Basic Concepts in Reaction Kinetics and Systems

Basic Terms

Stoichiometric Amount The stoichiometric amount is defined as the number of molecules of a particular reactant or product partaking in a reaction. Stoichiometric amounts will always be positive numbers.

Stoichiometric coefficient The stoichiometry coefficient refers to the relative amount of substance that is consumed and/or produced by a reaction.

Rate of Change The rate of change in concentration or amount of a specified molecular species.

Reaction Rate The rate of reaction, r, is defined to be the slope of the concentration-time plot for a species divided by the stoichiometric coefficient of that species.

Mass-action Ratio The ratio of the products to the reactants *in vivo* is called the mass-action ratio, denoted by the symbol Γ.

Disequilibrium Constant The ratio of the mass-action ratio to the equilibrium constant is called the disequilibrium ratio and denoted by the symbol, ρ.

Elasticity The elasticity describes how sensitive a reaction rate is to changes in reactant, product and effector concentrations, that is the degree to which changes are transmitted from the immediate environment of a reaction to the reaction rate.
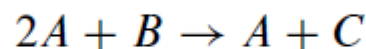
Kinetic order See elasticity

Stoichiometric Amounts

The **stoichiometric amount** is the number of molecules of a particular reactant or product taking part in a reaction.

List the stoichiometric amounts in the following reaction:

$$2A + B \rightarrow A + C$$

On the reactant side the stoichiometric amount for A is two and for B is one. On the product side, the stoichiometric amount for A is one and for C one.
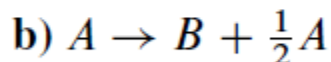
Stoichiometric Coefficients

The **stoichiometric coefficient**, c_i, for a molecular species A_i, is the difference between the stoichiometric amount of the species on the product side and the stoichiometric amount of the same species on the reactant side, that is:

$$c_i = \text{Stoichiometric Amount of Product, } A_i$$
$$- \text{ Stoichiometric Amount of Reactant, } A_i$$

Write down the stoichiometric coefficients for the following reactions:

a) $A + A \rightarrow A + B$
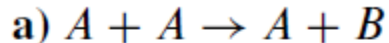
The stoichiometric amount of A on the reactant side is 2 and on the product side, 1. Therefore the stoichiometric coefficient for A is $1 - 2 = -1$. The stoichiometric amount of B on the product side is 1 and on the reactant side, 0, therefore the stoichiometric coefficient for B is $1 - 0 = 1$.

b) $A \rightarrow B + \frac{1}{2}A$

The stoichiometric amount of A on the reactant side is 1 and on the product side $\frac{1}{2}$, therefore the stoichiometric coefficient for A is $1/2 - 1 = -1/2$. The stoichiometric amount of B on the reactant side is 0 and on the product side, 1, therefore the stoichiometric coefficient for B is $1 - 0 = 1$.

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Rate of Change

The rate of change can be defined as the rate of change in concentration or amount (depending on units) of a designated species. If S is the species then the rate of change is given by:

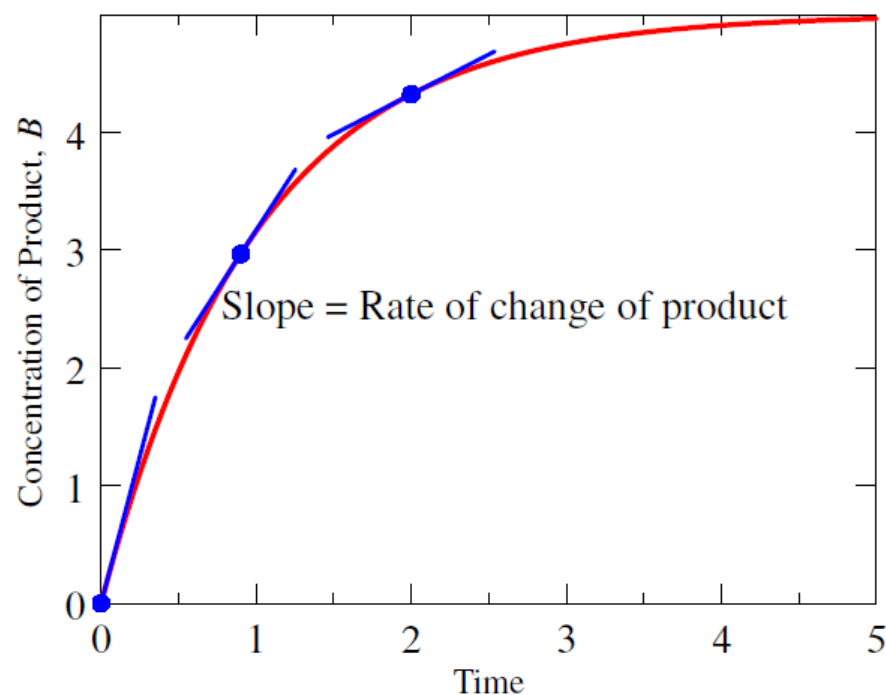$$\text{Rate} = \frac{\Delta S}{\Delta t} \qquad\qquad \text{Rate} = \frac{dS}{dt}$$
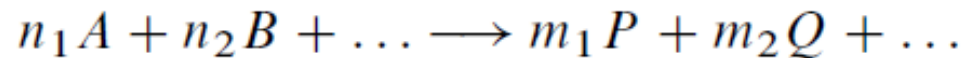

Figure 1.1: Progress curve for a simple irreversible reaction, $A \rightarrow B$.

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Reaction Rate (v)

For a reaction of the form

$$n_1 A + n_2 B + \ldots \longrightarrow m_1 P + m_2 Q + \ldots$$

where we assume that each species only occurs on one side of the reaction, and where $n_1, n_2, \ldots$ and $m_1, m_2, \ldots$ represent the stoichiometric amounts, the reaction rate is given by:

$$\text{Rate} = v \equiv -\frac{1}{n_1}\frac{dA}{dt} = -\frac{1}{n_2}\frac{dB}{dt} \ldots = \frac{1}{m_1}\frac{dP}{dt} = \frac{1}{m_2}\frac{dQ}{dt} \ldots \qquad (1.1)$$
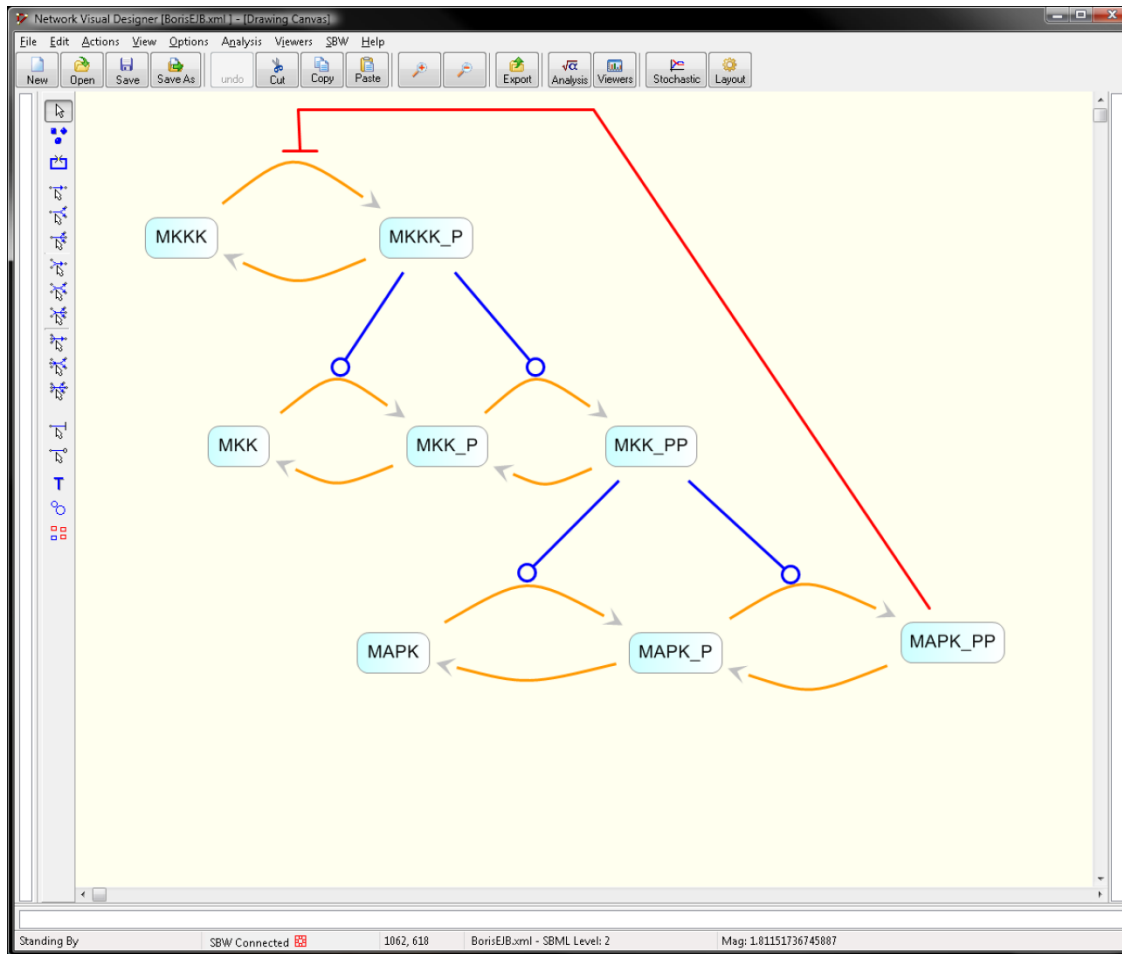
A reaction rate is the rate of change normalized with respect to the stoichiometric coefficient.
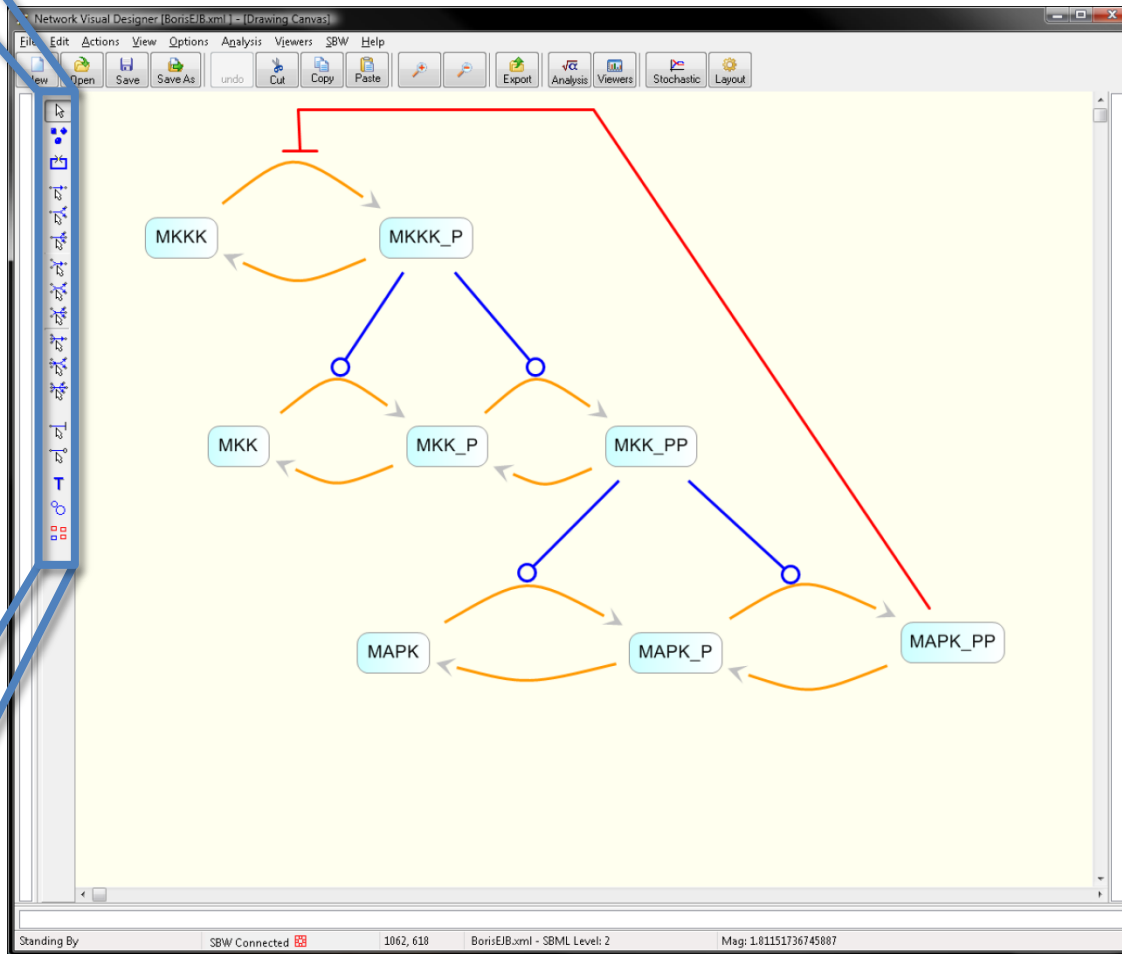
Simulation Tools

In this workshop we will use the following software tools:

- JDesigner
- JarnacLite
- Simulation Tool
- Jarnac

JDesigner

JDesigner
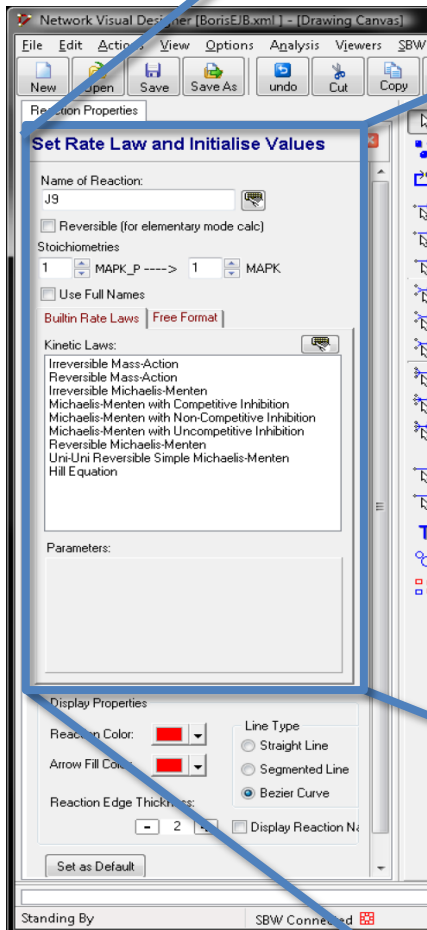
JDesigner

JDesigner
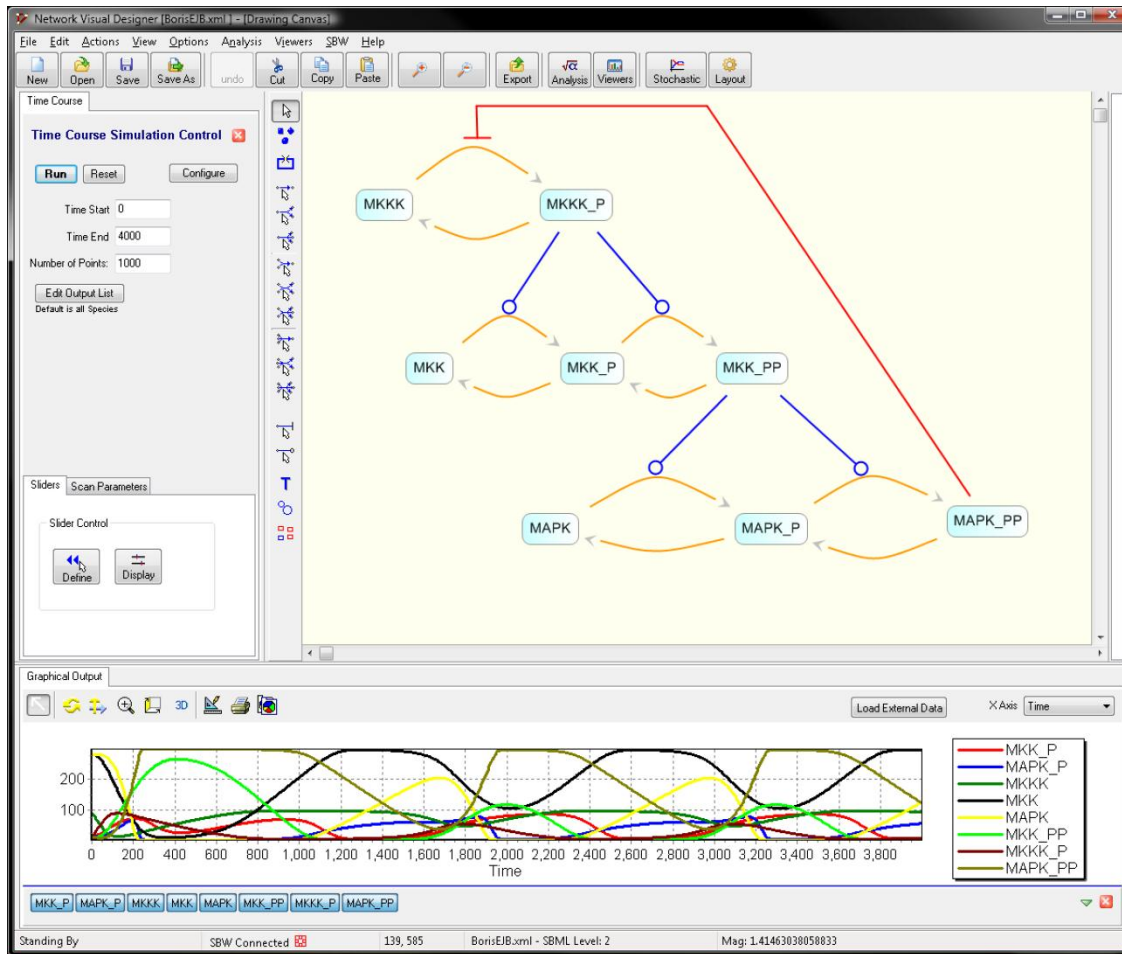
JarnacLite

```
// Model Definition
p = defn simple_reaction
    v1: $Xo -> S1;  k1*Xo;
    v2: S1 -> $w;    k2*S1;
end;

// Initialize Constants
p.k1 = 1; p.k2 = 1; p.S1 =20; p.Xo=1;
```

Simulation Tool

Jarnac

Jarnac:

Script-based Simulation Software
- ❖ Model Building
- ❖ Simulation
- ❖ Analysis
  (Deterministic and Stochastic)
- ❖ SBML file import and export

Console Window

Script Editor

Jarnac

```
// Model Definition
p = defn simple_reaction
    v1: $Xo -> S1;  k1*Xo;
    v2: S1 -> $w;   k2*S1;
end;

// Initialize constants
p.k1 = 1; p.k2 = 1; p.S1 =20; p.Xo=1;
m = p.sim.eval(0,20,100,[<p.Time>,<p.S1>]);
graph (m)
```

Most Important Jarnac Commands for the Week
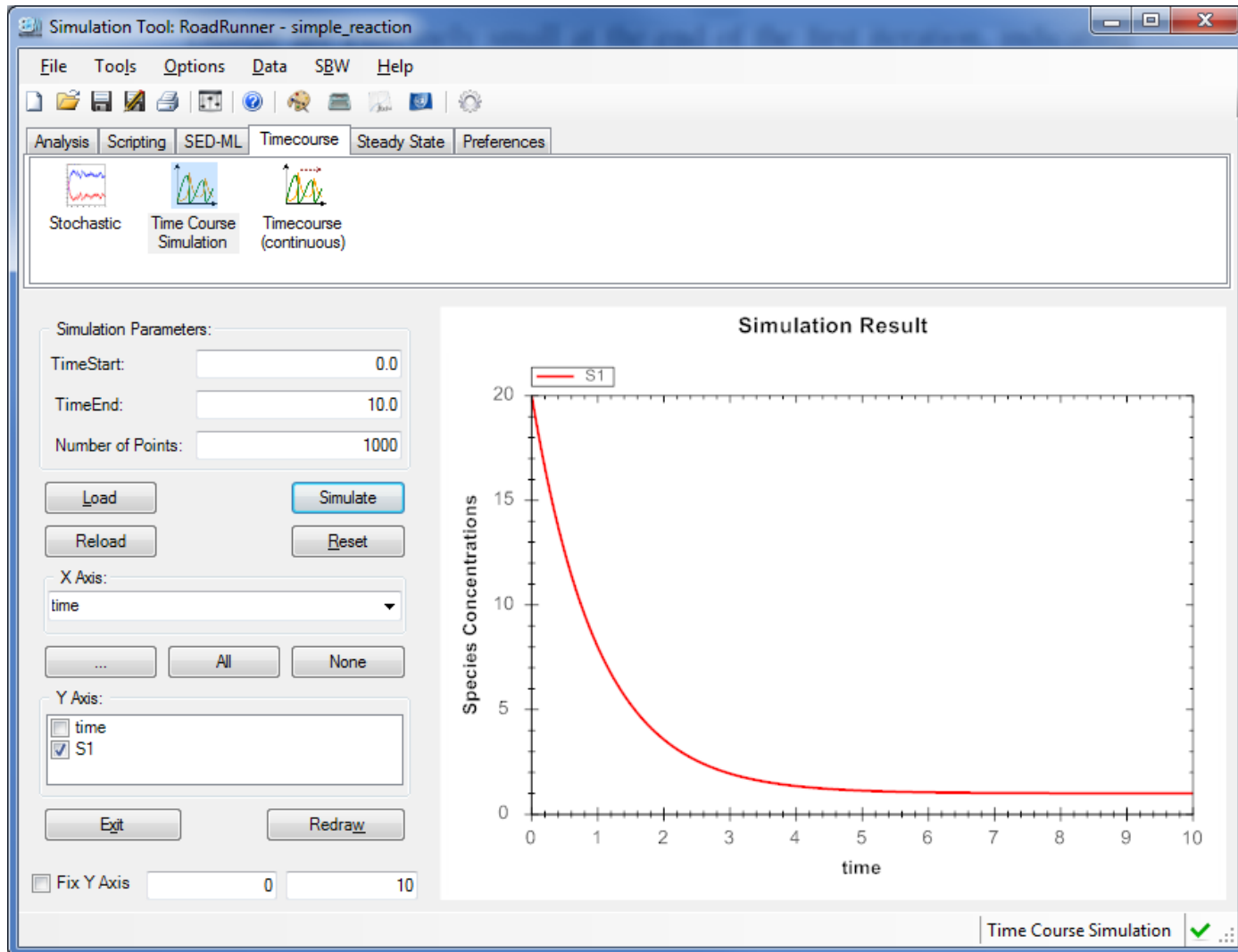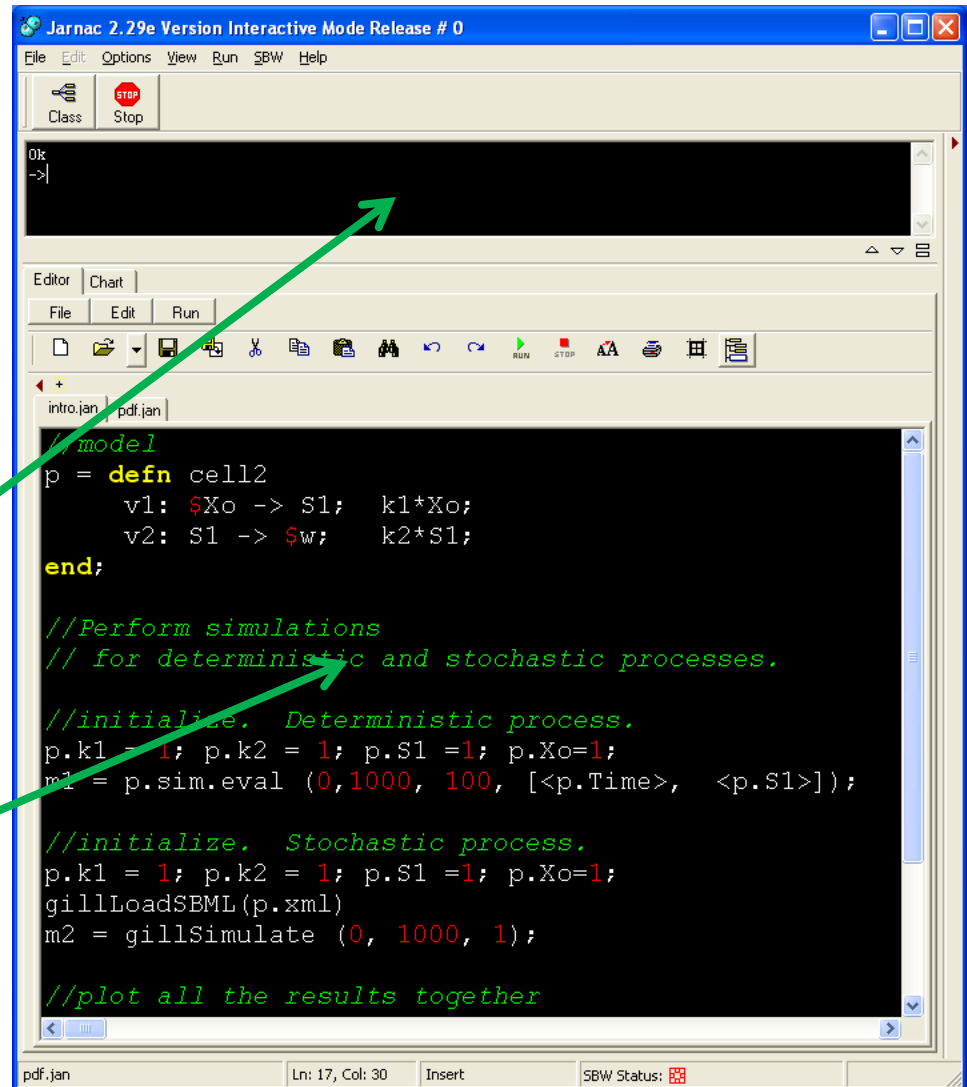
```
// Model Definition
p = defn simple_reaction
    v1: $Xo -> S1;  k1*Xo;
    v2: S1 -> $w;   k2*S1;
end;

// Initialize constants
p.k1 = 1; p.k2 = 1; p.S1 =20; p.Xo=1;

// Time course simulation
m = p.sim.eval(0,20,100,[<p.Time>,<p.S1>]);

// Plotting Graphs
graph (m);

// Steady State
p.ss.eval;

// Concatenating Matrices by row
m = augr (m1, m2);
```
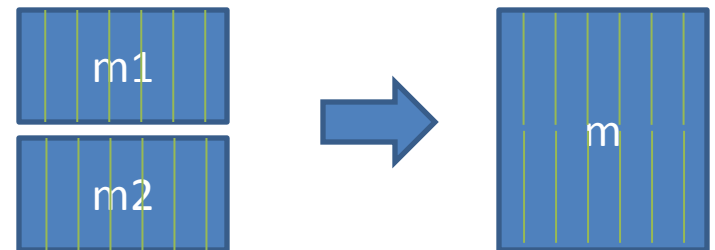

augr (m1, m2) -> m

Most Important Jarnac Commands for the Week

```
// Model Definition
p = defn simple_reaction
    v1: $Xo -> S1;  k1*Xo;
    v2: S1 -> $w;    k2*S1;
end;

// Initialize constants
p.k1 = 1; p.k2 = 1; p.S1 =20; p.Xo=1;

// Time course simulation
m1 = p.sim.eval(0, 20,100,[<p.Time>,<p.S1>]);
// Do something else here...
m2 = p.sim.eval(20,40,100,[<p.Time>,<p.S1>]);

m = augr (m1, m2);
graph (m);
```
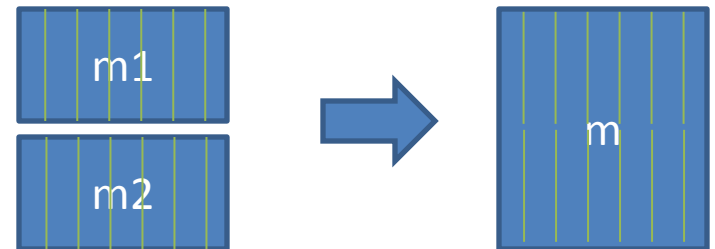


```
augr (m1, m2) -> m
```

Event Syntax in JarnacLite

```
// JarnacLite additional syntax (event control)


p = defn newModel
    $Xo -> S1; v;
    S1 -> $X1; k*S1;

    at(gt(time,10)): v = 2;
    at(gt(time,20)): v = 1;
end;


p.v = 1; p.k = 0.5; p.Xo = 0.5;
```

Equilibrium Constant (Keq)
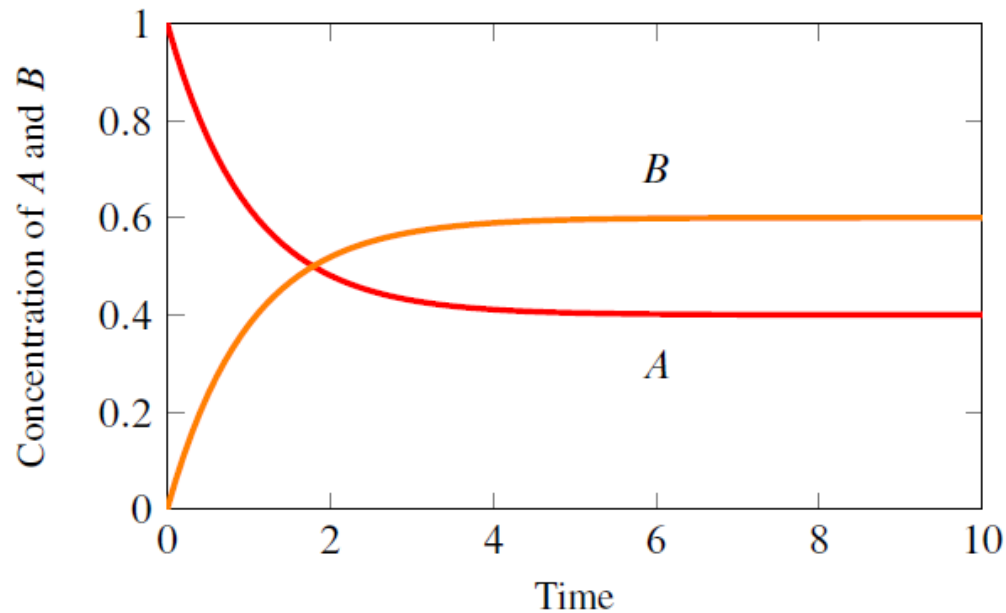
Figure 1.4: Approach to equilibrium for the reaction $A \rightleftharpoons B$, $k_1 = 0.6$, $k_2 = 0.4$, $A(0) = 1$, $B(0) = 0$. Progress curves calculated from the solution to the differential equation $dA/dt = k_2 B - k_1 A$.

$$\frac{k_1}{k_2} = \frac{B}{A} = K_{eq} \tag{1.12}$$

This ratio has special significance and is called the **equilibrium constant**,

Try a Simple Simulation

Implement a simple model that reaches equilibrium using the software tools in the following order:

- JDesigner

- JarnacLite, Simulation Tool

- Jarnac

Mass-Action Ratio and Disequilibrium Ratio

The ratio of the products to the reactants *in vivo* is called the **mass-action ratio**, Γ. For the system, $A \rightarrow B$:

$$\Gamma = \frac{B_{in\ vivo}}{A_{in\ vivo}}$$

At equilibrium $\Gamma = K_{eq}$. The ratio of the mass-action ratio to the equilibrium constant is often called the **disequilibrium ratio** and denoted by the symbol, ρ.

$$\rho = \frac{\Gamma}{K_{eq}} \qquad (1.16)$$

Disequilibrium Ratio and Free Energy

Page 23 in book

$\ln(\rho)$	Direction of Reaction	v	ΔG
< 0	Forward Direction	$v > 0$	$\Delta G < 0$
$= 0$	Equilibrium	$v = 0$	$\Delta G = 0$
> 0	Reverse Direction	$v < 0$	$\Delta G > 0$

Table 1.1: Relationship between ρ and ΔG.

If $\rho = 1$ then $v_r = v_f$, and the system is at equilibrium.

Finally if $\rho > 1$ then $v_r > v_f$, the reaction must be going in reverse.

If we take the natural log of equation (1.16) on both sides we get:

$$\ln(\rho) = \ln(\Gamma) - \ln(K_{eq})$$

$$\rho = \frac{\Gamma}{K_{eq}}$$

Those who are already familiar with the concept of free energy (ΔG) may realize that equation (1.18) is closely related to the free energy equation:

$$\Delta_r G = \Delta_r G^\circ + RT \ln \Gamma$$

$$\Delta_r G = RT \ln(\rho) \text{ and } \Delta_r G^\circ = -RT \ln K_{eq}$$

Application

A typical reversible mass-action rate law will require both the forward and the reverse rate constants to be fully defined. Often however, only one rate constant may be known. In these circumstances it is possible to express the reverse rate constant in terms of the equilibrium constant.

For example, given the simple unimolecular reaction, $A \rightleftharpoons B$. it is possible to derive the following:

$$v = k_1 A - k_2 B$$

$$v = k_1 A \left(1 - \frac{k_2 B}{k_1 A} \right)$$

Since $K_{eq} = \dfrac{k_1}{k_2}$

$$v = k_1 A \left(1 - \frac{\Gamma}{K_{eq}} \right) = k_1 A \left(1 - \rho \right)$$

Elasticities/Kinetic Orders

Page 37 in book

$$\varepsilon_{S_i}^{v} = \left(\frac{\partial v}{\partial S_i} \frac{S_i}{v} \right)_{S_j,S_k,\ldots} = \frac{\partial \ln v}{\partial \ln S_i} \approx v\%/S_i\% \qquad (2.1)$$

(a) $v = k$

    Elasticity: $\varepsilon_A^{v} = \dfrac{\partial v}{\partial A} \dfrac{A}{v} = 0$

(b) $v = kA$

    Elasticity: $\varepsilon_A^{v} = \dfrac{\partial v}{\partial A} \dfrac{A}{v} = \dfrac{A\,k}{kA} = 1$
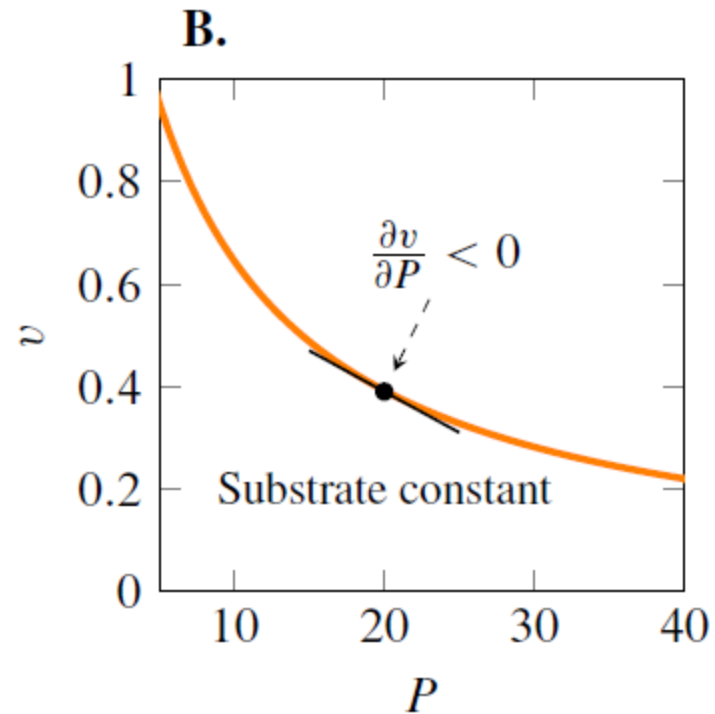
(c) $v = kA^2$

    Elasticity: $\varepsilon_A^{v} = \dfrac{\partial v}{\partial A} \dfrac{A}{v} = \dfrac{2kAA}{kA^2} = 2$

(d) $v = kA^n$

    Elasticity: $\varepsilon_A^{v} = \dfrac{\partial v}{\partial A} \dfrac{A}{v} = \dfrac{nkA^{n-1}A}{kA^n} = n$

Elasticities/Kinetic Orders

Page 42 in book

A. Product constant

$$\varepsilon_S^v = \frac{\partial v}{\partial S} \frac{S}{v}$$

$$\frac{\partial v}{\partial S} > 0$$

B. Substrate constant

$$\frac{\partial v}{\partial P} < 0$$
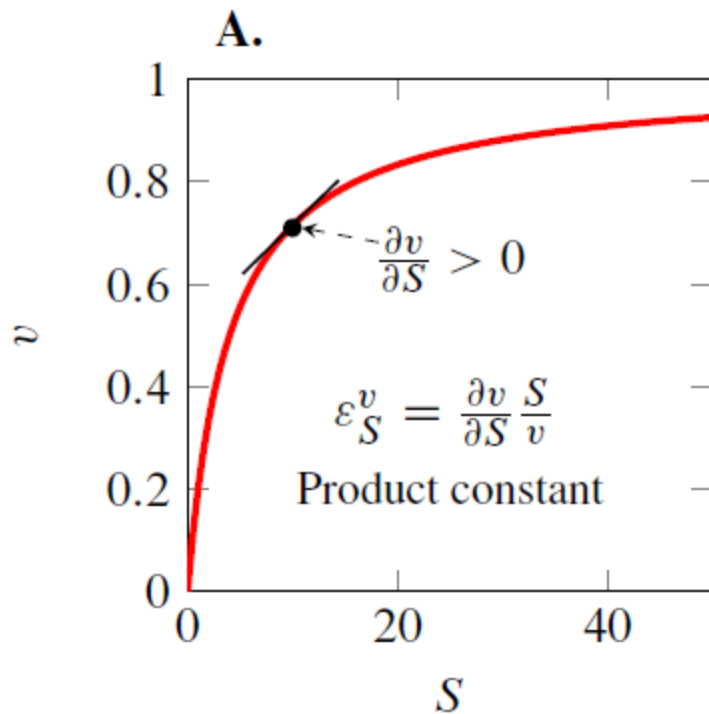
Elasticities/Kinetic Orders

Page 42 in book

For a simple irreversible mass-action reaction rate law such as:

$$v = k_1 S - k_2 P$$

The elasticities for the substrate and product are given by:

$$\varepsilon_S^v = \frac{k_1 S}{k_1 S - k_2 P} = \frac{v_f}{v}$$

$$\varepsilon_P^v = -\frac{k_2 P}{k_1 S - k_2 P} = -\frac{v_r}{v}$$

Elasticities/Kinetic Orders

Page 45 in book

$$\varepsilon^v_S = \frac{1}{1 - \Gamma/K_{eq}} = \frac{1}{1 - \rho}$$

$$\varepsilon^v_P = -\frac{\Gamma/K_{eq}}{1 - \Gamma/K_{eq}} = -\frac{\rho}{1 - \rho}$$

These expressions can vary over a wide range of values. Far from equilibrium ($\rho \simeq 0$) ε^v_S will lie close to 1.0, while ε^v_P will be close to -0.0. When operating close to equilibrium however ($\rho \approx 1$), the same elasticities will tend to $+\infty$ and $-\infty$, respectively.

$$\varepsilon^v_S + \varepsilon^v_P = 1 \tag{2.6}$$

$$\|\varepsilon^v_S\| > \|\varepsilon^v_P\|$$

Behavior Exhibited by Networks

1. Thermodynamic Equilibrium
2. Transients
3. Steady State

State	Reaction Rates	dX/dt
Thermo Equilibrium	0	0
Transient	≠ 0	≠ 0
Steady State	≠ 0	0

Steady State using Jarnac

```
// Define model
p = defn cell

    $Xo -> S1;   k1*Xo - k2*S1;
     S1 -> S2;   k3*S1 - k4*S2;
     S2 -> $X1; k4*S2 - k6*X1;
end;

// Initialize value
p.Xo = 10;   p.X1 = 0;
p.k1 = 3.4; p.k2 = 0.2;
p.k2 = 2.3; p.k3 = 0.56;
p.k4 = 5.6; p.k6 = 0.12;

// Initial starting point
p.S1 = 1; p.S2 = 1;

// Compute steady state
p.ss.eval;
println p.S1, p.S2;
```

Studies on the Mass-Action Ratio Using the Simulation Tool

```
p = defn cell
    G = S2/S1;
    rho = G/Keq;
    J1: S1 -> S2; k1*S1*(1 - rho);
end;

p.S1 = 1;
p.S2 = 0.45;
p.Keq = 4.5;
p.k1 = 1;
```

See Table 1.1 on page 23

Questions:

1. What happens at equilibrium?
2. What happens at +ve reaction rate
3. What happens at –ve reaction rate

This will illustrate:

JarnacLite
Simulation
Sliders
Selecting Y axis variables
Changing graph settings
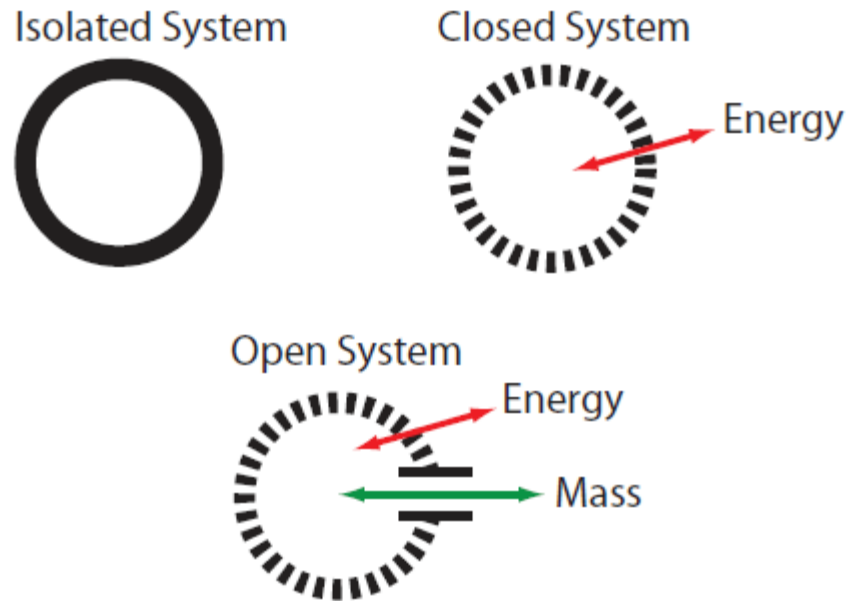
Basic Systems Concepts

Figure 3.1: Open and Closed Systems.

Experiments with simple networks

Closed System

```
p = defn cell
    Xo -> S1; k1*Xo - k2*S1;
    S1 -> S2; k3*S1 - k3*S2;
    S2 -> X1; k5*S2 - k6*X1;
end;


p.Xo = 4;
p.X1 = 0;
p.k1 = 1.2; p.k2 = 0.45;
p.k3 = 0.56; p.k4 = 0.2;
p.k5 = 0.89; p.k6 = 0;
```

This will illustrate:

JarnacLite
Help in picking rate laws
Simulation
Selecting Y axis variables
Changing graph settings

Experiments with simple networks

Open System

```
p = defn cell
    ext Xo, X1;

    Xo -> S1; k1*Xo - k2*S1;
    S1 -> S2;  k3*S1 - k3*S2;
    S2 -> X1; k5*S2 - k6*X1;
end;


p.Xo = 4;
p.X1 = 0;
p.k1 = 1.2; p.k2 = 0.45;
p.k3 = 0.56; p.k4 = 0.2;
p.k5 = 0.89; p.k6 = 0;
```

This will illustrate:

JarnacLite
Help in picking rate laws
Simulation
Selecting Y axis variables
Changing graph settings

System Quantities

1. Variables:

      State Variables, Dynamical Variables, Floating Species

In principle only indirectly under the control of the Experimentalist. <u>Determined</u> by the system.

2. Parameters:

      Kinetic Constants, Boundary Species (fixed)

In principle under the direct control of the experimentalist

Steady State

The steady state is one of the most important states to consider in a dynamical model. In the literature it is also sometimes referred to as the stationary solution or state, singular points, fixed points, or even equilibrium. We will

The steady state is the primary reference point from which to consider a model's behavior. At steady state, the concentrations of all molecular species are constant and there is a net flow of mass through the network.

$$X_o \xrightarrow{v_1} S_1 \xrightarrow{v_2} X_1$$
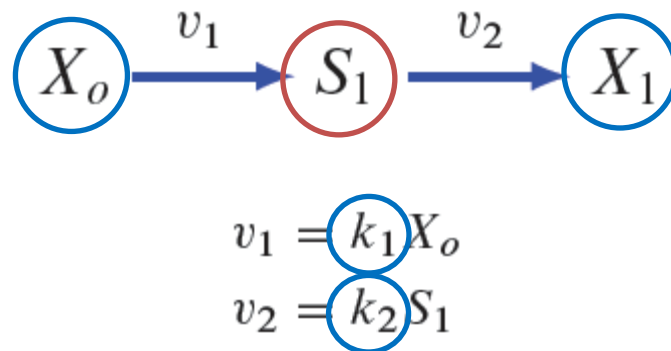
$$v_1 = k_1 X_o$$
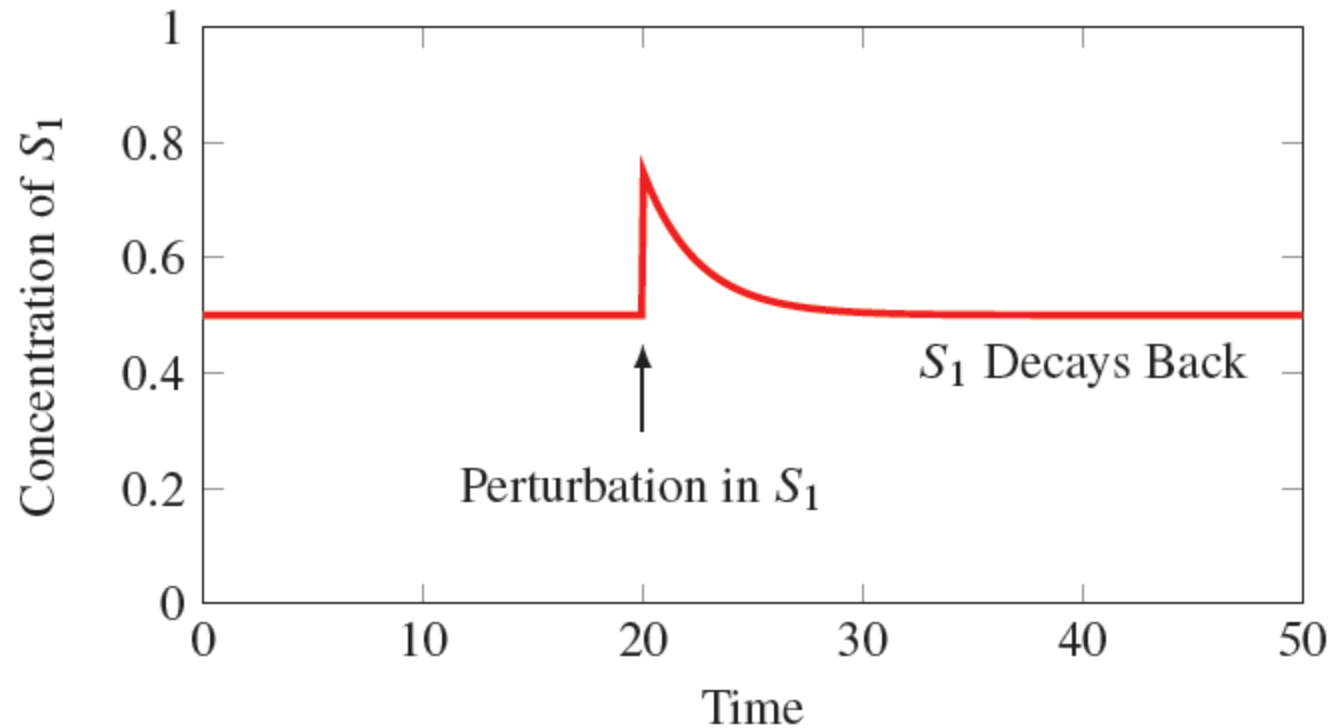$$v_2 = k_2 S_1$$
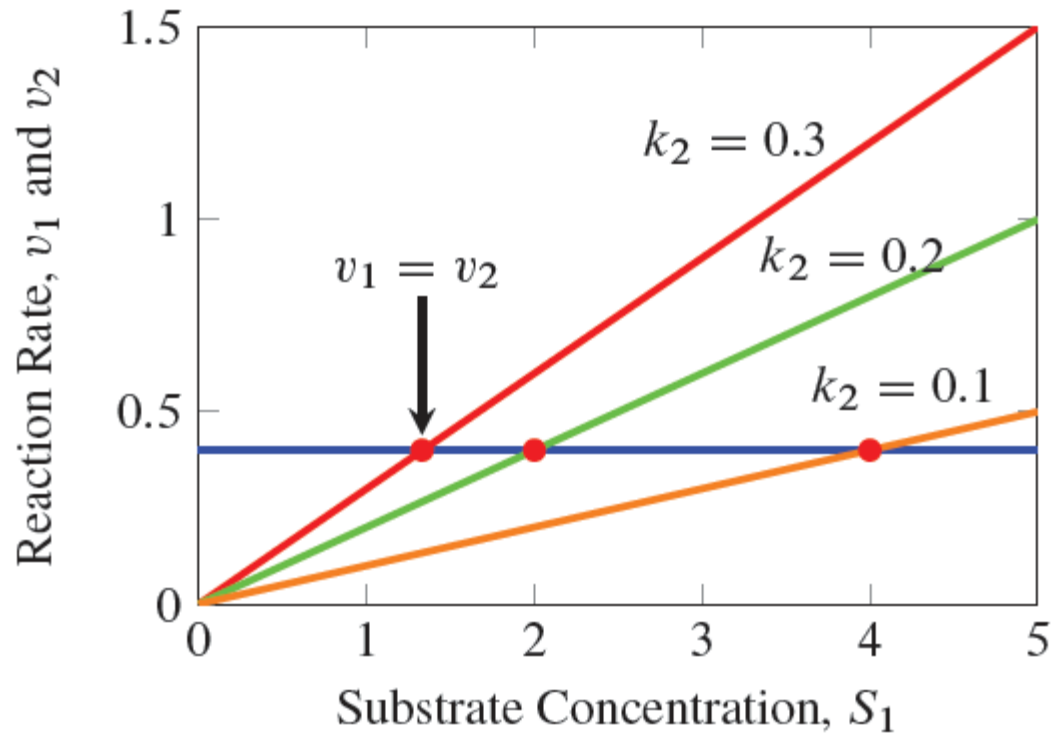
Steady State

Steady State

$$\frac{dS_1}{dt} = k_1 X_o - k_2 S_1$$

$$dS_1/dt = 0,$$

$$S_1 = \frac{k_1 X_o}{k_2}$$

$$J = k_2 \frac{k_1 X_o}{k_2} = k_1 X_o$$

Perturbations to Variables

Model Script

```
p = defn newModel
    $Xo -> S1; k1*Xo;
    S1 -> $X1; k2*S1;
end;

p.k1 = 0.2;
p.k2 = 0.4;
p.Xo = 1;
p.S1 = 0.5;
```

Why the disturbance is stable

$$dS_1/dt = k_1 X_o - k_2 S_1$$

If the system is at steady state, let us make a small perturbation to the steady state concentration of S_1, δS_1 and ask what is the rate of change of $S_1 + \delta S_1$ as a result of this perturbation, that is what is $d(S_1 + \delta S_1)/dt$? The new rate of change equation is rewritten as follows:
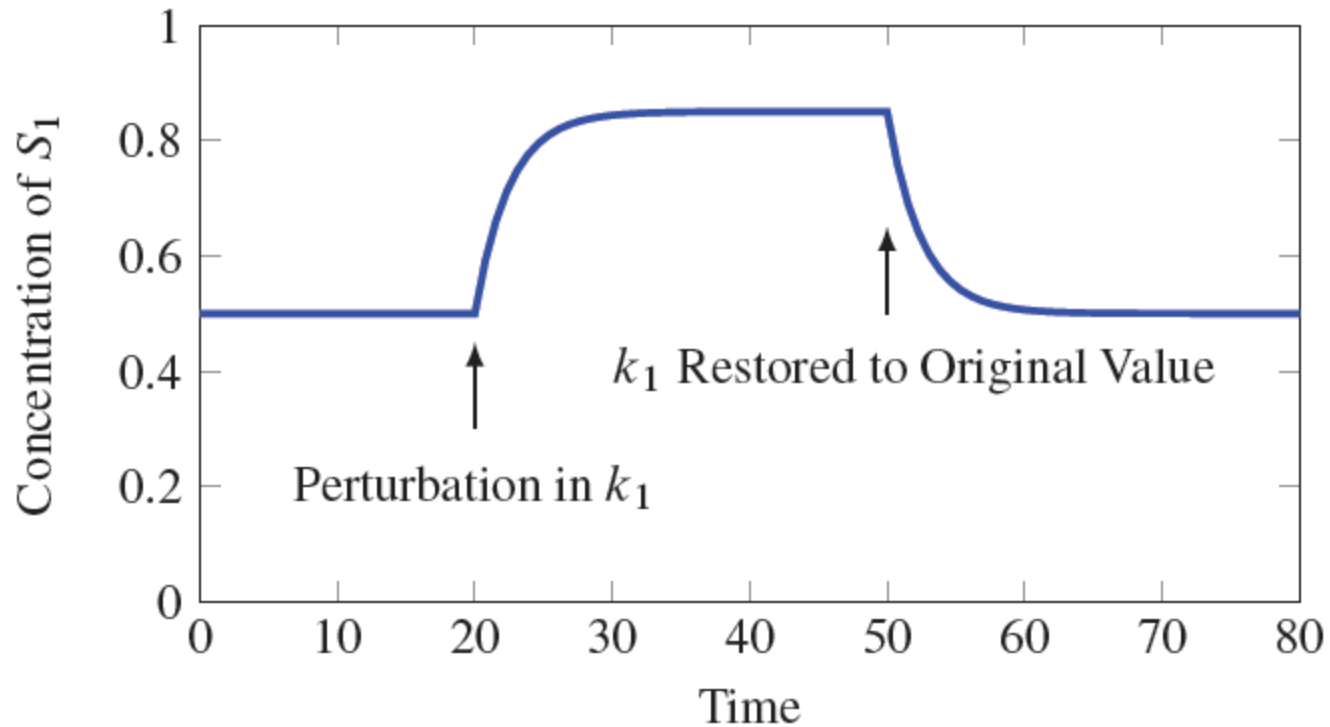
$$\frac{d(S_1 + \delta S_1)}{dt} = k_1 X_o - k_2(S_1 + \delta S_1)$$

If we insert the solution for S_1 (equation 5.1) into the above equation we are left with:

$$\frac{d\delta S_1}{dt} = -k_2 \delta S_1$$

In other words the rate of change of the disturbance itself, δS_1 is negative, that is, the system attempts to reduce the disturbance

Perturbations to Parameters

Model Script

```
p = defn newModel
  $Xo -> S1; k1*Xo;
  S1 -> $X1; k2*S1;
  end;

p.k1 = 0.2;
p.k2 = 0.4;
p.Xo = 1;
p.S1 = 0.5;
```

How would we do the same perturbations in JDesigner or the simulation tool?