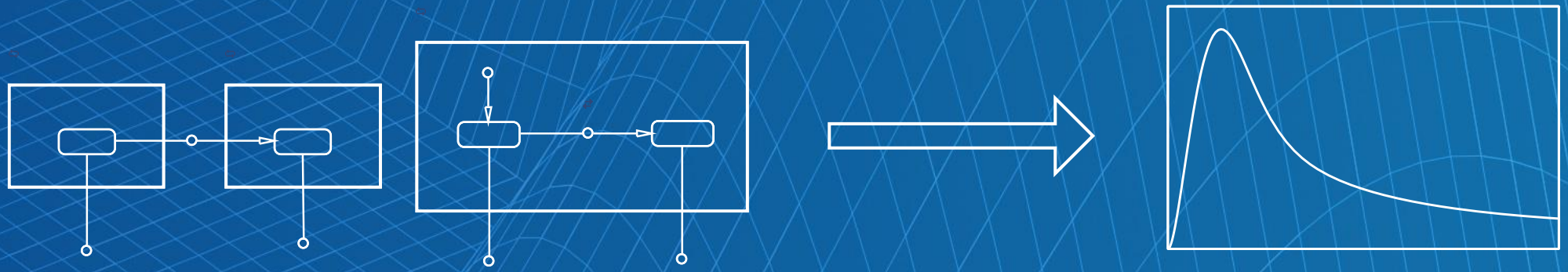
使用 MATLAB 进行新药发现及开发



许悦伊
MathWorks 中国

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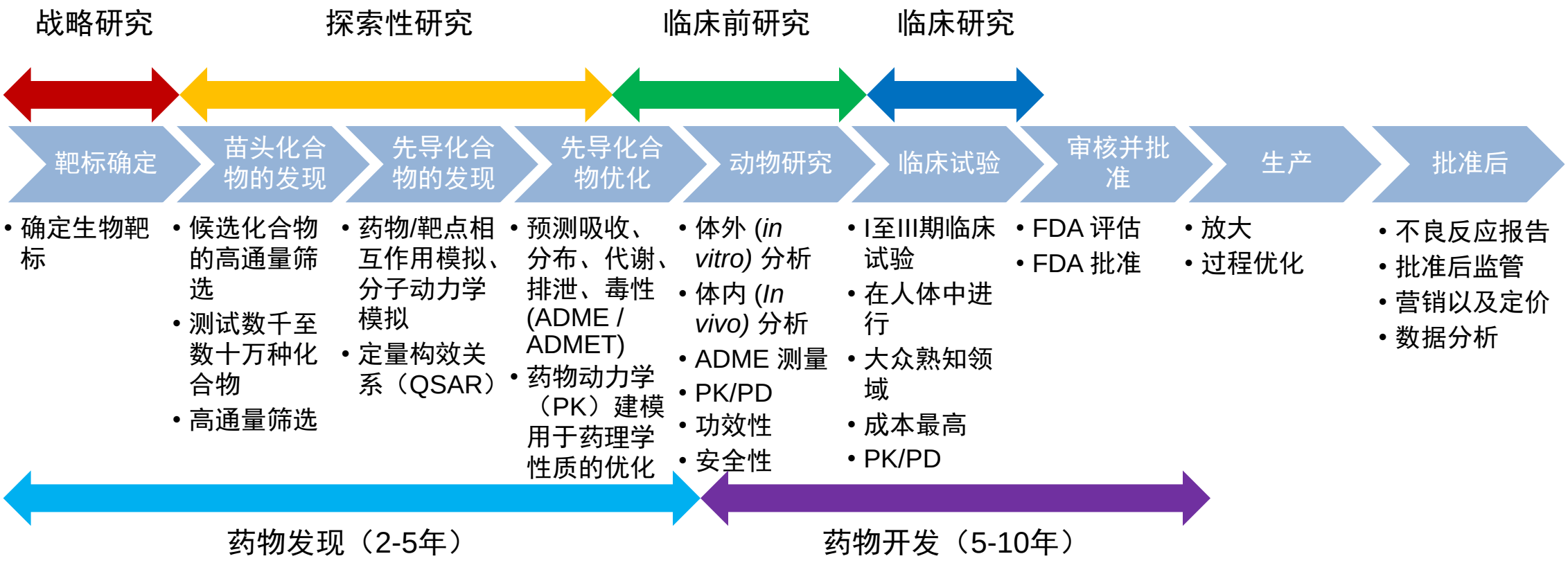
日程

1. 新药发现及开发流程
2. SimBiology是什么？
3. 示例展示
4. 您可以使用 SimBiology 做什么？
5. 用户案例
6. 分享模型以及仿真结果
7. MathWorks 以及社区提供的支持

新药发现及开发流程

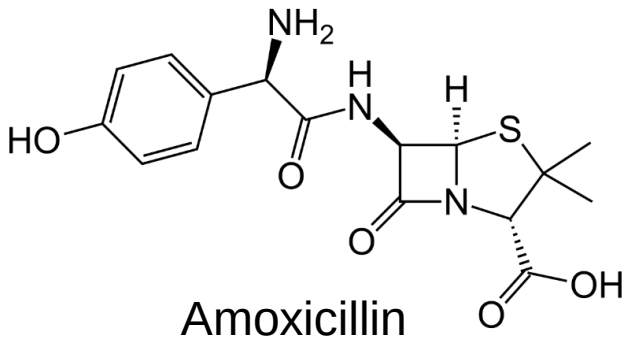


药物数量:	5000	3000	10	1

基于 Introduction to Biotech Entrepreneurship: From Idea to Business 和 Understanding the Drug Discovery Process

药物开发流程

化合物



Amoxicillin
（阿莫西林）

合成粉末

药物

目标：找到一个化合物，它可以：

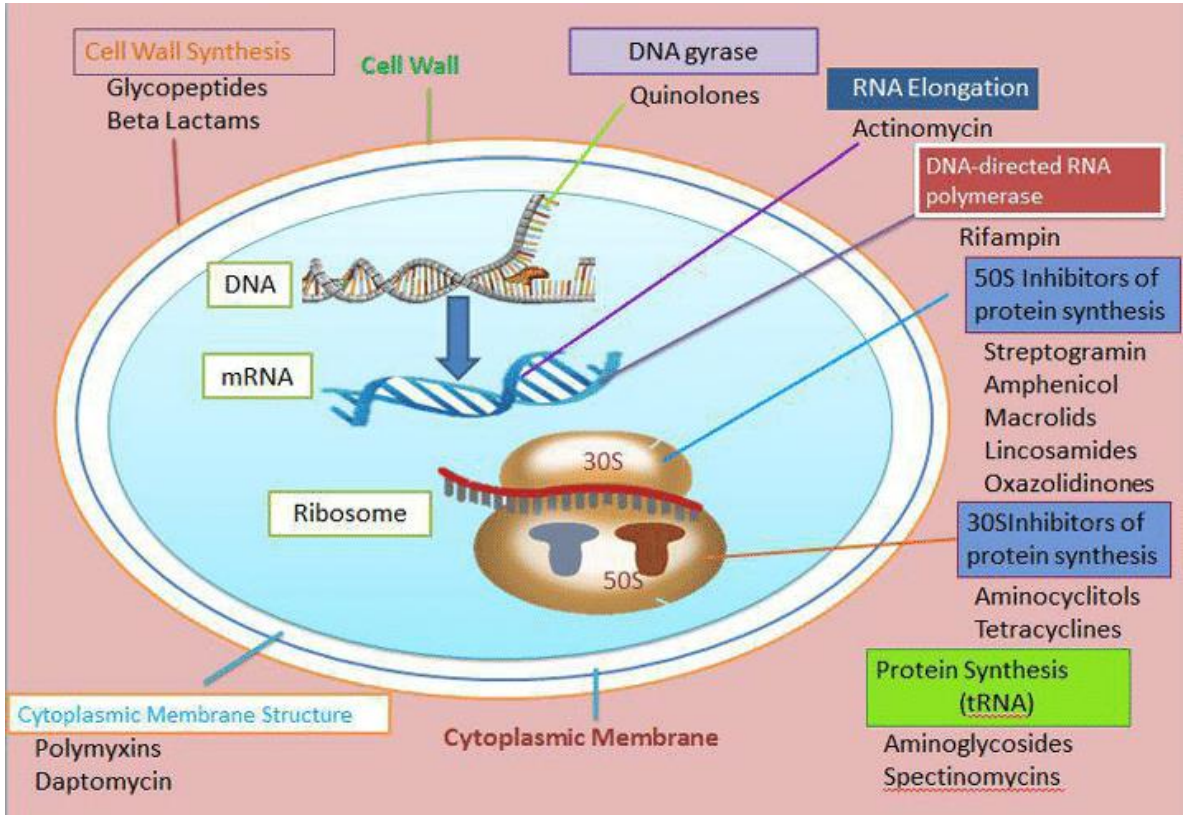
- 适合人类食用（安全性）
- 可以与靶标结合
- 发挥治疗作用（有效性）
- 可以从人体中代谢

药物发现与开发

发现	临床前研究	临床研究
▪ 确定药物靶标	▪ 药物会达到靶标吗？ ▪ 为首次人体试验找到安全有效的剂量	▪ 评估 ADME “吸收、分布、代谢和排泄” ▪ 定义目标人群

药物开发过程：靶标确定

发现 → 临床前研究 → 临床研究



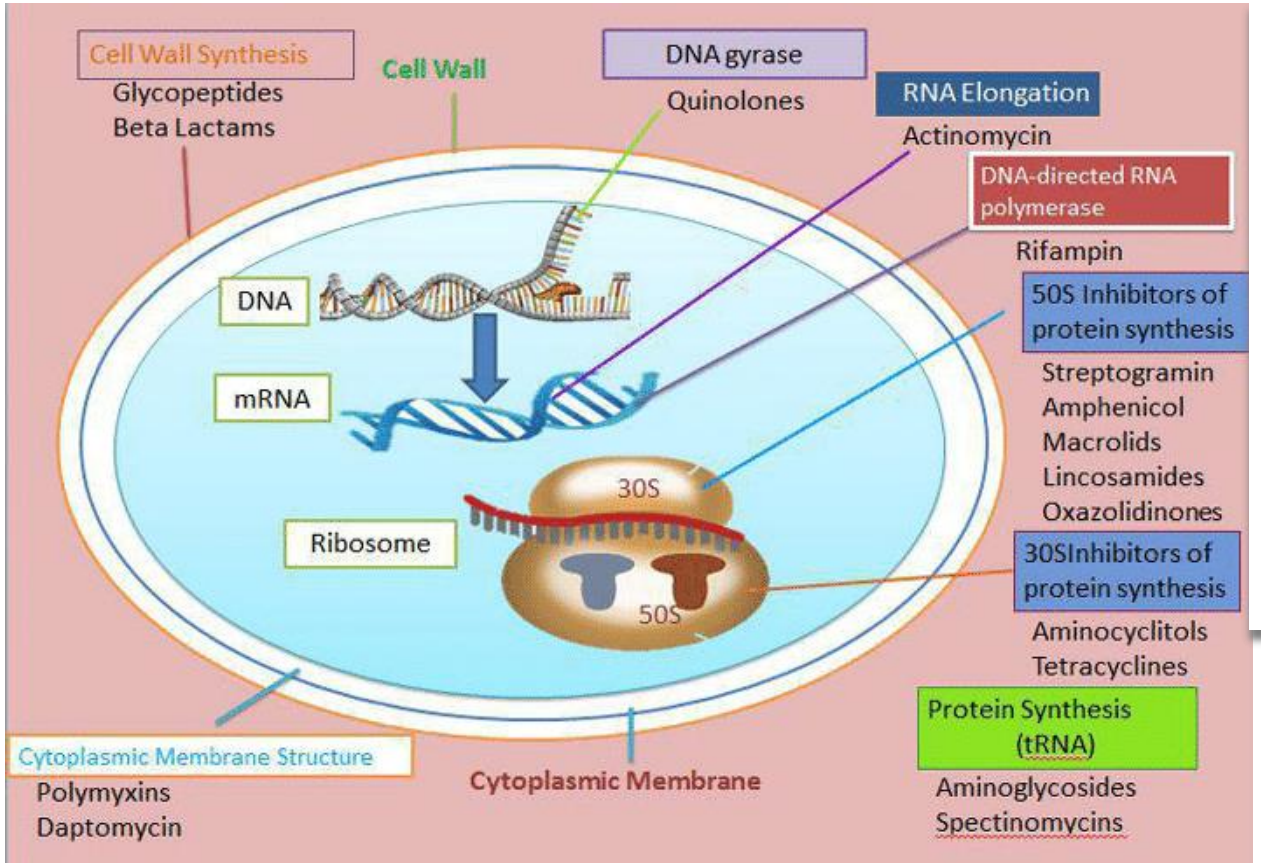
不同种类的抗生素机理

- 抑制或调节参与以下活动的酶 ——
  - 细胞膜生物合成
  - 核酸代谢与修复
  - 蛋白质合成
  - 膜结构的破坏

Ref: Review of new insights into antimicrobial agents

药物开发过程：靶标确定

发现 → 临床前研究 → 临床研究



你是否了解你的靶标：

- 为表型筛选启用基于靶点的药物发现
- 靶点的位置可能影响筛选实验或抑制剂设计
- 靶标的内源是什么

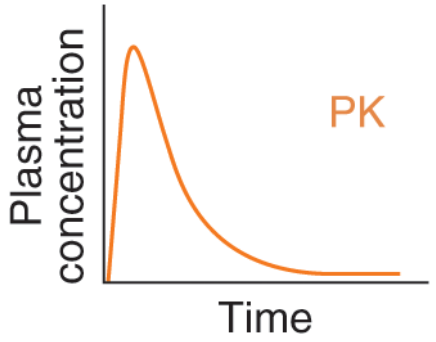
你是否了解你的化合物分子：

- 分子和哪些靶标和非靶标结合？
- 分子在哪里结合？
- 分子和靶标如何结合（结合动力学）？

Ref: Review of new insights into antimicrobial agents

药物开发流程：临床前研究和临床研究

发现 → 临床前研究 → 临床研究



Garrido, M., & Trocóniz, I. (2020). Pharmacokinetic and Pharmacodynamic Modelling in Anaesthesia. In P. Gambús & J. Hendrickx (Eds.), *Personalized Anaesthesia: Targeting Physiological Systems for Optimal Effect* (pp. 14-28). Cambridge: Cambridge University Press. doi:10.1017/9781316443217.002

MATLAB：一个可用于整个工作流的综合平台

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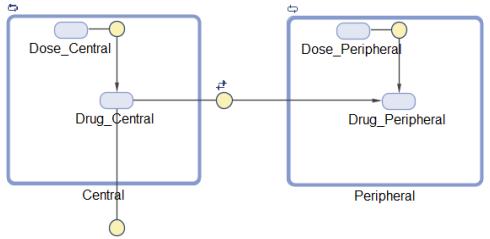
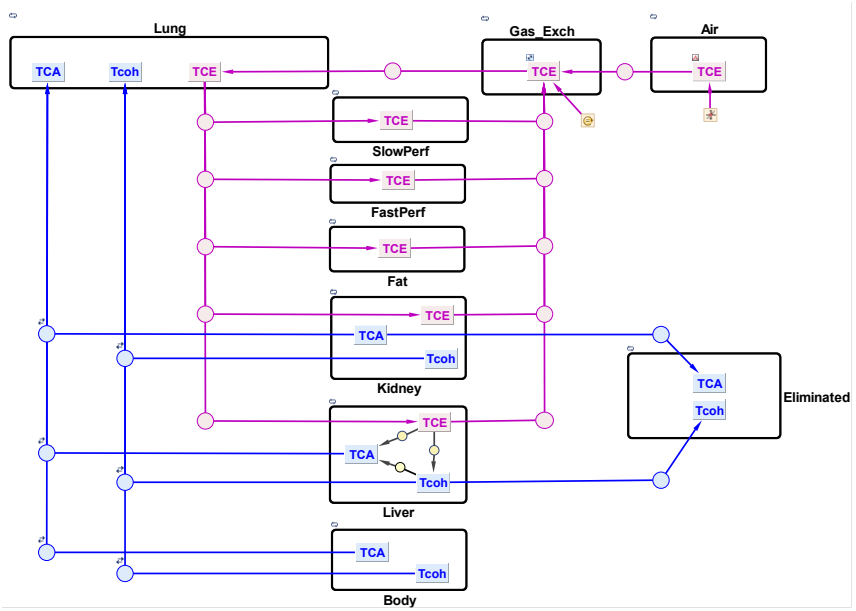
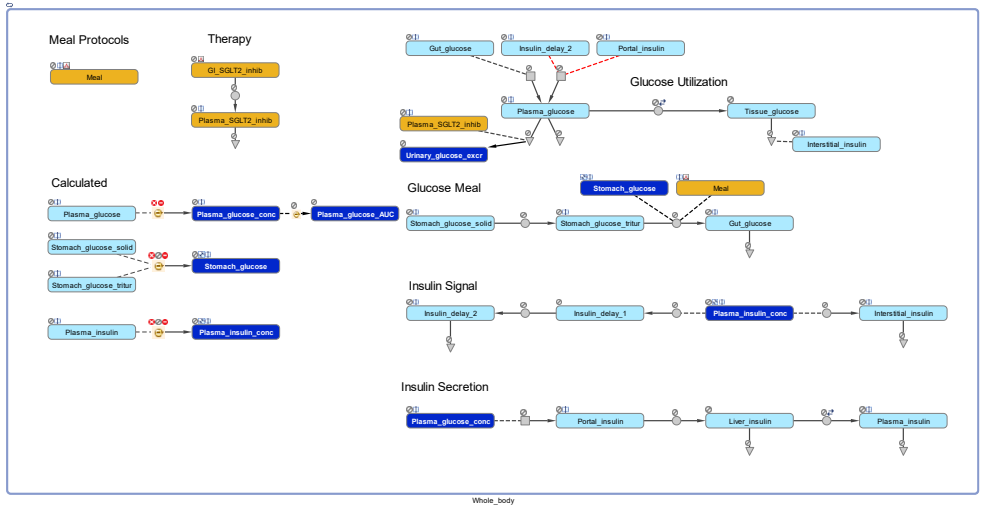
从 PK/PD 到定量系统药理学（QSP）





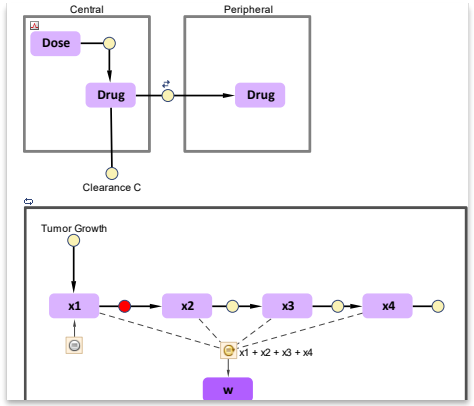


PK/PD　　PBPK　　QSP

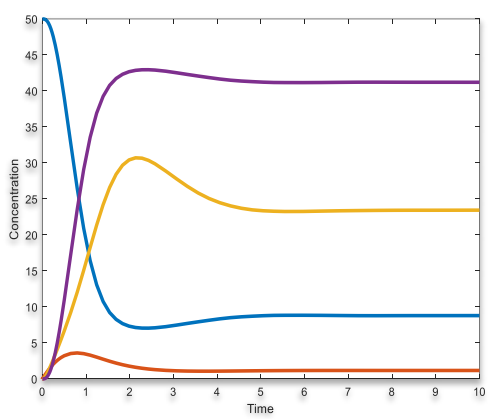
模型复杂性

SimBiology 是什么？

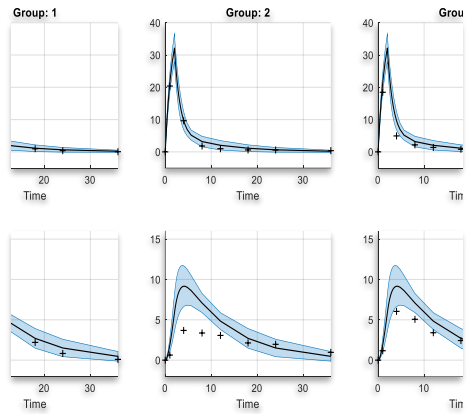
SimBiology® 为用户提供可操作 App 和编程工具，用于：



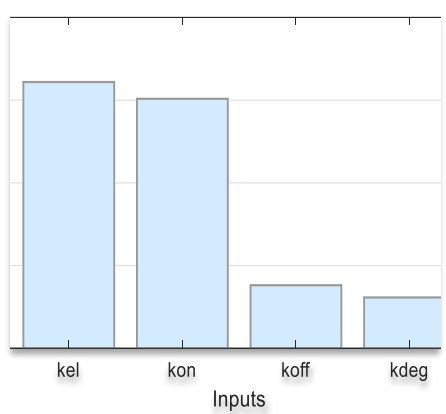
通过画图创建模型



仿真

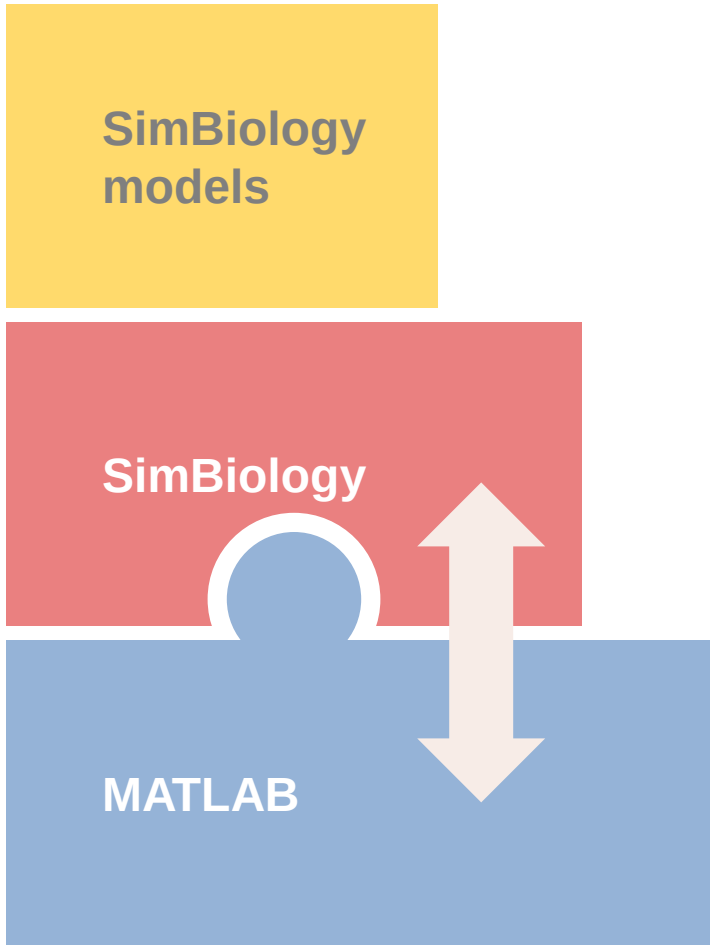


参数估计



模型分析

SimBiology 和它所在的 MATLAB 生态系统

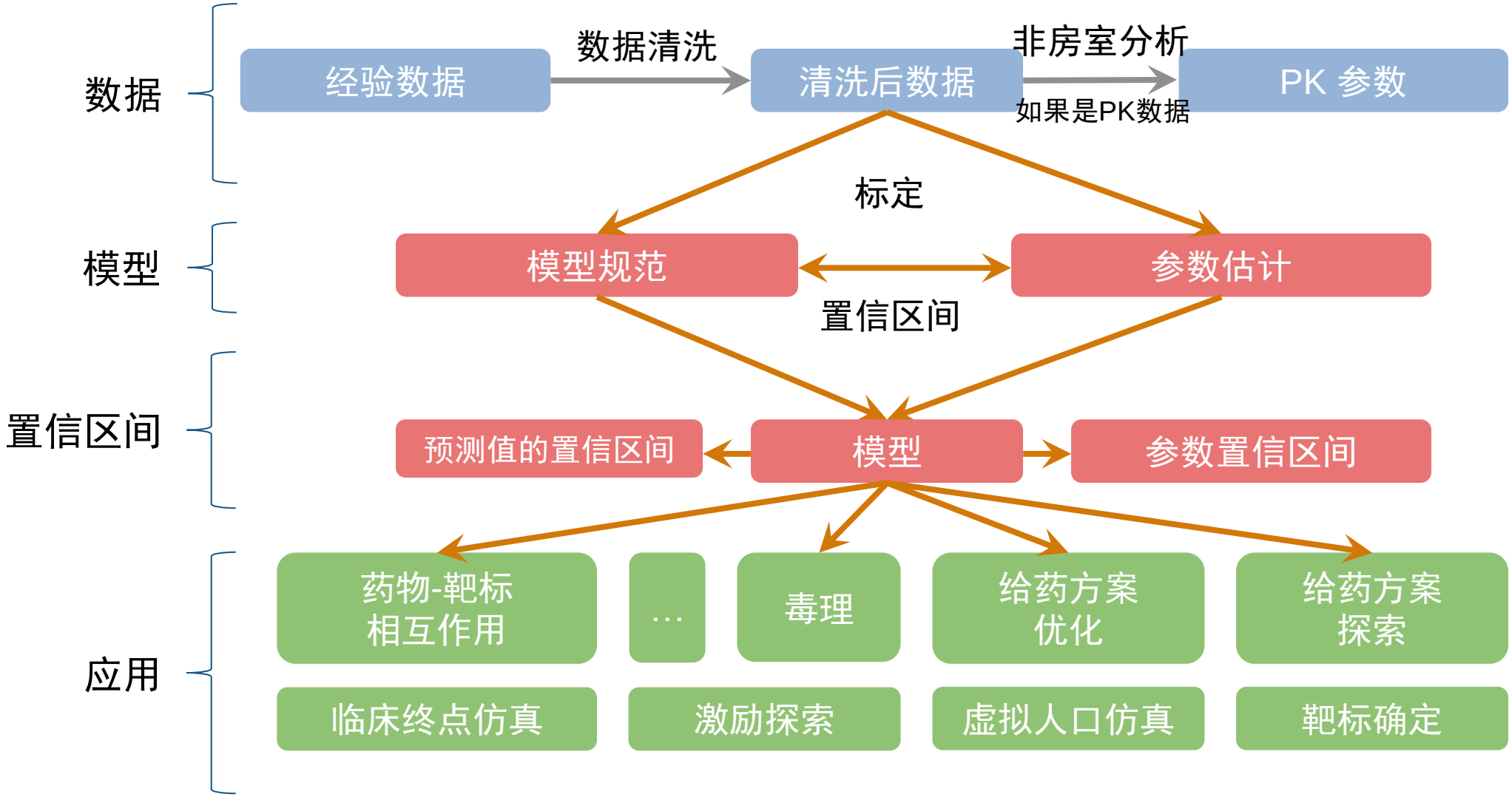


- 由终端用户开发
- 项目促进结果的连续性和可追溯性
- 图形化模型
- MATLAB 与 SimBiology 框架确保可重复性

- MATLAB 工具箱
- 基于图形或者代码的工作流
- 全面的内置分析工具集
- 通过编译成C代码实现模型加速

- 编程语言
- 多功能平台
- 专人维护并更新
- 严格的测试框架，确保平台质量

建模过程工作流示例


数据
模型
置信区间
应用
经验数据
数据清洗
清洗后数据
非房室分析
PK 参数
如果是PK数据
标定
模型规范
参数估计
置信区间
预测值的置信区间
模型
参数置信区间
药物-靶标
相互作用
…
毒理
给药方案
优化
给药方案
探索
临床终点仿真
激励探索
虚拟人口仿真
靶标确定

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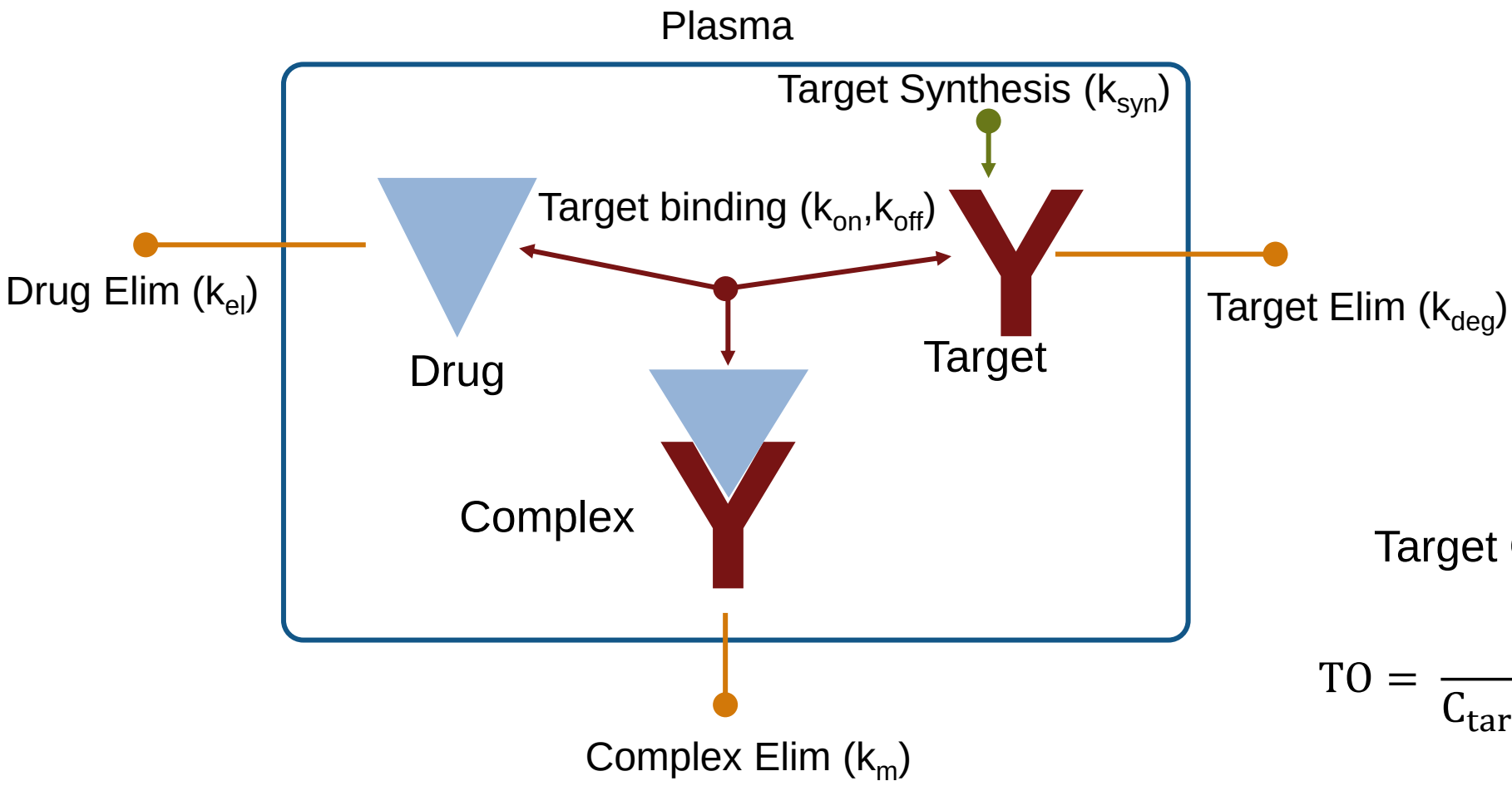
靶向介导药物处置 (TMDD) 模型

General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition
Donald E. Mager, William J. Jusko
Journal of Pharmacokinetics and Pharmacodynamics 2001; 28(6): 507–532

- 机械 PK 模型
- 适用于对药理靶点具有高结合亲和力的药物
- 结合靶向介导药物消除
- 目标：描述药物与药理靶点的非线性 PK 行为

TMDD 模型



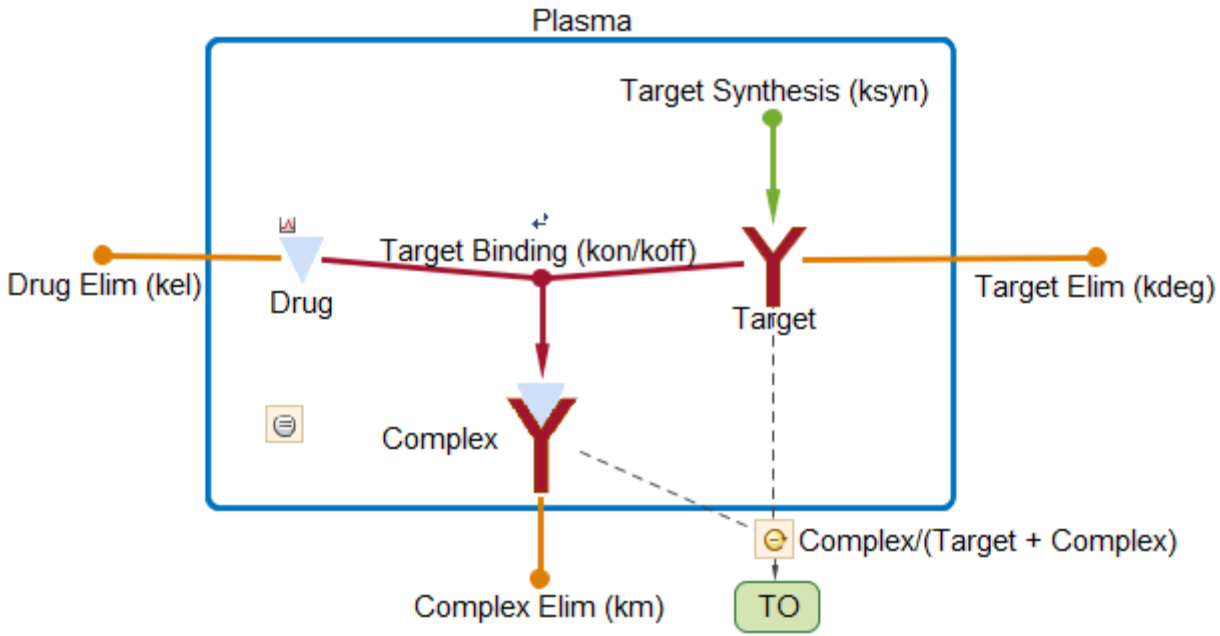
Target Occupancy:

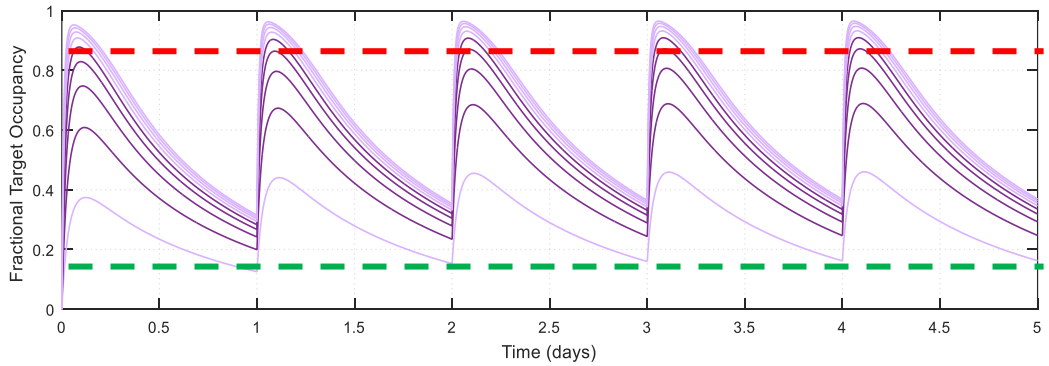
$$TO = \frac{C_{complex}}{C_{target} + C_{complex}}$$

示例链接：https://ww2.mathworks.cn/help/releases/R2022b/simbio/ug/parameter-scan-to-explore-dosing-regimens.html

在 SimBiology 中实现

- 图形化模型展示
- 模型可执行：
  - 仿真
  - 非房室分析（NCA）
  - 数据拟合
  - 给药方案优化
  - 等等等等
- 交互式分析模型表现
- 可以和 MATLAB 以及它的其他工具箱整合





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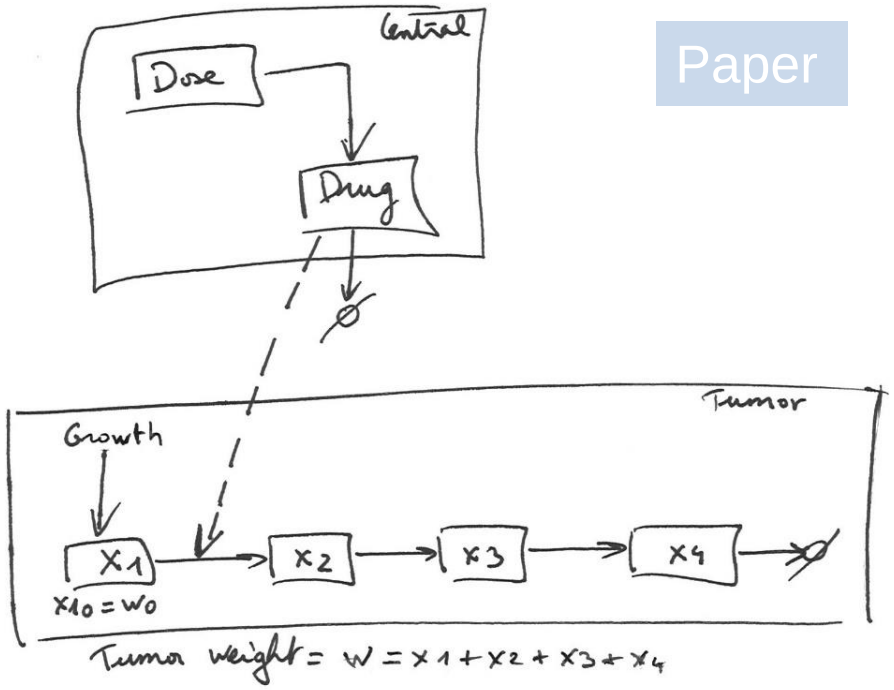
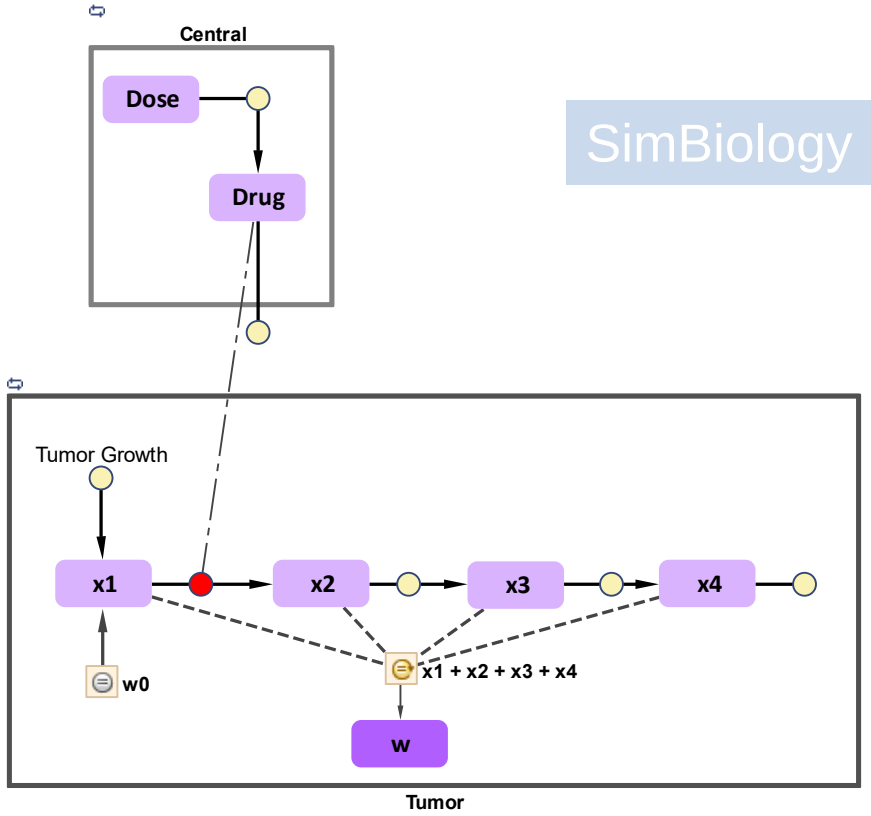
SimBiology 使您可以通过画图创建任何模型

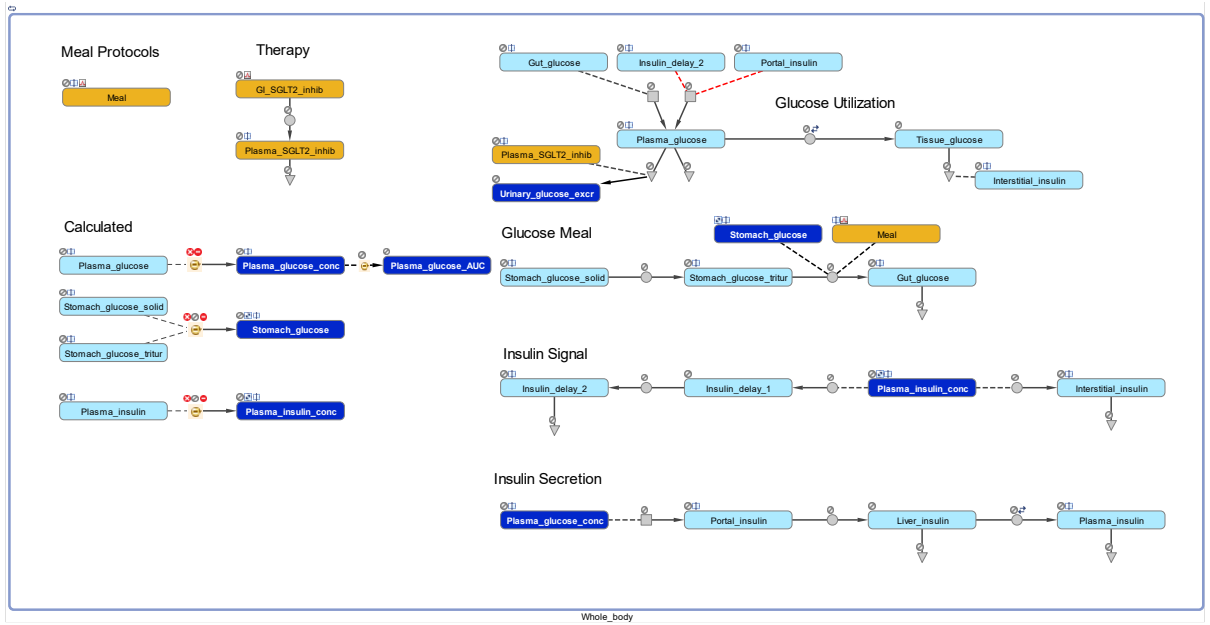
Paper

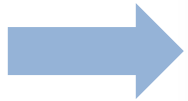


SimBiology



SimBiology 使您可以通过画图创建任何模型





Equations

Repeated Assignments

- plasma_glucose_AUC_24hr = Plasma_glucose_AUC*body_weight/(time+10080)*1440
- urinary_glucose_excr_24hr = Urinary_glucose_excr/1e3*body_weight/(time+10080)*1440
- renal_threshold = basal_renal_threshold*(1-compound_Imax*Whole_body.Plasma_SGLT2_inhib^2/(compound_IC50^2+Whole_body.Plasma_SGLT2_inhib^2))
- Plasma_insulin_conc = Plasma_insulin/plasma_vol_insulin
- insulin_secr = k_liver_portal*Portal_insulin
- hepatic_extract = -hepatic_extract_dep*insulin_secr+hepatic_extract_basal
- k_insulin_deg_liver = hepatic_extract*k_insulin_plasma_liver/(1-hepatic_extract)
- glucose_excretion = (Plasma_glucose>renal_threshold)*GFR*(Plasma_glucose-renal_threshold)
- Vmax_glucose_util = Vmax_basal_glucose_util+Vmax_dep_glucose_util*Interstitial_insulin
- insulin_dep_glucose_util = Vmax_glucose_util*Tissue_glucose/(Km_glucose_util+Tissue_glucose)
- glucose_utilization = insulin_indep_glucose_util+insulin_dep_glucose_util
- glucose_appearance_rate = fraction_abs*k_glucose_abs*Gut_glucose*(basis/body_weight)
- glucose_prod = EGP_max-LGE*Plasma_glucose-IAL*Insulin_delay_2-PIAL*Portal_insulin
- plasma_glucose_conc_rate = (glucose_prod+glucose_appearance_rate-insulin_indep_glucose_util-glucose_excretion-k_tissue_plasma*Plasma_glucose+k_plasma_tissue*Tissue_glucose)/plasma_vol_glucose
- insulin_prod = delayed_glucose_signal+basal_insulin_secr+(plasma_glucose_conc_rate>0"plasma_glucose_conc_rate&&Plasma_glucose_conc>basal_plasma_glucose_conc)*K_insulin_prod"plasma_glu...
- Stomach_glucose = Stomach_glucose_solid+Stomach_glucose_tritur
- k_emptying = gastric_emptying_kmin+0.5*(gastric_emptying_kmax-gastric_emptying_kmin)*(tanh(gastric_emptying_a*(Stomach_glucose-gastric_emptying_b*[Stomach Glucose After Dosing]))-tanh(gastric_emptying_c*(Stomach_glucose-gastric_emptying_d*[Stomach Glucose After Dosing]))+2)

ODEs

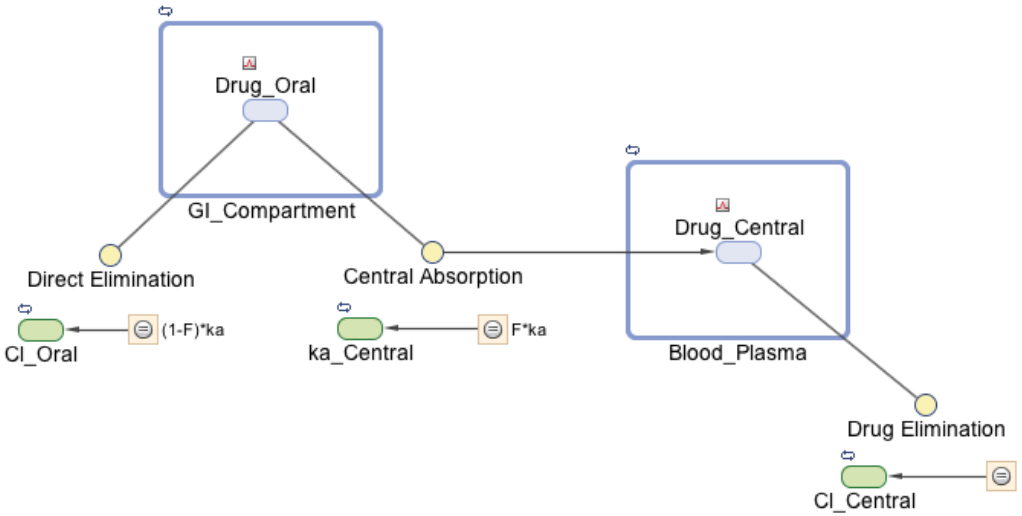
- d(Stomach_glucose_solid)/dt = -(k_grinding*Stomach_glucose_solid)
- d(Stomach_glucose_tritur)/dt = (k_grinding*Stomach_glucose_solid) - (k_emptying*Stomach_glucose_tritur)
- d(Gut_glucose)/dt = (k_emptying*Stomach_glucose_tritur) - (k_glucose_abs*Gut_glucose)
- d(Plasma_glucose)/dt = (glucose_appearance_rate) - (k_tissue_plasma*Plasma_glucose-k_plasma_tissue*Tissue_glucose) + (glucose_prod) - (insulin_indep_glucose_util) - (glucose_excretion)
- d(Tissue_glucose)/dt = (k_tissue_plasma*Plasma_glucose-k_plasma_tissue*Tissue_glucose) - (insulin_dep_glucose_util)
- d(GI_SGLT2_inhib)/dt = -(k_compound_absorption*GI_SGLT2_inhib)
- d(Plasma_SGLT2_inhib)/dt = (k_compound_absorption*GI_SGLT2_inhib) - (CL/Vd*Plasma_SGLT2_inhib)
- d(Insulin_delay_2)/dt = 1/Whole_body*(((k_insulin_delay*Insulin_delay_1)*Whole_body) - ((k_insulin_delay*Insulin_delay_2)*Whole_body))
- d(Insulin_delay_1)/dt = 1/Whole_body*(((k_insulin_delay*Plasma_insulin_conc)*Whole_body) - ((k_insulin_delay*Insulin_delay_1)*Whole_body))
- d(Interstitial_insulin)/dt = 1/Whole_body*((((Plasma_insulin_conc>basal_plasma_insulin_conc)*IAGU*(Plasma_insulin_conc-basal_plasma_insulin_conc))*Whole_body) - ((IAGU*Interstitial_insulin)*Whole_body))
- d(Plasma_insulin)/dt = (k_insulin_plasma_liver*Liver_insulin-k_insulin_liver_plasma*Plasma_insulin) - (k_insulin_deg_plasma*Plasma_insulin)
- d(Liver_insulin)/dt = (insulin_secr) - (k_insulin_plasma_liver*Liver_insulin-k_insulin_liver_plasma*Plasma_insulin) - (k_insulin_deg_liver*Liver_insulin)
- d(Portal_insulin)/dt = (insulin_prod) - (insulin_secr)
- d(Urinary_glucose_excr)/dt = (glucose_excretion)
- d(Plasma_glucose_AUC)/dt = 1/Whole_body*(((Plasma_glucose_conc*AUC_rate)*Whole_body))

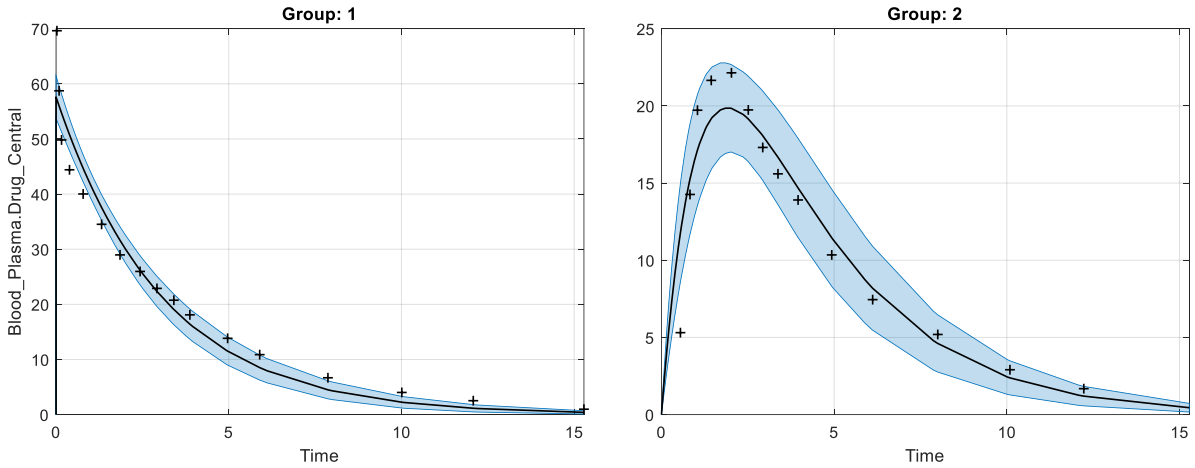
优点：

- 充分的灵活性
- 图表 = 可以进行仿真的模型
- 方便与实验人员交流

参数估计并计算置信区间

- 使用非线性回归和非线性混合效应技术
- 示例：估计药物昂丹司琼（ondansetron）的生物利用度：





	Group	Name	Estimate	ConfidenceInterval		Type	Alpha	Status
1	pooled	'ka'	0.78292	0.41447	1.1514	Gaussian	0.05	success
2	pooled	'clearance'	45.007	39.145	50.869	Gaussian	0.05	success
3	pooled	'Blood_Pla...	138.9	129.6	148.19	Gaussian	0.05	success
4	pooled	'F'	0.64302	0.50814	0.77789	Gaussian	0.05	success

示例链接：https://ww2.mathworks.cn/help/releases/R2022b/simbio/ug/estimating-the-bioavailability-of-a-drug.html

SimBiology中参数估计的支持方法

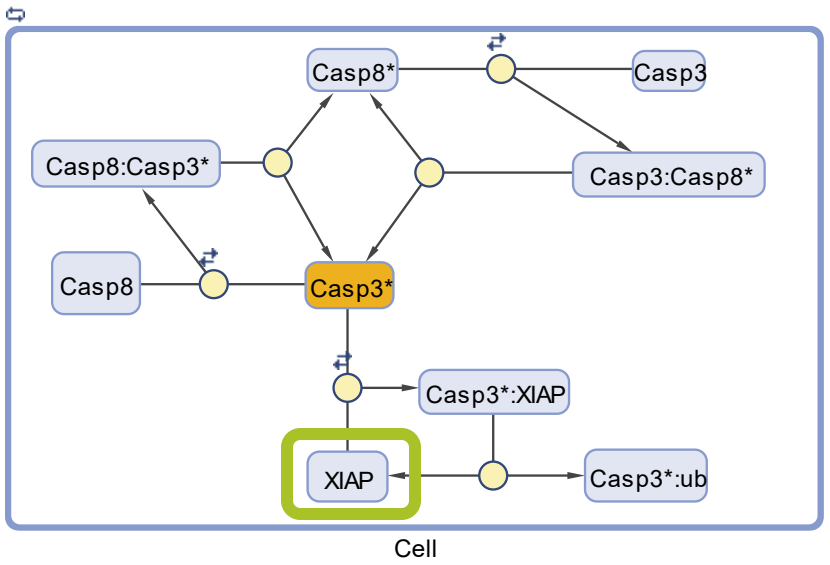
Method	Additional Toolbox Required	Supports Parameter Bounds	Uses Parameter Sensitivities†	Response-specific Error Models	Fixed or Mixed Effects	Supports Stochastic EM Algorithm	SimBiology Function to Use
`fminsearch`	—	Yes*	No	Yes	Fixed	No	`sbiofit` or `fitproblem`
`scattersearch`	—	Yes	Depends on the selected local solver.	Depends on the selected local solver.	Fixed	No	
`nlinfit` (Statistics and Machine Learning Toolbox)	Statistics and Machine Learning Toolbox™	Yes*	No	No	Fixed	No	
`fminunc` (Optimization Toolbox)	Optimization Toolbox™	Yes*	Yes	Yes	Fixed	No	
`fmincon` (Optimization Toolbox)	Optimization Toolbox	Yes	Yes	Yes	Fixed	No	
`lsqcurvefit` (Optimization Toolbox)	Optimization Toolbox	Yes	Yes	Yes	Fixed	No	
`lsqnonlin` (Optimization Toolbox)	Optimization Toolbox	Yes	Yes	Yes	Fixed	No	
`patternsearch` (Global Optimization Toolbox)	Global Optimization Toolbox	Yes	No	Yes	Fixed	No	
`ga` (Global Optimization Toolbox)	Global Optimization Toolbox	Yes	No	Yes	Fixed	No	
`particleswarm` (Global Optimization Toolbox)	Global Optimization Toolbox	Yes	No	Yes	Fixed	No	
`nlmefit` (Statistics and Machine Learning Toolbox)	Statistics and Machine Learning Toolbox	No	No	No	Mixed	No	`sbiofitmixed` or `fitproblem`
`nlmefitsa` (Statistics and Machine Learning Toolbox)	Statistics and Machine Learning Toolbox	No	No	No	Mixed	Yes	

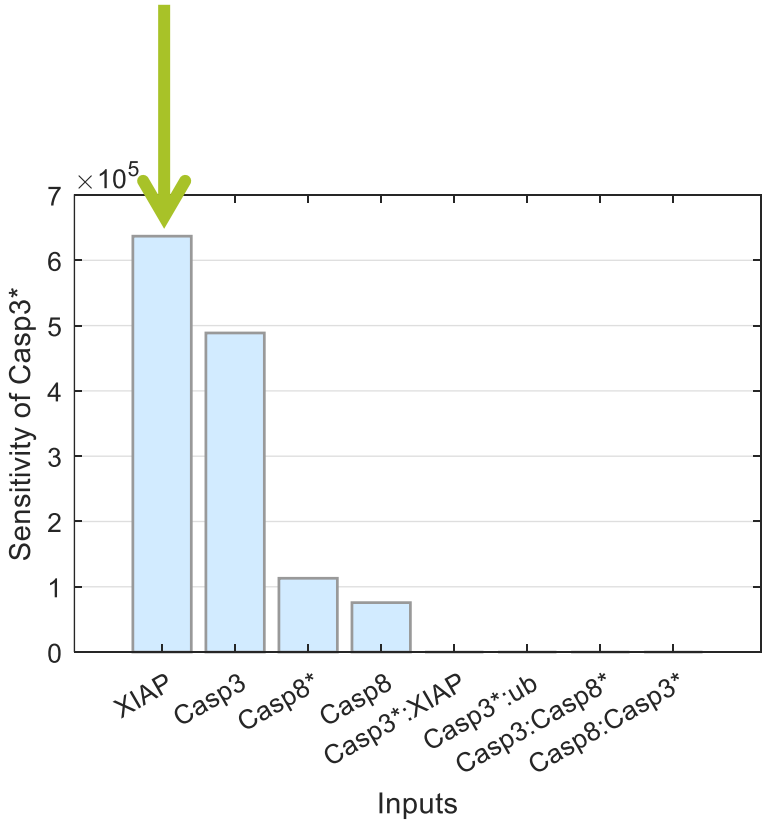
https://ww2.mathworks.cn/help/simbio/ug/supported-methods-for-parameter-estimation.html

敏感度分析

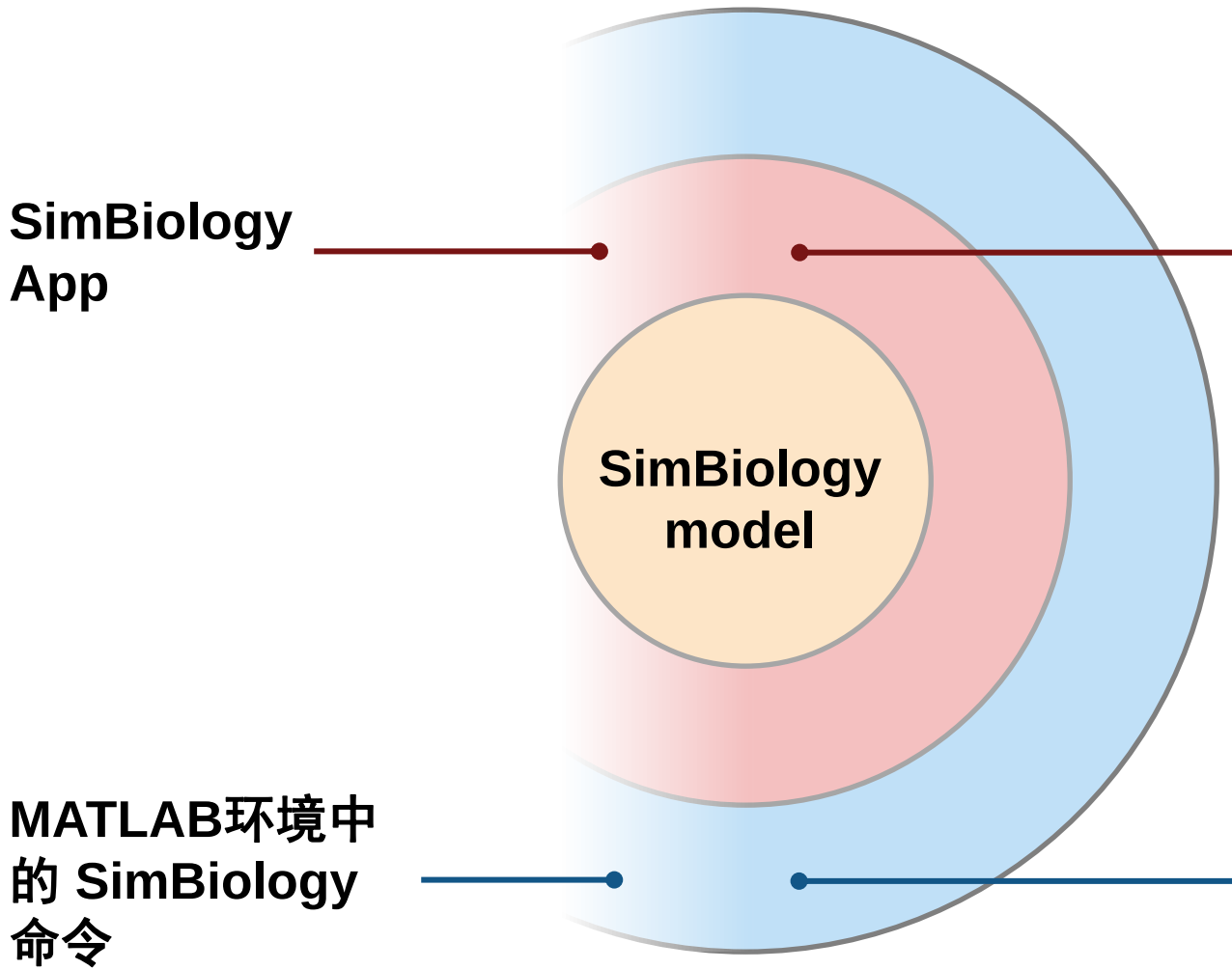
- 寻找影响模型结果的重要参数
- 寻找需要仔细估计的参数
- 寻找潜在的药物靶点

- 示例：凋亡通路模型





MATLAB 中的 SimBiology 生态系统



内置分析工具：

- 仿真
- 数据拟合
- NCA
- 敏感度分析
- 参数扫描
- 定制化任务
- 等等等等

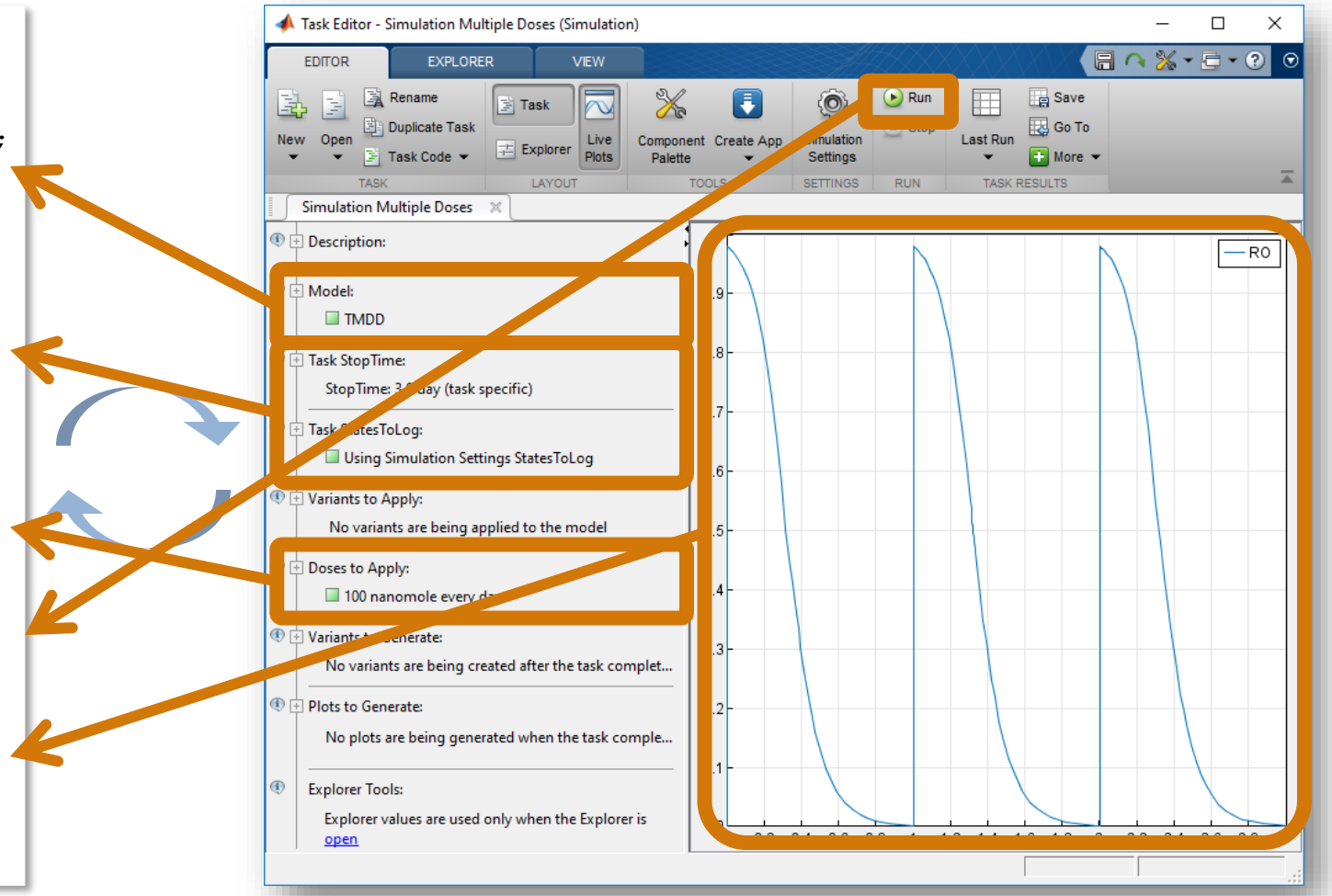
利用MATLAB环境

- 定制化分析
- 批处理
- 报告生成
- 等等等等

非一成不变！

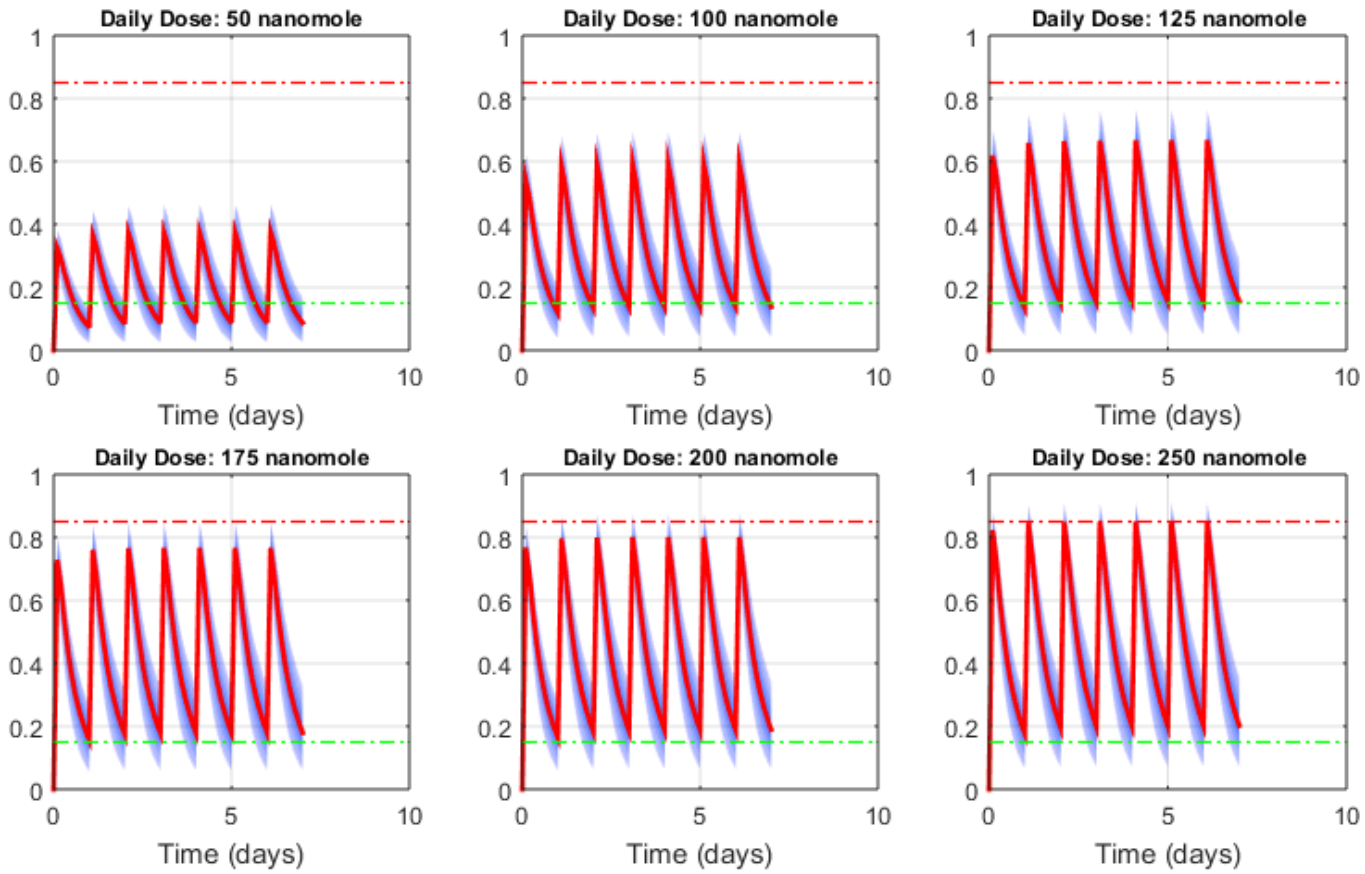
SimBiology App *vs.* script

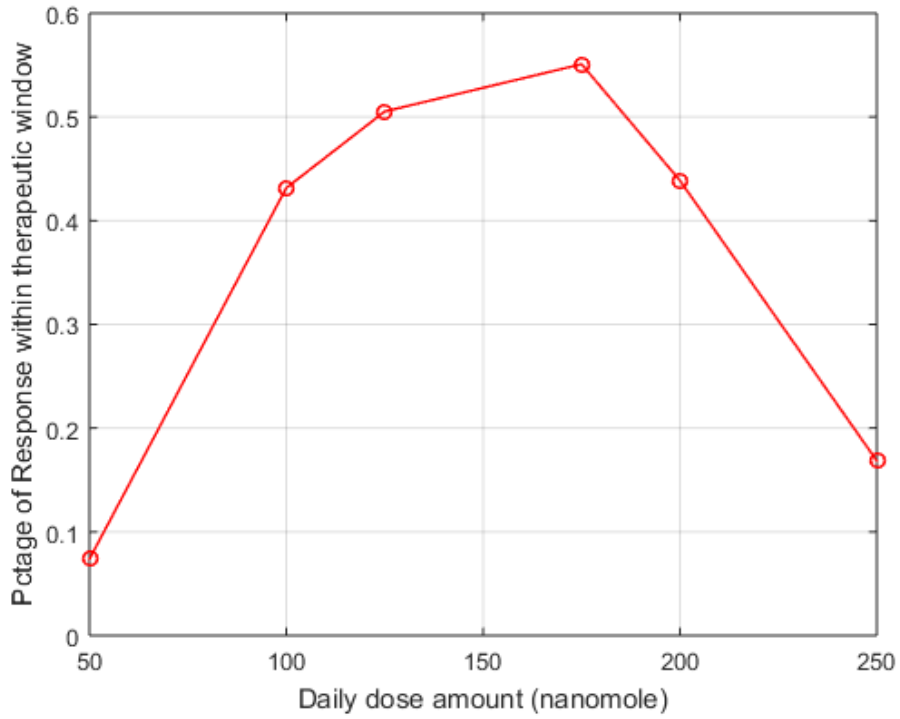
```
% model
proj = sbioloadproject('TMDD_training.sbproj','m1');
model = proj.m1;
```



模拟虚拟人群，假设场景

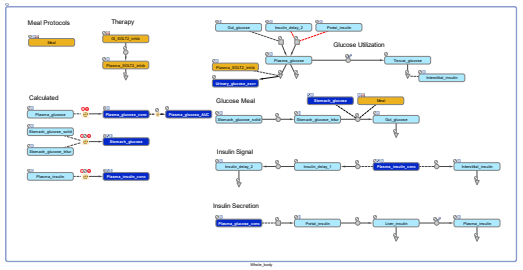
- 示例：使用TMMD模型优化给药方案



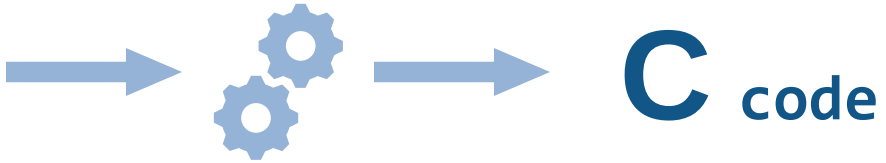


在各种设备上进行快速仿真

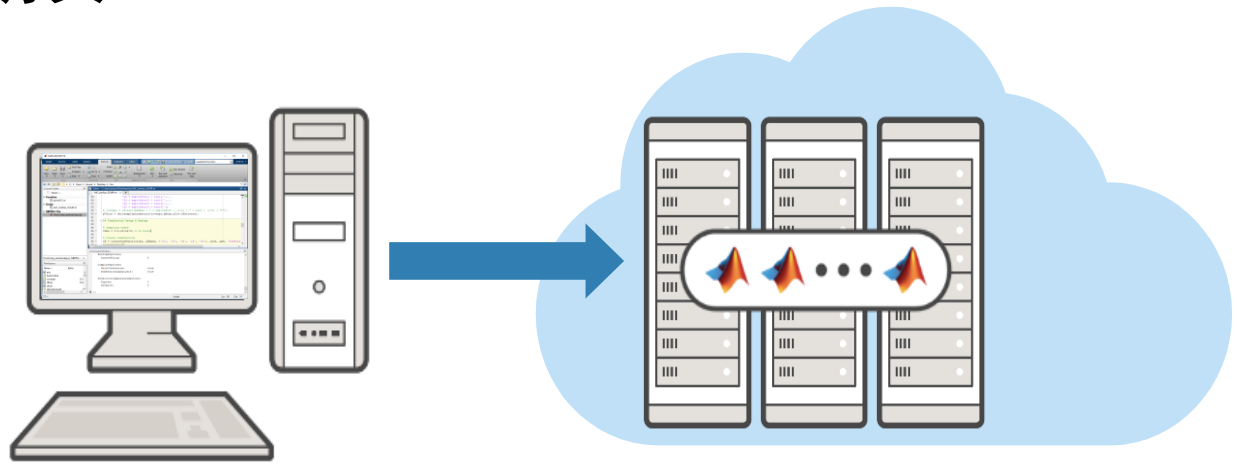
- 快速地进行单次仿真



加速模式



- 并行运行多个仿真



扩展至集群或者云端

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6. 分享模型以及仿真结果
7. MathWorks 以及社区提供的支持

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 650–659; doi:10.1002/psp4.12035
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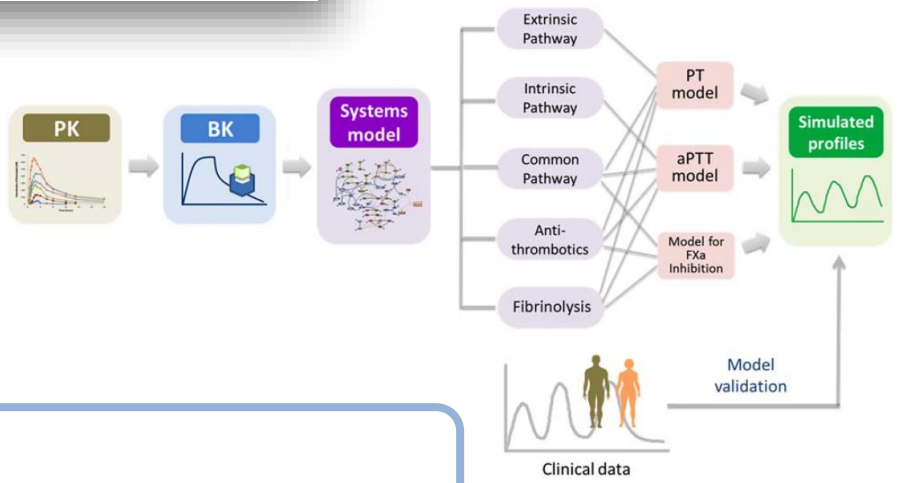
ORIGINAL ARTICLE

A Systems Pharmacology Model for Predicting Effects of Factor Xa Inhibitors in Healthy Subjects: Assessment of Pharmacokinetics and Binding Kinetics

X Zhou[1]*, DRH Huntjens[2] and RAHJ Gilissen[1]

- **背景：**
  - Xa 因子 (FXa) = 有效抗凝预防静脉血栓栓塞的有希望的靶点
  - 没有模型可以预测 FXa 抑制剂的临床凝血行为
  - Zhou *et al.开发了一个详细的 QSP 模型来回答以下问题*



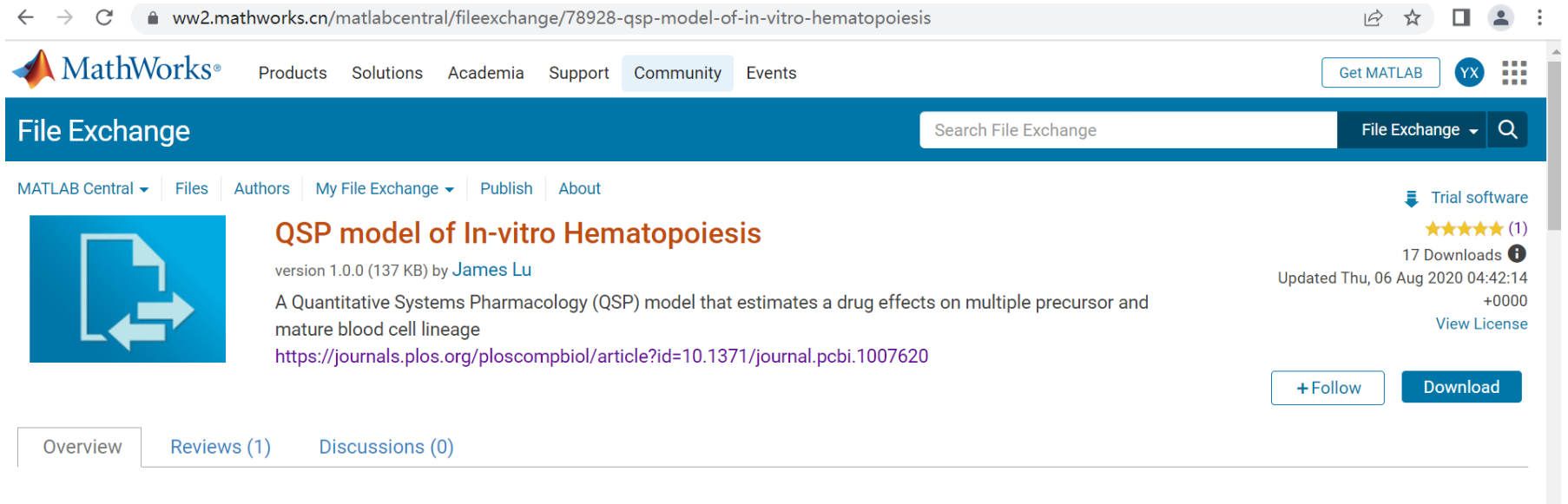
我们能否通过药物发现阶段的动力学数据来预测 FXa 抑制剂的药物作用？
药物靶点结合动力学是药物作用的重要决定因素吗？

- **结论：**
  - 不仅与药物和靶点相关的特性，而且与生物系统相关的参数和物种都是药物作用的重要决定因素。
  - 系统药理学模型可用于识别和验证凝血级联中的目标。

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716584/

Genentech: 体外造血 QSP 模型

- 骨髓抑制是与抗癌治疗相关的最常见和最严重的不良反应之一，并且可能是药物损耗的来源。
- 本文开发了体外造血的定量系统药理学 (QSP) 模型用于量化抗癌剂对多种造血细胞谱系的影响。
- 源代码可以在 MathWorks 官网访问：https://ww2.mathworks.cn/matlabcentral/fileexchange/78928-qsp-model-of-in-vitro-hematopoiesis、



哈佛医学院使用 SimBiology 教学

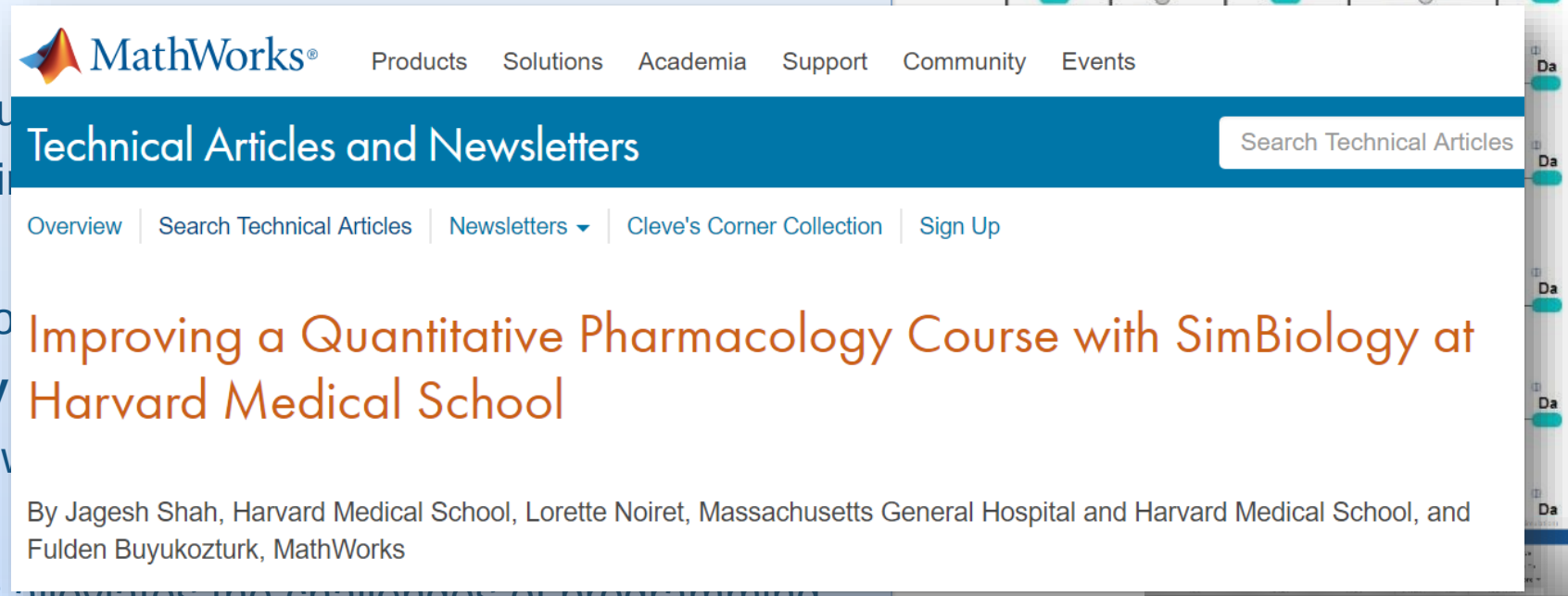
改进定量药理学课程

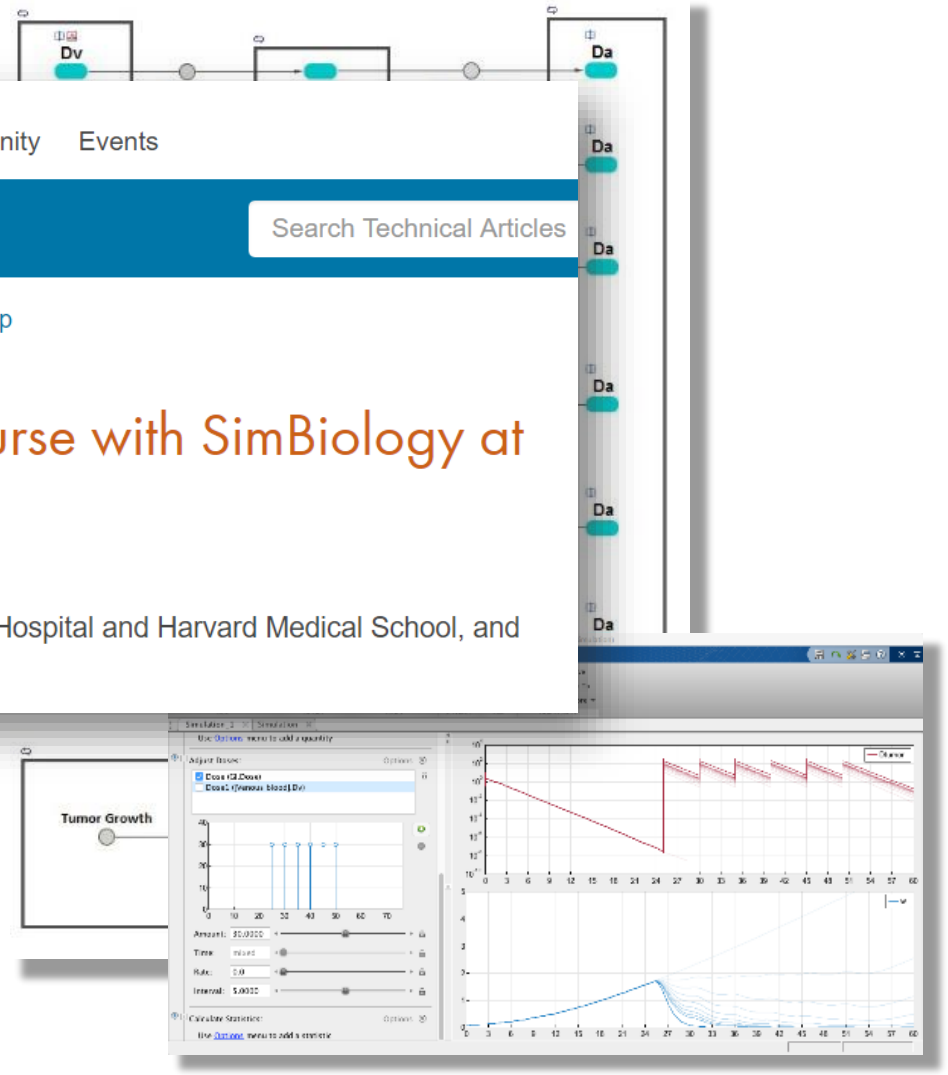
"Basing the
offer the cou
programmi

With SimBio
graphically
estimation, v

This aspect alleviates the challenges of programming and helps the students to **focus on the modeling** aspects."

Dr. Jagesh Shah
Harvard Medical School





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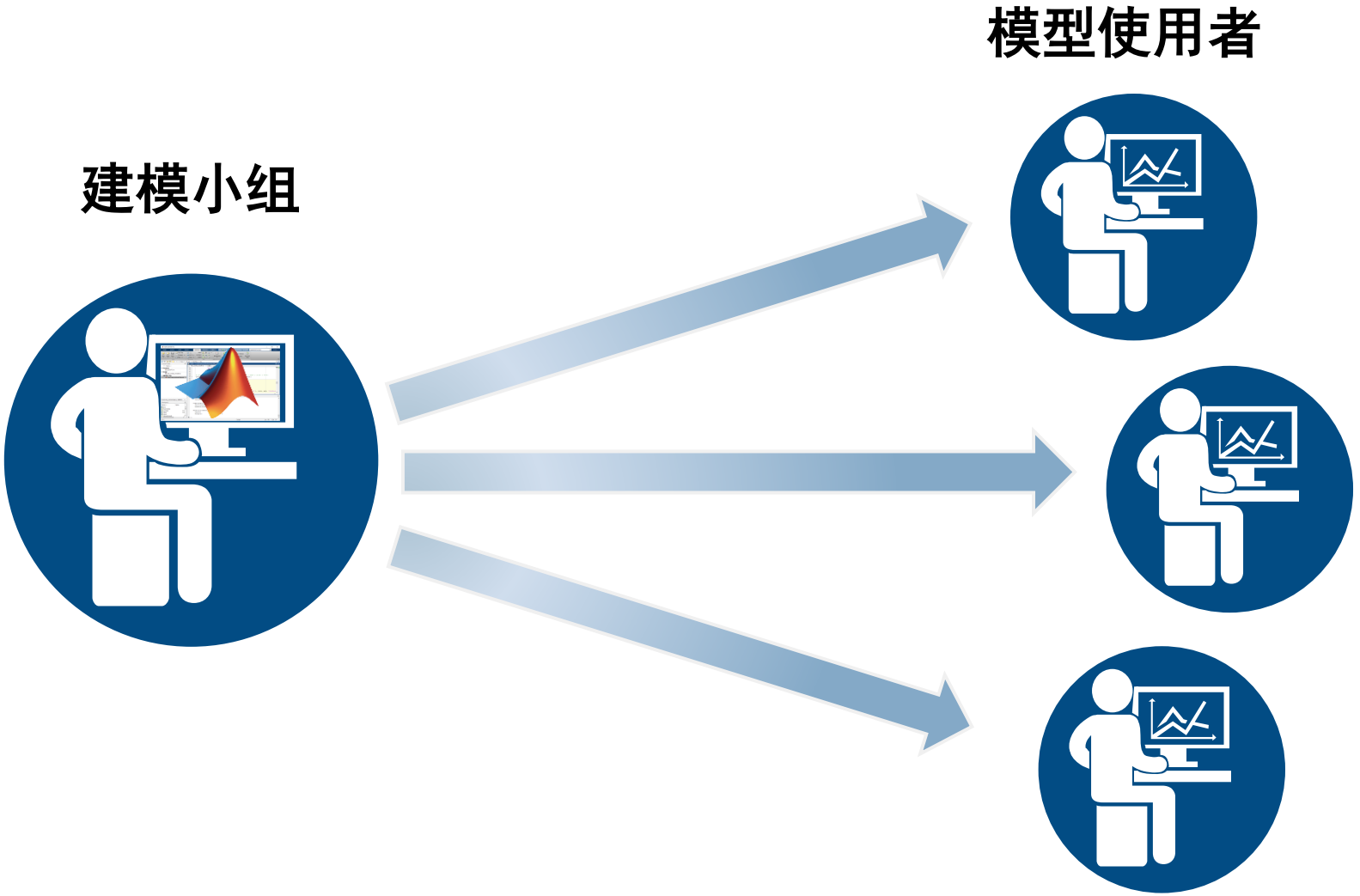
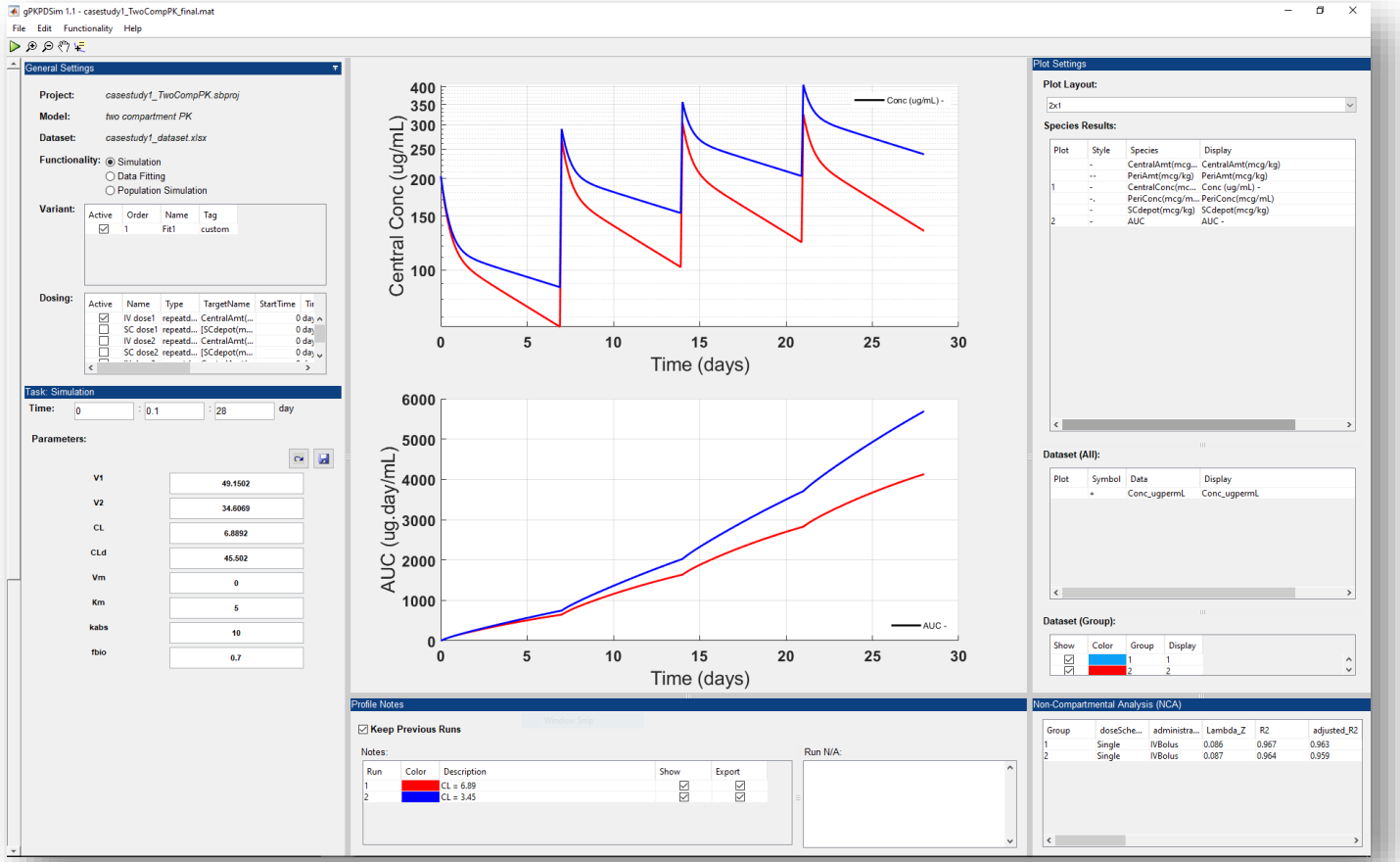
为仿真生成可以部署的 App



gPKPDSim: 一个基于 SimBiology® 的 GUI 应用程序，用于药物开发中的 PKPD 建模

- Genentech 希望能够轻松使用复杂模型来执行各种常见的 PKPD 分析，即使是非建模人员也可以操作
- 该项目为 MathWorks 咨询项目



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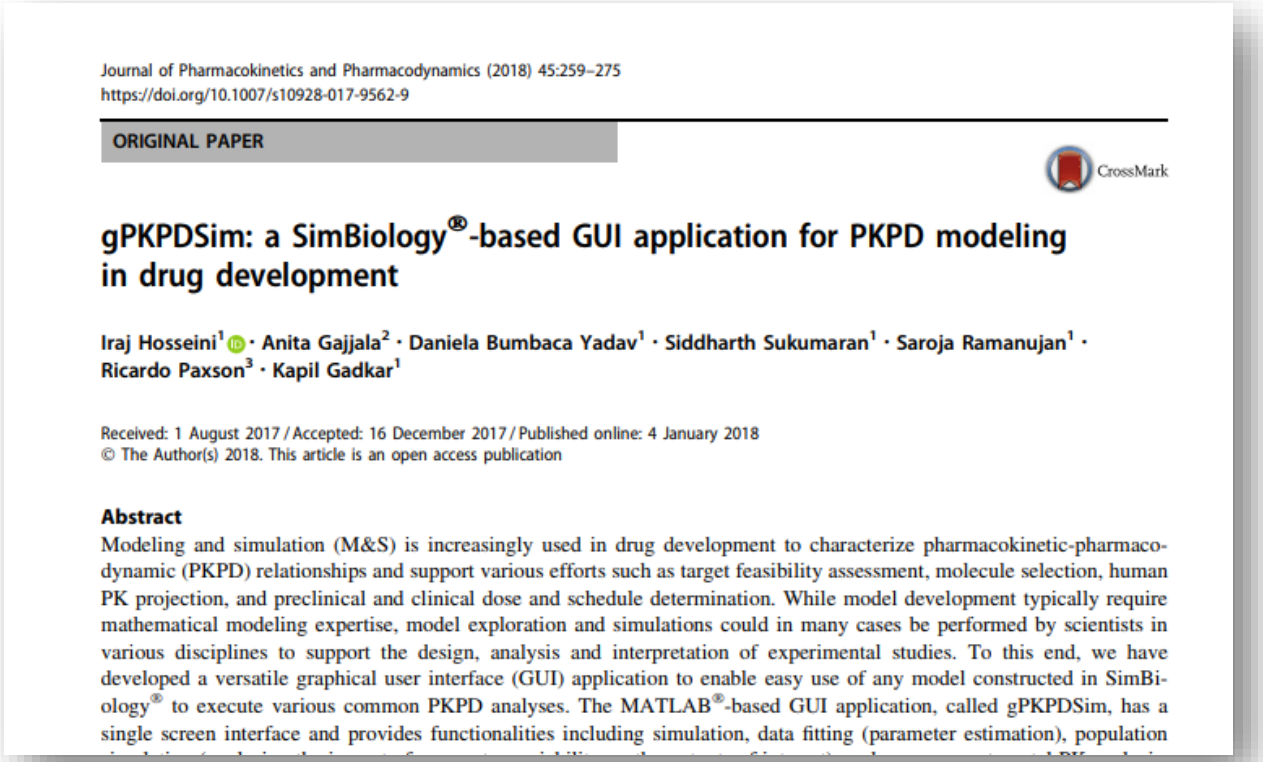

Journal of Pharmacokinetics and Pharmacodynamics (2018) 45:259–275
https://doi.org/10.1007/s10928-017-9562-9

ORIGINAL PAPER

CrossMark

gPKPDSim: a SimBiology®-based GUI application for PKPD modeling in drug development

Iraj Hosseini[1] · Anita Gajjala[2] · Daniela Bumbaca Yadav[1] · Siddharth Sukumaran[1] · Saroja Ramanujan[1] · Ricardo Paxson[3] · Kapil Gadkar[1]

Received: 1 August 2017 / Accepted: 16 December 2017 / Published online: 4 January 2018
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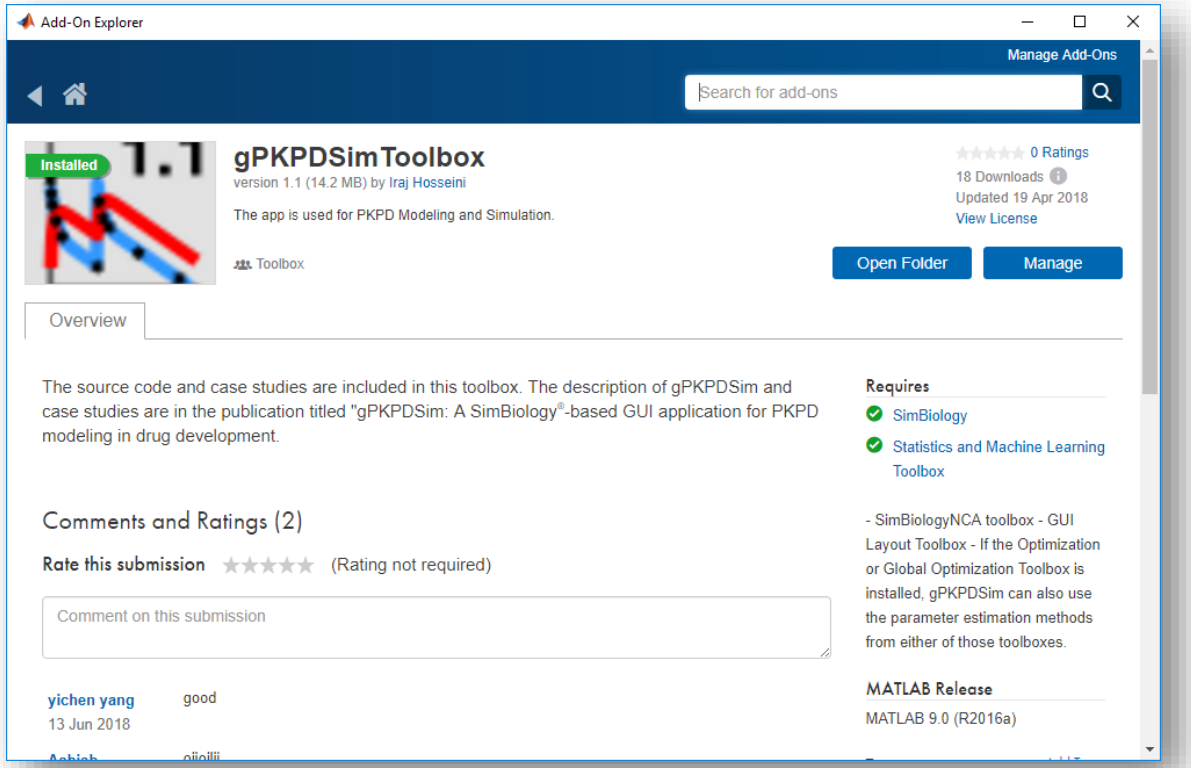
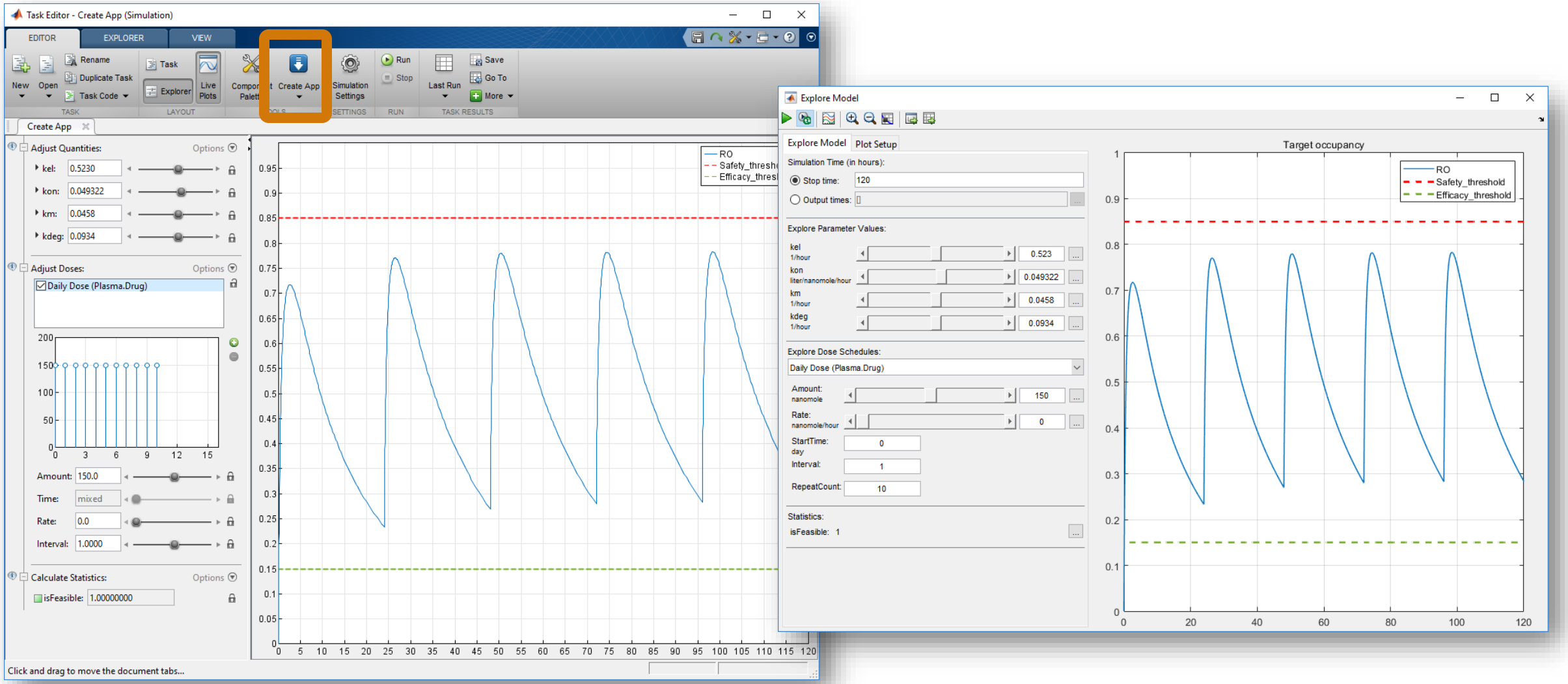
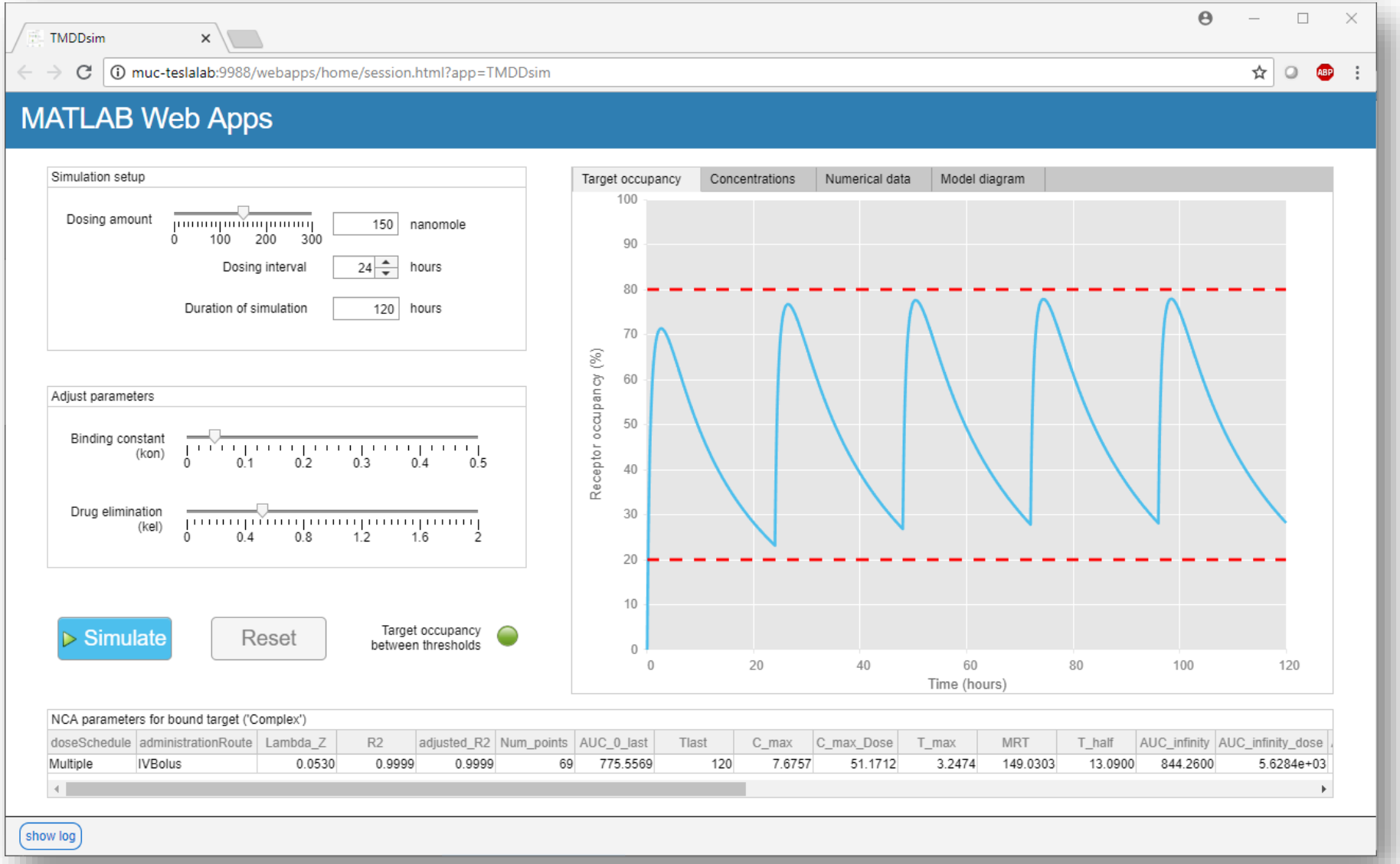
Abstract
Modeling and simulation (M&S) is increasingly used in drug development to characterize pharmacokinetic-pharmacodynamic (PKPD) relationships and support various efforts such as target feasibility assessment, molecule selection, human PK projection, and preclinical and clinical dose and schedule determination. While model development typically require mathematical modeling expertise, model exploration and simulations could in many cases be performed by scientists in various disciplines to support the design, analysis and interpretation of experimental studies. To this end, we have developed a versatile graphical user interface (GUI) application to enable easy use of any model constructed in SimBiology® to execute various common PKPD analyses. The MATLAB®-based GUI application, called gPKPDSim, has a single screen interface and provides functionalities including simulation, data fitting (parameter estimation), population



为仿真生成可部署 App



在您的局域网中通过 URL 分享您的仿真 App



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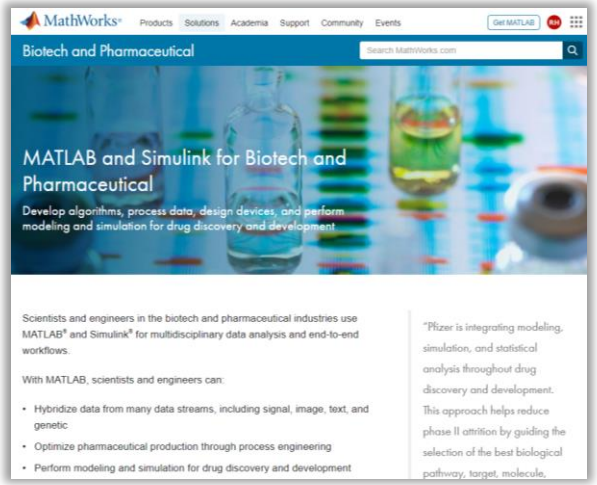
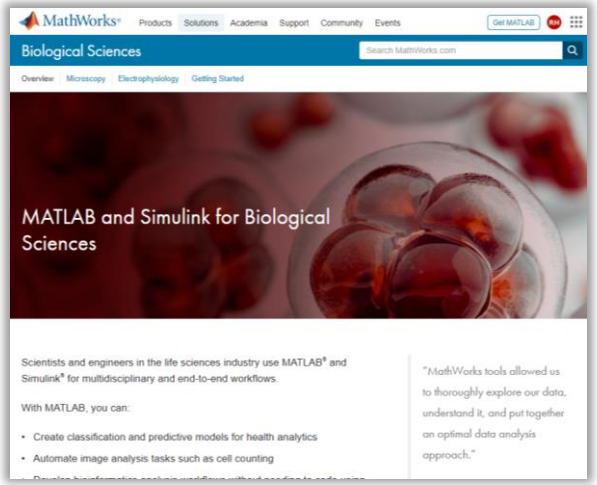
制药行业相关网页

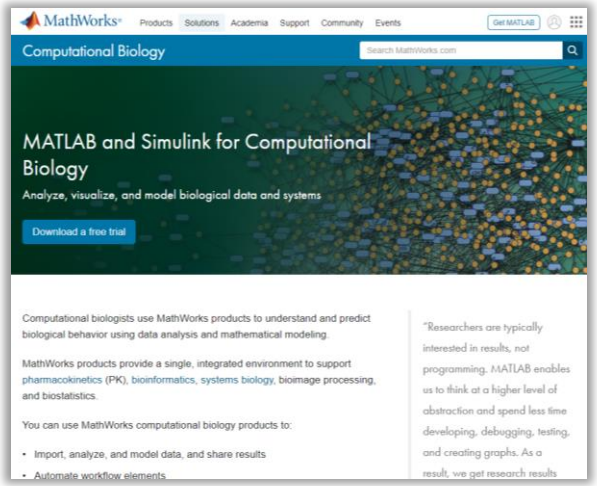


[Biotech and Pharmaceutical Solutions Page]

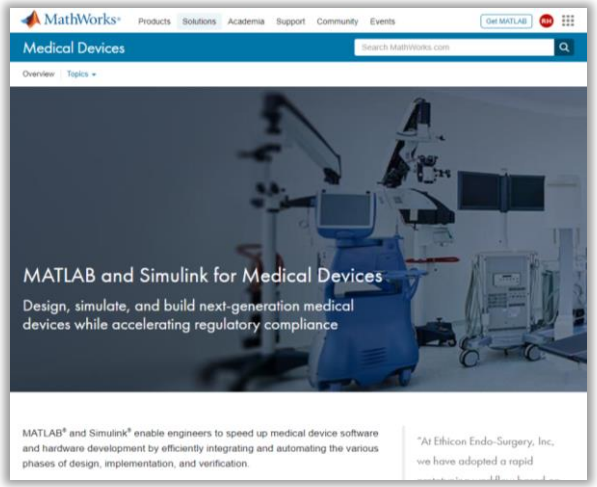
[SimBiology Product Page]



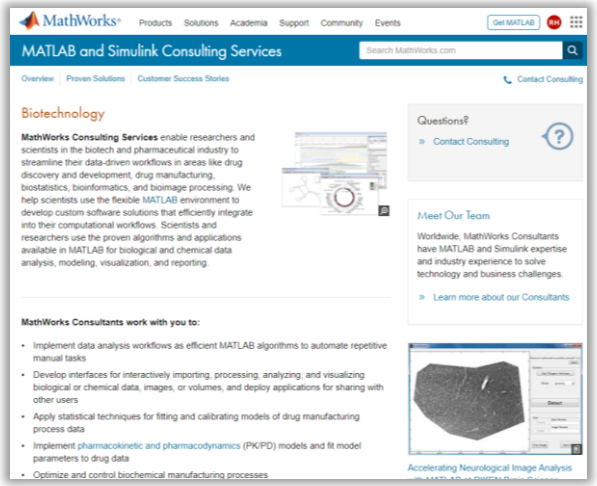
[Biological Sciences Solutions Page]



[Computational Biology Solutions Page]

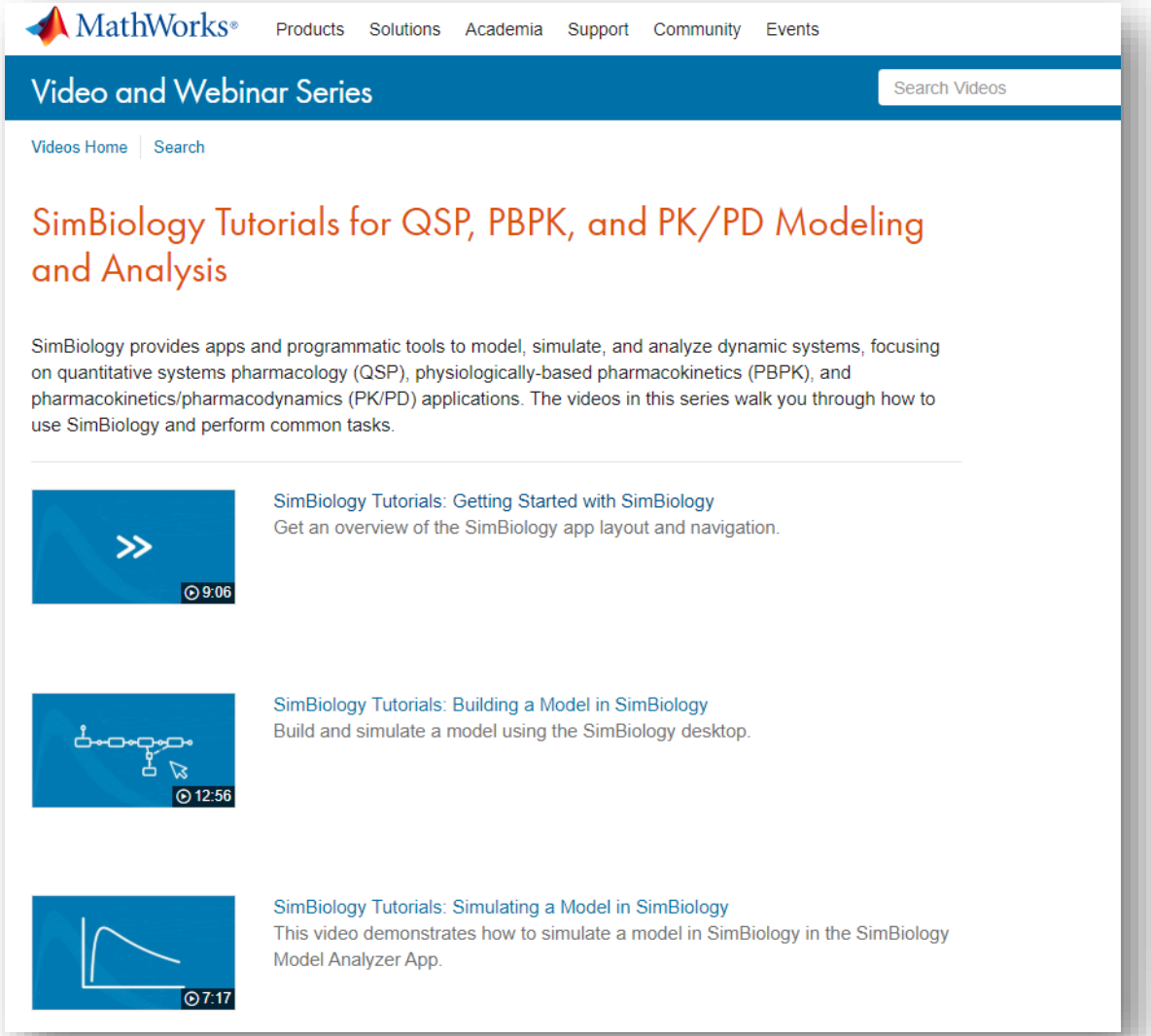


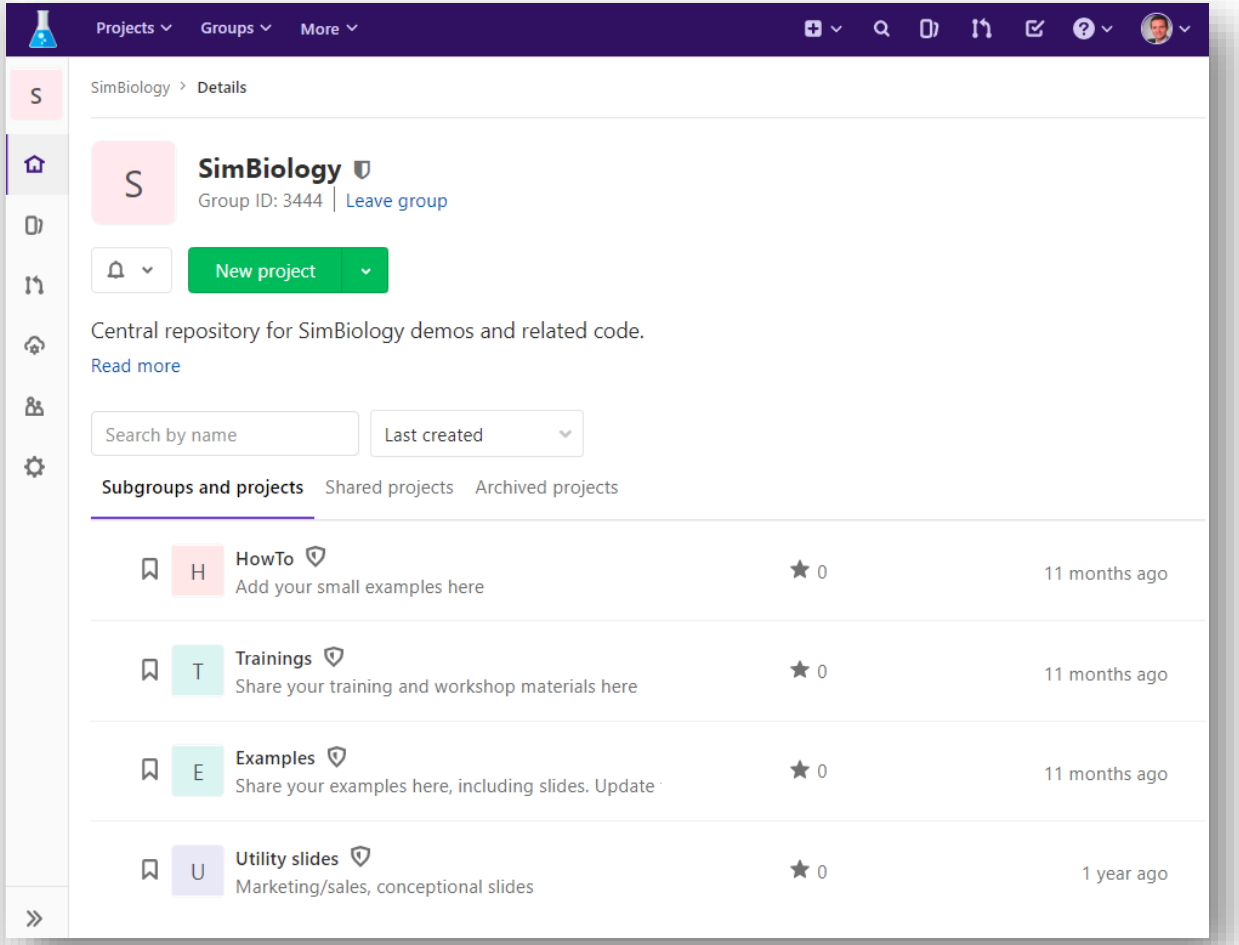
[Medical Devices Solutions Page]



[Biotechnology Consulting Page]

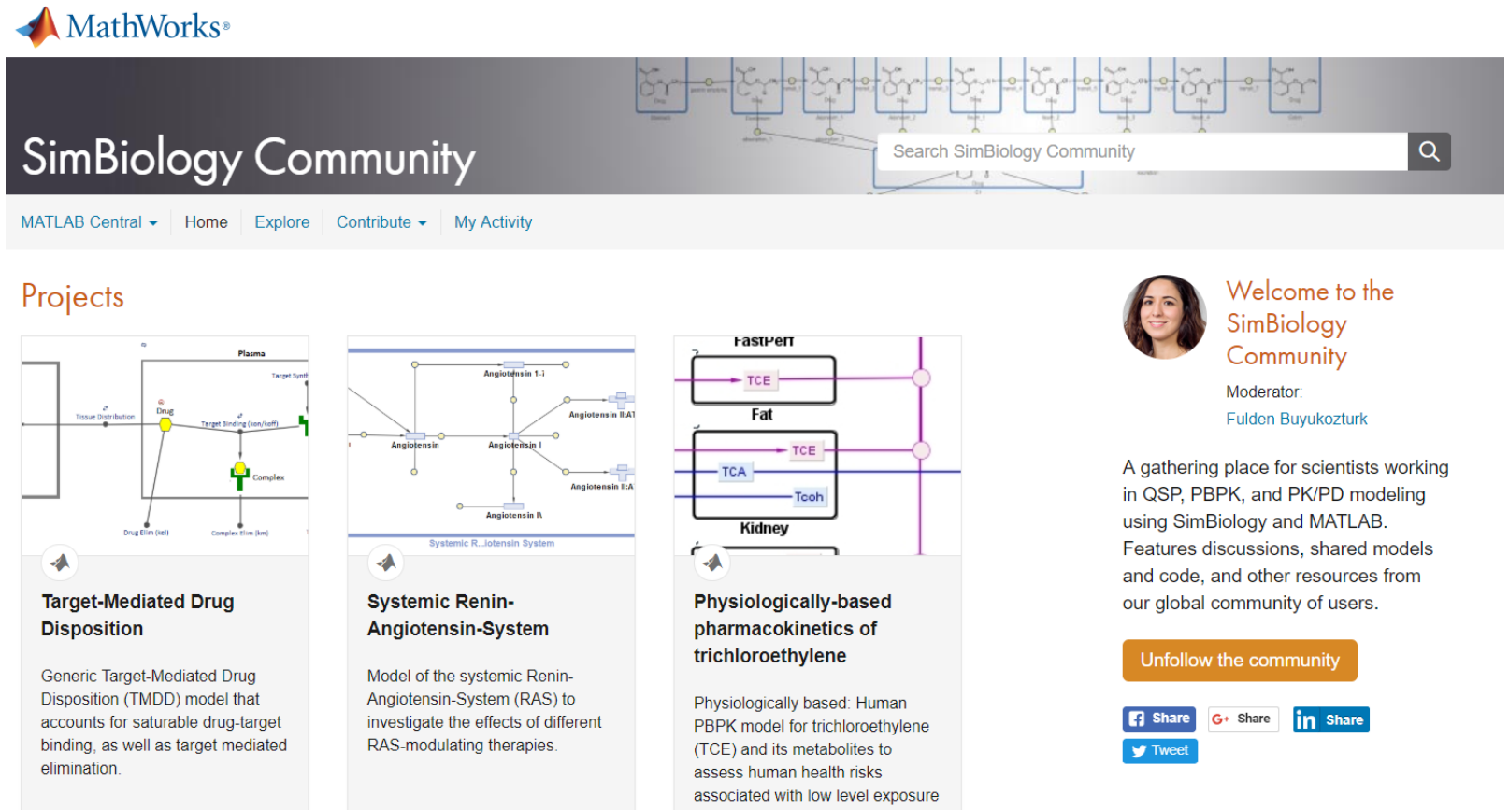
MathWorks 教程与示例





https://ww2.mathworks.cn/videos/series/simbiology-tutorials-for-qsp-pbpk-and-pk-pd-modeling-and-analysis.html
https://github.com/mathworks-simbiology

支持：SimBiology 专属社区



- 问答
- 讨论
- 模型
- 代码
- 您也可以向我们寻求技术支持

https://www.mathworks.com/matlabcentral/simbiology.html

MATLAB 中国官方B站

https://space.bilibili.com/1768836923

礼物领取地址：

仙林信息化中心楼一楼前台，上班时间带本人证件来领取