Quasi Steady State Petri Net (QSSPN)

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Tripos

Pharsight

2008

CERTARA

Formed by the merging of Tripos and Pharsight

2012

simcyp

Mechanistic-based PBPK modeling, DDI and special population simulation

2013

Drug development consultancy, program management and model based drug management

2014

synchrogenix

Regulatory writing and document focused services

2015

ClinGenuity

Disclosure and transparency focused services, medical writing

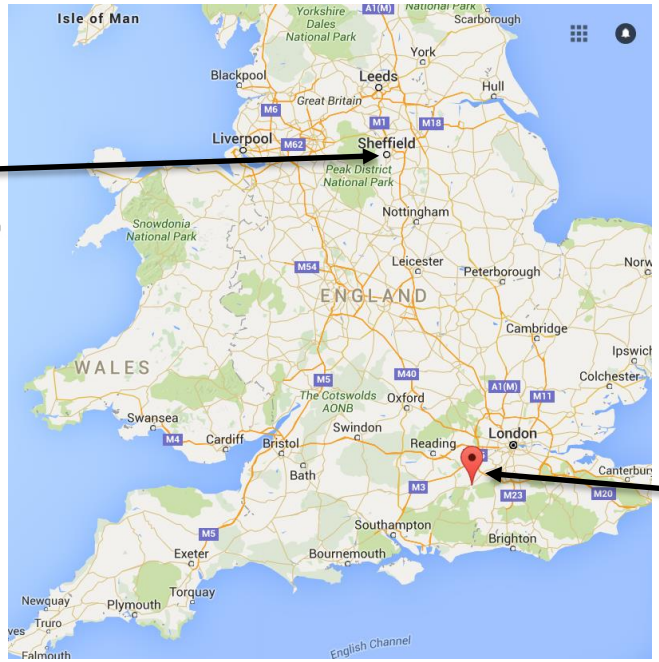
2015

Quantitative Solutions

Model-based Meta-analysis, clinical databases, full M&S/pharmacometric services

XenologiQ

Quantitative Systems Pharmacology



From 2004: Lecturer Reader, Professor, Visiting Professor of Systems Biology,

University of Surrey, Guildford, UK

From 2016:

Head of Systems Modelling,

Simcyp, a Certara Company

Sheffield, UK

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Outline

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- Motivation: Computer simulation of molecular cell biology
- Motivation: Large mechanistic models in Large Pharma
- Flux Balance Analysis of Genome Scale Metabolic Networks
- **Quasi-Steady State Petri Nets (QSSPN)**

Statistical inference of genotype-phenotype relationship.

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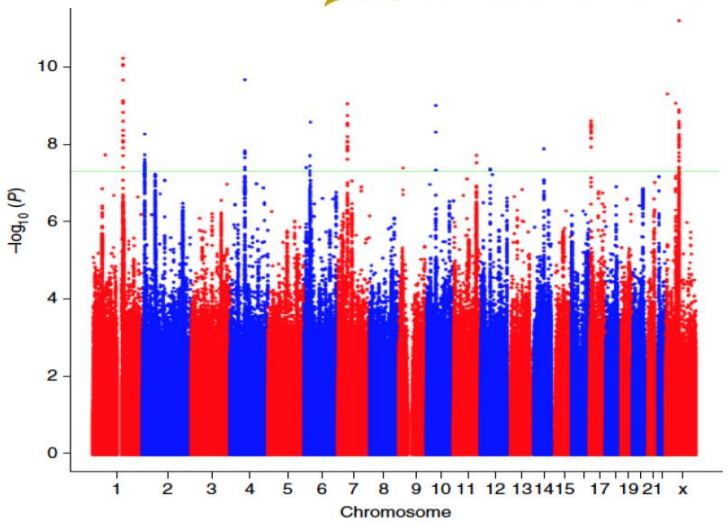


LETTERS

nature genetics

A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer

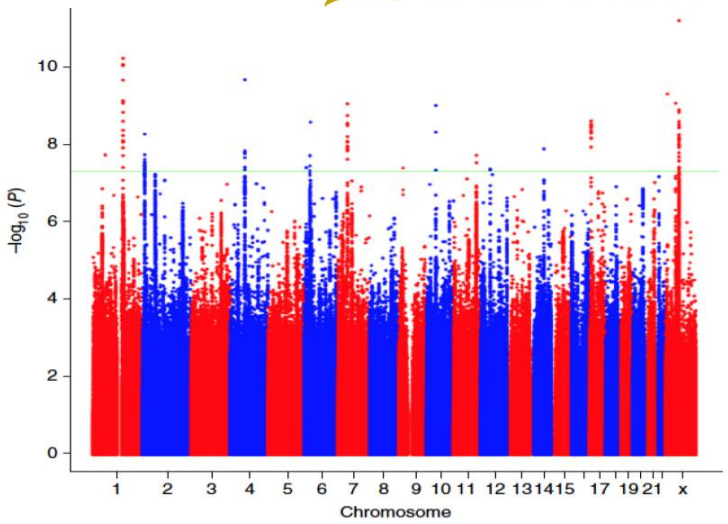
Al Olama AA[1], Kote-Jarai Z[2], Berndt SI[3], Conti DV[4], Schumacher F[4], Han Y[5], Benlloch S[6], Hazelett DJ[4], Wang Z[7], Saunders E[8], Leongamornlert D[8], Lindstrom S[9], Jugurnauth-Little S[8], Dadaev T[8], Tymrakiewicz M[8], Stram DO[4], Rand K[5], Wan P[5], Stram A[5], Sheng X[5], Pooler LC[5], Park K[5], Xia L[5], Tyrer J[6], Kolonel LN[10], Le Marchand L[10], Hoover RN[3], Machiela MJ[3], Yeager M[3], Burdette L[3], Chung CC[3], Hutchinson A[3], Yu K[3], Goh C[8], Ahmed M[8], Govindasami K[8], Guy M[8], Tammela TL[11], Auvinen A[12], Wahlfors T[13], Schleutker J[14], Visakorpi T[15], Leinonen KA[15], Xu J[16], Aly M[17], Donovan J[18], Travis RC[19], Key TJ[19], Siddiq A[20], Canzian F[21], Khaw KT[22], Takahashi A[23], Kubo M[24], Pharoah P[25], Pashayan N[25], Weischer M[26], Nordestgaard BG[27], Nielsen SF[27], Klarskov P[28], Røder MA[29], Iversen P[29], Thibodeau SN[30], McDonnell SK[30], Schaid DJ[30], Stanford JL[31], Kolb S[32], Holt S[33], Knudsen B[34], Coll AH[35], Gapstur SM[36], Diver WR[36], Stevens VL[36], Maier C[37], Luedeke M[37], Herkommer K[38], Rinckleb AE[37], Strom SS[39], Pettaway C[40], Yeboah ED[41], Tettey Y[41], Biritwum RB[41], Adjei AA[41], Tay E[41], Truelove A[42], Niwa S[42], Chokkalingam AP[43], Cannon-Albright L[44], Cybulski C[45], Wokołorczyk D[45], Kluźniak W[45], Park J[46], Sellers T[46], Lin HY[47], Isaacs WB[48], Partin AW[48], Brenner H[49], Dieffenbach AK[49], Stegmaier C[50], Chen C[9], Giovannucci EL[51], Ma J[52], Stampfer M[53], Penney KL[54], Mucci L[54], John EM[55], Ingles SA[4], Kittles RA[56], Murphy AB[57], Pandha H[58], Michael A[58], Kierzek AM[58], Blot W[59], Signorello LB[54], Zheng W[60], Albanes D[61], Virtamo J[62], Weinstein S[61], Nemesure B[63], Carpten J[64], Leske C[63], Wu SY[63], Hennis A[65], Kibel AS[66], Rybicki BA[67], Neslund-Dudas C[67], Hsing AW[55], Chu L[55], Goodman PJ[68], Klein EA[69], Zheng SL[16], Batra J[70], Clements J[70], Spurdle A[71], Teixeira MR[72], Paulo P[73], Maia S[73], Slavov C[74], Kaneva R[75], Mitev V[75], Witte JS[76], Casey G[4], Gillanders EM[77], Seminara D[77], Riboli E[78], Hamdy FC[79], Coetzee GA[4], Li Q[80], Freedman ML[80], Hunter DJ[9], Muir K[81], Gronberg H[82], Neal DE[83], Southey M[84], Giles GG[85], Severi G[86]; Breast and Prostate Cancer Cohort Consortium (BPC3); PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; COGS (Collaborative Oncological Gene-environment Study) Consortium; GAME-ON/ELLIPSE Consortium, Cook MB[87], Nakagawa H[88], Wiklund F[89], Kraft P[90], Chanock SJ[87], Henderson BE[91], Easton DF[1], Eeles RA[92], Haiman CA[91].

We can determine any genotype of interest, including full genome sequence of an individual.

Genotype-phenotype relationship is fundamental problem in basic and applied science. Knowledge will revolutionise medicine and biotechnology.

Currently, statistical inference is attractive approach to study genotype-phenotype relationship.

Statistical inference of genotype-phenotype relationship.



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What molecular/physiological mechanisms associate these 23 genes with cancer? How complex genotype-environment-phenotype interactions could be studied with GWAS approach?

We can determine any genotype of interest, including full genome sequence of an individual.

Genotype-phenotype relationship is fundamental problem in basic and applied science. Knowledge will revolutionise medicine and biotechnology.

Currently, statistical inference is attractive approach to study genotype-phenotype relationship.

Mechanistic computer simulation of genotype-phenotype relationship.

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BIBLIOME* OF MOLECULAR BIOLOGY

***Formerly known as library**

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Mechanistic computer simulation of genotype-phenotype relationship.

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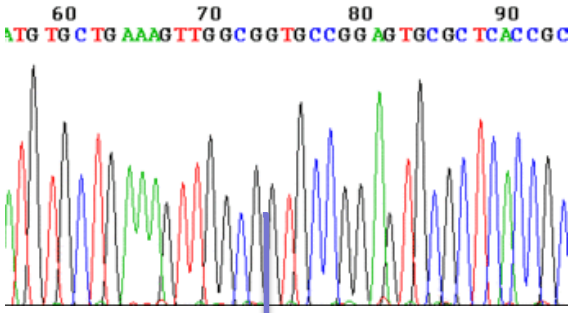
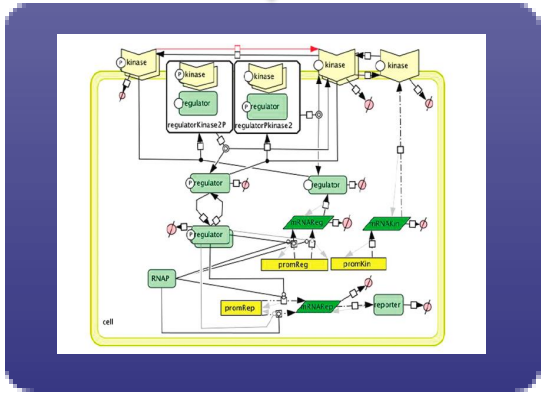
GENOTYPE



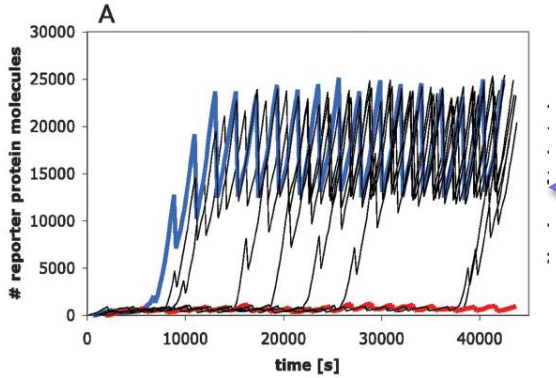
BIBLIOME* OF MOLECULAR BIOLOGY

ENVIRONMENT



Computer simulation of molecular cell biology.

SIMULATED PHENOTYPE



***Formerly known as library**

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Physiologically Based Pharmacokinetics (PBPK) – whole system mechanistic simulation routinely used in Large Pharma.

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Non-eliminating tissues:

$$\frac{dC_T}{dt} = \frac{Q_T C_A - Q_T C_{v,T}}{V_T}$$

Eliminating tissues (liver, kidney):

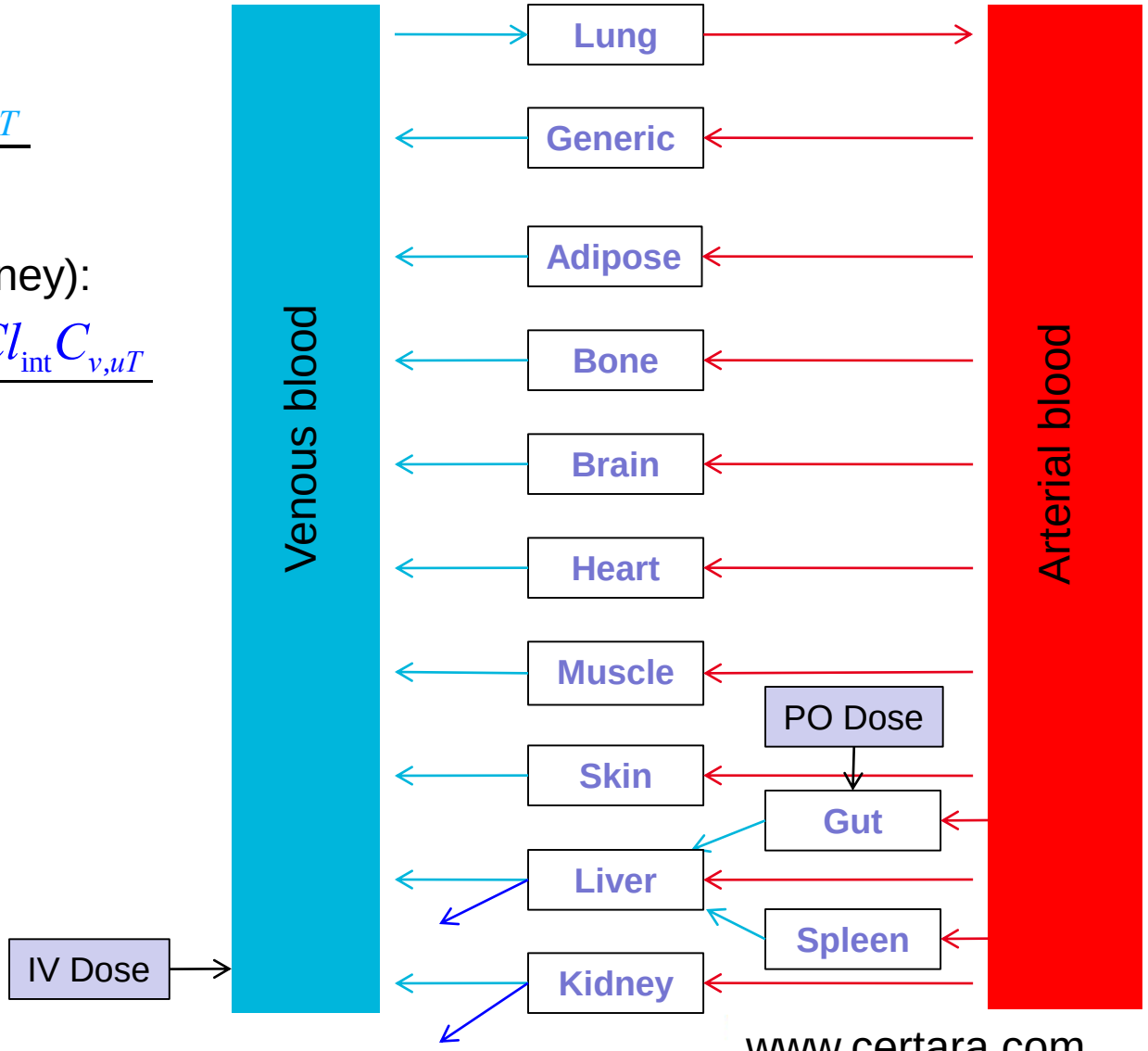
$$\frac{dC_T}{dt} = \frac{Q_T C_A - Q_T C_{v,T} - Cl_{\text{int}} C_{v,uT}}{V_T}$$

where:

Q	Blood flow [L/h]
V	Volume [L/h]
T	Tissue
A, v, u	Arterial, venous, unbound

$$C_{v,T} = \frac{K_p}{B:P}$$

$B:P$	Blood/plasma partition coefficient
K_P	Tissue/plasma partition coefficient
Cl_{int}	Intrinsic clearance



Physiologically Based Pharmacokinetics (PBPK) – whole system mechanistic simulation routinely used in Large Pharma.

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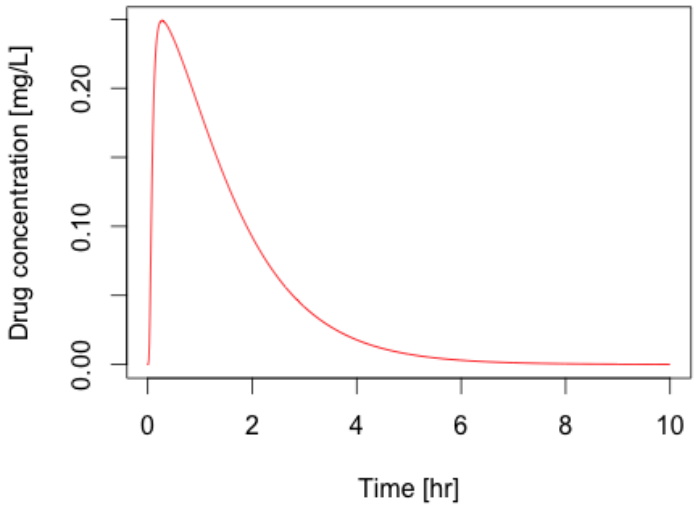
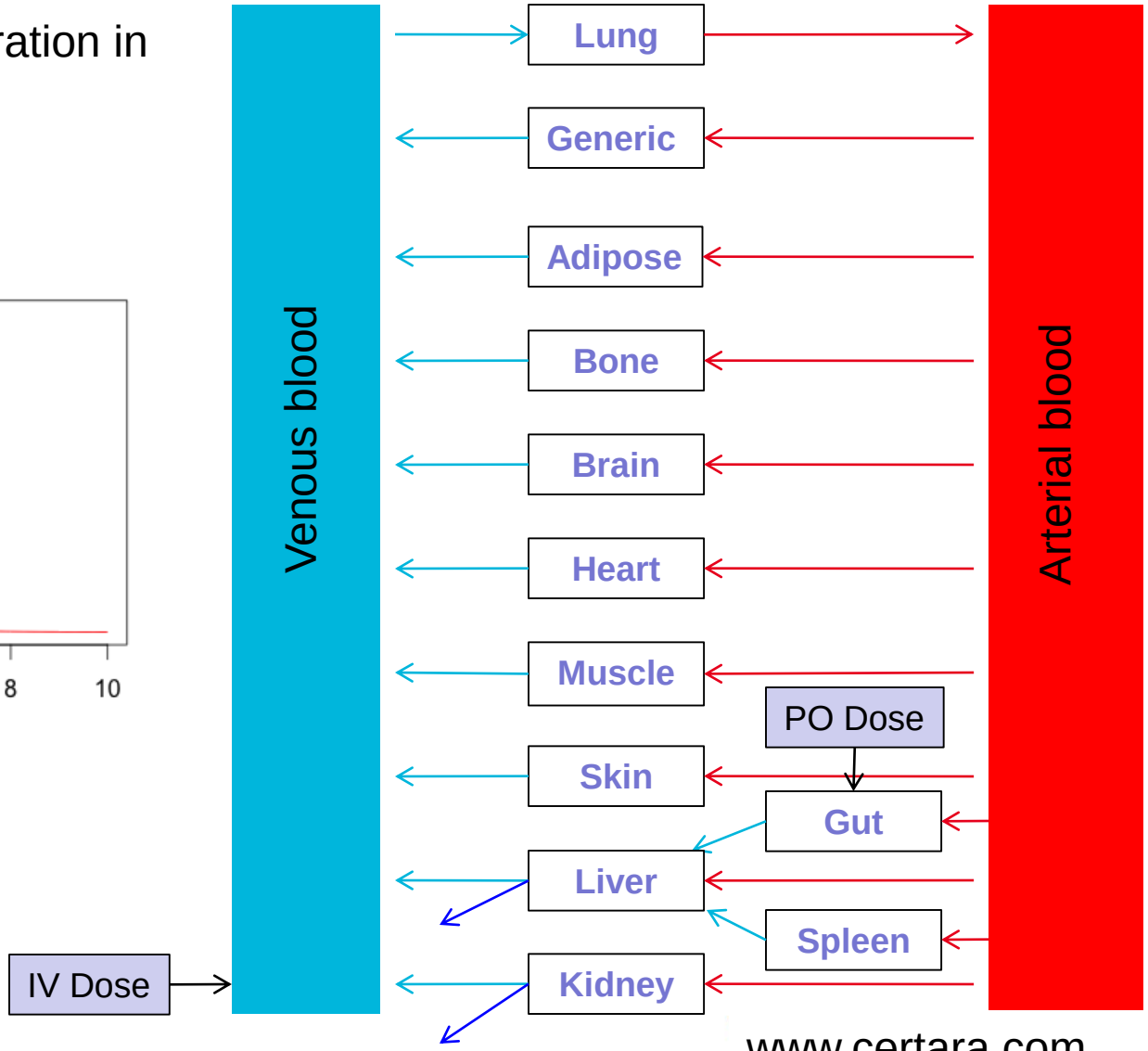
Simulation of drug concentration in Heart:





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Physiologically Based Pharmacokinetics (PBPK) – whole system mechanistic simulation routinely used in Large Pharma.

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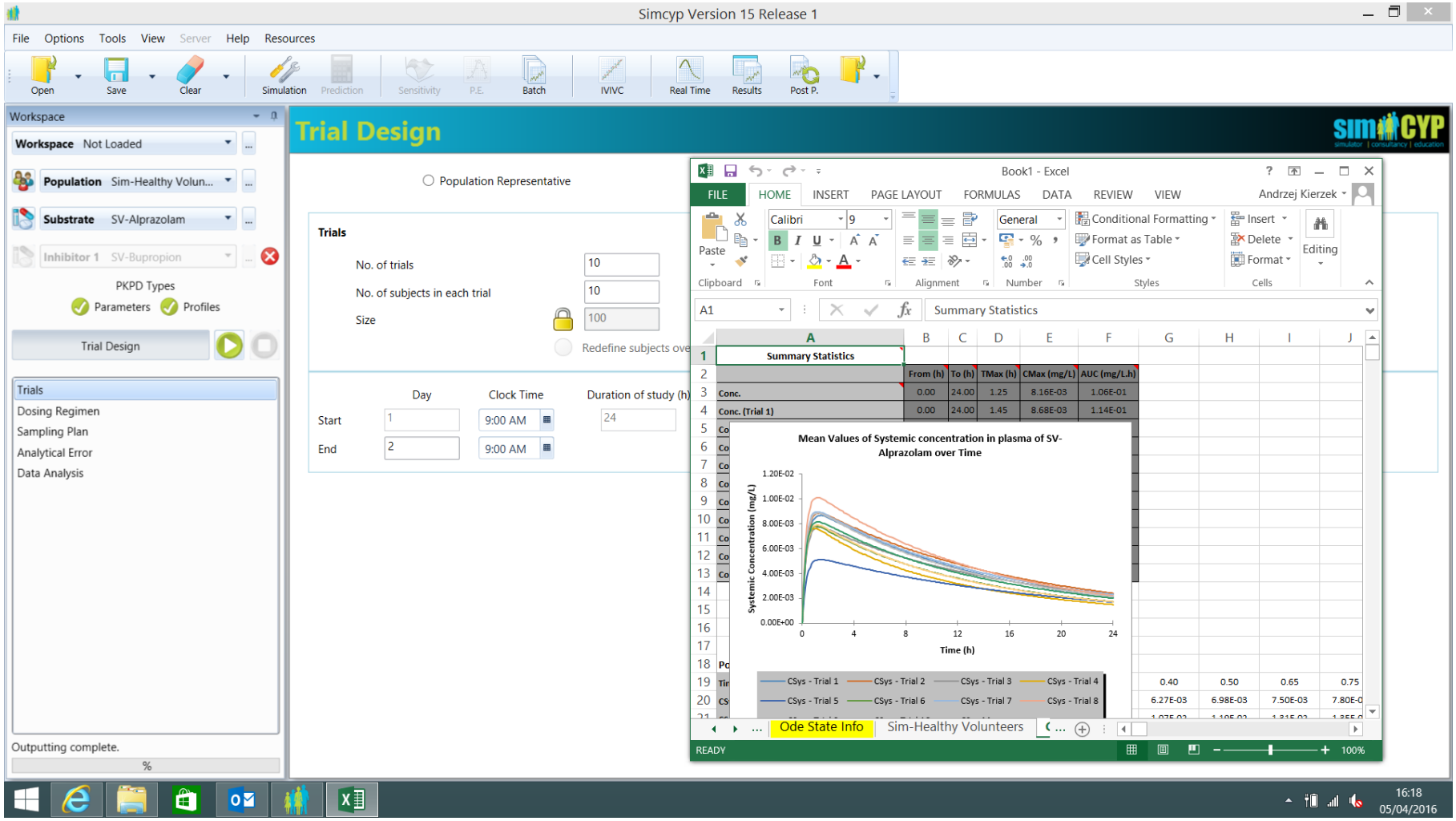

Simcyp simulator

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PBPK: – whole system scale, bottom-up, literature-based mechanistic simulation routinely used in Large Pharma.

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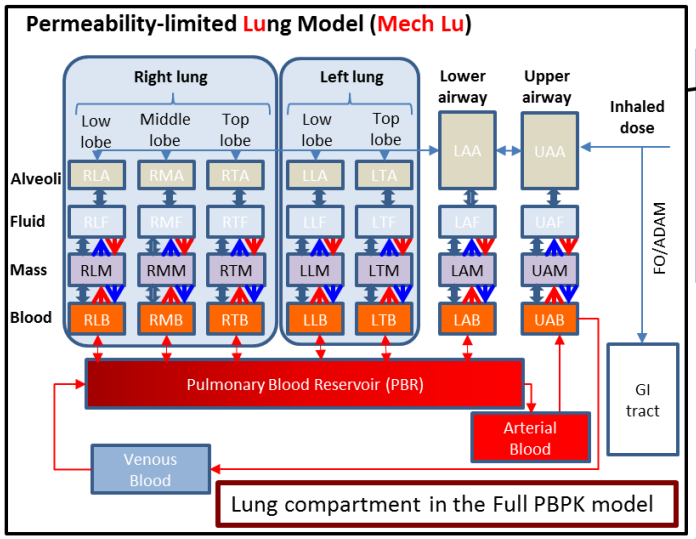

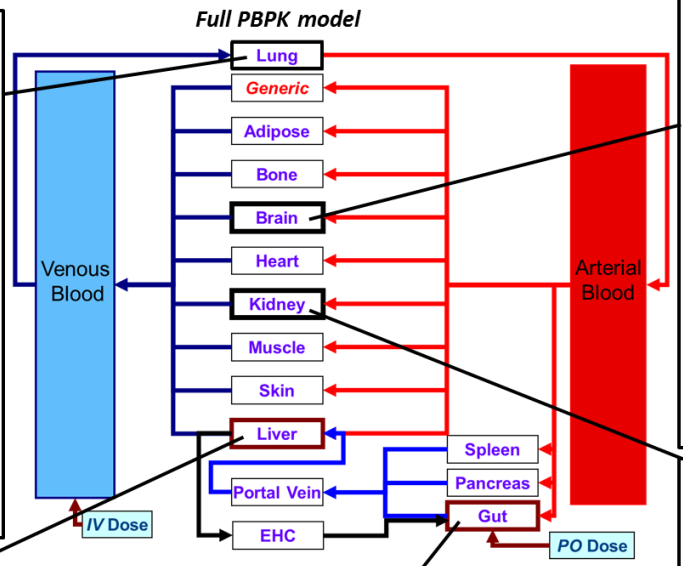

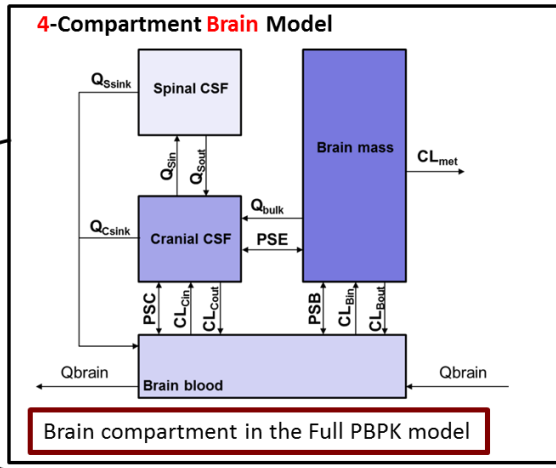

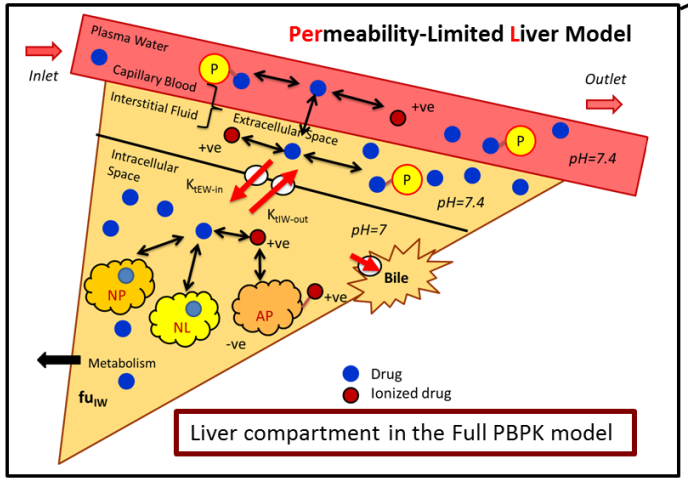

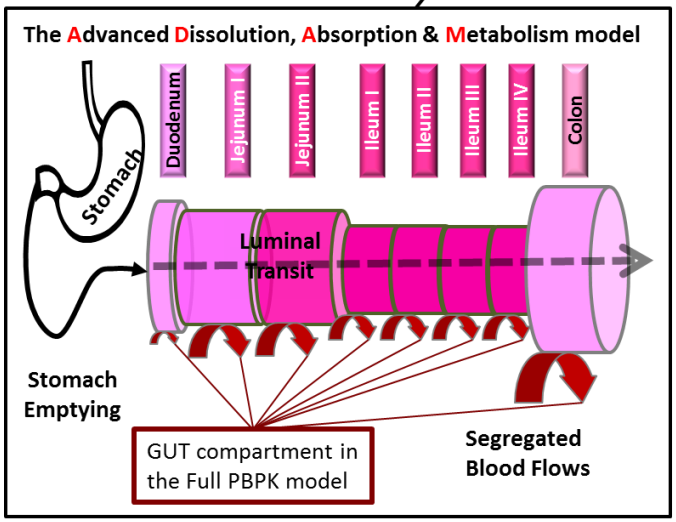

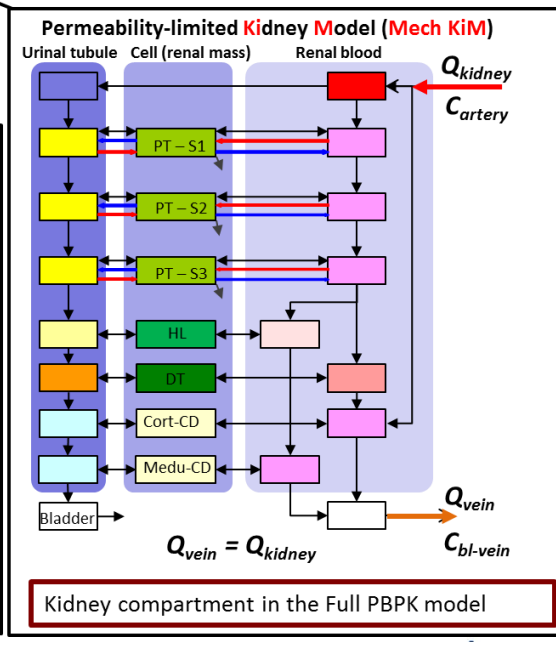

Permeability-limited model are available for the intestine, liver, kidney, brain and lung.

Example drug label claim based on PBPK simulation.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA® (ibrutinib) capsules, for oral use

Initial U.S. Approval: 2013

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

Coadministration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C_{max} and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

PBPK impact on new drug approvals.

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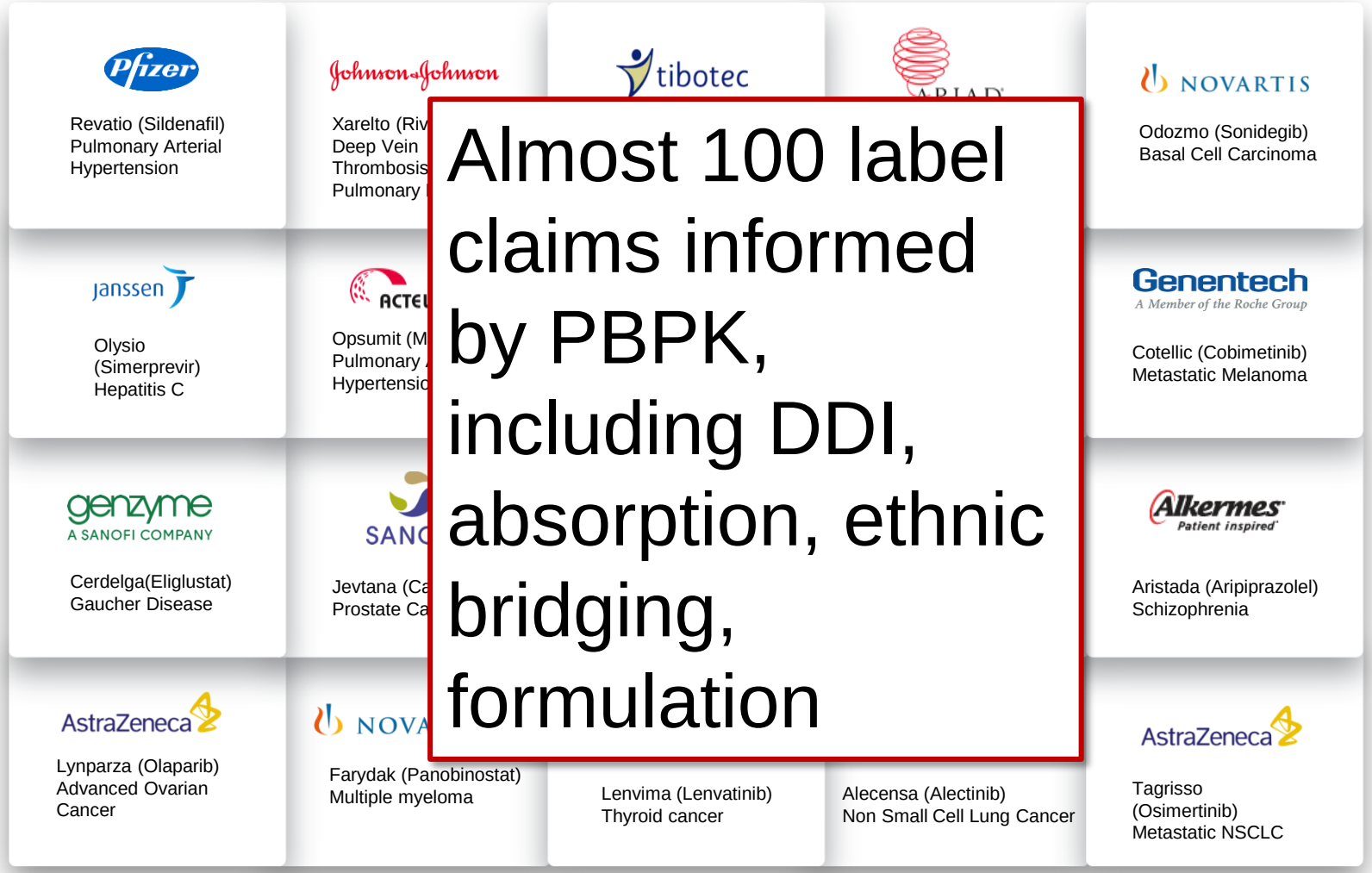

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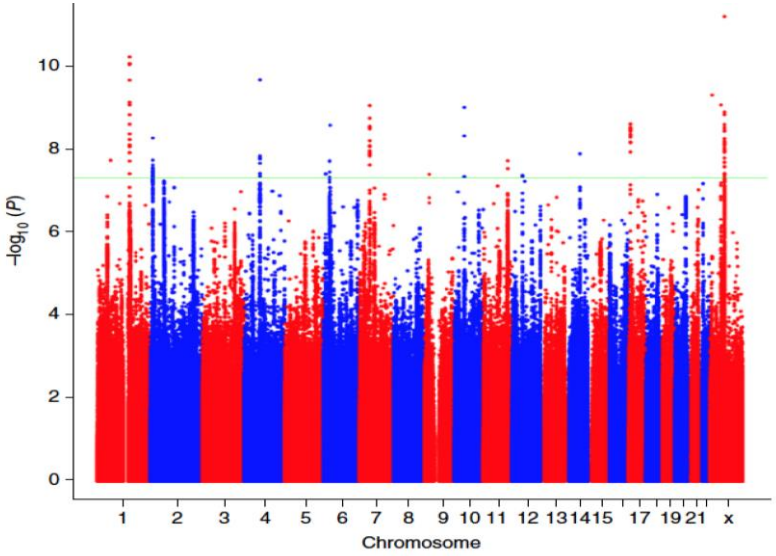
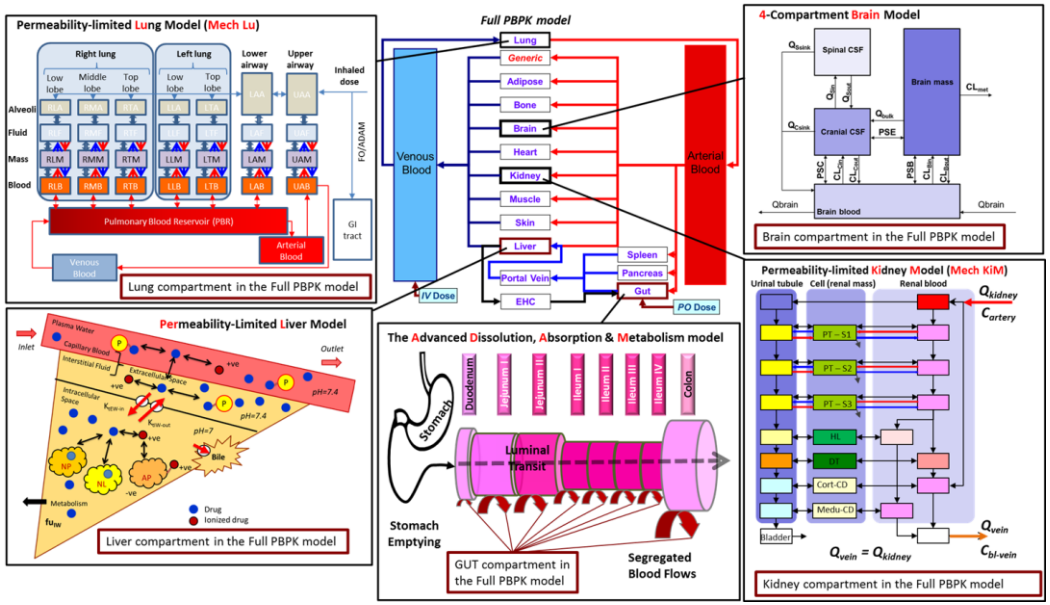


MIND THE GAP



We can determine full genome sequence of an individual. Genomics has entered clinical research and healthcare (UK NHS 100K genomes project).

Currently, Simcyp simulator can mechanistically account for polymorphism of only about 20 genes (drug metabolism and drug transporters).

Bridging the gap between genomics and physiology through mechanistic modelling of "intracellular space" is a major challenge and solutions will revolutionise model-based drug development.

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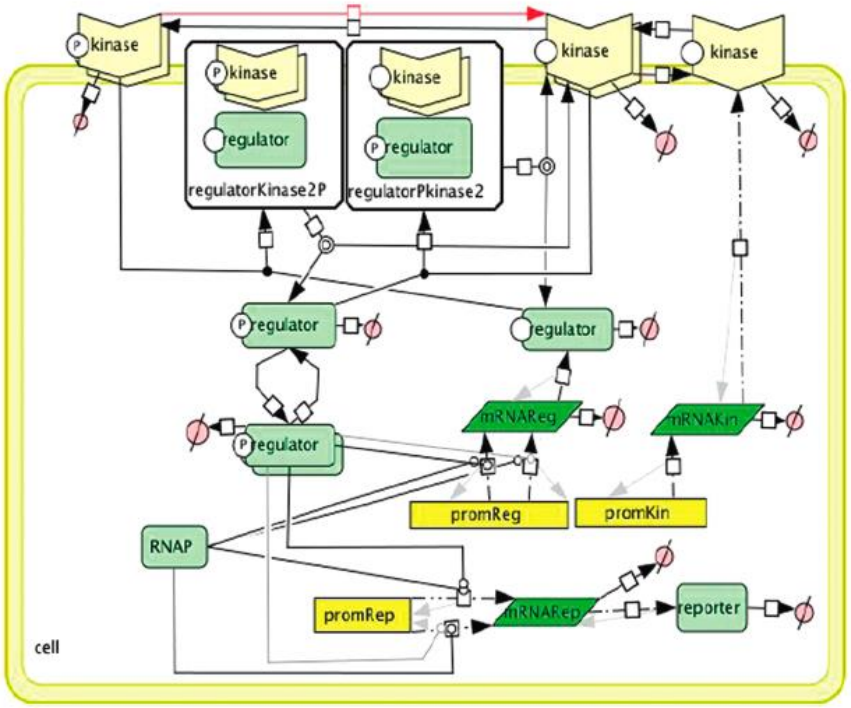
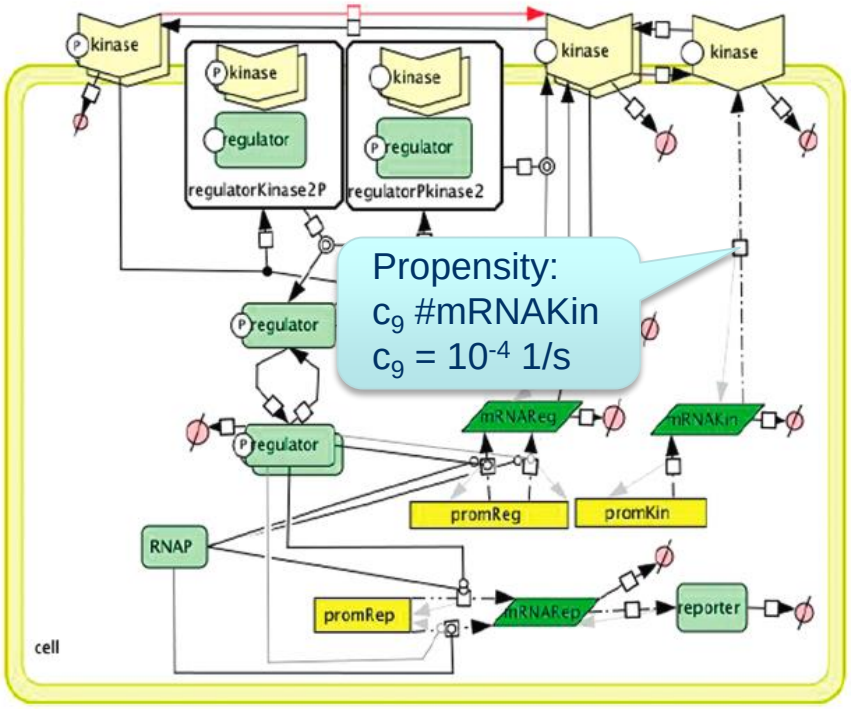
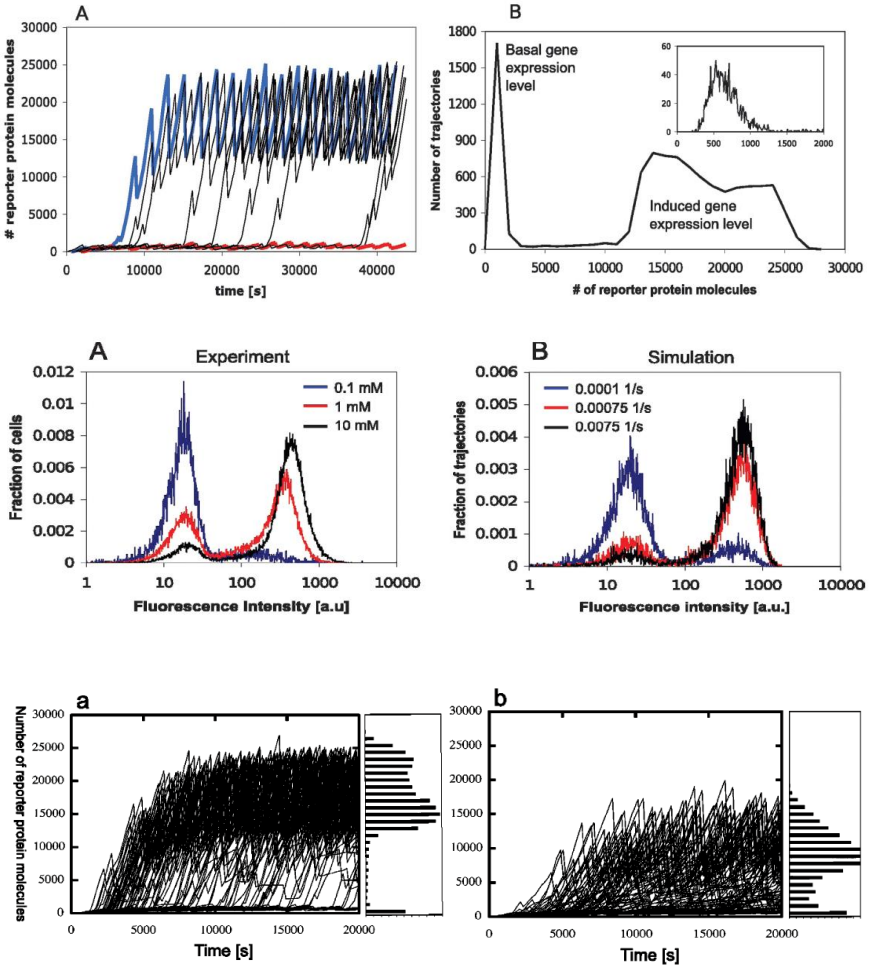
Quantitative simulation of molecular network dynamics



Stochastic kinetic model of two component system signalling. Kierzek, Zhou, Wanner, Molecular Biosystems, 2010, Hoyle, Avitabile, Kierzek, PLoS Comp Biol 2012

Quantitative simulation of molecular network dynamics





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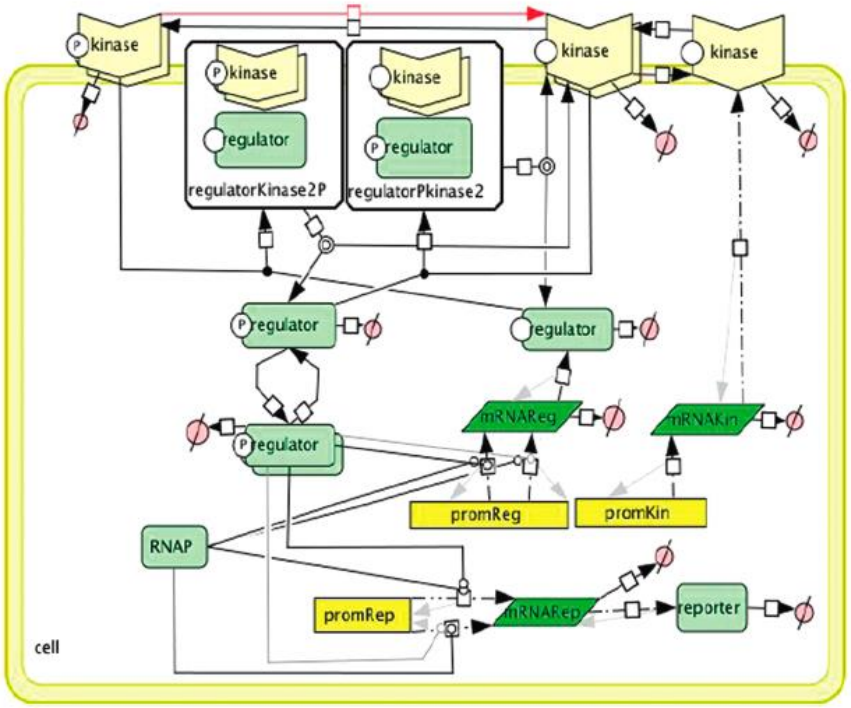
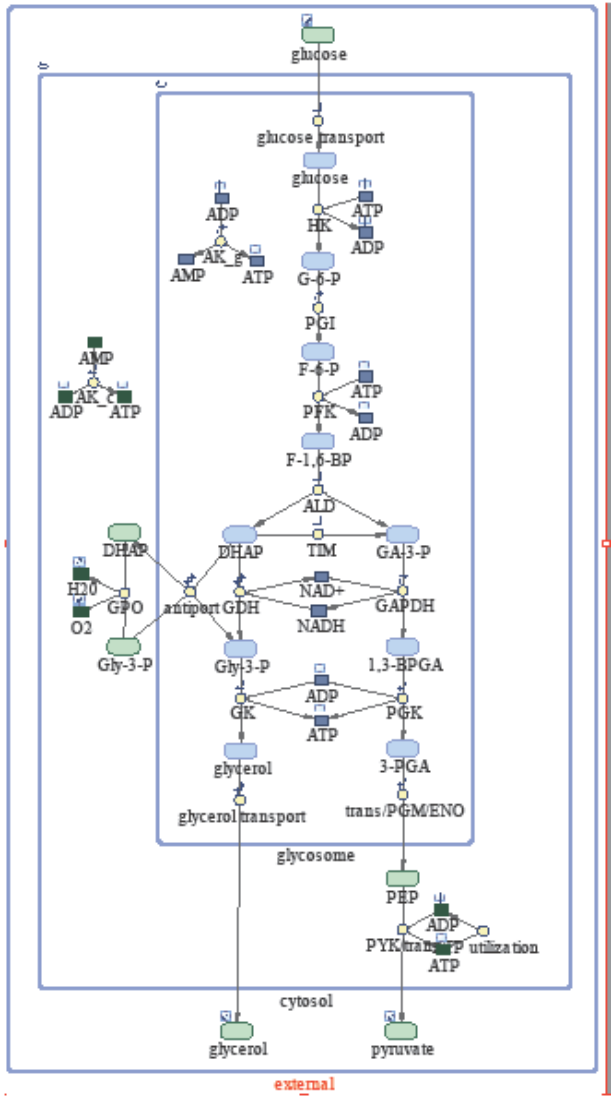
By the way ....



Molecular networks are commonly represented as bipartite graphs even if it is not referred to as a Petri Net. SBGN and CellDesigner (above) as well as Matlab Simbiology (right) are good examples.



Mechanistic simulation of the relationship between genotype and metabolic phenotype with Flux Balance Analysis (FBA) of Genome Scale Metabolic Network.

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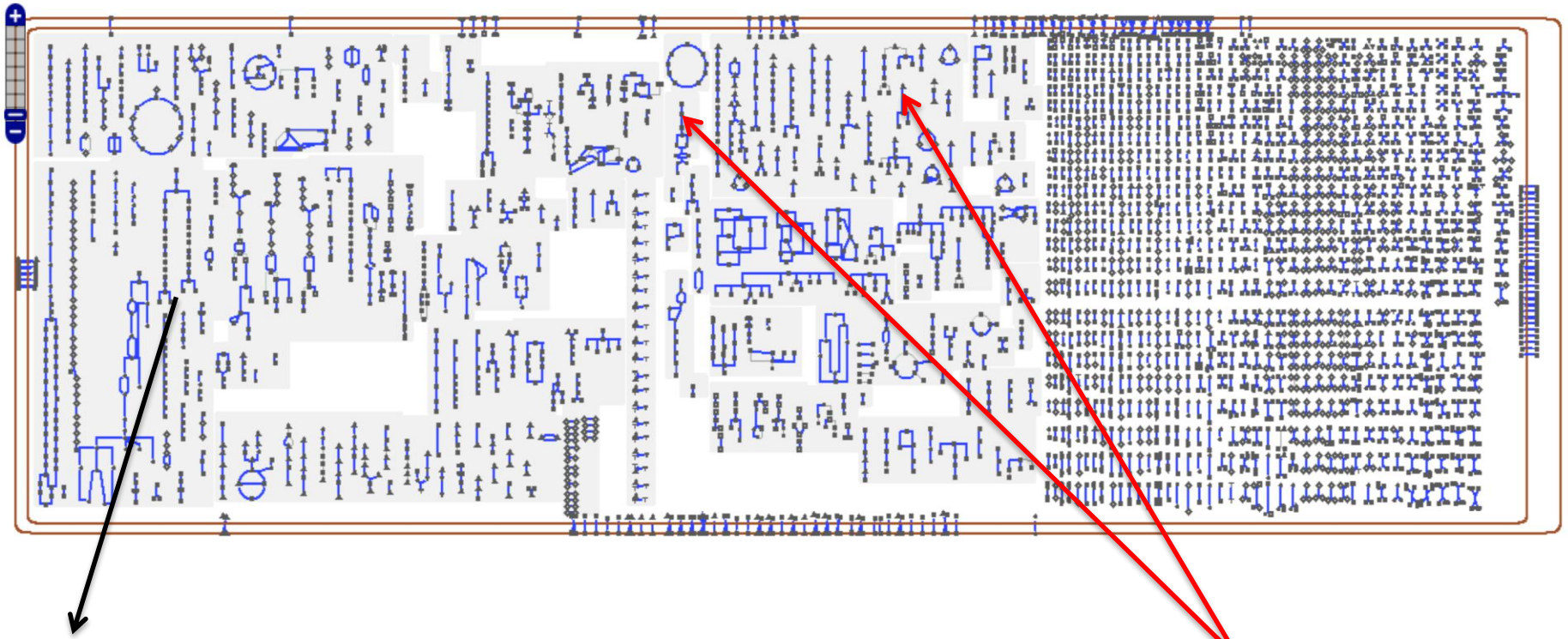
Nutrients available in cell environment (external metabolites)

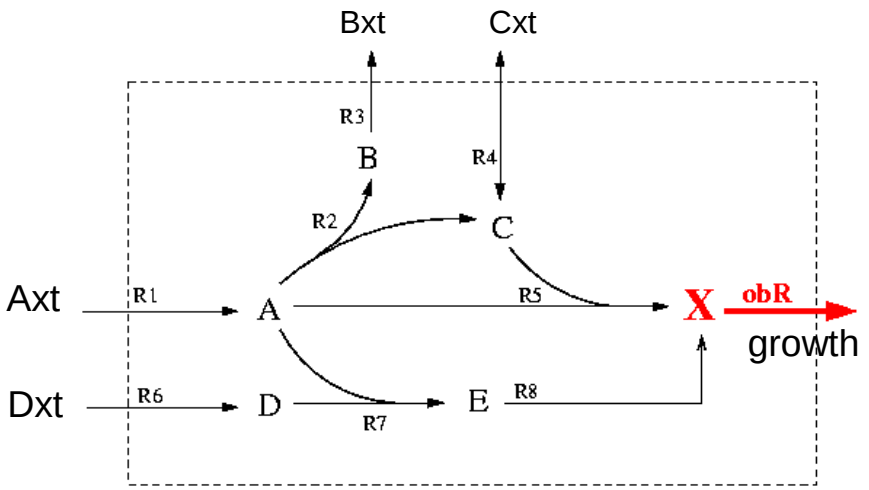


Maximal possible flux through selected reaction in the system (objective function).

Genetic polymorphism.

ASSUMPTION: Internal metabolites are at steady state.

Flux Balance Analysis – a constraint based approach



Adapted from FluxAnalyzer software (Steffen Klamt,MPI Magdeburg)

$$\frac{d\mathbf{c}}{dt} \quad \mathbf{S} \quad \mathbf{v}$$

$$\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 & 0 & -1 & 0 & -1 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} F_1 \\ F_2 \\ F_3 \\ F_4 \\ F_5 \\ F_6 \\ F_7 \\ F_8 \end{bmatrix}$$

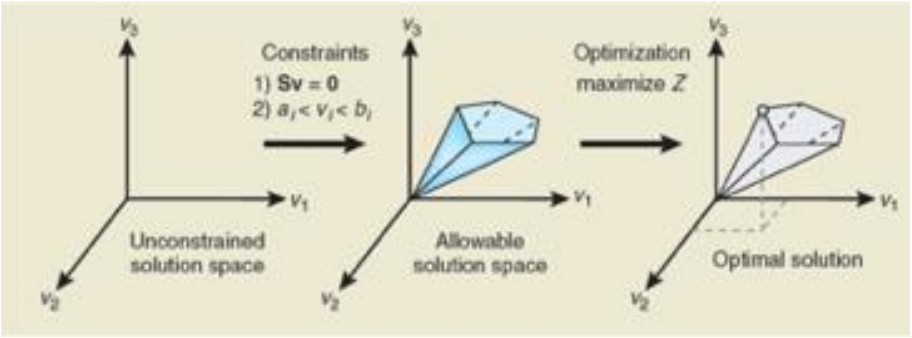
$$\textit{Maximise}: \quad F_5 + F_8$$

$$\textit{such that}$$

$$S\vec{v} = \vec{0}$$

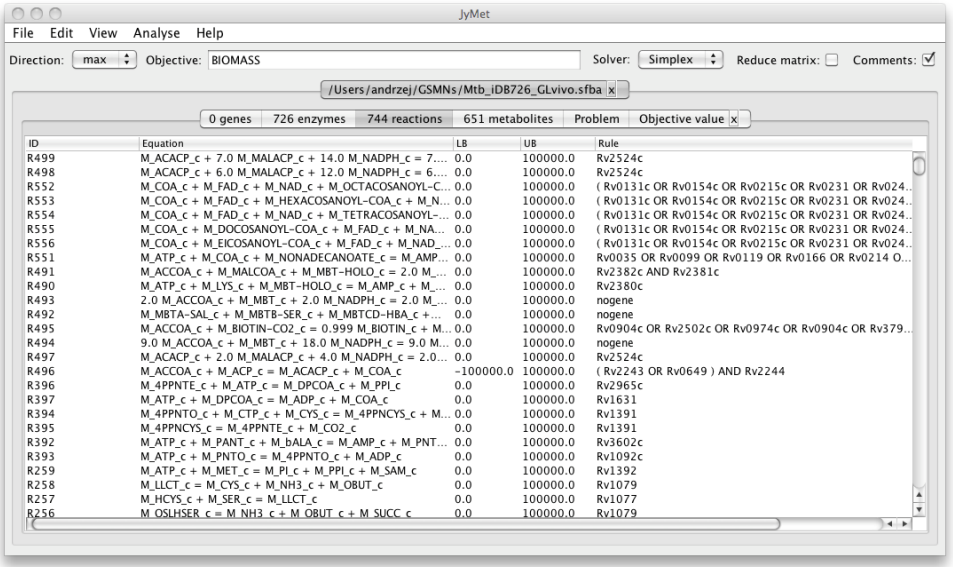
$$l_i \le v_i < u_i$$

Variables of the model are reaction fluxes at steady state F_1,..,F_8. Stoichiometric matrix **S** represents contribution of metabolites (rows) to reactions (columns). The unique maximal value of any linear combination of fluxes can be calculated by linear programming. Maximal objective value can be achieved by many flux distributions (solutions). **FBA generates insightful qualitative predictions based on network connectivity alone, but quantitative information can be used to constraint solution space**.

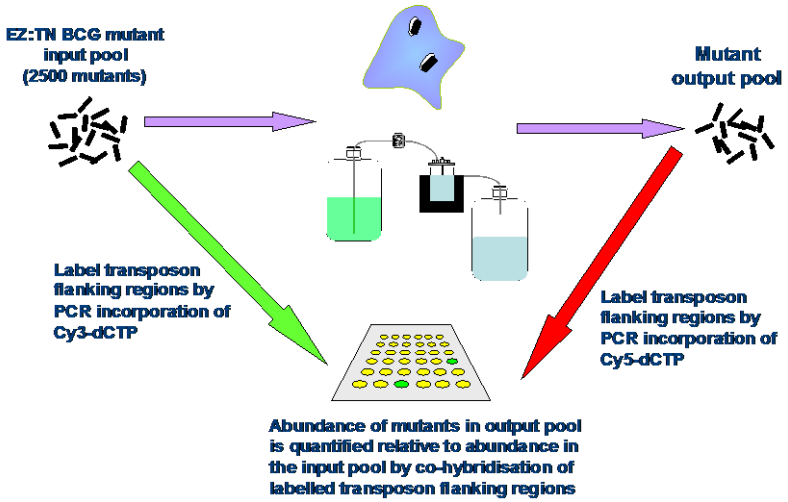


From Orth, Thiele, Palsson Nature Biotechnology 2010, 28:245

Computer simulation of genotype-phenotype relationship.



SurreyFBA software: Gevorgyan, Bushell, Avignone-Rossa, Kierzek, Bioinformatics 2011.



Sensitivity 71%, Specificity 80%, Correct predictions 78%.

Research

Highly accessed | Open Access

GSMN-TB: a web-based genome-scale network model of *Mycobacterium tuberculosis* metabolism

Dany JV Beste[¤*], Tracy Hooper[¤*], Graham Stewart[*], Bhushan Bonde[*], Claudio Avignone-Rossa[*], Michael E Bushell[*], Paul Wheeler[†], Steffen Klamt[‡], Andrzej M Kierzek[¤*] and Johnjoe McFadden[¤*]

Addresses: *School of Biomedical and Molecular Sciences, University of Surrey, Stag Hill, Guildford, Surrey, GU2 7XH, UK. †Tuberculosis Research Group, Veterinary Laboratories Agency (Weybridge), New Haw, Addlestone KT15 3NB, UK. ‡Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstrasse, D-39106 Magdeburg, Germany.

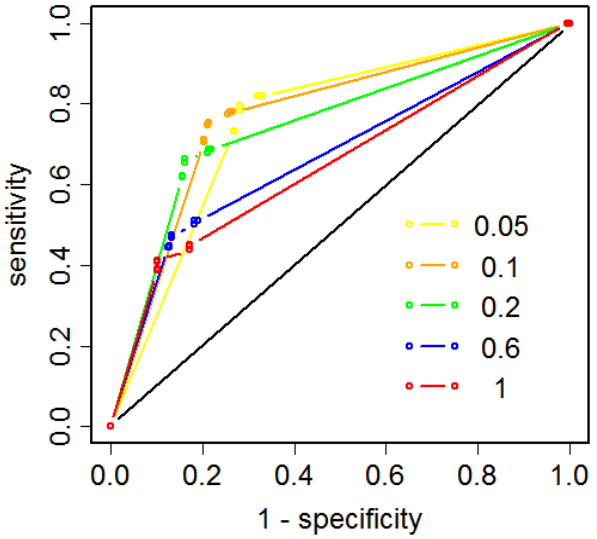
¤ These authors contributed equally to this work.

Correspondence: Johnjoe McFadden. Email: j.mcfadden@surrey.ac.uk

Published: 23 May 2007
Genome Biology 2007, 8:R89 (doi:10.1186/gb-2007-8-5-r89)

Received: 25 January 2007
Revised: 16 April 2007
Accepted: 23 May 2007

Genome Biology 2007, **106 citations**.



Reconstruction and Simulation of Genome Scale Metabolic Networks @Surrey

UNIVERSITY OF SURREY

Mendum *et al. BMC Genomics* (2015) 16:372
DOI 10.1186/s12864-015-1569-2

BMC Genomics

RESEARCH ARTICLE Open Access

Lipid metabolism and Type VII secretion systems dominate the genome scale virulence profile of *Mycobacterium tuberculosis* in human dendritic cells

Tom A Mendum*, Huihai Wu, Andrzej M Kierzek and Graham R Stewart

Metabolic Engineering 10 (2008) 227–233

Contents lists available at ScienceDirect

Metabolic Engineering

journal homepage: www.elsevier.com/locate/ymben

Selection of objective function in genome scale flux balance analysis for process feed development in antibiotic production

Chiraphan Khannapho [1], Hongjuan Zhao, Bhushan K. Bonde, Andrzej M. Kierzek, Claudio A. Avignone-Rossa, Michael E. Bushell *

Microbial Science Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

OPEN ACCESS Freely available online PLoS COMPUTATIONAL BIOLOGY

Differential Producibility Analysis (DPA) of Transcriptomic Data with Metabolic Networks: Deconstructing the Metabolic Response of *M. tuberculosis*

Bhushan K. Bonde, Dany J. V. Beste, Emma Laing, Andrzej M. Kierzek, Johnjoe McFadden*

Microbial Sciences Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom

Mendum *et al. Genome Biology* 2011, **12**:R127
http://genomebiology.com/2012/12/12/R127

Genome Biology

RESEARCH Open Access

Interrogation of global mutagenesis data with a genome scale model of *Neisseria meningitidis* to assess gene fitness *in vitro* and in sera

Tom A Mendum, Jane Newcombe, Ahmad A Mannan, Andrzej M Kierzek and Johnjoe McFadden*

Research Open Access

GSMN-TB: a web-based genome-scale network model of *Mycobacterium tuberculosis* metabolism

Dany JV Beste¤*, Tracy Hooper¤*, Graham Stewart*, Bhushan Bonde*, Claudio Avignone-Rossa*, Michael E Bushell*, Paul Wheeler†, Steffen Klamt‡, Andrzej M Kierzek¤* and Johnjoe McFadden¤*

Addresses: *School of Biomedical and Molecular Sciences, University of Surrey, Stag Hill, Guildford, Surrey, GU2 7XH, UK. †Tuberculosis Research Group, Veterinary Laboratories Agency (Weybridge), New Haw, Addlestone KT15 3NB, UK. ‡Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstrasse, D-39106 Magdeburg, Germany.

¤ These authors contributed equally to this work.

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Published: 23 May 2007
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Received: 25 January 2007
Revised: 16 April 2007
Accepted: 23 May 2007

MRC Medical Research Council

C1net gas fermentation

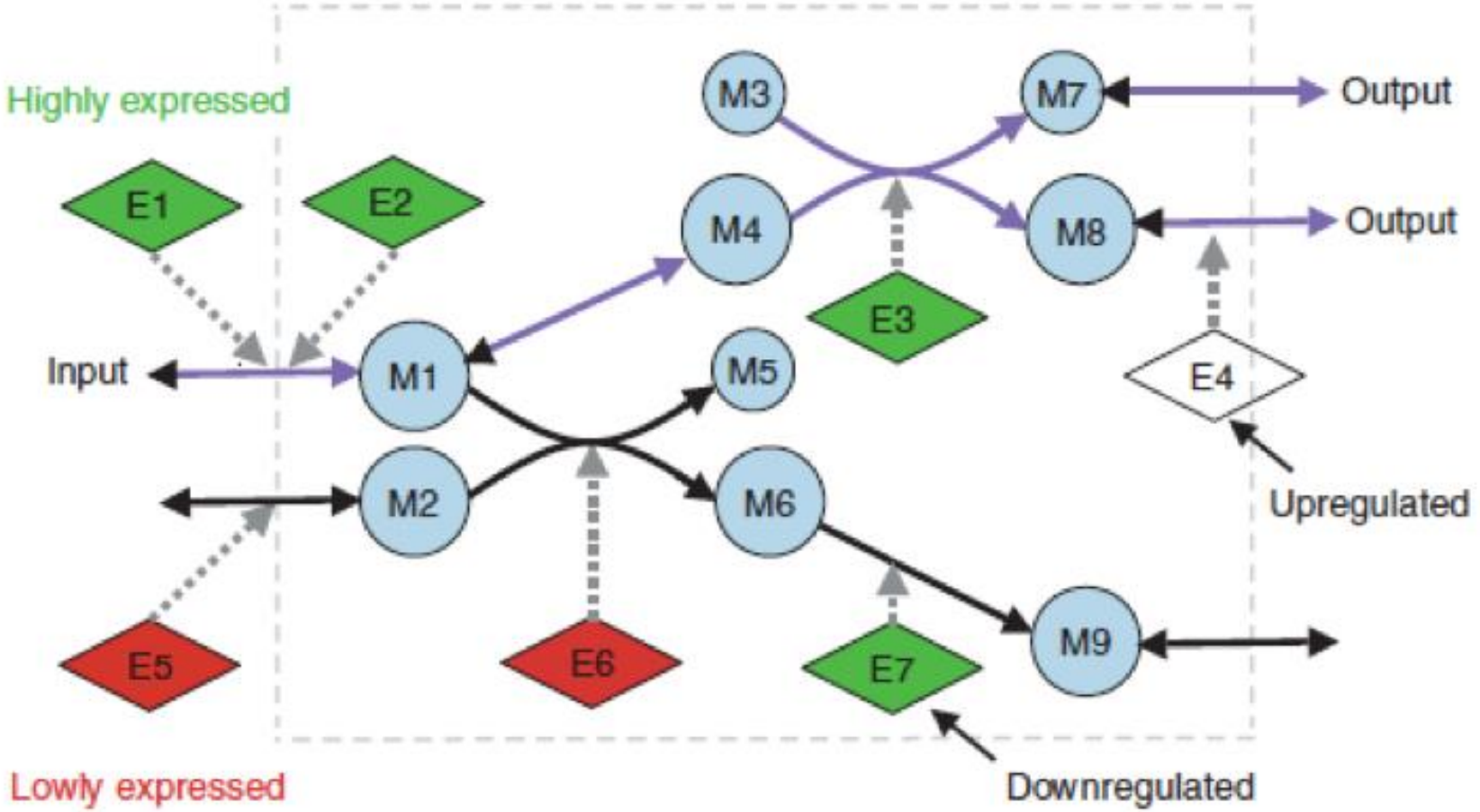
wellcome trust

ERASysBio Plus

bbsrc biotechnology and biological sciences research council

www.surrey.ac.uk

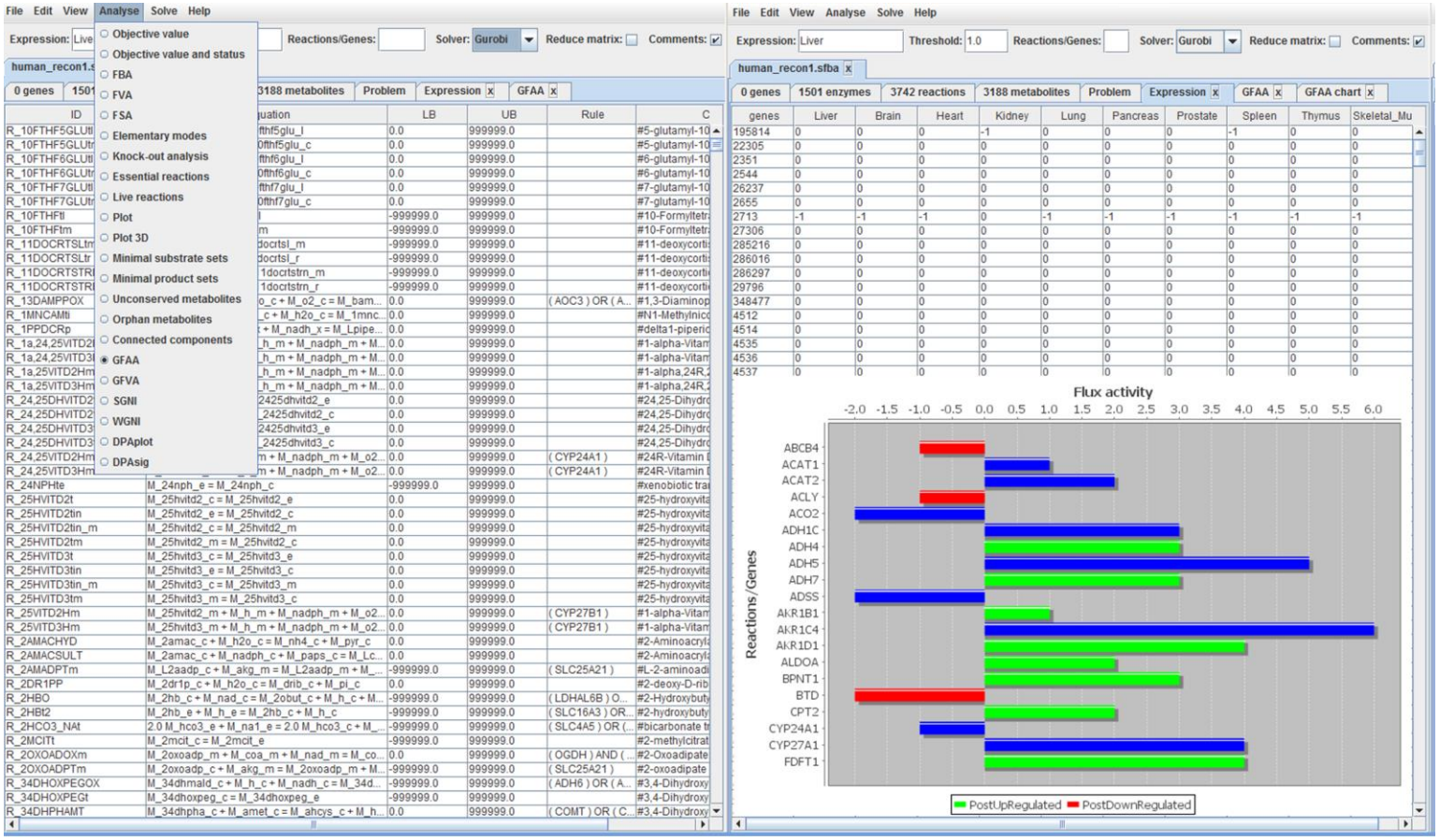
Mechanistic interpretation of transcriptome data.



Shlomi T, Cabili MN, Herrgård MJ, Palsson BØ, Ruppin E. Network-based prediction of human tissue-specific metabolism. Nature Biotechnology. 2008 26(9):1003-10.

Mechanistic interpretation of omics data in JyMet GUI and sfba command line tool.

Huihai Wu



Large number of ~omics data analysis approaches available through Graphics User Interface: iMAT, GIMME,GIM3E, DPA, Fast iMAT, GNI

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www.nature.com/scientificreports

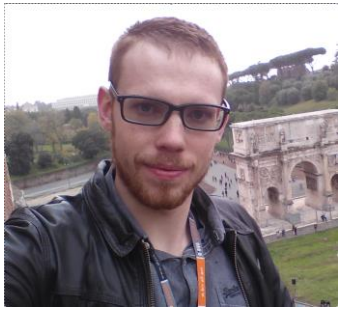
SCIENTIFIC REPORTS

OPEN

Generation of 2,000 breast cancer metabolic landscapes reveals a poor prognosis group with active serotonin production

Received: 24 June 2015
Accepted: 07 December 2015
Published: 27 January 2016

Vytautas Leoncikas[1], Huihai Wu[1], Lara T. Ward[2], Andrzej M. Kierzek[1,*] & Nick J. Plant[1,*]



Vytautas Leoncikas

bbsrc
biotechnology and biological sciences research council

AstraZeneca

www.surrey.ac.uk

Summary

UNIVERSITY OF SURREY

ARTICLE

doi:10.1038/nature10983

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Christina Curtis[1,2]†*, Sohrab P. Shah[3,4]*, Suet-Feung Chin[1,2]*, Gulisa Turashvili[3,4]*, Oscar M. Rueda[1,2], Mark J. Dunning[2], Doug Speed[2,5]†, Andy G. Lynch[1,2], Shamith Samarajiwa[1,2], Yinyin Yuan[1,2], Stefan Gräf[1,2], Gavin Ha[3], Gholamreza Haffari[3], Ali Bashashati[3], Roslin Russell[2], Steven McKinney[3,4], METABRIC Group‡, Anita Langerød[6], Andrew Green[7], Elena Provenzano[8], Gordon Wishart[8], Sarah Pinder[9], Peter Watson[3,4,10], Florian Markowetz[1,2], Leigh Murphy[10], Ian Ellis[7], Arnie Purushotham[9,11], Anne-Lise Børresen-Dale[6,12], James D. Brenton[2,13], Simon Tavaré[1,2,5,14], Carlos Caldas[1,2,8,13] & Samuel Aparicio[3,4]

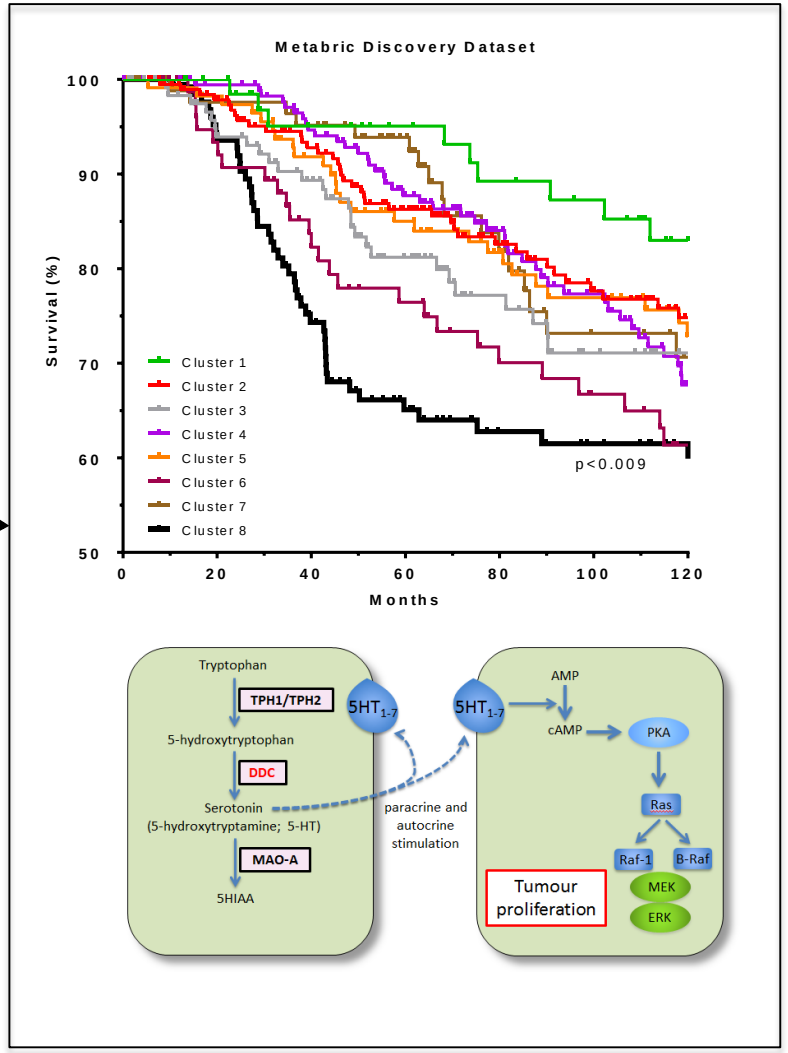
Nature. 2012 486:346-52. doi: 10.1038/nature10983.

computational BIOLOGY RESOURCE

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

Nat Biotechnol. 2013 31:419-25. doi: 10.1038/nbt.2488.



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Mechanistic model-based meta-analysis of clinical transcriptomes to stratify disease progression in individual patients.

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METABRICK transcriptome arrays, 2000 individual tumours

Recon 2, Genome Scale Metabolic Network (GSMN), 7440 reactions

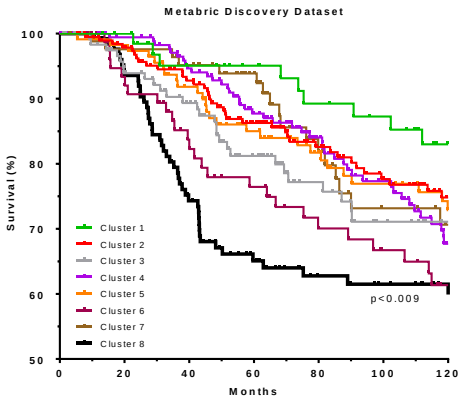
Array data pre-processing and classification of transcripts to absent (-1) and present (0) based on detection p-values.

Classification of GSMN reactions to absent (-1) and present (0) based on GSMN gene-reaction rules and transcript classification.

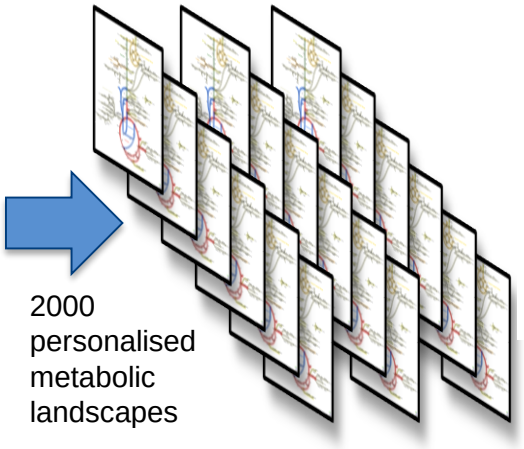
Optimisation of congruency between GSMN constraints and transcriptome-based reaction classification.

Determination of metabolic landscape by assigning non-active (-1) or active (0) state to each GSMN reaction based on Flux Variability Analysis ranges.

2000 samples

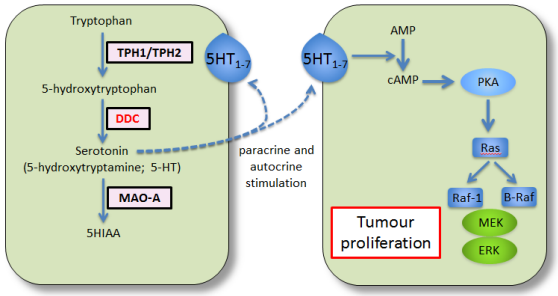


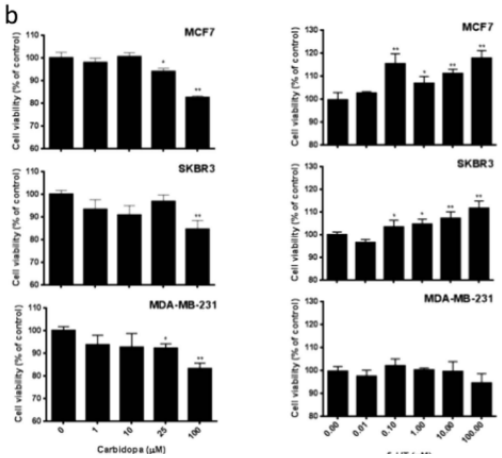
K-means clustering and comparison with survival data.

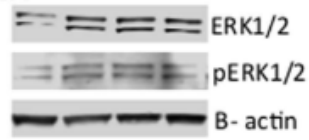


2000 personalised metabolic landscapes

Potential DDI between chemotherapy and SSRI antidepressants.







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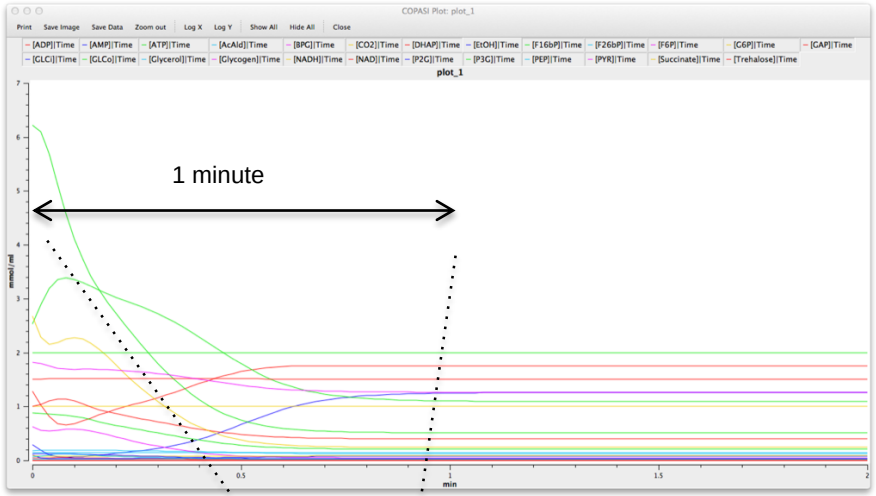
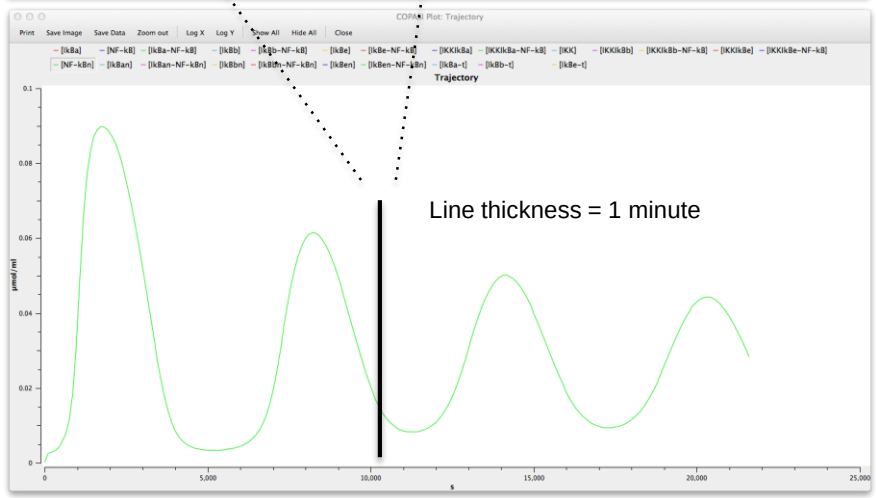
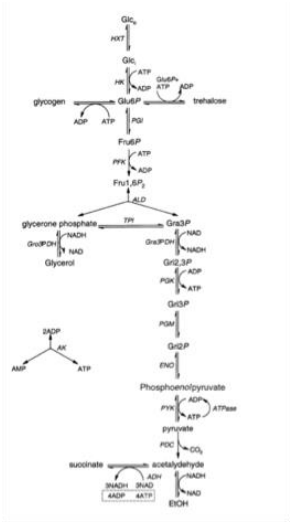
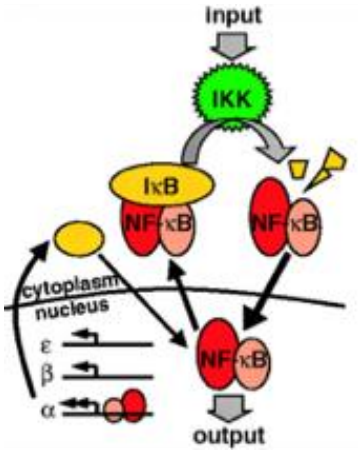
Quasi-steady state metabolic fluxes.









Metabolism: COPASI example file YeastGlycolysis

From Pritchard and Kell (2002) Eur. J. Biochem. , modified from Teusink et al.(2000) Eur J Biochem 267, 5313-5329.

Gene regulation: COPASI example file NF-kappaB

NELSON, D.E., IHEKWABA, A.E., et al.(2004). Science 306, 704-708.HOFFMANN, A., LEVCHENKO, A., SCOTT, M. L. & BALTIMORE, D. (2002). Science 298, 1241-1245.

The timescale separation between gene regulation and metabolism justifies Quasi-Steady State assumption: **Following the change of gene expression state metabolism quickly reaches state where metabolic flux is constant and metabolite concentrations are balanced.**

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BIOINFORMATICS ORIGINAL PAPER

Vol. 29 no. 24 2013, pages 3181–3190
doi:10.1093/bioinformatics/btt552

Systems biology

Advance Access publication September 23, 2013

QSSPN: dynamic simulation of molecular interaction networks describing gene regulation, signalling and whole-cell metabolism in human cells

Ciarán P. Fisher, Nicholas J. Plant, J. Bernadette Moore and Andrzej M. Kierzek*

Faculty of Health and Medical Sciences, School of Biosciences and Medicine, University of Surrey, Guildford, Surrey GU2 7XH, UK

Associate Editor: Igor Jurisica

Ciaran Fisher

Nick Plant

Bernadette Moore

Andrzej Kierzek

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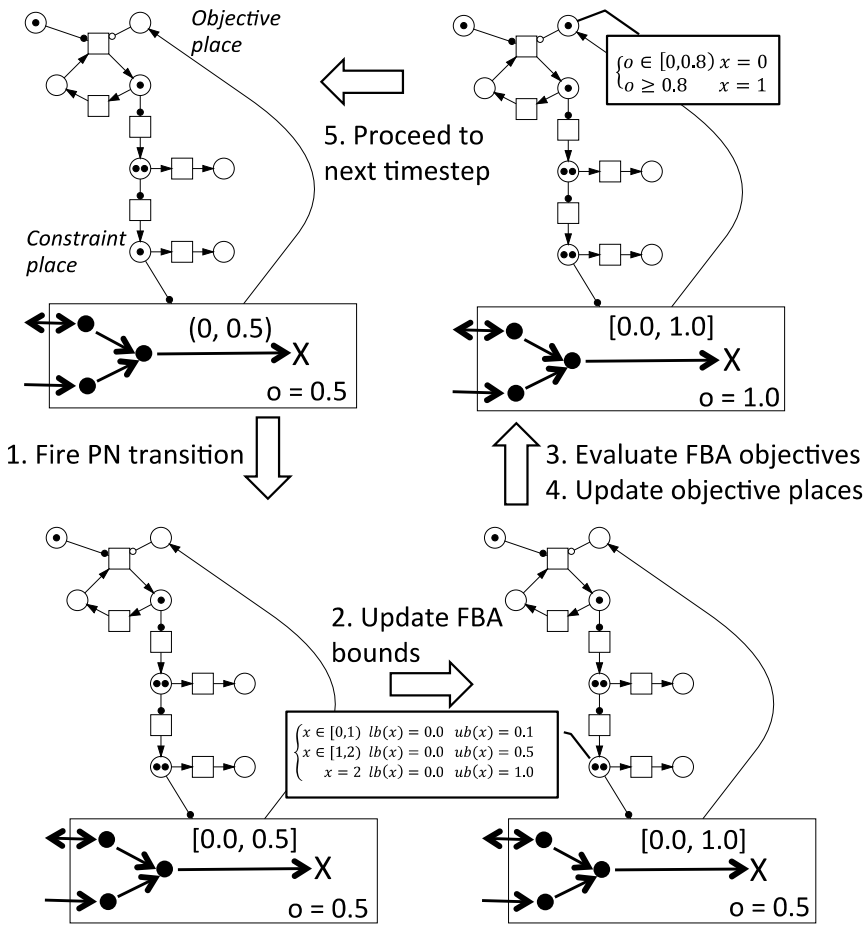
Quasi Steady State Petri Net (QSSPN)



1. Method integrates Petri Net simulations with Flux Balance Analysis using quasi-steady state approximation.
2. Slow, dynamic, regulatory processes are modelled by Petri Net
3. For each state of regulatory network fast metabolic reactions are assumed to be at steady state.
4. **Constraint places** set flux bounds of FBA fluxes. **Objective places** execute FBA evaluation of objective functions.

Fisher, Plant, Moore, Kierzek Bioinformatics 29, 3181-3190 (2013)

Propensity function and transition types.

To allow formulation of general rules involving token number thresholds, we define transition propensity:

$$P_t = c_t \prod_{i=1}^{N} \mu_i(x_i)$$

where P_t is a propensity function of transition t, c_t is a rate constant, N is the number of pre-places of transition t, x_i is the number of tokens at preplace i and μ_i is the pre-place activity in the transition depending on the pre-place state. The activity function is a look-up table of T thresholds t_i and activities a_i allowing general definition of the pre-place contribution to the transition propensity

$$\mu(x) = \left\{ \begin{array}{ll} x \in [t_1, t_2), & \mu(x) = a_1 \\ x \in [t_i, t_{i+1}), & \mu(x) = a_i \\ & \cdots \\ x \in [t_{T-1}, t_T), & \mu(x) = a_T \end{array} \right\}$$

In new version of the software any arithmetic expression involving pre-place states x_i can also be used to calculate propensity P_t

The interpretation of a transition propensity during simulations is dependent on the transition class:

Stochastic transition - propensity is interpreted as the probability density of the transition firing in the next, infinitesimally small, time step. We allow stochastic transitions to be **delayed**.

Continuous transitions – propensity is interpreted as reaction rate.

Immediate transition - fires once whenever its propensity function is different than 0.

In new version of the QSSPN software the following transition classes were added:

Reset transition – sets state of post places to the value specified by arithmetic expression involving pre-place states x_i.

Flux transition has only one pre-place which has to be objective node. It resets state of one post-place to one of FBA solution fluxes.

QSSPN simulation algorithm.

setQSSFbounds() - This function sets the bounds of fluxes in the quasi-steady state flux (QSSF) part of the model according to the state of the constraint node.

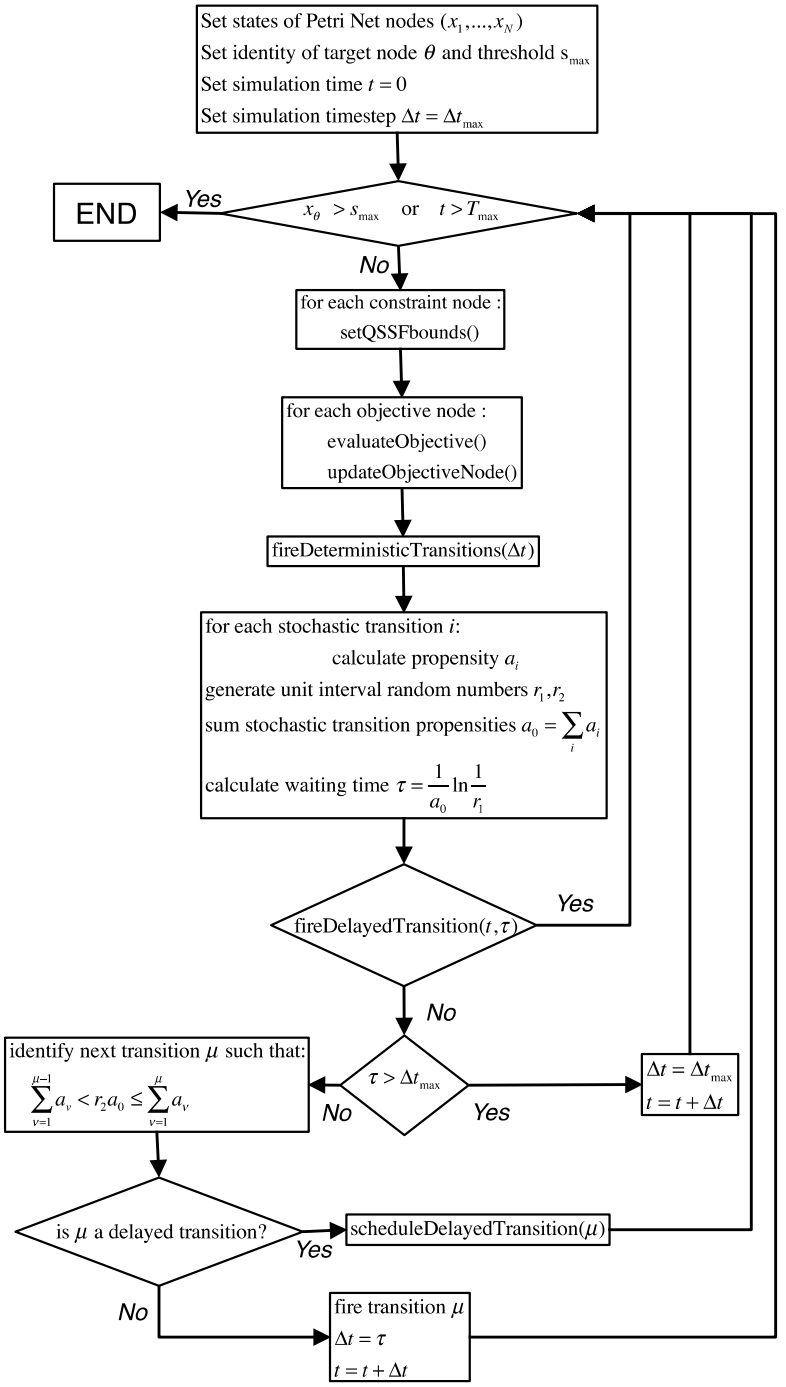
evaluateObjective() - This function uses Flux Balance Analysis to evaluate the objective function specified by a particular objective node. The objective function is specified as the name of the flux or the name of the metabolite in the QSSF network. If the objective is specified as the flux the linear programming (LP) maximises value of this flux. If the objective is specified as a metabolite, the sum of fluxes producing this metabolite is maximised.

updateObjectiveNode() - This function sets the state of a particular objective node according to the objective function value, thus feeding back information about steady state metabolic capabilities to the dynamic part of the model.

fireDeterministicTransitions(Δt) - Each immediate transition for which propensity function is greater than 0 is fired once. In recent version of the software adaptive timestep Euler algorithm is used to simulate state change of places connected to continous transitions within Δt. All node state updates within this function are executed synchronously.

fireDelayedTransition(t, t_d) - This function returns a Boolean value; the function checks if there are any delayed transitions to be fired in the time interval (t, t+t_d). If there are no delayed transitions scheduled to fire the function returns FALSE. Otherwise, it fires one delayed transition and sets simulation time t to the time t_s at which this transition has been scheduled. The Δt parameter is then set to t_s – t. If there are multiple delayed transitions set to fire in the time interval (t, t+t_d) the transition that is scheduled at the earliest time is fired. After firing the transition the function returns TRUE.

scheduleDelayedTransition(m) - If the stochastic transition m selected to be fired has delay time td greater than 0 this function adds the transition to the list of delayed transi-tions to be fired. The transition is scheduled to fire at time ts = t + td.



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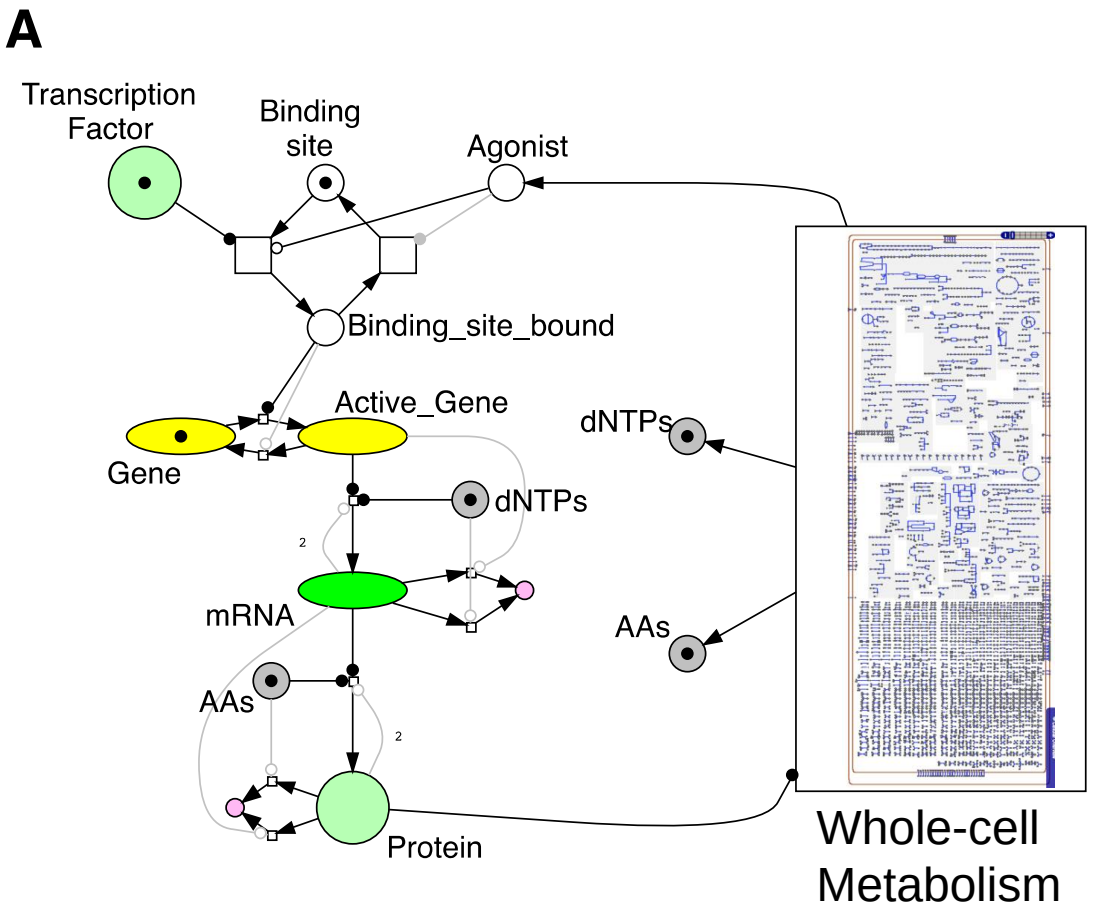
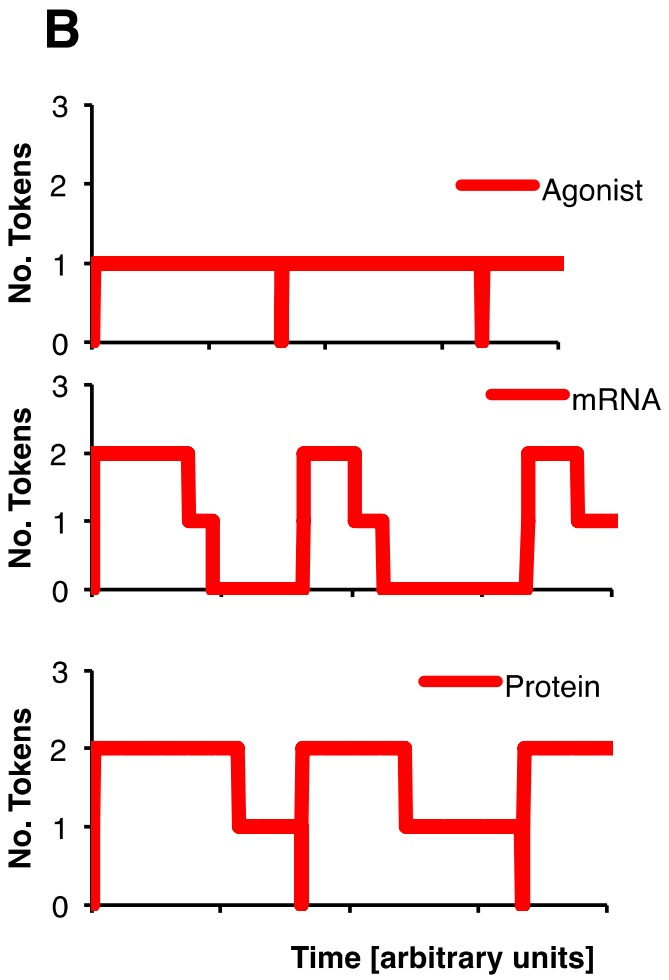
QSSPN = HPN + FBA

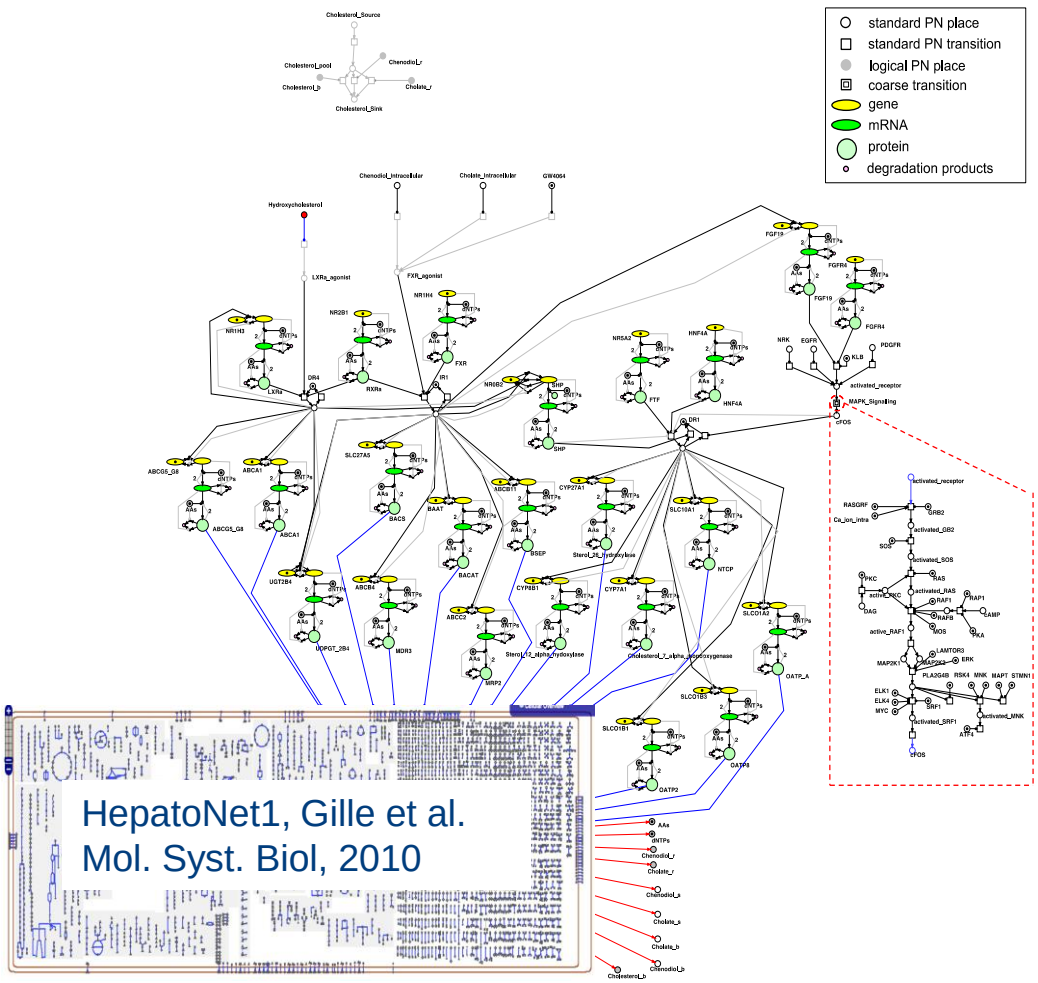
Qualitative gene expression model

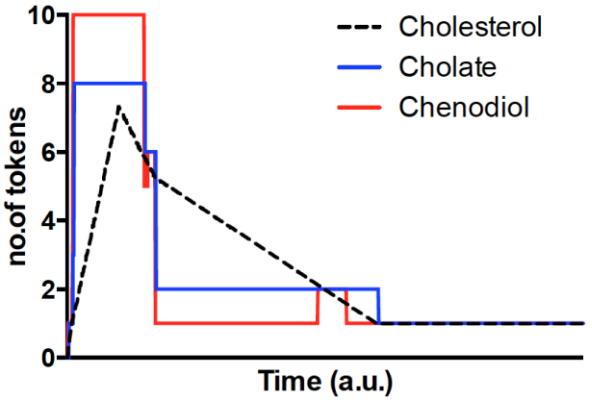




Fisher, Plant, Moore, Kierzek Bioinformatics 29, 3181-3190 (2013)

The model of bile acid homeostasis in human hepatocyte.

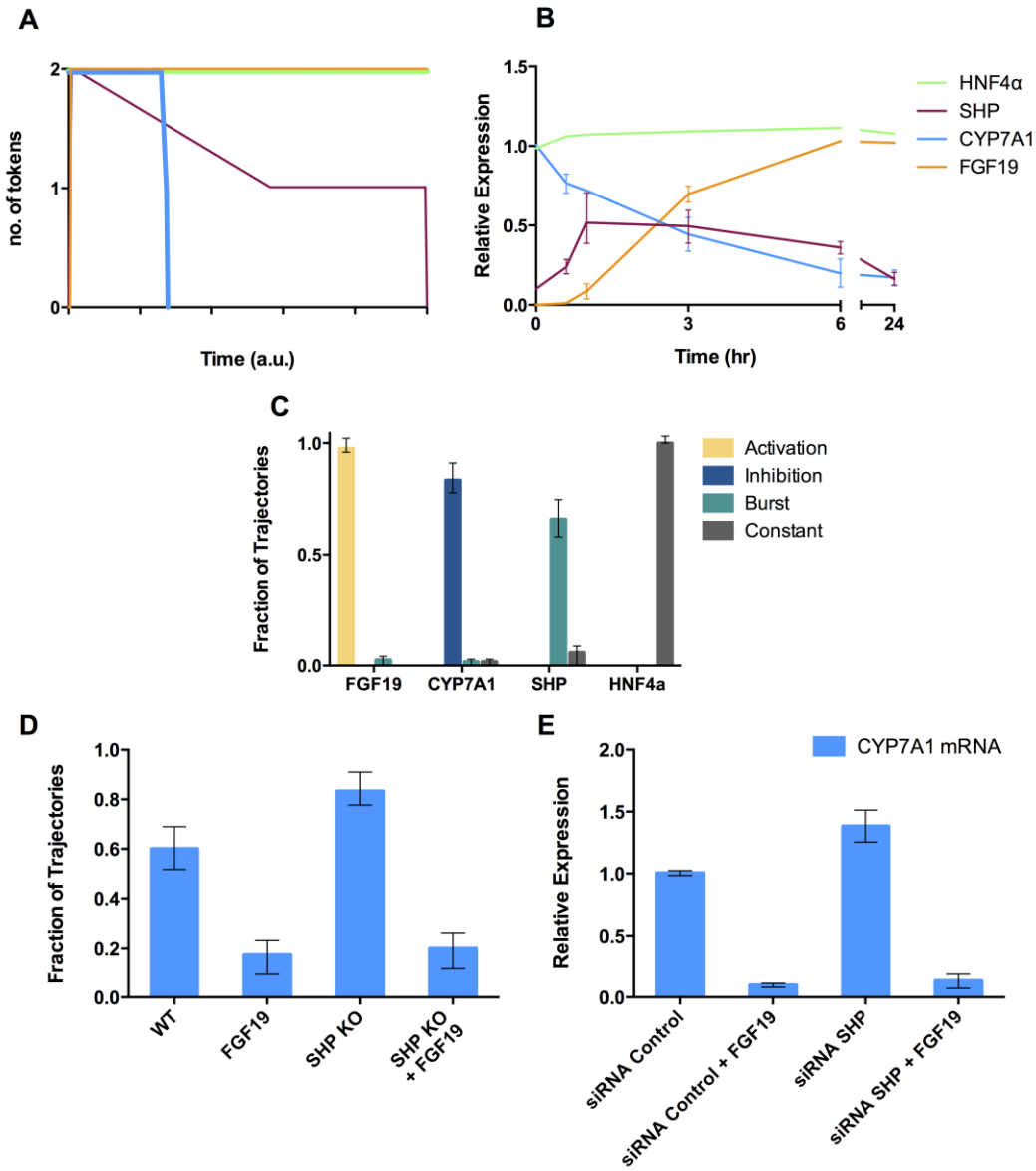




Hepatocyte QSSPN Model	
Petri net Places	206
Enzymes	6
Transporters	9
Nuclear Receptors	6
Petri net Transitions	214
Hepatocyte-specific Reactions	2539
Enzymatic	953
Transport	1454
Hepatocyte-specific Metabolites	777
Reactions dynamically regulated	**11.1%**

Fisher, Plant, Moore, Kierzek Bioinformatics 29, 3181-3190 (2013)

Model validation



Fraction of trajectories exhibiting dynamic qualitative behaviour of interest has been compared with experimental data of Song and Chiang, Hepatology 2009.

Fisher, Plant, Moore, Kierzek Bioinformatics 29, 3181-3190 (2013)

Model validation

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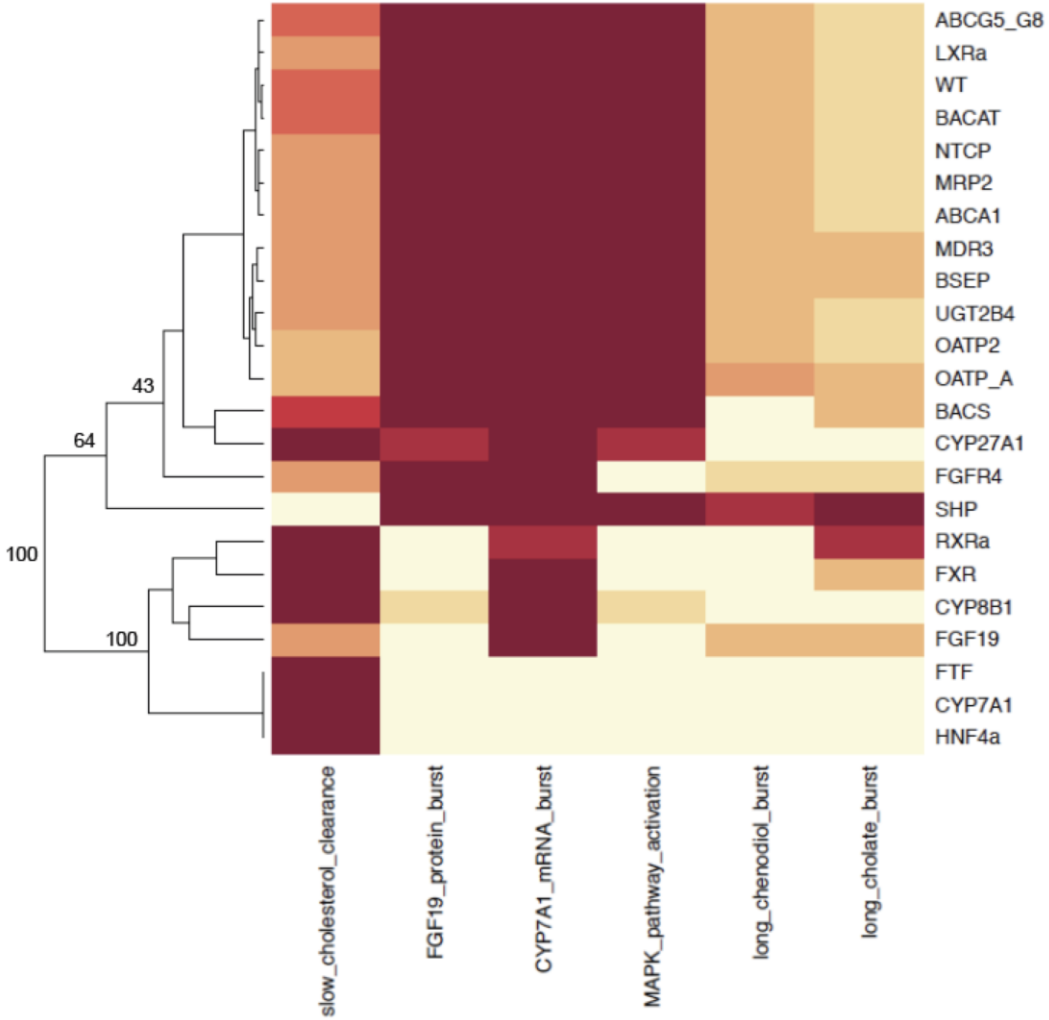
Supplementary Table 4.16. Comparison of behaviours exhibited by experimental data and simulation results.

Molecule	Experimental data	Experimental behaviour	Simulation behaviour
FGF19 transcript	Relative amount after treatment with GW4064 for 0, 0.6, 1, 3, 6, 24 hours (Section 4.2.1).	activation	activation
CYP7A1 transcript	Relative amount after treatment with GW4064 for 0, 0.6, 1, 3, 6, 24 hours (Section 4.2.2).	inhibition	inhibition
SHP transcript	Relative amount after treatment with GW4064 for 0, 0.6, 1, 3, 6, 24 hours (Section 4.2.3).	burst	burst
HNF4α transcript	Relative amount after treatment with GW4064 for 0, 0.6, 1, 3, 6, 24 hours (Section 4.2.4).	constant	constant
CYP7A1 transcript	Relative amount after treatment with FGF19 for 0, 0.6, 1, 3, 6, 24, 48 hours (Section 4.2.5).	inhibition	inhibition
SHP transcript	Relative amount after treatment with FGF19 for 0, 0.6, 1, 3, 6, 24, 48 hours (Section 4.2.6).	burst	burst
CYP7A1 transcript	Relative amount with respect to untreated control after treatment with FGF19 (Section 4.2.7)	decrease	decrease
CYP7A1 transcript	Relative amount with respect to untreated control after treatment with SHP siRNA (Section 4.2.8)	increase	increase
CYP7A1 transcript	Relative amount with respect to untreated control after treatment with SHP siRNA and FGF19 (Section 4.2.9)	decrease	decrease
SHP transcript	Relative amount with respect to untreated control after treatment with FGF19 (Section 4.2.10)	equal	equal
CYP7A1 transcript	Relative amount with respect to GW4064 treatment after FGF19 antibody treatment (Section 4.2.11)	increase	equal
CYP7A1 transcript	Relative amount with respect to GW4064 treatment after FGFR4 siRNA (Section 4.2.12)	increase	equal
Chenodiol	Physiological response to rise of cholesterol. (Section 4.2.13)	burst	burst
Cholate	Physiological response to rise of cholesterol. (Section 4.2.13)	burst	burst

Number of True Positive predictions (TP)	12
Number of True Negative predictions (TN)	42
Number of False Positive predictions (FP)	2
Number of False Negative predictions (FN)	2
Matthews Correlation Coefficient (MCC)	**0.812**

Fisher, Plant, Moore, Kierzek Bioinformatics 29, 3181-3190 (2013)

Mechanistic simulation of genotype-phenotype relationship.



Colour spectrum represents fraction of trajectories exhibiting behaviour of interest. Increasing colour intensity represents higher fraction of trajectories. The knockdown/behaviour pairs where fractions are within 95% CIs of WT are assigned the same colour as WT.

Model of signalling pathways regulating translation in mammalian cells.

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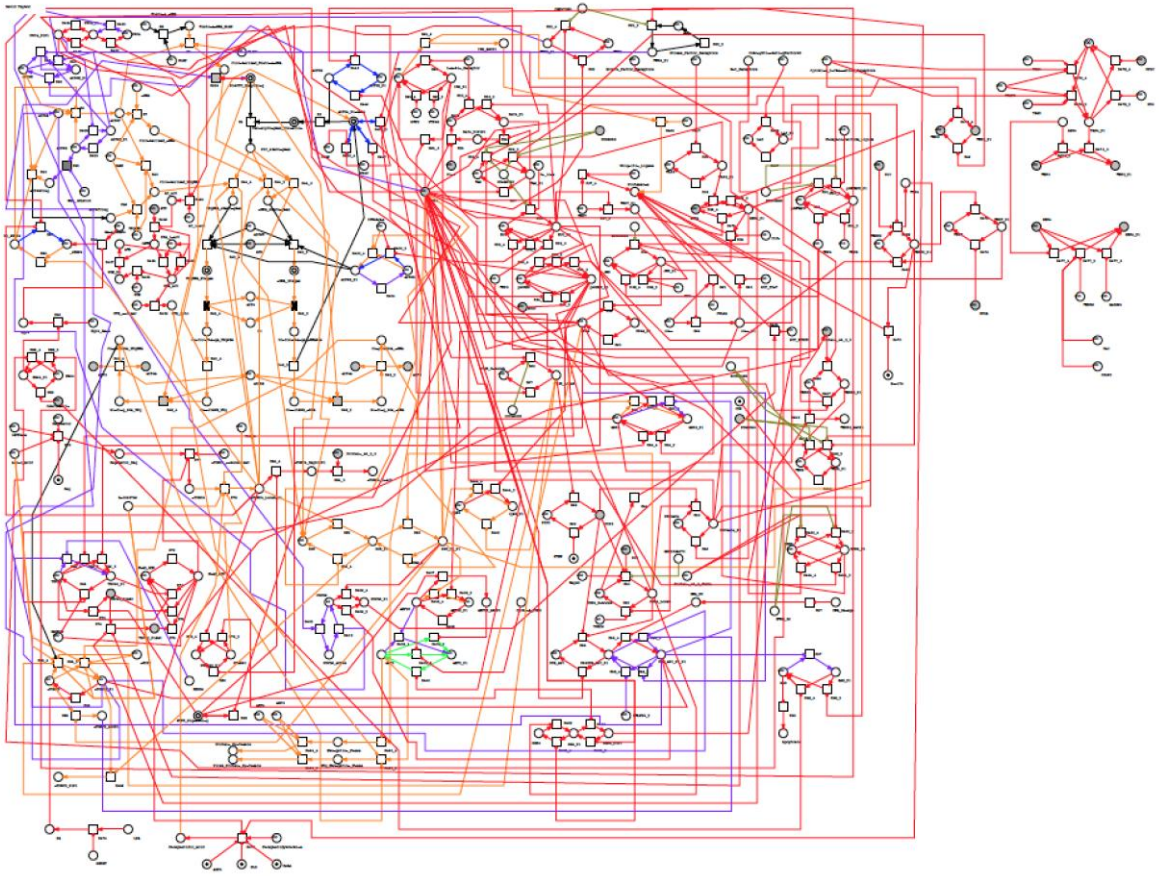
Work of David Taylor.



Significant predictive power evaluated by comparison with comprehensive benchmark of literature data on signalling network inhibitors (MCC = 0.45)

300 molecular species, 241 interactions based on 1,158 literature references.

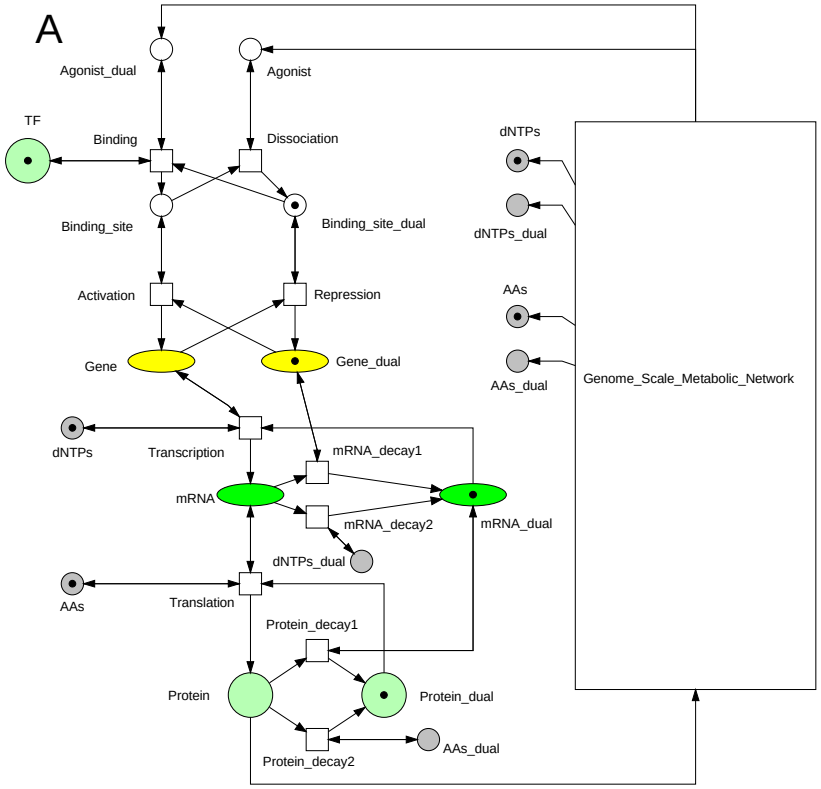
Reachability of molecular targets under experimental conditions (input) studied by Statistical Model Checking.

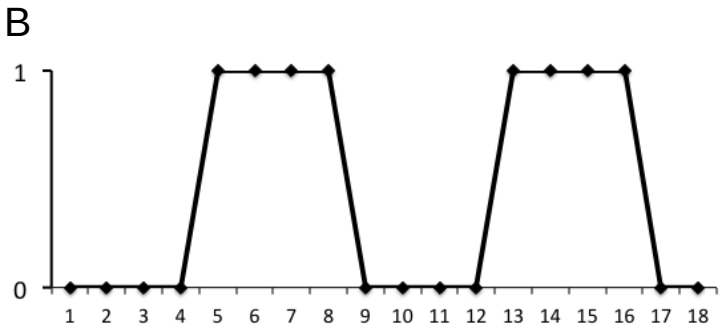
Colour reflect the change in the number of transition firings resulting from application of Ku0063794 inhibitor of mTOR pathway.

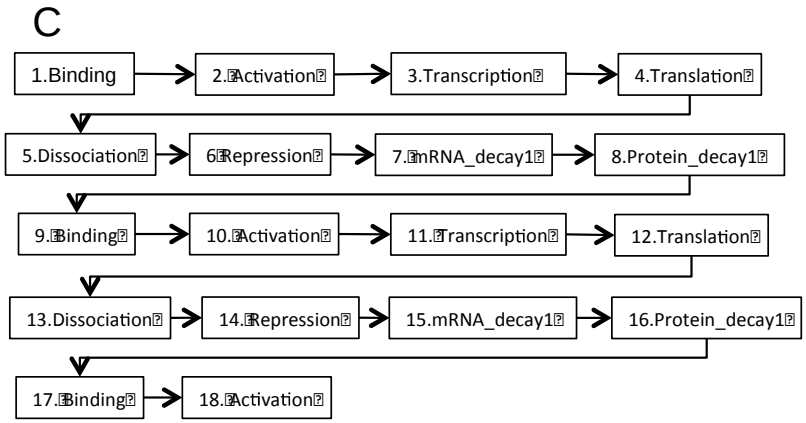
Simulation led to hypotheses that were experimentally validated.

Manuscript in preparation.

Formal verification of qualitative QSSPN model.







All possible sequences of transitions (reachability graph) are examined to prove that certain behaviour is not feasible.

Marek Grabowski (University of Warsaw, now Google), Ciaran P. Fisher, Nick J. Plant, J. Bernadette Moore, Andrzej M. Kierzek, Jacek Sroka (University of Warsaw). Formal verification of dynamic behaviour existence in molecular networks describing gene regulation, signalling and whole-cell metabolism. (in preparation).

Multi-scale, multi-formalism simulation.

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Nilgun Sahin

Andrzej Kierzek

Hans Westerhoff

Nick Plant

The dynamic model of cortisol mediated signalling integrated with Recon 2 FBA model of human metabolism and PBPK models.

Multi-scale, multi-formalism simulation to integrate existing models.

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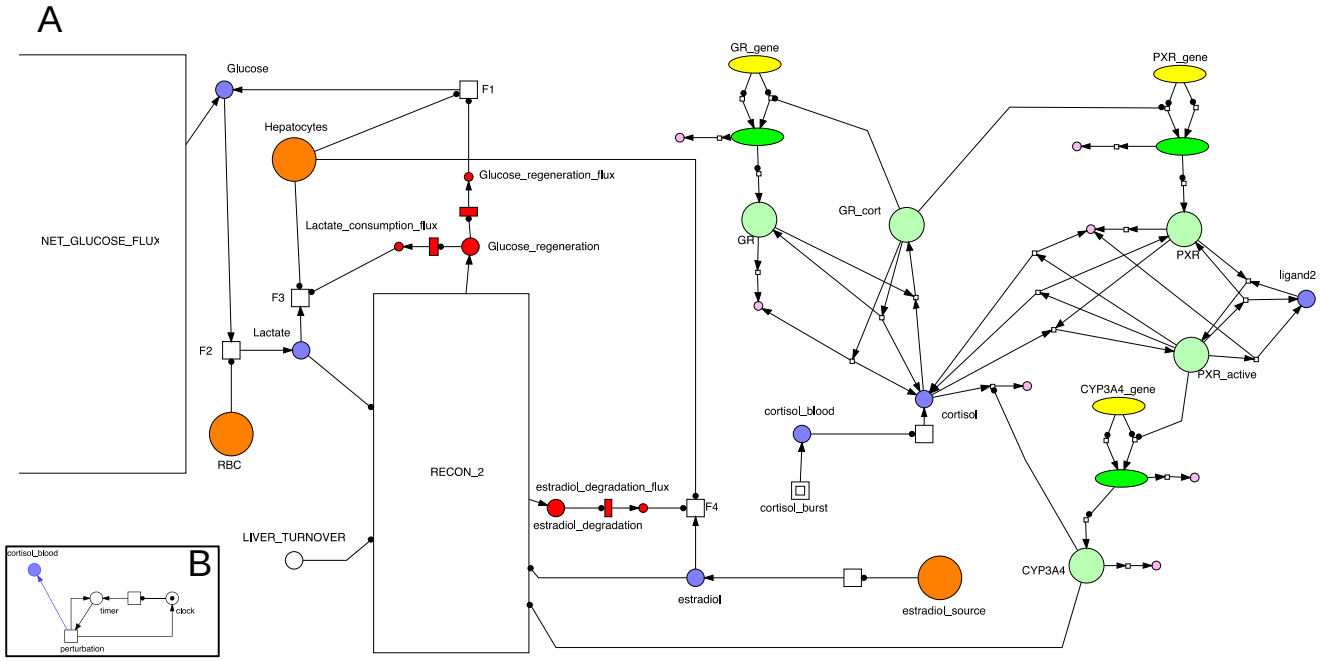

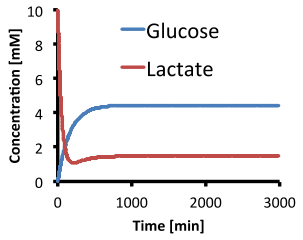

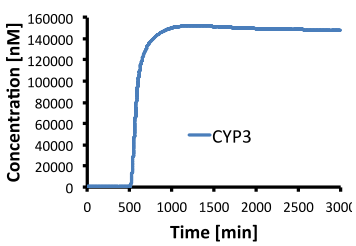

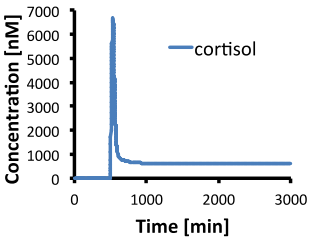

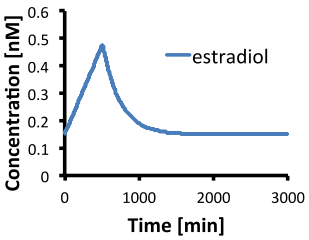

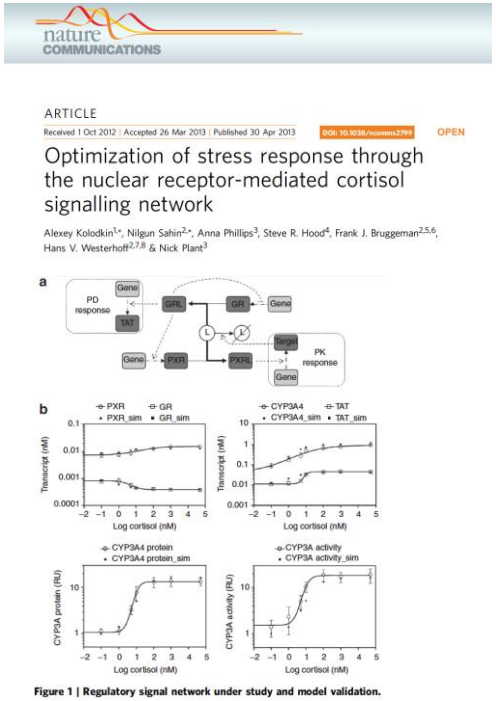

nature COMMUNICATIONS

ARTICLE

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Optimization of stress response through the nuclear receptor-mediated cortisol signalling network

Alexey Kolodkin[1,*], Nilgun Sahin[2,*], Anna Phillips[3], Steve R. Hood[4], Frank J. Bruggeman[2,5,6], Hans V. Westerhoff[2,7,8] & Nick Plant[3]

Figure 1 | Regulatory signal network under study and model validation.

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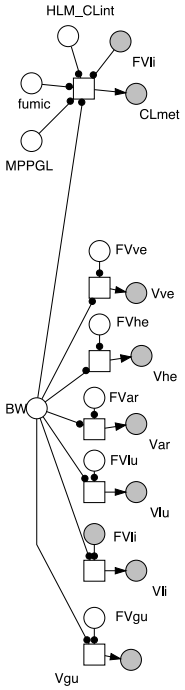
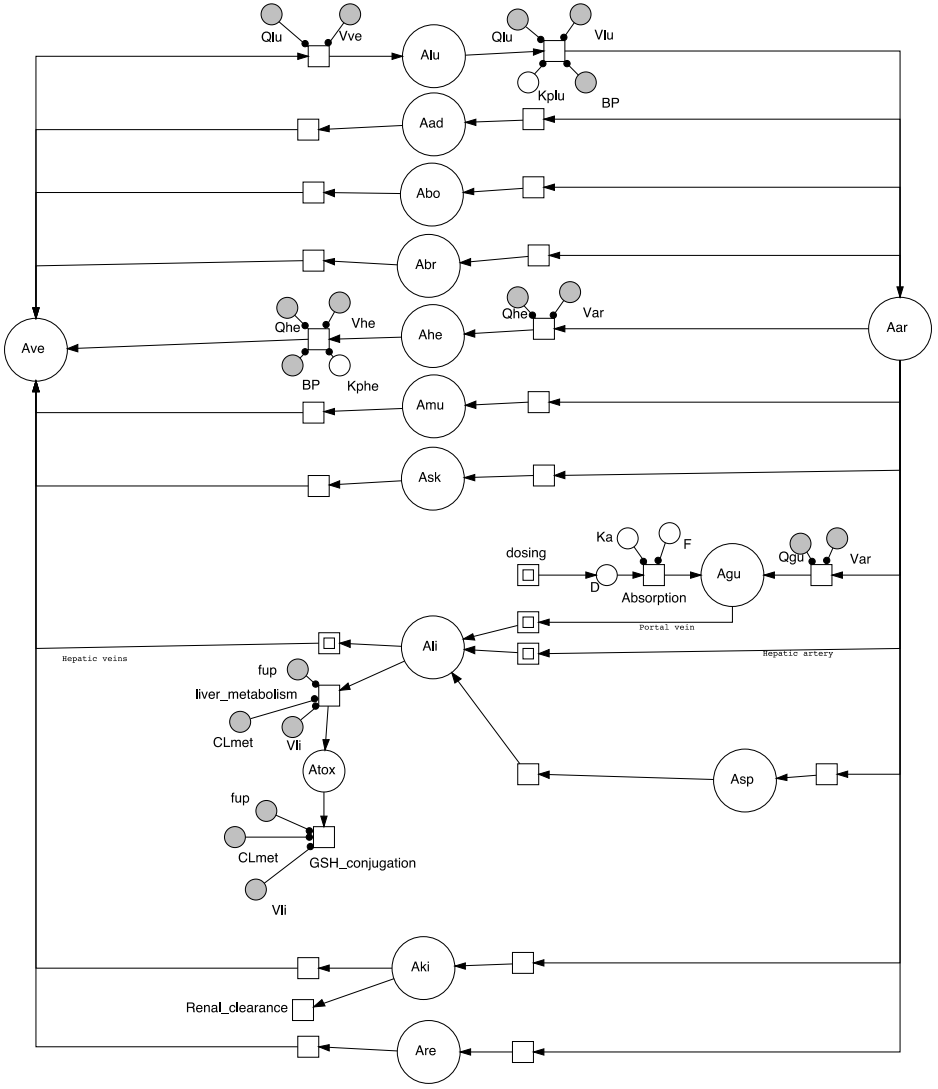
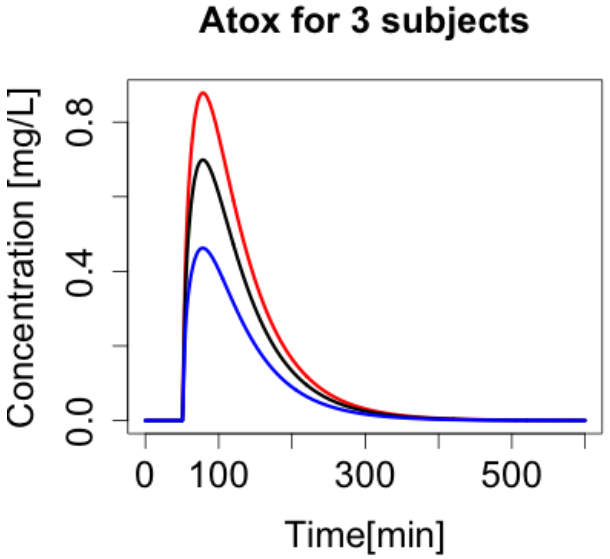
Physiologically Based Pharmacokinetic Models (PBPK)





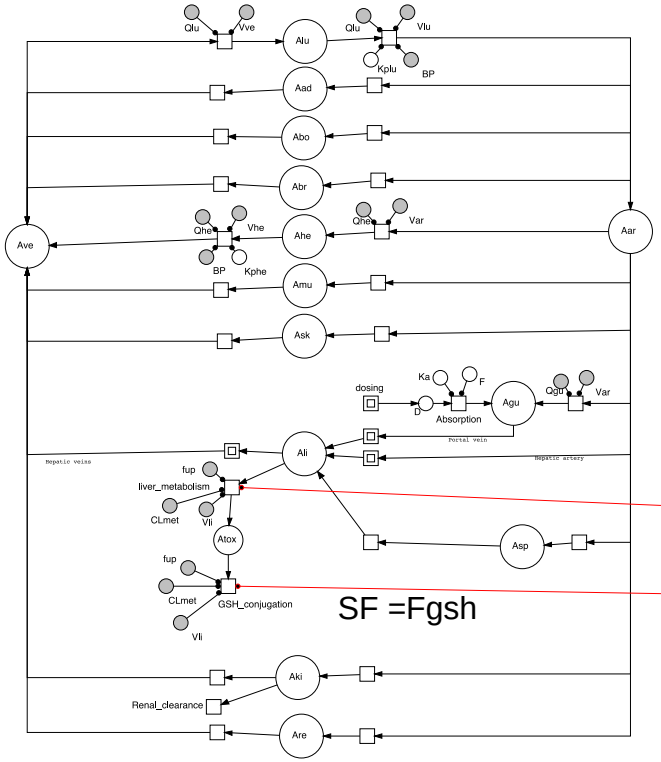


PBPK model of drug A and its toxic liver metabolite Atox detoxified through GSH conjugation (e.g. paracetamol and NAPQI).

Model structure and parameters adapted from Jones and Rowland Yeo 2013 CPT: Pharmacometrics & Systems Pharmacology Volume 2, Issue 8, pages 1–12, August 2013.

Simulation in qsspn.

Integration of molecular network models with PBPK.



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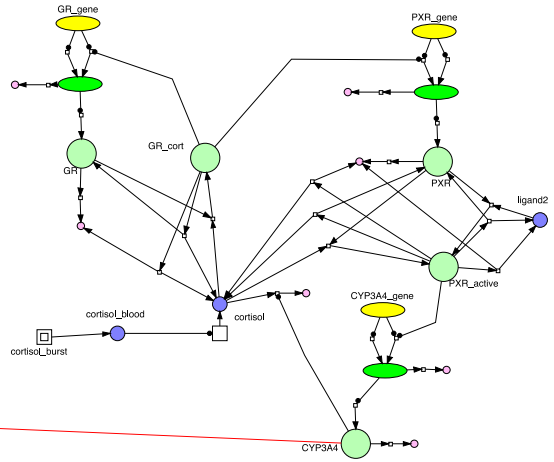

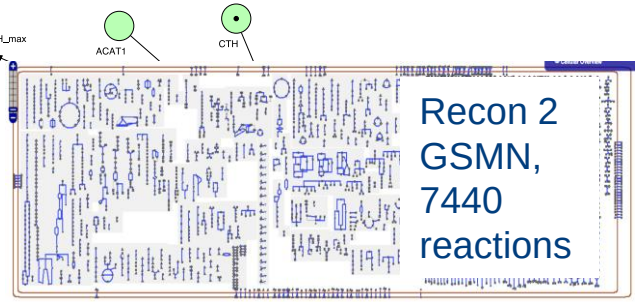

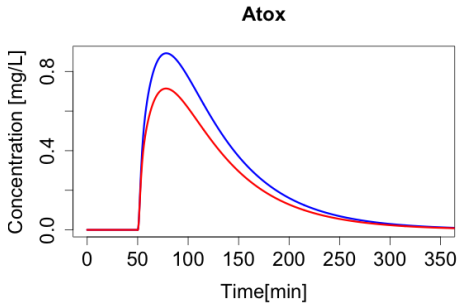

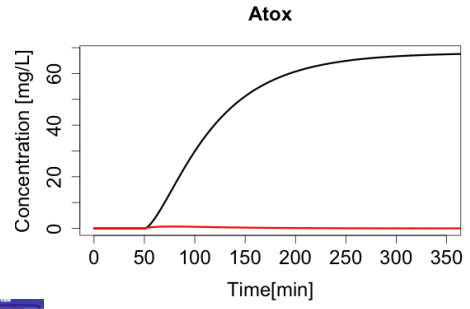

Control
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Expanding Pharmacogenomics by 2192 genes. Expanding DDI analysis by 7440 potential targets. Enabling incorporation of ~omics data.

FVA simulation: 127 reactions affect glutathione production. Recon 2 model constrained by ~200 exametabolome fluxes from Jain et al, Science, 2012

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MUFINS: Multi-Formalism Interaction Networks Simulator.

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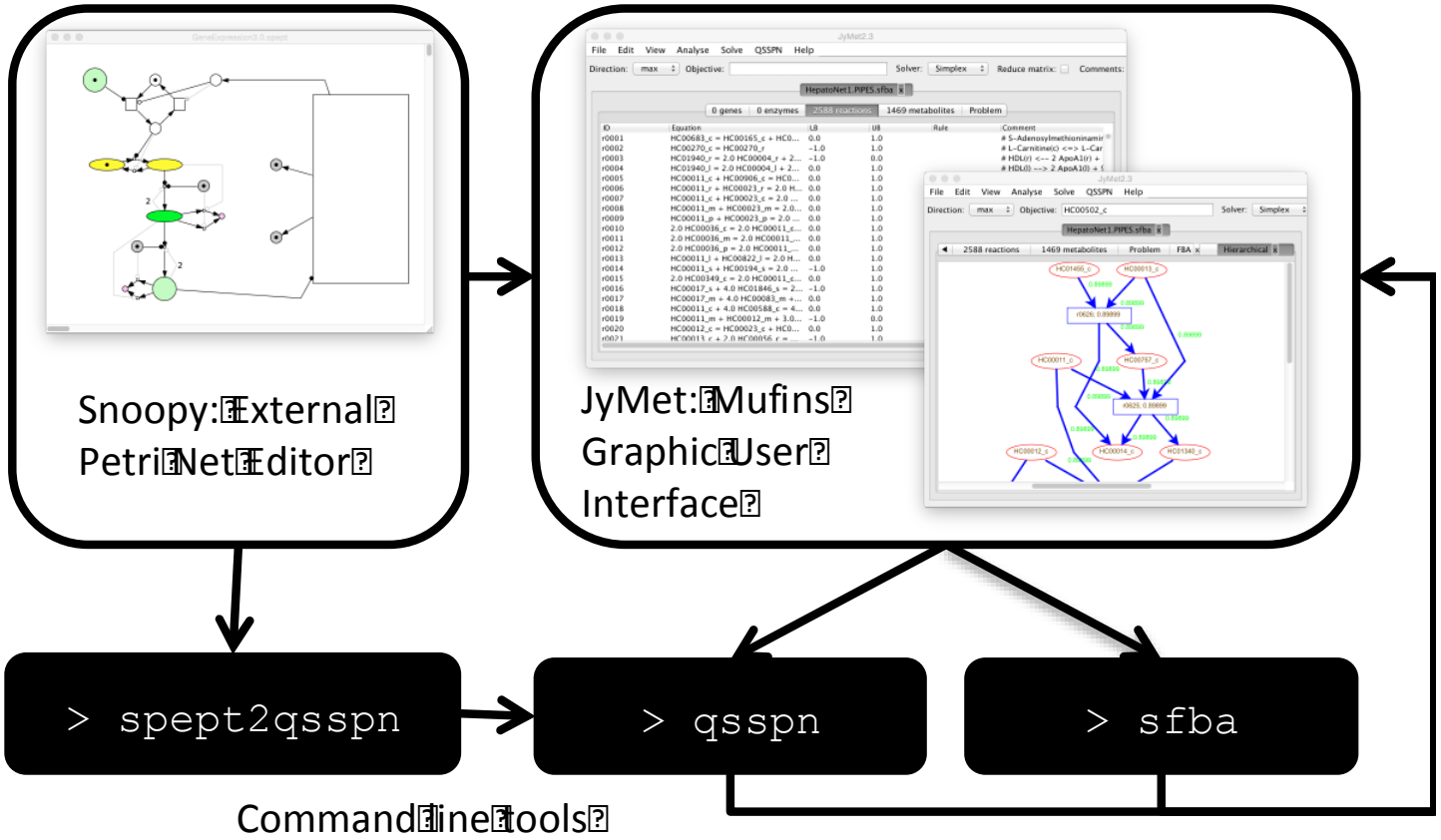

http://sysbio3.fhms.surrey.ac.uk/mufins/

Manuscript in third stage of review in NPJ: Systems Biology & Applications.

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