系统生物学

(Systems Biology)

马彬广

通用建模工具

（第十四讲）

梗概（Synopsis）

- 通用建模工具（数学计算软件）
- 专用建模工具（细胞生化体系建模）

通用建模工具

主要是各种数学计算软件，有些是商业软件，有些是自由软件。

- 商业软件，主要介绍： MatLab, Mathematica, Maple，另有MuPAD，现已被MatLab收购。

- 自由软件： R, Maxima, sagemath, 另外，Octave，也很有用。

举例：SOD模型

反应体系：$\xrightarrow{c_1} O_2^{\cdot -} \xrightarrow[\text{SOD}]{c_2} H_2O_2 \xrightarrow[\text{cat}]{c_3} H_2O$

系统动力学方程：

$$\begin{cases} \dfrac{dO_2^{\cdot -}}{dt} = c_1 - c_2 \cdot SOD \cdot O_2^{\cdot -} \\ \dfrac{dH_2O_2}{dt} = c_2 \cdot SOD \cdot O_2^{\cdot -} - c_3 \cdot cat \cdot H_2O_2 \end{cases}$$

可简写为：

$$\begin{cases} \dfrac{dx}{dt} = a - bx \\ \dfrac{dy}{dt} = bx - cy \end{cases}$$

$\left(\text{其中，} x = O_2^{\cdot -},\ y = H_2O_2,\ a = c_1,\ b = c_2 \cdot SOD,\ c = c_3 \cdot cat\right)$

给定参数值：

$$c_1 = 6.6\times10^{-7},\quad c_2 = 1.6\times10^{9},\quad c_3 = 3.4\times10^{7},\quad SOD = 10^{-5},\quad cat = 10^{-5}$$

和初始条件：$O_2^{\cdot -}(0) = 0,\ H_2O_2(0) = 0$

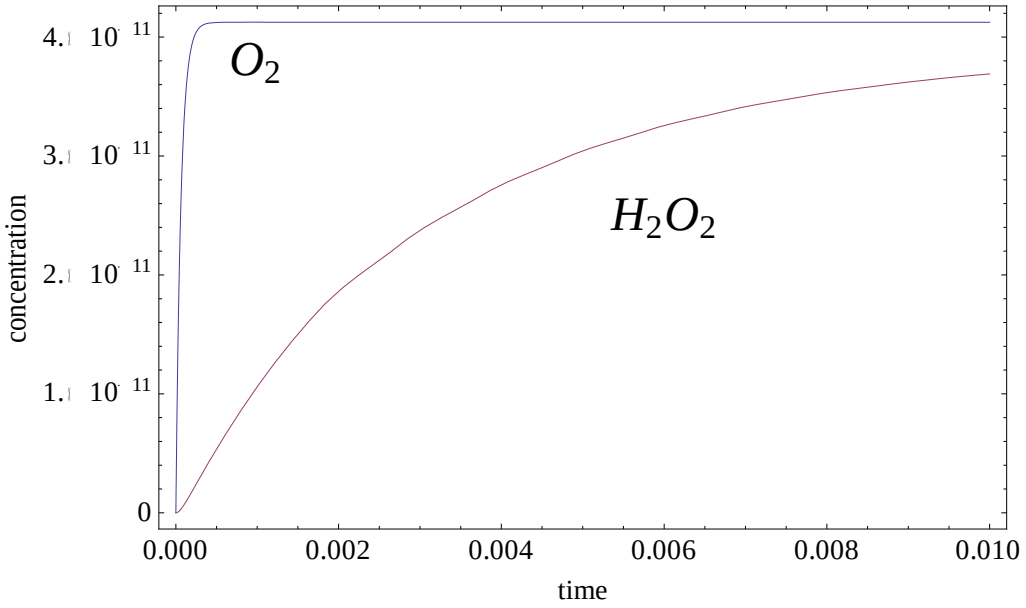
则可解出其时间过程（数值解），并作图如后。

Mathematica

- 开发商： Wolfram Research
- 当前版本： 8.x
- 特点：符号计算、数值计算、可视化并重，综合性好
- 公司网址：www.wolfram.com

用Mathematica求解SOD模型

```
eq1 = O2'[t] == c1 - c2*SOD*O2[t];
eq2 = H2O2'[t] == c2*SOD*O2[t] - c3*cat*H2O2[t];
par = {c1-> 6.6*10^-7, c2-> 1.6*10^9,c3-> 3.4*10^7, SOD-> 10^-5, cat-> 10^-5};
sol = NDSolve[{eq1, eq2, O2[0]==0,H2O2[0]==0}/.par,{O2, H2O2},{t,0,0.01}]
Plot[Evaluate[{O2[t], H2O2[t]/50}/.sol,{t, 0, 0.01}], PlotRange->All, FrameLabel ->
{"time", "concentration"}, Frame-> True, LabelStyle -> Directive[FontSize-
>14],Epilog -> {Text[Style["Subscript[O, 2]",Large], {0.001, 3.8*10^-
11} ],Text[Style["Subscript[H, 2]Subscript[O, 2]", Large], {0.006, 2.5*10^-11}]}]
```

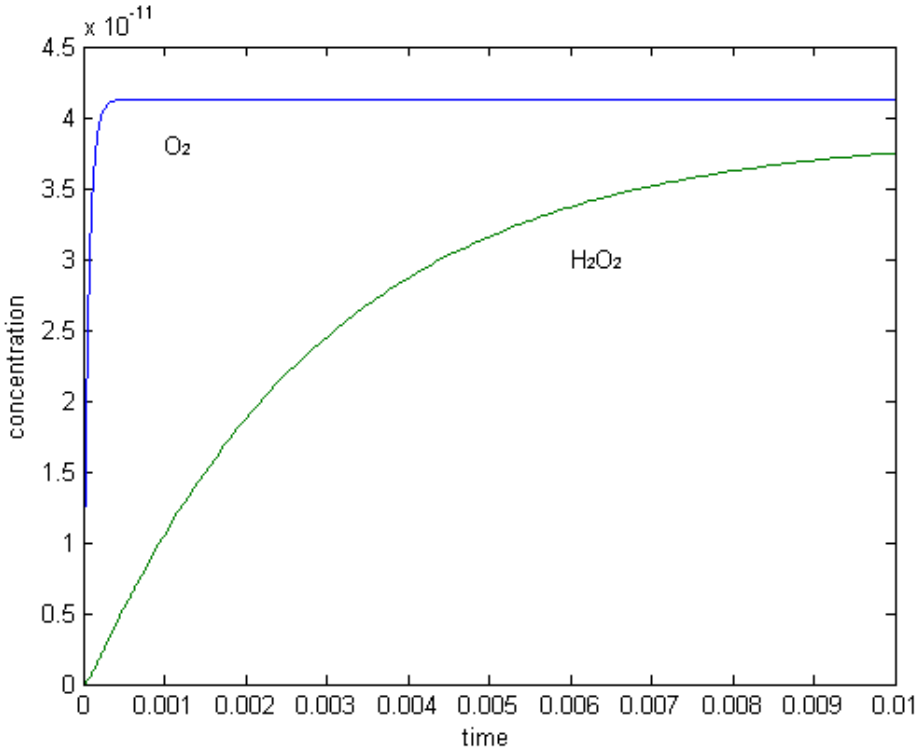


MatLab

- 开发商： Mathworks, Inc.
- 当前版本： 2012b
- 特点：符号计算、数值计算、可视化并重，综合性好
- 公司网址：www.mathworks.com
- 收购 MuPAD 后，符号计算能力得到加强

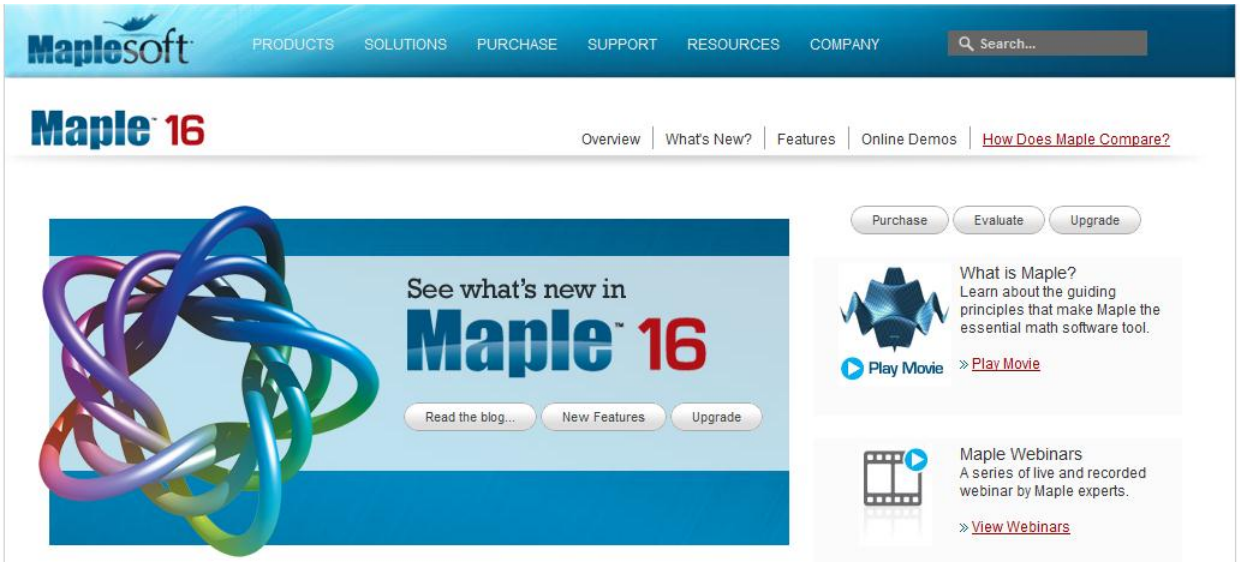
用MatLab求解SOD模型

```
dydt = inline('[c1-c2*SOD*y(1); c2*SOD*y(1)-c3*cat*y(2)]', 't', 'y', 'tmp','SOD',
'cat', 'c1', 'c2', 'c3');
options = odeset('AbsTol', 1e-30, 'RelTol', 1e-6);
[t, y] = ode45(dydt, [0, 0.01], [0; 0], options, 1e-5, 1e-5, 6.6e-7, 1.6e9, 3.4e7);
plot(t, y(:,1), t, y(:, 2)/50);
xlabel('time');
ylabel('concentration');
text(0.001, 3.8E-11, 'O2');
text(0.006, 3.0E-11, 'H2O2');
```



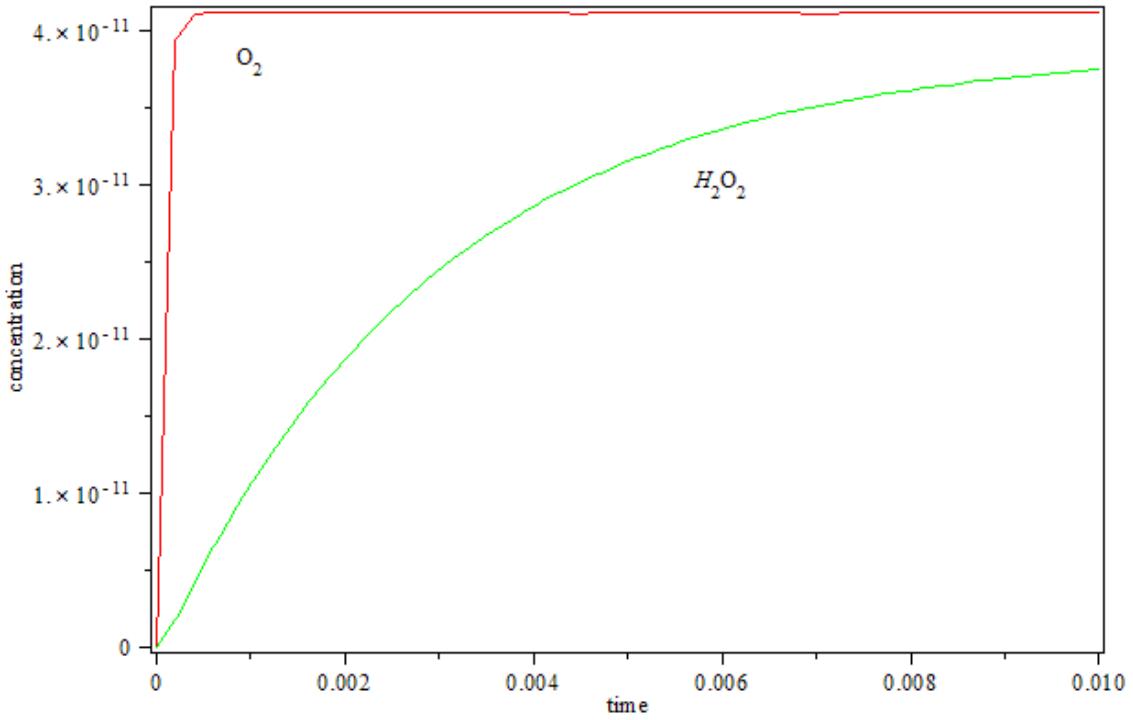
Maple

- 开发商： Maplesoft, Waterloo Maple Inc.
- 当前版本： 16.x
- 特点：符号计算、数值计算、可视化并重，符号好
- 公司网址：www.maplesoft.com
- 开发 MapleSim 后，系统建模能力得到加强

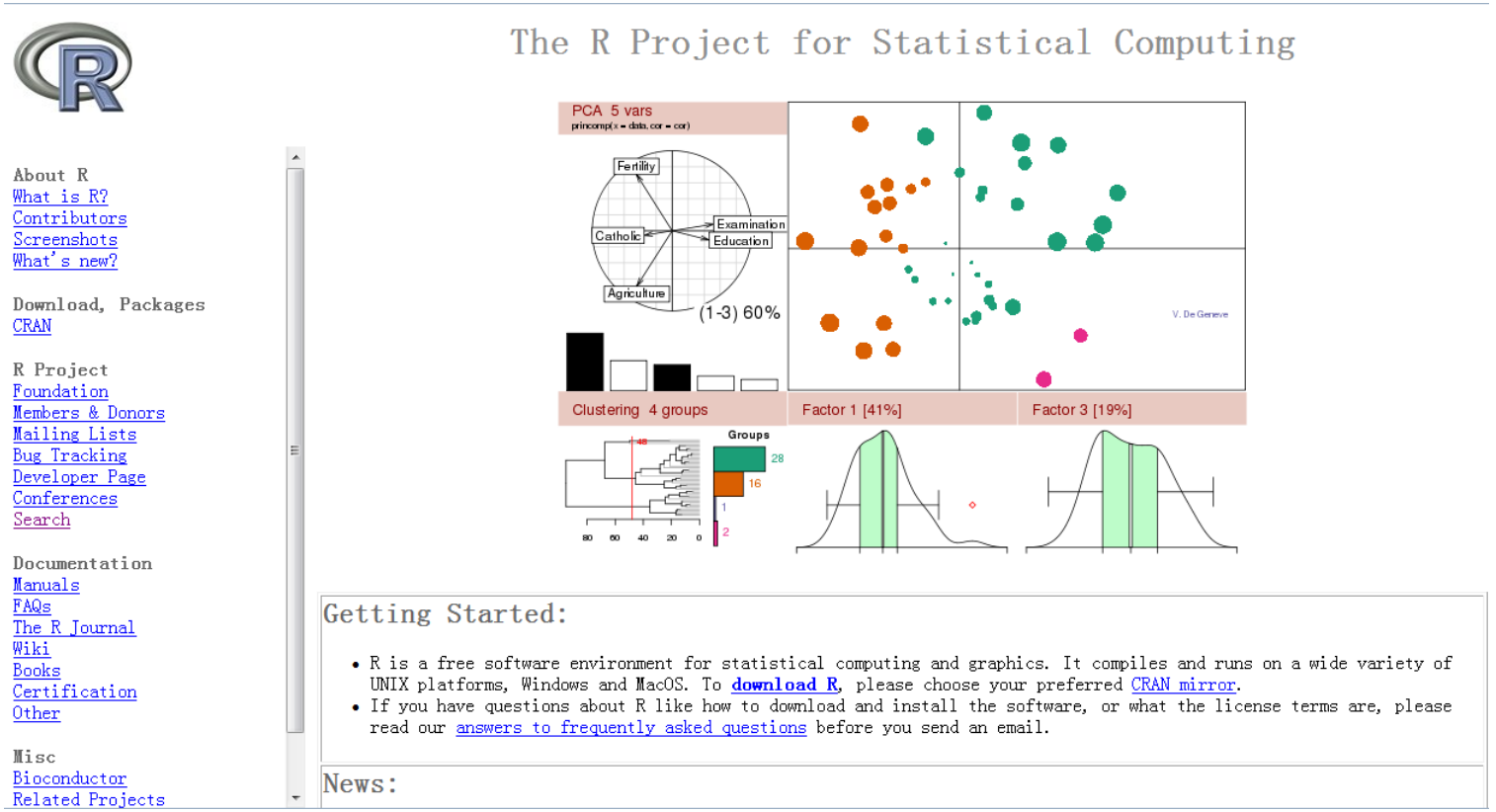


用Maple求解SOD模型

```
sol1 := dsolve([diff(H2O2(t), t) = 0.16e5*O2(t)-0.34e3*H2O2(t), diff(O2(t), t) =
0.66e-6-0.16e5*O2(t), H2O2(0) = 0, O2(0) = 0], numeric, method = dverk78):
with(plots):
pic := plots[odeplot](sol1, [[t, O2(t), color = red], [t, (1/50)*H2O2(t), color =
green]], 0 .. 0.1e-1, axes = FRAME, labeldirections = [horizontal, vertical],
labels = ["time", "concentration"]):
txt := textplot({[0.1e-2, 0.38e-10, O[2]], [0.6e-2, 0.30e-10, H[2]O[2]]}):
display({pic, txt});
```



R language



- 开发组织：R team
- 当前版本： 2.15.x
- 特点：符号计算、数值计算、可视化并重，统计好
- 网址：www.r-project.org

R package deSolve

R package deSolve can be used to solve initial value problems (IVP) of:

- ordinary differential equations (ODE),
- differential algebraic equations (DAE),
- partial differential equations (PDE),
- delay differential equations (DeDE).

Implementation of an IVP ODE in R can be separated in two parts: the model specification and the model application.

Model specification consists of:

- Defining model parameters and their values,
- Defining model state variables and their initial conditions,
- Implementing the model equations that calculate the rate of change (e.g. dX/dt) of the state variables.

The model application consists of:

- Specification of the time at which model output is wanted,
- Integration of the model equations,
- Plotting of model results.

举例：SOD模型

反应体系：$\xrightarrow{c_1} O_2^{\cdot -} \xrightarrow[\text{SOD}]{c_2} H_2O_2 \xrightarrow[\text{cat}]{c_3} H_2O$

系统动力学方程：

$$\begin{cases} \dfrac{dO_2^{\cdot -}}{dt} = c_1 - c_2 \cdot SOD \cdot O_2^{\cdot -} \\ \dfrac{dH_2O_2}{dt} = c_2 \cdot SOD \cdot O_2^{\cdot -} - c_3 \cdot cat \cdot H_2O_2 \end{cases}$$

可简写为：

$$\begin{cases} \dfrac{dx}{dt} = a - bx \\ \dfrac{dy}{dt} = bx - cy \end{cases}$$

$\left(\text{其中，} x = O_2^{\cdot -},\ y = H_2O_2,\ a = c_1,\ b = c_2 \cdot SOD,\ c = c_3 \cdot cat\right)$

给定参数值：

$$c_1 = 6.6\times10^{-7},\quad c_2 = 1.6\times10^{9},\quad c_3 = 3.4\times10^{7},\quad SOD = 10^{-5},\quad cat = 10^{-5}$$

和初始条件：$O_2^{\cdot -}(0) = 0,\ H_2O_2(0) = 0$

则可解出其时间过程（数值解），并作图如后。

Model Specification

```
#Model parameters:
parameters <- c(c1=6.6E-7,  c2=1.6E9, c3=3.4E7, SOD=1.0E-5, cat=1.0E-5)

#State variables:
state <- c(O2=0, H2O2=0)

#Model equations:
SODmodel <- function(t, state, parameters) {
   with(as.list(c(state, parameters)), {
   # rate of change
      dO2 <- c1 - c2*SOD*O2
      dH2O2 <- c2*SOD*O2 - c3*cat*H2O2

   # return the rate of change
      list(c(dO2, dH2O2))
   }) # end with
}
```

Modeling Application

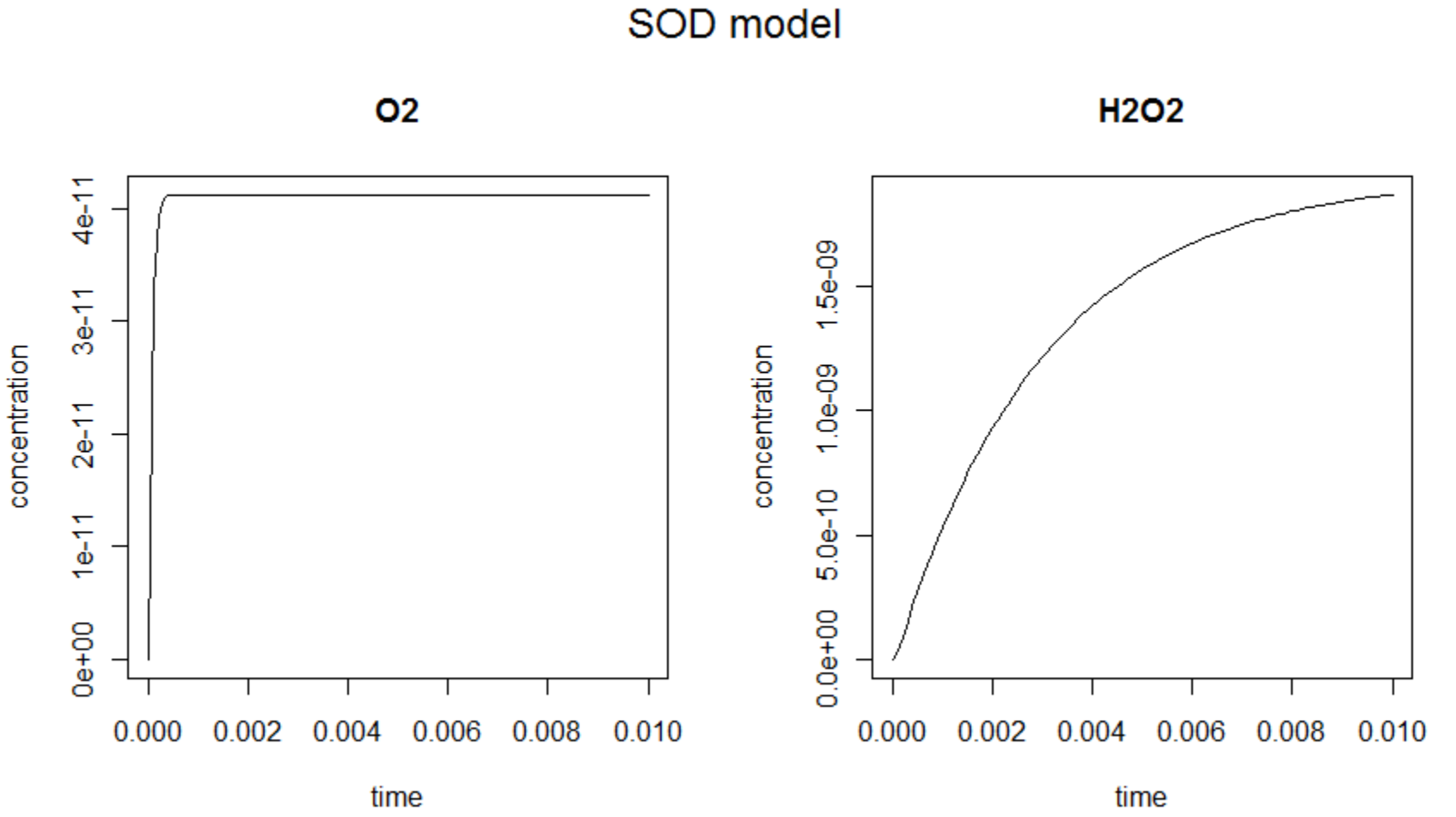
```
#Time specification:
times <- seq(0, 0.01, by=0.0001)

#Model integration:
require(deSolve)
out <- ode(y=state, times=times, func=SODmodel, parms=parameters)
head(out)
```

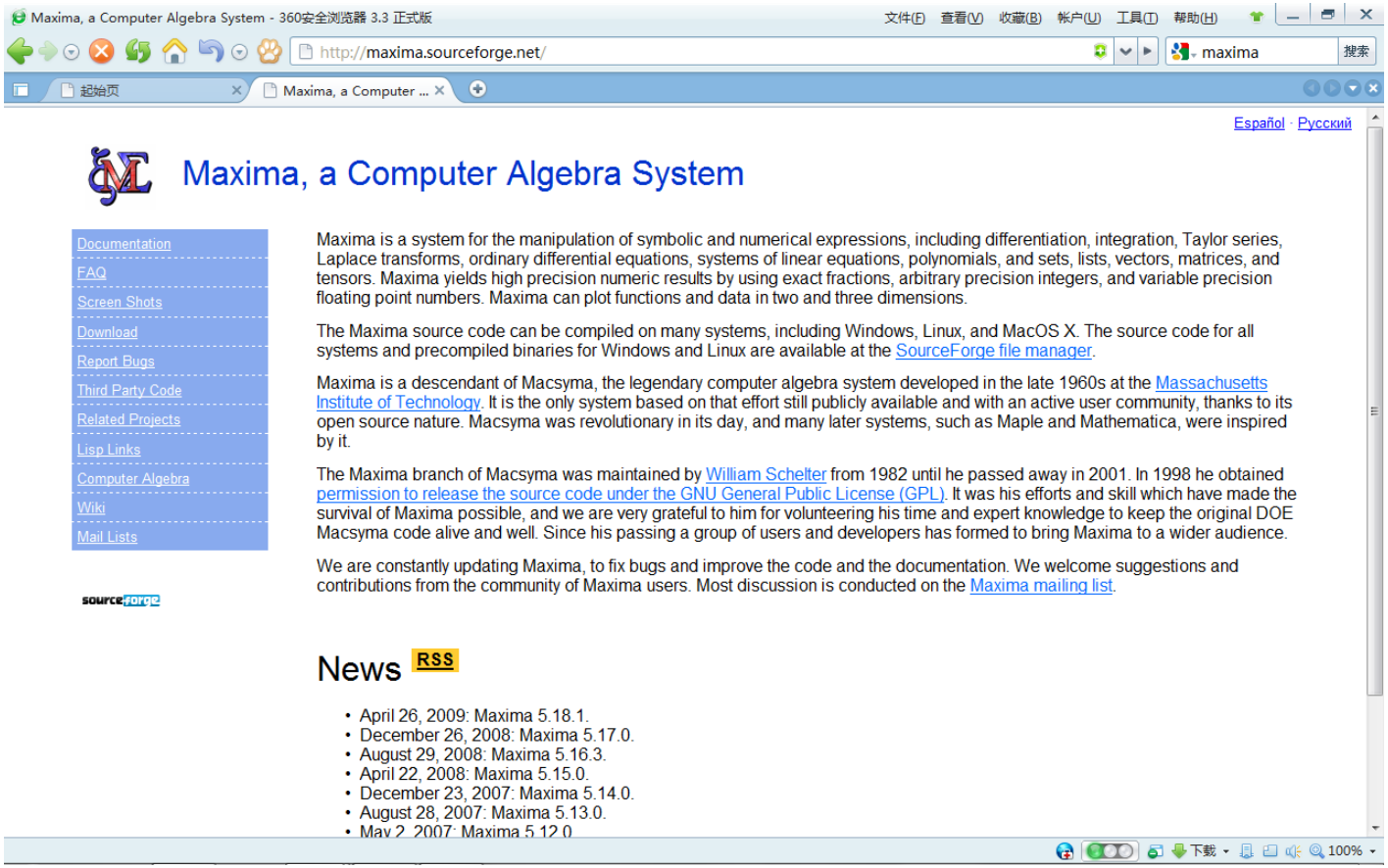
	time	O2	H2O2
[1,]	0e+00	0.000000e+00	0.000000e+00
[2,]	1e-04	3.276534e-11	3.282355e-11
[3,]	2e-04	3.943006e-11	9.009806e-11
[4,]	3e-04	4.086067e-11	1.505780e-10
[5,]	4e-04	4.116716e-11	2.101359e-10
[6,]	5e-04	4.123242e-11	2.679388e-10

```
#Plotting
par(oma = c(0, 0, 3, 0))
plot(out, type = "l", xlab = "time", ylab = "concentration")
mtext(outer = TRUE, side = 3, "SOD model", cex = 1.5)
```

Plotting of model results



Maxima



- 开发组织： Maxima team，France
- 当前版本： 5.22.x
- 特点：符号计算、数值计算、可视化并重，还可以
- 网址：http://maxima.sourceforge.net/

Maxima package “dynamics”

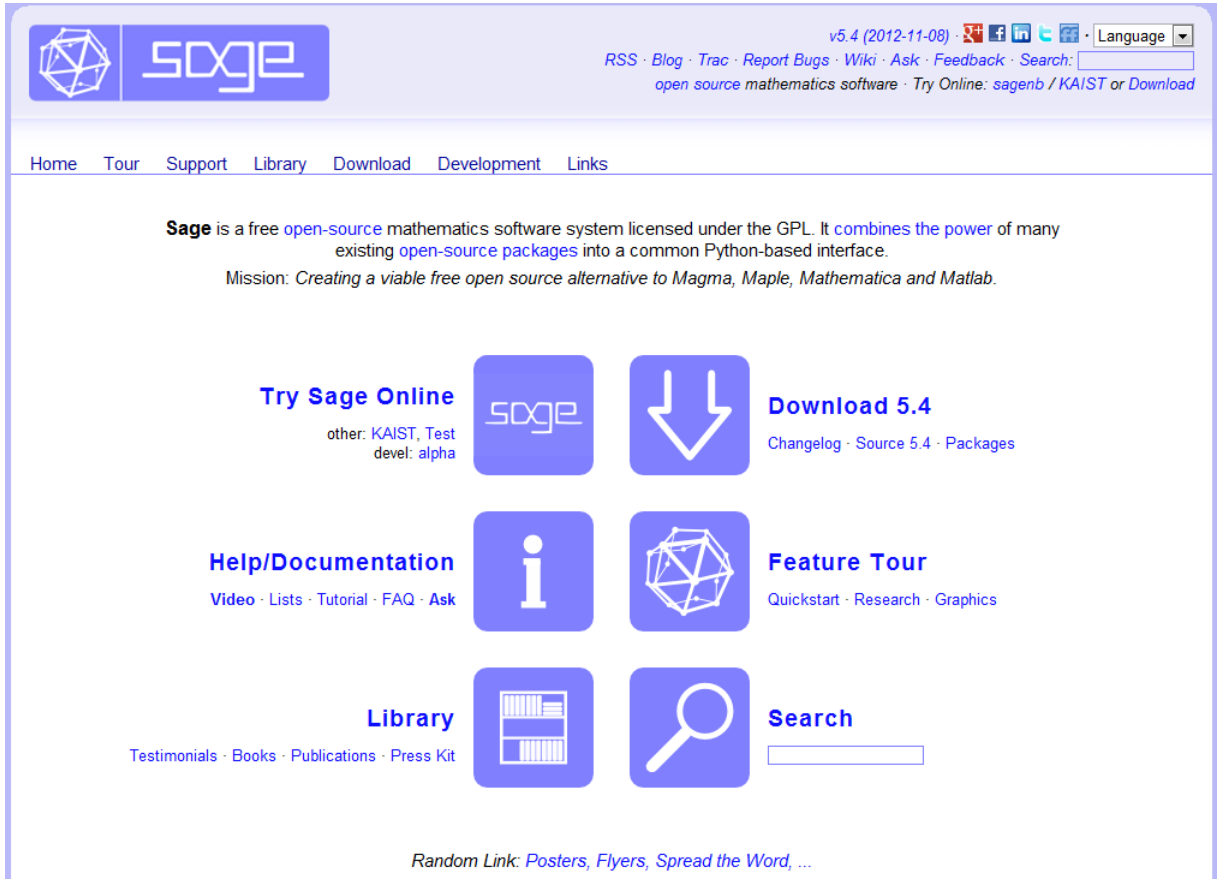
For numerical solutions, use the function rk (the 4th order Runge-Kutta method)

The general form for rk function is:
Function: **rk** *([ODE1,...,ODEm], [v1,...,vm], [init1,...,initm], domain)*

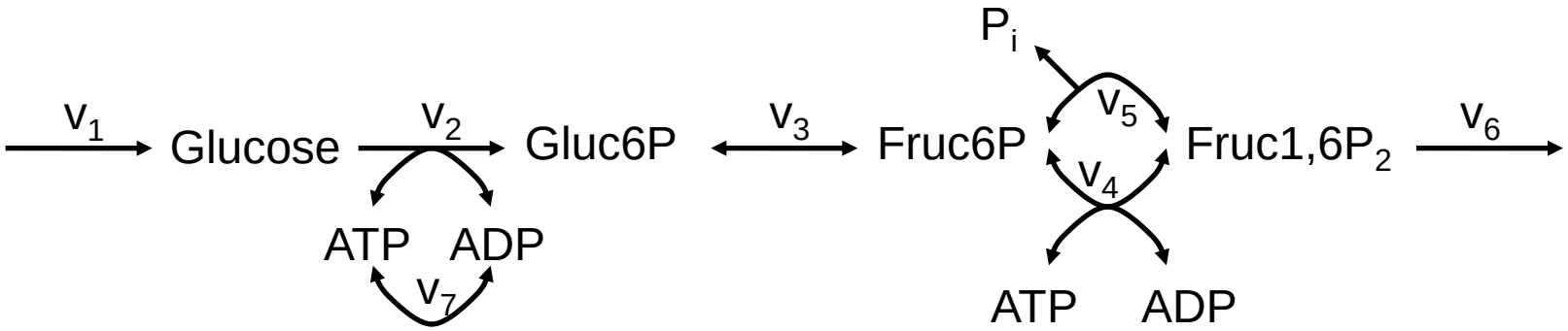
For the above SOD model, the command is:
load("dynamics")
sol1: rk([6.6E-7-1.6E9*1E-5*O2, 1.6E9*1E-5*O2-3.4E7*1E-5*H2O2], [O2, H2O2], [0, 0], [t, 0, 0.01, 0.0001])

Sagemath

- 开发组织： sagemath team
- 当前版本： 5.4.x
- 特点：符号计算、数值计算、可视化并重，前景好
- 网址：www.sagemath.org



糖酵解反应模型



$$\begin{cases} \frac{d}{dt}Glucose = v_1 - v_2 \\ \frac{d}{dt}Gluc6P = v_2 - v_3 \\ \frac{d}{dt}Fruc6P = v_3 - v_4 + v_5 \\ \frac{d}{dt}Fruc1,6P_2 = v_4 - v_5 - v_6 \\ \frac{d}{dt}ATP = -\frac{d}{dt}ADP = -v_2 - v_4 + v_7 \end{cases}$$

$$\begin{cases} v_1 = \text{constant} = k_1 \\ v_2 = k_2 \cdot Glucose \cdot ATP \\ v_3 = k_3 \cdot Gluc6P - k_{-3} \cdot Fruc6P \\ v_4 = k_4 \cdot Fruc6P \cdot ATP \\ v_5 = k_5 \cdot Fruc1,6P_2 \\ v_6 = k_6 \cdot Fruc1,6P_2 \\ v_7 = k_7 \cdot ADP \end{cases}$$

糖酵解反应模型

$$
\begin{cases}
\dfrac{d}{dt}Glucose = v_1 - v_2 = k_1 - k_2 \cdot Glucose \cdot ATP = 0.25 - Glucose \cdot ATP \\
\dfrac{d}{dt}Gluc6P = v_2 - v_3 = k_2 \cdot Glucose \cdot ATP - k_3 \cdot Gluc6P + k_{-3} \cdot Fruc6P = Glucose \cdot ATP - Gluc6P + Fruc6P \\
\dfrac{d}{dt}Fruc6P = v_3 - v_4 + v_5 = k_3 \cdot Gluc6P - k_{-3} \cdot Fruc6P - k_4 \cdot Fruc6P \cdot ATP + k_5 \cdot Fruc1,6P_2 = Gluc6P - Fruc6P - Fruc6P \cdot ATP + Fruc1,6P_2 \\
\dfrac{d}{dt}Fruc1,6P_2 = v_4 - v_5 - v_6 = k_4 \cdot Fruc6P \cdot ATP - k_5 \cdot Fruc1,6P_2 - k_6 \cdot Fruc1,6P_2 = Fruc6P \cdot ATP - 2Fruc1,6P_2 \\
\dfrac{d}{dt}ATP = -\dfrac{d}{dt}ADP = -v_2 - v_4 + v_7 = -k_2 \cdot Glucose \cdot ATP - k_4 \cdot Fruc6P \cdot ATP + k_7 \cdot ADP = ADP - (Glucose + Fruc6P) \cdot ATP
\end{cases}
$$

$$
\begin{cases}
v_1 = \text{constant} = k_1 \\
v_2 = k_2 \cdot Glucose \cdot ATP \\
v_3 = k_3 \cdot Gluc6P - k_{-3} \cdot Fruc6P \\
v_4 = k_4 \cdot Fruc6P \cdot ATP \\
v_5 = k_5 \cdot Fruc1,6P_2 \\
v_6 = k_6 \cdot Fruc1,6P_2 \\
v_7 = k_7 \cdot ADP
\end{cases}
$$

糖酵解反应模型

令, $k_1=0.25,\ k_2=1,\ k_3=1,\ k_{-3}=1,\ k_4=1,\ k_5=1,\ k_6=1,\ k_7=2.5$

则有：

$$\begin{cases} \dfrac{d}{dt}Glucose = 0.25 - Glucose \cdot ATP \\ \dfrac{d}{dt}Gluc6P = Glucose \cdot ATP - Gluc6P + Fruc6P \\ \dfrac{d}{dt}Fruc6P = Gluc6P - Fruc6P - Fruc6P \cdot ATP + Fruc1,6P_2 \\ \dfrac{d}{dt}Fruc1,6P_2 = Fruc6P \cdot ATP - 2Fruc1,6P_2 \\ \dfrac{d}{dt}ATP = -\dfrac{d}{dt}ADP = ADP - (Glucose + Fruc6P) \cdot ATP \end{cases}$$

设$t=0$时的初始浓度为：

$$Glucose(0) = Gluc6P(0) = Fruc6P(0) = Fruc1,6P_2(0) = 0,\quad ATP(0) = ADP(0) = 0.5 \ \text{(任意单位)}$$

演示用MatLab、sagemath、R进行求解