parameters: constants such as K, diameter of the tank

State variables: Height of water in the tanks (h)

Inputs: Flow of water into the tank (Q)

Equations I

Using the conservation of mass we can write:

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

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

But we want to predict height changes not volume. However we know that $V = Ah$ where A is the cross-sectional area of the tank.

Differentiating $V = Ah$ with respect to time gives:

$$\frac{dV}{dt} = A\frac{dh}{dt}$$

Equations II

Since

$$\frac{dV_1}{dt} = A\frac{dh_1}{dt} \quad \text{and} \quad \frac{dV_1}{dt} = Q_1 - Q_2$$

then

$$\frac{dh_1}{dt} = \frac{Q_1 - Q_2}{A}$$

We can do the same for V_2

Use a Simulation

$$\frac{dh_1}{dt} = \frac{Q_1 - K_1\sqrt{h_1}}{A}$$

$$\frac{dh_2}{dt} = \frac{K_1\sqrt{h_1} + Q_4 - K_2\sqrt{h_2}}{A}$$

Rather than solve the equations analytically we can solve then numerically.

Run a Simulation: I

```
import numpy as np
from scipy.integrate import odeint
import matplotlib.pyplot as plt
import math

# function that returns dy/dt
def model(y,t):
    K1 = 0.3; K2 = 0.4; # Assume Area = 1
    Q1 = 5; Q4 = 1 # Units:volume per time
    dh1dt = Q1 - K1*math.sqrt (y[0])
    dh2dt = K1*math.sqrt (y[0]) + Q4 - K2*math.sqrt(y[1])
    return [dh1dt, dh2dt]
```

Run a Simulation: II

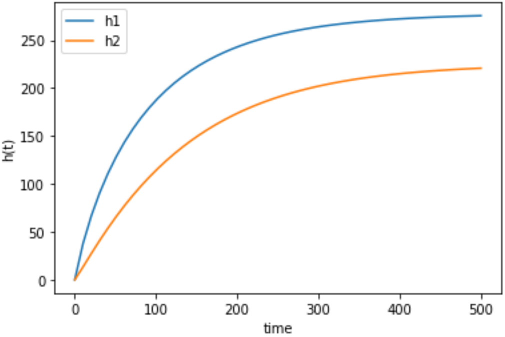
```
# initial condition
y0 = [0, 0]

# time points
t = np.linspace(0,500)

# solve ODE
y = odeint(model,y0,t)

# plot results
plt.plot(t,y[:,0], label="h1")
plt.plot(t,y[:,1], label="h2")
plt.xlabel('time')
plt.ylabel('h(t)')
plt.legend()
plt.show()
```

Run a Simulation: II



Models of Reaction Networks

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

Rate of reaction:

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

Example:

$$A \to B$$

$$v = k_1 A$$

Reversible:

$$v = k_1 A - k_2 B$$

Models of Reaction Networks

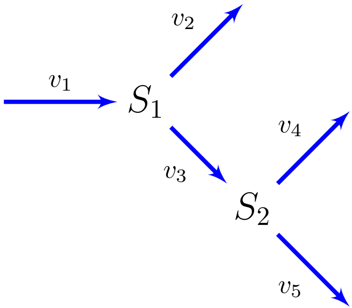
Mass-Balance Equation:

$$\xrightarrow{v_1} S \xrightarrow{v_2}$$

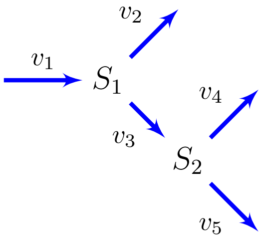
$$\frac{dS}{dt} = v_1 - v_2$$

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

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

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

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

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

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

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

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

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

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

$$\mathbf{N} = \begin{array}{c} \begin{array}{cccc} v_1 & v_2 & v_3 & v_4 \end{array} \\ \left[\begin{array}{rrrr} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{array}\right] \end{array} \begin{array}{c} \\ S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array}$$

System Equation

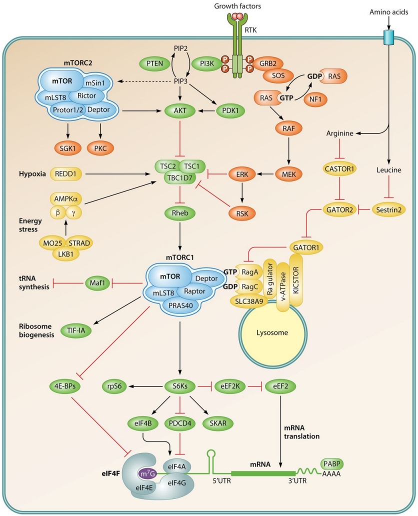
$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v}$$

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

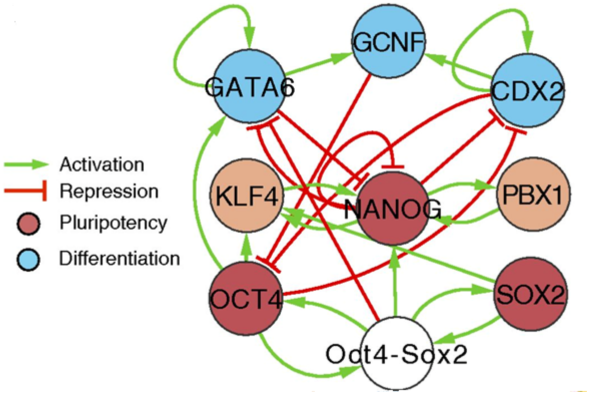
Pathway Regulation

How to interpret biochemical writing diagrams

Pathway Regulation



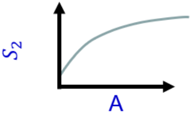
Pathway Regulation



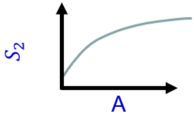
Regulatory Links—Interpretation

A regulatory link indicates that the rate of the reaction link depends on the concentration or amount in the source node

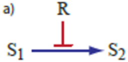
Regulatory links may be **activating** (excitatory), in which case a larger amount of the species at the node **increases** the rate of the reaction or the level of the response. **The rate at $A = 0$ need not be 0.** Note the alternative notation which is ambiguous

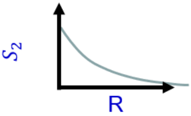


$A \multimap S_2$

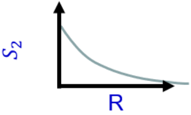


Regulatory links may be **inhibiting**, in which case a larger amount of the species at the node **decreases** the rate of the reaction or the level of the response. Note the alternative notation which is ambiguous



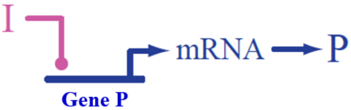


$R \dashv S_2$

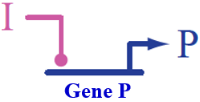


Gene Regulatory Networks—Notation

Models (and graphical notation) for GRNs focus on the transcription factors, RNAs and other molecules that turn genes on and off by binding



Binding of an **Inducer** I to the DNA for Gene P produces mRNA, which is translated into protein P. Neglects editing, transport and post-translational steps



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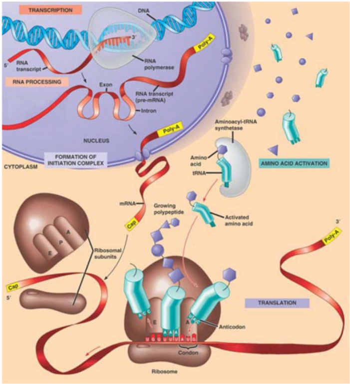


https://www.thinglink.com/scene/616264922585628674

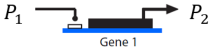
Based on biotapestry standard http://www.biotapestry.org/

Interpreting Gene Regulatory Networks into Chemical Reactions

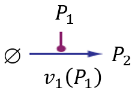
If we interpret P_1 as a protein transcription factor that determines the rate of production of protein P_2 (neglecting mRNA)

P_1 and P_2 are not used up in these interactions

So we interpret the regulation as



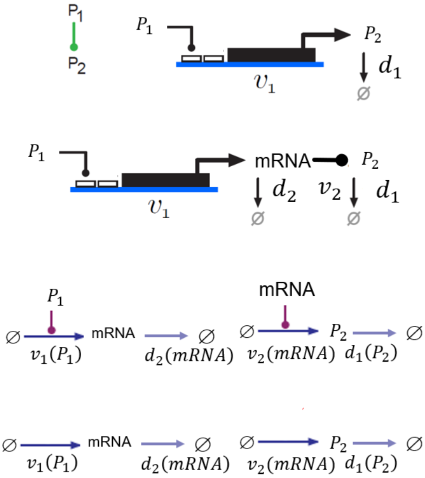
Which we translate into a chemical reaction of augmented form



Pathway Regulation

Gene Regulatory Networks: Including Translation

Sometimes the extra step of translation of mRNA into protein is regulated or the time delay associated with it is critical, in this case, we need to extend our interpretation to include the production, translation and degradation of mRNA



So simple arrow becomes 4 reactions with 4 rate laws!

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)