



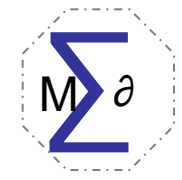
系统生物学 (Systems Biology)

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



系统动力学方程：

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

可简写为：

$$\begin{cases} \frac{dx}{dt} = a - bx \\ \frac{dy}{dt} = bx - cy \end{cases} \quad (\text{其中, } x = O_2^-, y = H_2O_2, a = c_1, b = c_2 \cdot SOD, c = c_3 \cdot cat)$$

给定参数值：

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

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

则可解出其时间过程（数值解），并作图如后。



Mathematica



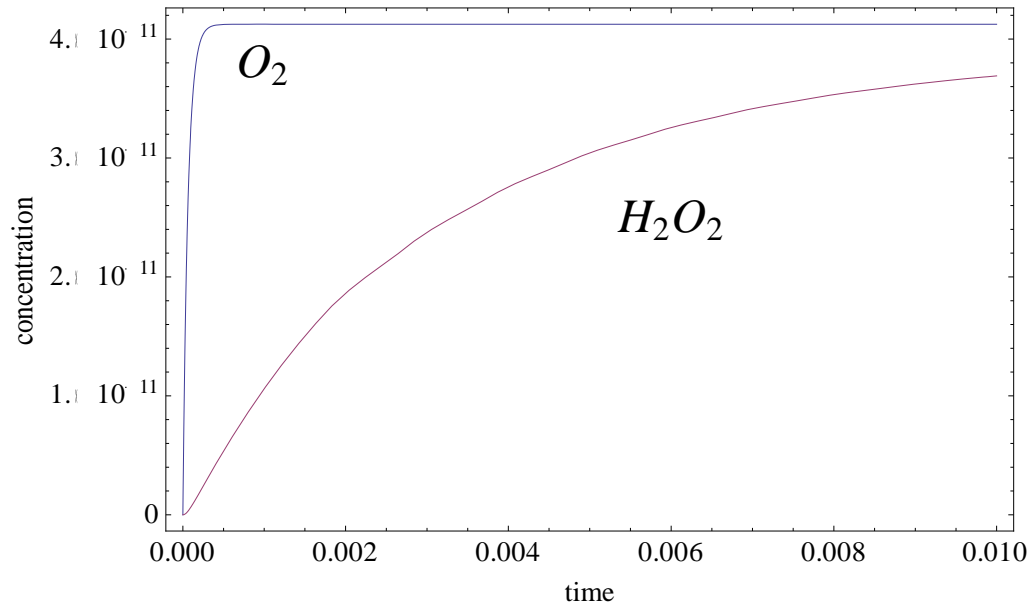
- ❑ 开发商：Wolfram Research
- ❑ 当前版本：8.x
- ❑ 特点：符号计算、数值计算、可视化并重，综合性好
- ❑ 公司网址：www.wolfram.com



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



MATLAB 技术计算语言

MATLAB® 是一种用于数值计算、可视化及编程的高级语言和交互式环境。使用 MATLAB，可以分析数据，开发算法，创建模型和应用程序。借助其语言、工具和内置数学函数，您可以探求多种方法，比电子表格或传统编程语言（如 C/C++ 或 Java™）更快地求得结果。

MATLAB 应用广泛，其中包括信号处理和通信、图像和视频处理、控制系统、测试和测量、计算金融学及计算生物学等众多应用领域。在各行各业和学术机构中，有一百多万工程师和科学家使用 MATLAB 这一技术计算语言。

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» 了解更多
- 应用程序的开发和部署**
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» 了解更多

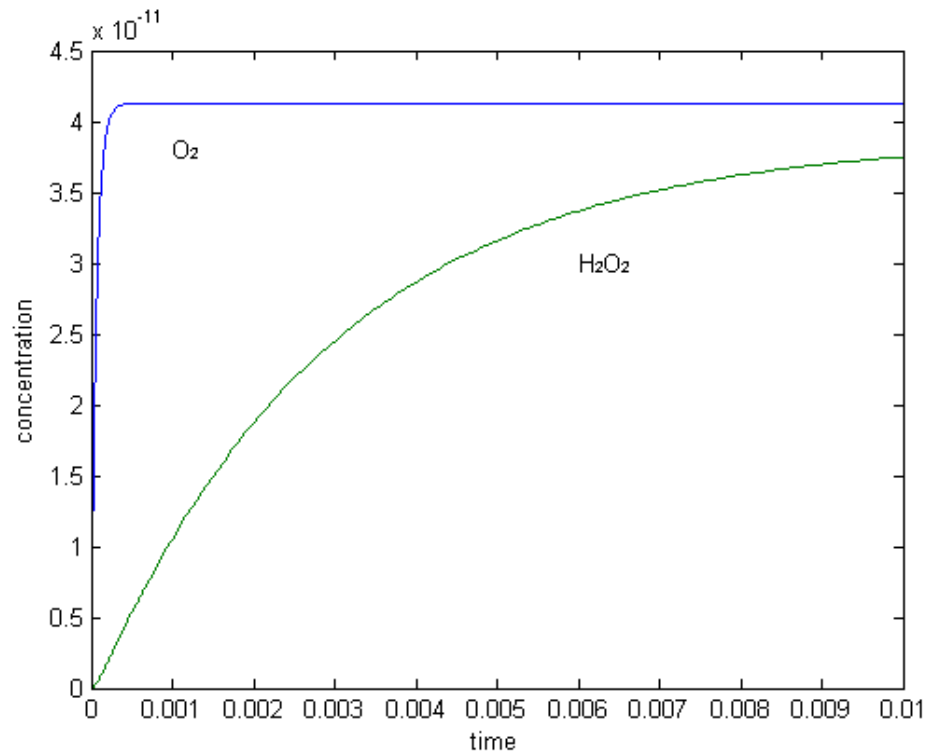
- ❑ 开发商：Mathworks, Inc.
- ❑ 当前版本：2012b
- ❑ 特点：符号计算、数值计算、可视化并重，综合性好
- ❑ 公司网址：www.mathworks.com
- ❑ 收购 MuPAD 后，符号计算能力得到加强



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

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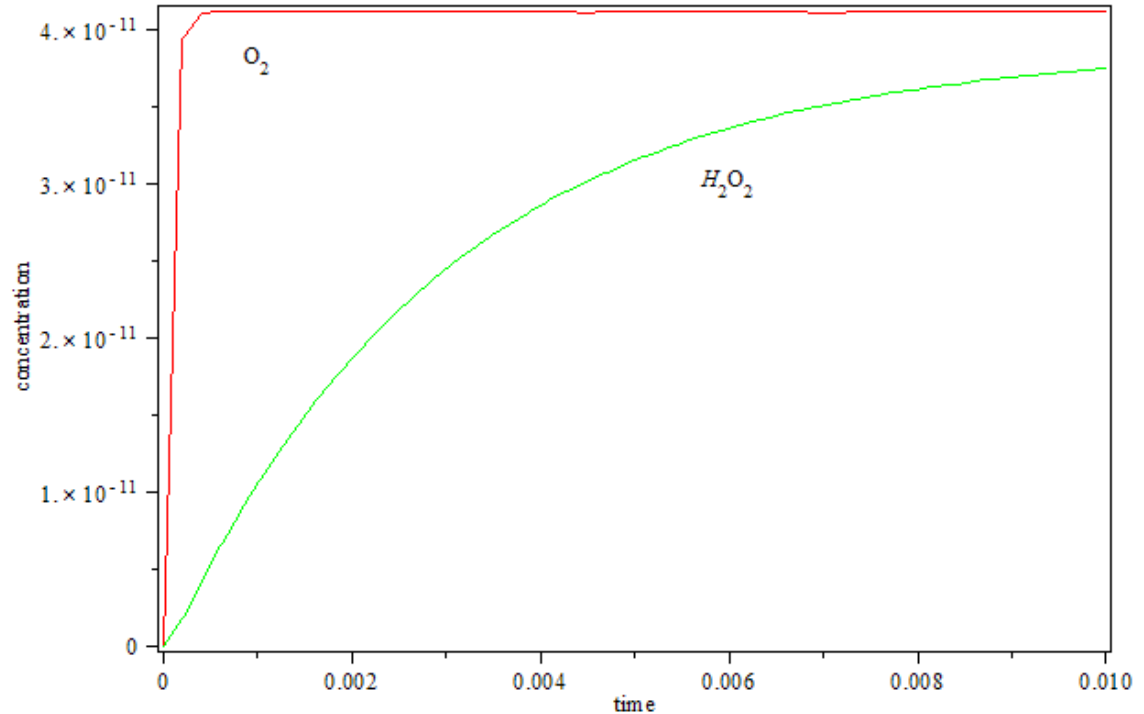
Maple Webinars
A series of live and recorded webinar by Maple experts.
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用Maple求解SOD模型



```
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, laeldirections = [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



The R Project for Statistical Computing

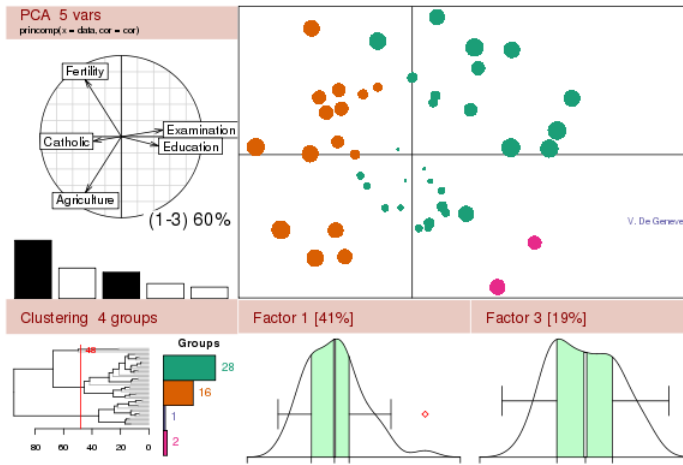
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Getting Started:

- R is a free software environment for statistical computing and graphics. It compiles and runs on a wide variety of UNIX platforms, Windows and MacOS. To [download R](#), please choose your preferred [CRAN mirror](#).
- If you have questions about R like how to download and install the software, or what the license terms are, please read our [answers to frequently asked questions](#) before you send an email.

News:

- ❑ 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



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给定参数值：

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

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

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)
```

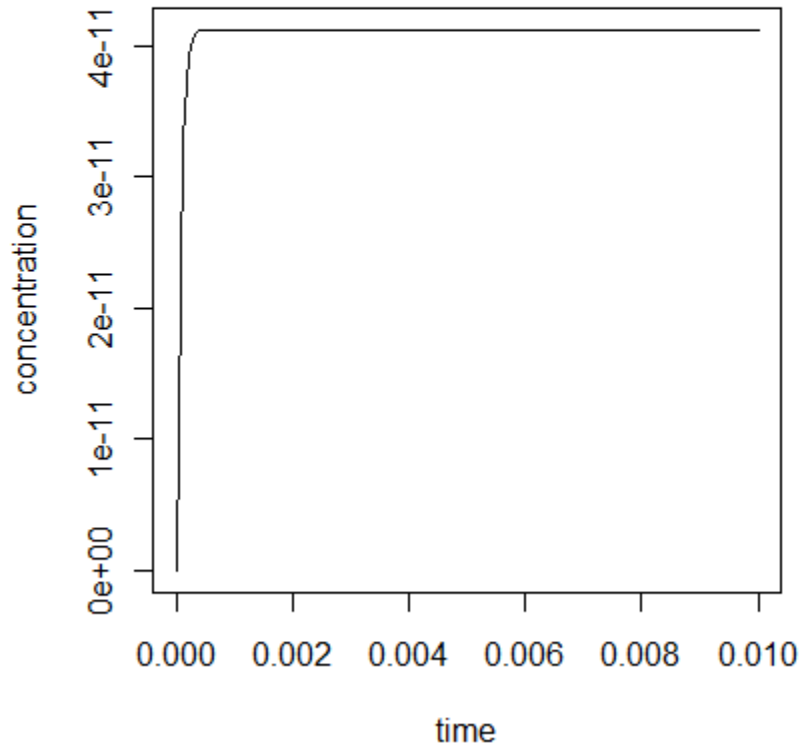



Plotting of model results

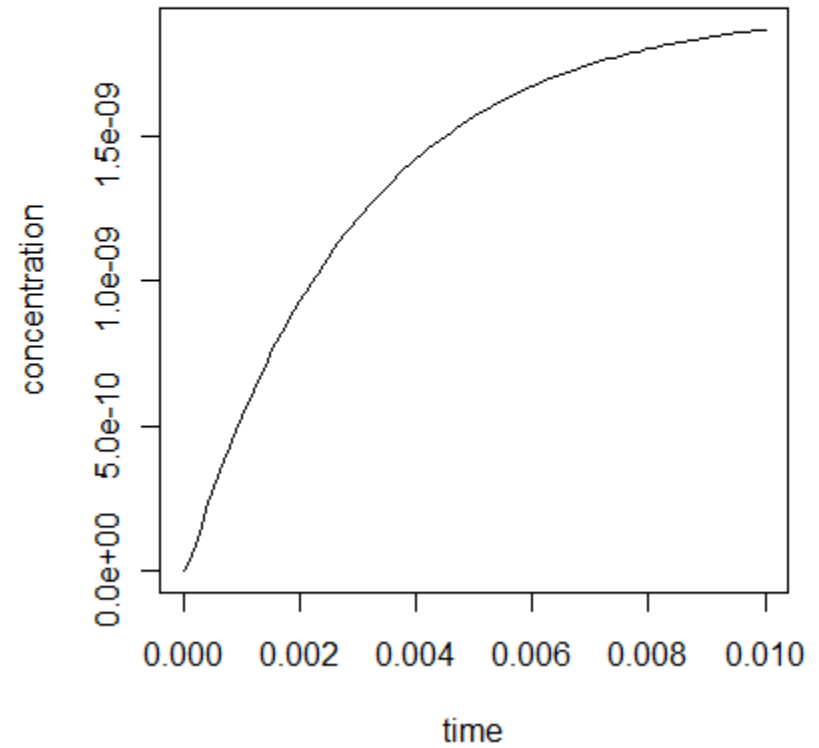


SOD model

O₂



H₂O₂





Maxima



Maxima, a Computer Algebra System - 360安全浏览器 3.3 正式版

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http://maxima.sourceforge.net/

Maxima, a Computer Algebra System

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Maxima is a system for the manipulation of symbolic and numerical expressions, including differentiation, integration, Taylor series, Laplace transforms, ordinary differential equations, systems of linear equations, polynomials, and sets, lists, vectors, matrices, and tensors. Maxima yields high precision numeric results by using exact fractions, arbitrary precision integers, and variable precision floating point numbers. Maxima can plot functions and data in two and three dimensions.

The Maxima source code can be compiled on many systems, including Windows, Linux, and MacOS X. The source code for all systems and precompiled binaries for Windows and Linux are available at the [SourceForge file manager](#).

Maxima is a descendant of Macsyma, the legendary computer algebra system developed in the late 1960s at the [Massachusetts Institute of Technology](#). It is the only system based on that effort still publicly available and with an active user community, thanks to its open source nature. Macsyma was revolutionary in its day, and many later systems, such as Maple and Mathematica, were inspired by it.

The Maxima branch of Macsyma was maintained by [William Schelter](#) from 1982 until he passed away in 2001. In 1998 he obtained [permission to release the source code under the GNU General Public License \(GPL\)](#). It was his efforts and skill which have made the survival of Maxima possible, and we are very grateful to him for volunteering his time and expert knowledge to keep the original DOE Macsyma code alive and well. Since his passing a group of users and developers has formed to bring Maxima to a wider audience.

We are constantly updating Maxima, to fix bugs and improve the code and the documentation. We welcome suggestions and contributions from the community of Maxima users. Most discussion is conducted on the [Maxima mailing list](#).

News [RSS](#)

- April 26, 2009: Maxima 5.18.1.
- December 26, 2008: Maxima 5.17.0.
- August 29, 2008: Maxima 5.16.3.
- April 22, 2008: Maxima 5.15.0.
- December 23, 2007: Maxima 5.14.0.
- August 28, 2007: Maxima 5.13.0.
- May 2, 2007: Maxima 5.12.0

- ❑ 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

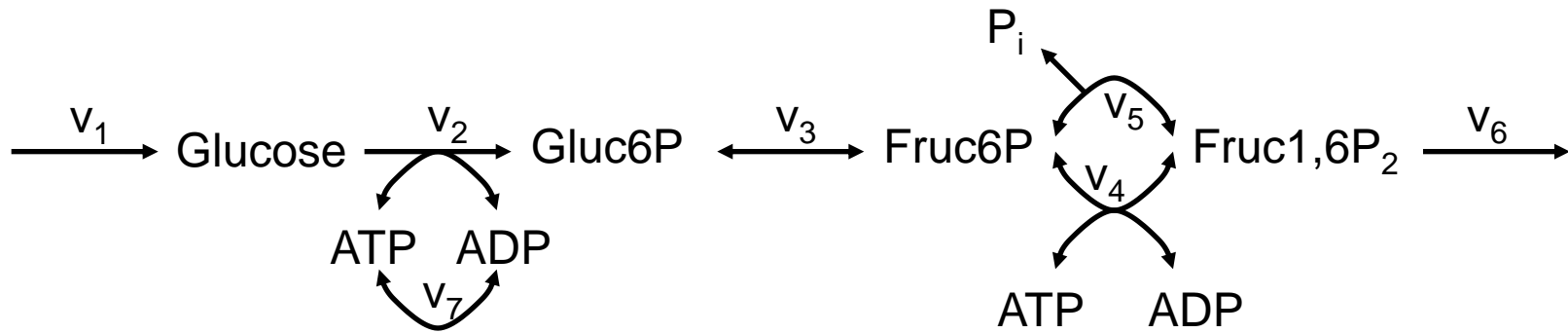


- ❑ 开发组织: sagemath team
- ❑ 当前版本: 5.4.x
- ❑ 特点: 符号计算、数值计算、可视化并重, 前景好
- ❑ 网址: www.sagemath.org

The screenshot shows the Sagemath website homepage. At the top left is the Sagemath logo, which consists of a geometric shape and the word "sage". To the right of the logo is the version number "v5.4 (2012-11-08)" and a "Language" dropdown menu. Below this is a navigation bar with links for "Home", "Tour", "Support", "Library", "Download", "Development", and "Links". The main content area features a paragraph describing Sage as a free open-source mathematics software system licensed under the GPL, combining the power of many existing open-source packages into a common Python-based interface. Below this is a mission statement: "Creating a viable free open source alternative to Magma, Maple, Mathematica and Matlab." The page is divided into several sections, each with a blue icon and text: "Try Sage Online" (with subtext "other: KAIST, Test devel: alpha"), "Download 5.4" (with subtext "Changelog · Source 5.4 · Packages"), "Help/Documentation" (with subtext "Video · Lists · Tutorial · FAQ · Ask"), "Feature Tour" (with subtext "Quickstart · Research · Graphics"), "Library" (with subtext "Testimonials · Books · Publications · Press Kit"), and "Search" (with a search input field). At the bottom of the page, there is a "Random Link" section with the text "Posters, Flyers, Spread the Word, ...".



糖酵解反应模型



$$\left\{ \begin{array}{l} \frac{d}{dt} \text{Glucose} = v_1 - v_2 \\ \frac{d}{dt} \text{Gluc6P} = v_2 - v_3 \\ \frac{d}{dt} \text{Fruc6P} = v_3 - v_4 + v_5 \\ \frac{d}{dt} \text{Fruc1,6P}_2 = v_4 - v_5 - v_6 \\ \frac{d}{dt} \text{ATP} = -\frac{d}{dt} \text{ADP} = -v_2 - v_4 + v_7 \end{array} \right.$$

$$\left\{ \begin{array}{l} v_1 = \text{constant} = k_1 \\ v_2 = k_2 \cdot \text{Glucose} \cdot \text{ATP} \\ v_3 = k_3 \cdot \text{Gluc6P} - k_{-3} \cdot \text{Fruc6P} \\ v_4 = k_4 \cdot \text{Fruc6P} \cdot \text{ATP} \\ v_5 = k_5 \cdot \text{Fruc1,6P}_2 \\ v_6 = k_6 \cdot \text{Fruc1,6P}_2 \\ v_7 = k_7 \cdot \text{ADP} \end{array} \right.$$



糖酵解反应模型



$$\begin{cases} \frac{d}{dt} \text{Glucose} = v_1 - v_2 = k_1 - k_2 \cdot \text{Glucose} \cdot \text{ATP} = 0.25 - \text{Glucose} \cdot \text{ATP} \\ \frac{d}{dt} \text{Gluc6P} = v_2 - v_3 = k_2 \cdot \text{Glucose} \cdot \text{ATP} - k_3 \cdot \text{Gluc6P} + k_{-3} \cdot \text{Fruc6P} = \text{Glucose} \cdot \text{ATP} - \text{Gluc6P} + \text{Fruc6P} \\ \frac{d}{dt} \text{Fruc6P} = v_3 - v_4 + v_5 = k_3 \cdot \text{Gluc6P} - k_{-3} \cdot \text{Fruc6P} - k_4 \cdot \text{Fruc6P} \cdot \text{ATP} + k_5 \cdot \text{Frucl,6P}_2 = \text{Gluc6P} - \text{Fruc6P} - \text{Fruc6P} \cdot \text{ATP} + \text{Frucl,6P}_2 \\ \frac{d}{dt} \text{Frucl,6P}_2 = v_4 - v_5 - v_6 = k_4 \cdot \text{Fruc6P} \cdot \text{ATP} - k_5 \cdot \text{Frucl,6P}_2 - k_6 \cdot \text{Frucl,6P}_2 = \text{Fruc6P} \cdot \text{ATP} - 2\text{Frucl,6P}_2 \\ \frac{d}{dt} \text{ATP} = -\frac{d}{dt} \text{ADP} = -v_2 - v_4 + v_7 = -k_2 \cdot \text{Glucose} \cdot \text{ATP} - k_4 \cdot \text{Fruc6P} \cdot \text{ATP} + k_7 \cdot \text{ADP} = \text{ADP} - (\text{Glucose} + \text{Fruc6P}) \cdot \text{ATP} \\ v_1 = \text{constant} = k_1 \\ v_2 = k_2 \cdot \text{Glucose} \cdot \text{ATP} \\ v_3 = k_3 \cdot \text{Gluc6P} - k_{-3} \cdot \text{Fruc6P} \\ v_4 = k_4 \cdot \text{Fruc6P} \cdot \text{ATP} \\ v_5 = k_5 \cdot \text{Frucl,6P}_2 \\ v_6 = k_6 \cdot \text{Frucl,6P}_2 \\ v_7 = k_7 \cdot \text{ADP} \end{cases}$$



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:

$$\left\{ \begin{array}{l} \frac{d}{dt} \text{Glucose} = 0.25 - \text{Glucose} \cdot \text{ATP} \\ \frac{d}{dt} \text{Gluc6P} = \text{Glucose} \cdot \text{ATP} - \text{Gluc6P} + \text{Fruc6P} \\ \frac{d}{dt} \text{Fruc6P} = \text{Gluc6P} - \text{Fruc6P} - \text{Fruc6P} \cdot \text{ATP} + \text{Fruc1,6P}_2 \\ \frac{d}{dt} \text{Fruc1,6P}_2 = \text{Fruc6P} \cdot \text{ATP} - 2\text{Fruc1,6P}_2 \\ \frac{d}{dt} \text{ATP} = -\frac{d}{dt} \text{ADP} = \text{ADP} - (\text{Glucose} + \text{Fruc6P}) \cdot \text{ATP} \end{array} \right.$$

设 $t = 0$ 时的初始浓度为:

$$\text{Glucose}(0) = \text{Gluc6P}(0) = \text{Fruc6P}(0) = \text{Fruc1,6P}_2(0) = 0, \quad \text{ATP}(0) = \text{ADP}(0) = 0.5 \quad (\text{任意单位})$$

演示用MatLab、sagemath、R进行求解