Universiteit Leiden

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Introduction to QSP in Drug Discovery and Development: a Historical, Current and Future Perspective

Piet van der Graaf

ASCPT, Washington DC

13th March 2019

The birth of QSP?

Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms

An NIH White Paper by the QSP Workshop Group – October, 2011

Peter K. Sorger (co-chair), Sandra R.B. Allerheiligen (co-chair)

Darrell R. Abernethy, Russ B. Altman, Kim L. R. Brouwer, Andrea Califano, David Z. D'Argenio, Ravi Iyengar, William J. Jusko, Richard Lalonde, Douglas A. Lauffenburger, Brian Shoichet, James L. Stevens, Shankar Subramaniam, Piet Van der Graaf and Paolo Vicini

Rebecca Ward (editor)

Definitions: QSP is defined as an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs. QSP will provide an integrated "systems-level" approach to determining mechanisms of action of new and existing drugs in preclinical and animal models and in patients. QSP will create the knowledge needed to change complex cellular networks in a specified way with mono or combination therapy, alter the pathophysiology of disease so as to maximize therapeutic benefit and minimize toxicity and implement a "precision medicine" approach to improving the health of individual patients.

https://www.nigms.nih.gov/Training/Documents/SystemsPharmaWPSorger2011.pdf

NIH Workshop follow up

National Institute of Neurological Disorders and Stroke

Quantitative Systems Pharmacology and Drug Discovery: Filling the Gaps in Current Models of the R&D

July 26, 2017 to July 27, 2017
Bethesda North Marriott Hotel & Conference Center (Conference Room:Salon C)
North Bethesda, Maryland
United States

Deliverables of Workshop

- White Paper: Merged Systems Biology and Pharmacology as an approach to CNS Drug Discovery: Filling the Gaps in Current Models of the R&D Process for Neurotherapeutics: NINDS/NIH Workshop, Summer, 2017
- Recommendations regarding the utility of this approach to CNS Drug Discovery and Development
- Posted WS summary on ADDS website to foster collaborations between data science and systems biology PI's (post → advertisement of WS to ADDS blog and its participants)

Summary and Recommendations from the 2017 NIH Workshop, "Quantitative Systems Pharmacology (QSP) and Drug Discovery: Filling the Gaps in Current Models of the R&D Process for Neurotherapeutics"

Hugo Geerts, In Silico Biosciences, Berwyn, PA
John Wikswo, Vanderbilt University, Nashville, TN, USA
Piet van der Graaf, Certara, Canterbury, UK
Jane Bai, Center for Drug Evaluation and Research, FDA, Silver Spring, MD, USA
Chris Gaiteri, Rush Alzheimer' Disease Center, Rush University, Chicago IL, USA
David Bennett, Rush Alzheimer' Disease Center, Rush University, Chicago, IL, USA
Susan Swalley, Novartis Biomedical Research Institute, Cambridge, MA, USA
Nancy Klimas, Miami VA Healthcare, Miami, FL, USA
Suzana Petanceska, Division of Neuroscience, NIA, Bethesda, MD, USA
MaryAnn Pelleymounter, Division of Translational Research, NINDS, Bethesda, MD, USA

Pre-Conference Programming

ADVANCING QSP TOWARD PREDICTIVE DRUG DEVELOPMENT: FROM TARGETS TO TREATMENTS

WEDNESDAY, MARCH 13, 2019 | 8:00 AM – 5:00 PM

Co-Sponsors: ASCPT, US Food and Drug Administration (FDA), IQ Consortium, and the International Society of Pharmacometrics (ISoP)
Chairs: Cynthia J. Musante, PhD, Jane Bai, PhD, and Suzana Petanceska, PhD

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Earlier versions of Systems Pharmacology

Peter C. Preusch, PhD
Pharmacological Sciences
Training Grant Program Director
NIGMS/NIH
Department of Health and
Human Services
E-mail preuschp@nigms.nih.gov.

LACDR

Universiteit Leiden
The Netherlands

Integrative and Organ Systems Pharmacology:
A New Initiative from the National Institute of General Medical Sciences

molecular interventions

April 2004
Volume 4, Issue 2

BRITISH PHARMACOLOGICAL SOCIETY

About the Integrated Systems Pharmacology Affinity Group

The Integrated Systems Pharmacology Affinity Group serves members who study complex systems or take a whole animal approach to understand drug action or toxicity at molecular, cellular or organ system levels. Those working across several systems, or working in systems without a defined Affinity Group, might be expected to align with Integrated Systems Pharmacology .

INNOVATION

Rescuing drug discovery: *in vivo* systems pathology and systems pharmacology

Jan van der Greef and Robert N. McBurney

NATURE REVIEWS | DRUG DISCOVERY VOLUME 4 | DECEMBER 2005 | 961

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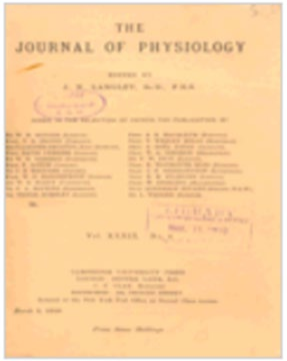
Even earlier versions of Systems Pharmacology

Volume 39, Issue 6
March 8, 1910



THE NATURE OF OXYHÆMOGLOBIN, WITH A NOTE ON ITS MOLECULAR WEIGHT.

By J. BARCROFT, M.A., B.Sc., *Fellow of King's College, Cambridge,* AND A. V. HILL, B.A., *Scholar of Trinity College, Cambridge.*

(*From the Physiological Laboratory, Cambridge.*)

[1] **The responsibility for the mathematical portion of the work rests with Hill and for the oxygen estimations with Barcroft.**

If $[O_2]$ be the concentration of oxygen in the solution we have the equation

$$HbO_2 \rightleftharpoons Hb + O_2.$$

Now at the surface of any bubbles of gas we have a diffusion of gas into the bubble from the solution and its rate of diffusion is proportional to $[O_2]$.

Hence if the rate of bubbling is always the same the rate of loss of oxygen from the solution is proportional at any moment to $[O_2]$.

Now let $100x/\alpha$ be the percentage saturation, x the number of molecules of HbO_2 present (assuming the Hb to be present as molecules), α the total number of molecules present whether as Hb or HbO_2.

The amount of O_2 present $= x +$ the amount in simple solution. The latter term is small compared with the first and may be neglected.

$\therefore -\frac{dx}{dt}$ = the rate of loss of oxygen from the solution $= \lambda[O_2]$.

Now the laws of mass action give us

$$-\frac{dx}{dt} \propto k[HbO_2] - k'[Hb][O_2],$$

$$\text{i.e.} \quad -\frac{dx}{dt} = k_0[HbO_2] + \frac{\mu k'}{\lambda}[Hb]\frac{dx}{dt},$$

$$\text{i.e.} \quad -\frac{dx}{dt}(\lambda + \mu k'[Hb]) = \mu k_0 x,$$

$$\text{i.e.} \quad -\frac{dx}{dt} = \frac{\mu k_0 x}{\lambda + \mu k'\alpha - \mu k' x},$$

$$\text{i.e.} \quad +\frac{dx\,(\mu k' x - \lambda - \mu k'\alpha)}{\mu k_0 x} = dt,$$

$$\text{i.e.} \quad dx\left\{\frac{k'}{k_0\lambda} - \frac{\lambda + \mu k'\alpha}{\mu k_0 \lambda}\frac{1}{x}\right\} = dt,$$

and integrating,

$$\left[x\frac{k'}{k_0\lambda} - \frac{\lambda + \mu k'\alpha}{\mu k_0 \lambda}\log_e x\right] = t,$$

where the square brackets signify "between the limits of integration."

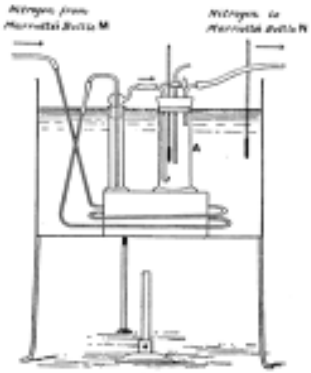


Fig. 1.

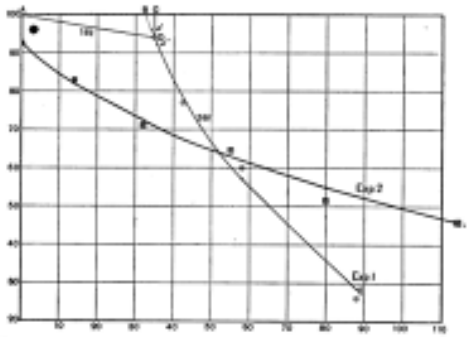


Fig. 2. Curves representing the calculated degree of dissociation at any time in Expts. 1 and 2. Percentage saturation plotted vertically, time in minutes horizontally. The points represent the actual observations.

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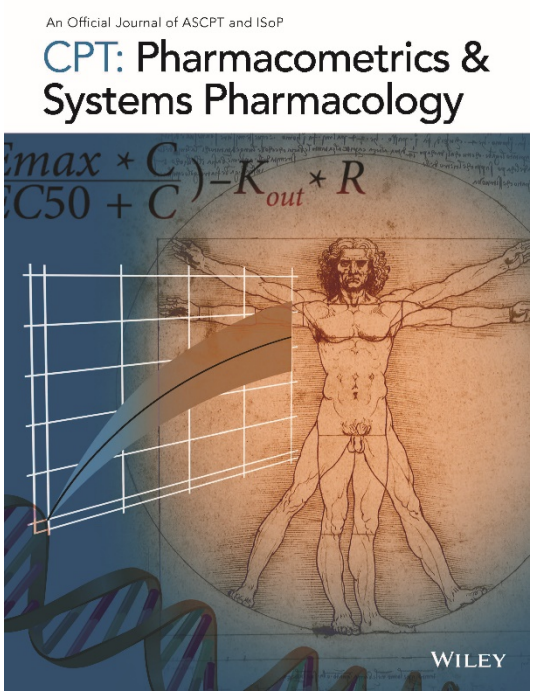
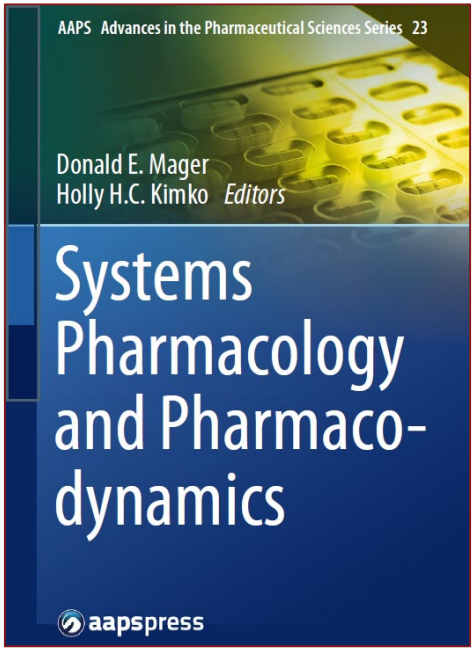
QSP: An established discipline

Journal



2012

Book



2016

Networks and Communities

ASCPT American Society for Clinical Pharmacology & Therapeutics

Member Services › Networks and Communities › Quantitative Pharmacology › S

Systems Pharmacology (SP) Community

aaps American Association of Pharmaceutical Scientists

SYSTEMS PHARMACOLOGY COMMUNITY

ISoP Special Interest Group

QSP

Quantitative Systems Pharmacology

UK Quantitative Systems Pharmacology NETWORK

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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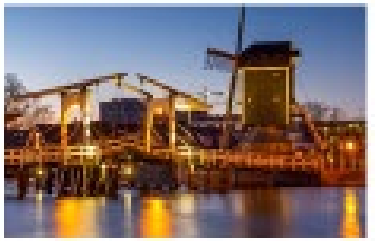
…and a meeting!





QSPC2020
Quantitative Systems Pharmacology Conference 2020

April 22-24, 2020

Leiden, The Netherlands

www.qspc.eu

Universiteit Leiden
The Netherlands

Stadsgehoorzaal

LACDR

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Application of QSP in Regulatory Review: FDA

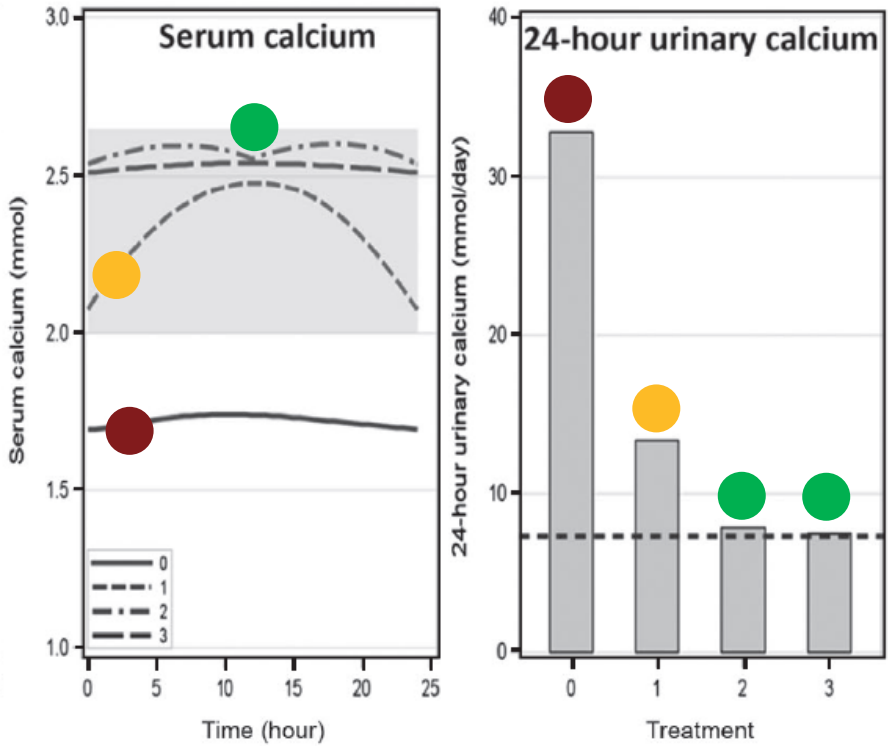
CLINICAL PHARMACOLOGY & THERAPEUTICS

doi:10.1002/cpt.1200

Use of a Systems Pharmacology Model Based Approach Toward Dose Optimization of Parathyroid Hormone Therapy in Hypoparathyroidism

Manoj Khurana[1], Immo Zadezensky[2,*], Naomi Lowy[3], Dragos Roman[3], Jean-Marc Guettier[4,*], Liang Li[1], Jeffry Florian[3], Chandrahas G. Sahajwalla[1], Vikram Sinha[5,*] and Nitin Mehrotra[5,*]

- Placebo
- Proposed regimen
- QSP suggested regimen



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Application of QSP in Regulatory Review: EMA

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 5 | NOVEMBER 2018

The Role of Quantitative Systems Pharmacology in the Design of First-in-Human Trials

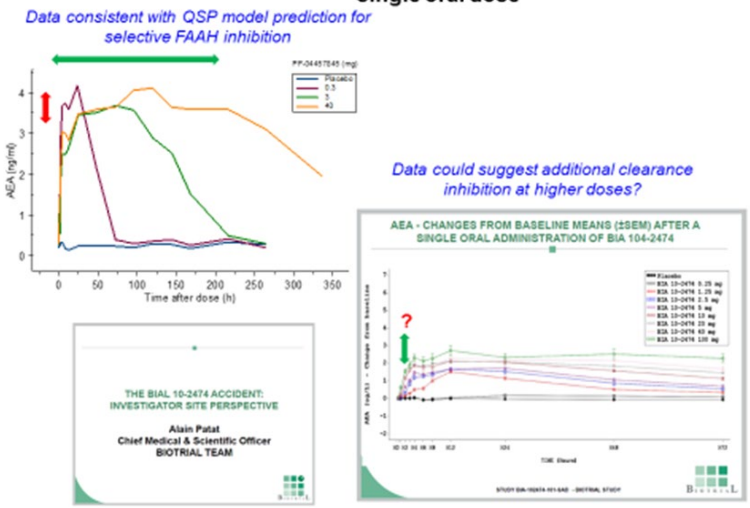
Piet H. van der Graaf[1,2] and Neil Benson[2]

ORIGINAL ARTICLE

A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain

N Benson[1], E Metelkin[2], O Demin[2], GL Li[3], D Nichols[4] and PH van der Graaf[5]

Elevation of AEA observed in healthy volunteers following a single oral dose



Response to: "The Role of Quantitative Systems Pharmacology in the Design of First-in-Human Trials"

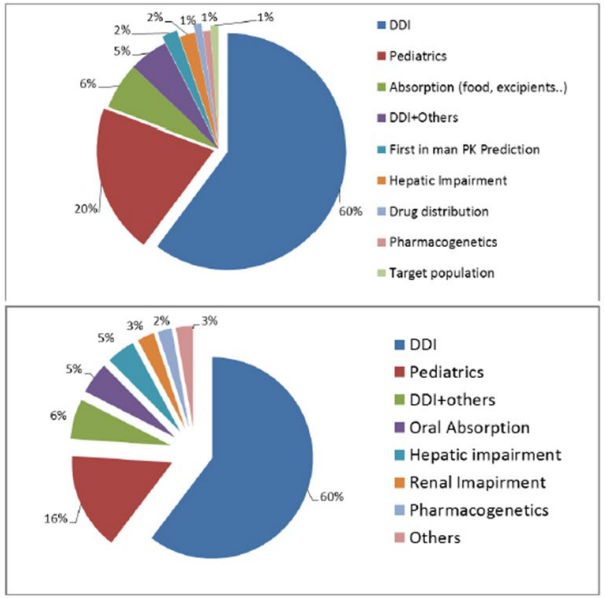
Kevin Blake[1], Milton Bonelli[1], Stefano Ponzano[1], Harald Enzmann[2], on behalf of the European Medicines Agency Committee for Human Medicinal Products "First-in-Human Guideline Drafting Group"[†]

EMA encourages the development and use of complementary mechanistic models in translational drug research, such as the present example. Guidance on novel technologies can be obtained from EMA under the form of a qualification advice or a qualification opinion (Qualification of novel methodologies for medicine development: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0. Accessed 8 June 2018). Their inclusion in future guidelines will be further considered in line with increasing scientific knowledge.

Still some way to go: comparison with PBPK

Currently ~10 FDA submissions containing QSP per year

FDA submissions using PBPK modelling



Cumulative as of June 18, 2014 (n=96)

Sinha, MHRA PBPK Workshop 2014, London, UK

Cumulative as of Aug 1, 2016 (n=217)

Majority related to drug-drug interactions (DDIs, ~ 60%); pediatrics ranks the second

Ping Zhao

41 Labels with *in-silico* substitutes for clinical data informed by Simcyp

Pfizer Revatio (Sildenafil) Pulmonary Arterial Hypertension	**Johnson & Johnson** Xarelto (Rivaroxaban) Deep Vein Thrombosis and Pulmonary Embolism	**Tibotec** Edurant (Rilpivirine) HIV infection	**Ariad** Iclusig (Ponatinib) Chronic Myeloid Leukemia	**GW Pharma** Epidiolex (Cannabidiol) Epilepsy	**Lilly** Olumiant (Baricitinib) Rheumatoid Arthritis
Novartis Odomzo (Sonidegib) Basal Cell Carcinoma	**Janssen** Olysio (Simeprevir) Hepatitis C	**Actelion** Opsumit (Macitentan) Pulmonary Arterial Hypertension	**Pharmacyclics** Imbruvica (Ibrutinib) Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	**AstraZeneca** Movantik (Naloxegol) Opioid Induced Constipation	**Genentech** Cotellic (Cobimetinib) Metastatic Melanoma
Genzyme Cerdelga (Eliglustat) Gaucher Disease	**Sanofi** Jevtana (Cabazitaxel) Prostate Cancer	**Novartis** Zykadia (Ceritinib) Metastatic Non-small Cell Lung Cancer	**Pfizer** Bosulif (Bosutinib) Chronic Myelogenous Leukemia	**Alkermes** Aristada (Aripiprazole lauroxil) Schizophrenia	**AstraZeneca** Lynparza (Olaparib) Advanced Ovarian Cancer
Novartis Farydak (Panobinostat) Multiple myeloma	**Eisai** Lenvima (Lenvatinib) Thyroid cancer	**Genentech** Alecensa (Alectinib) Non-small Cell Lung Cancer	**AstraZeneca** Tagrisso (Osimertinib) Metastatic NSCLC	**Amgen** Blincyto (Blinatumomab) Acute Lymphoblastic Leukemia	**AstraZeneca** Calquence (Acalabrutinib) Mantle Cell Lymphoma
Eli Lilly Verzenio (Abemaciclib) Metastatic Breast Cancer	**Intercept** Ocaliva (Obeticholic acid) Primary Biliary Cholangitis	**Actelion** Uptravi (Selexipag) Pulmonary Arterial Hypertension	**Janssen** Invokana (Canagliflozin) Type 2 Diabetes	**Merck** Prevymis (Letermovir) Cytomegalovirus	**Merck** Steglujan (Ertugliflozin) Type 2 Diabetes
Novartis Kisqali (Ribociclib succinate) Metastatic Breast Cancer	**PTC Therapeutics** Emflaza (Deflazacort) Duchenne Muscular Dystrophy	**Shionogi** Symproic (Naldemedine) Opioid Induced Constipation	**Spectrum** Beleodaq (Belinostat) Peripheral T-cell Lymphoma	**UCB** Briviact (Brivaracetam) Epilepsy	**Vertex** Symdeko (Tezacaftor/ivacaftor) Cystic Fibrosis
Novartis Rydapt (Midostaurin) Acute Myeloid Leukemia	**Ariad** Alunbrig (Brigatinib) Metastatic Non-small Cell Lung Cancer	**Janssen** Erleada (Apalutamide) Non-metastatic Prostate Cancer	**Helsinn** Akynzeo (fosnetupitant/palonosetron) Acute and Delayed Nausea	**AkaRx** Doptelet (Avatrombopag maleate) Thrombocytopenia	

QSP: Dose (regimen) prediction and Target validation?

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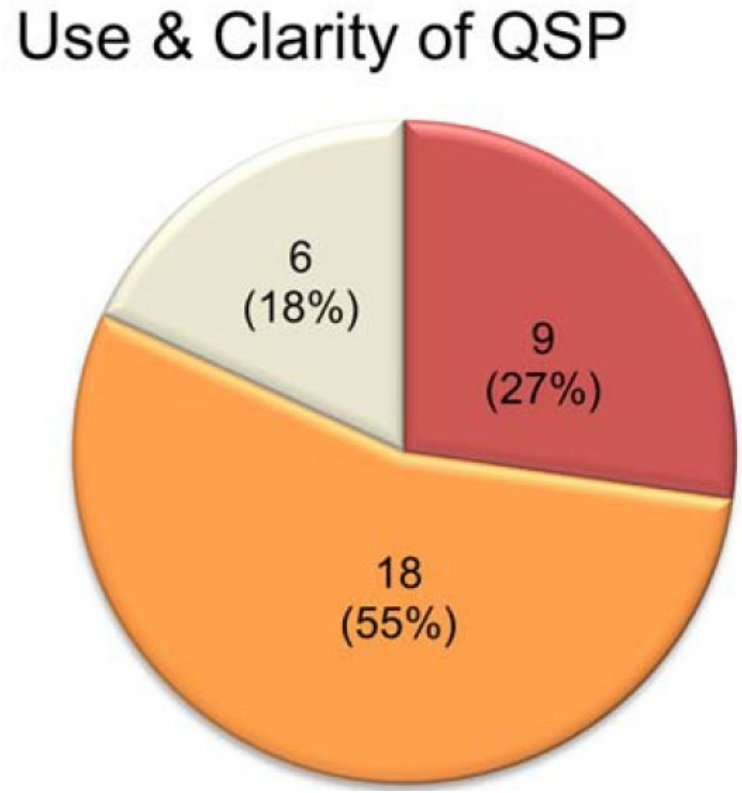
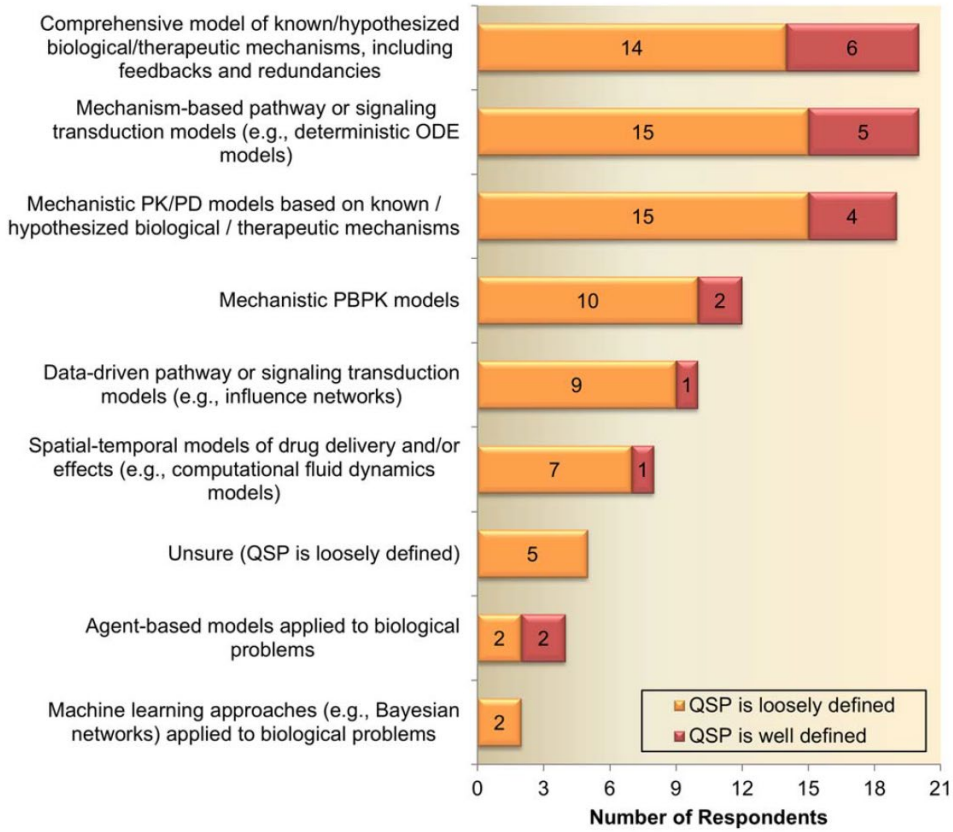
QSP definition: confusion?

REVIEW

Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape





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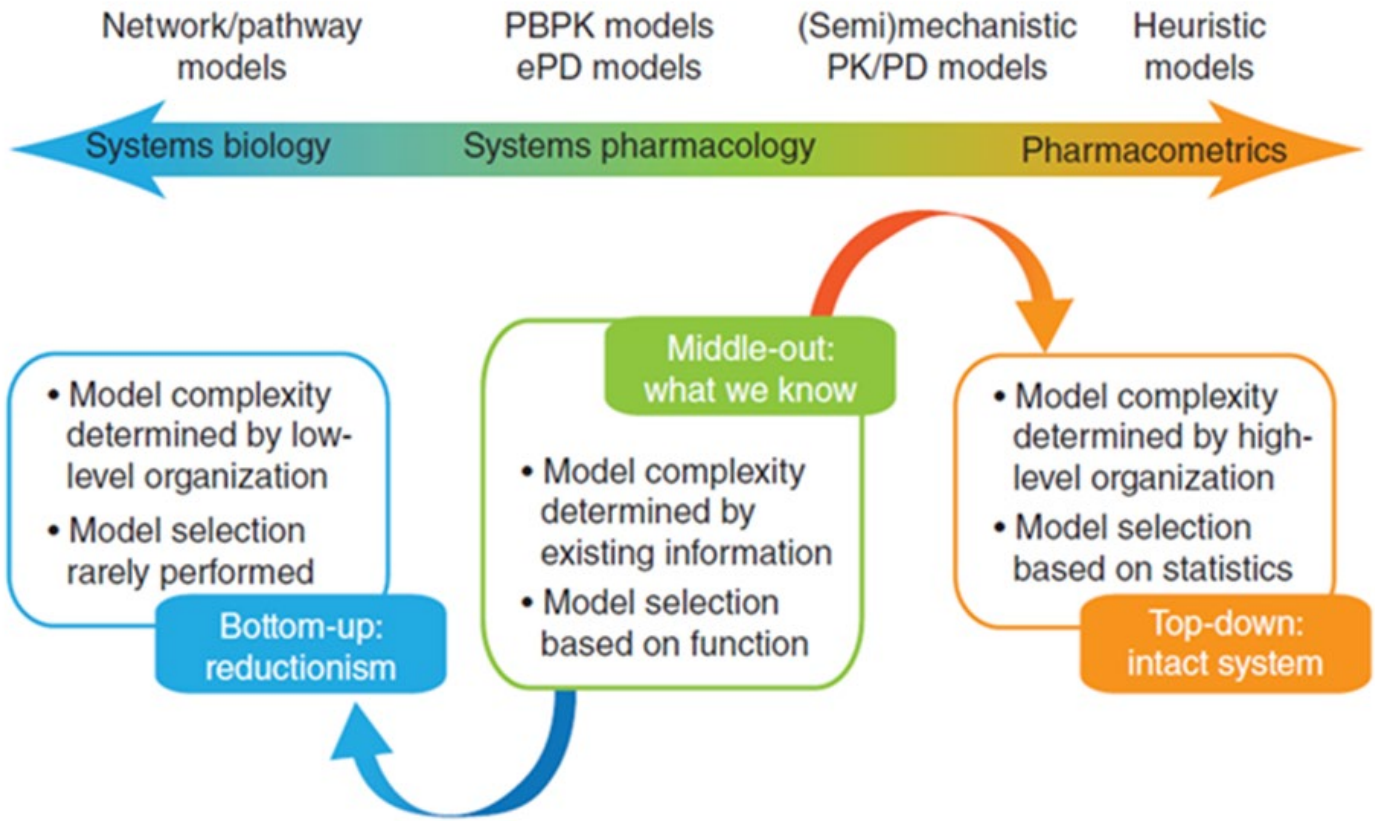


CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 93 NUMBER 5 | MAY 2013

nature publishing group

PERSPECTIVES

COMMENTARIES

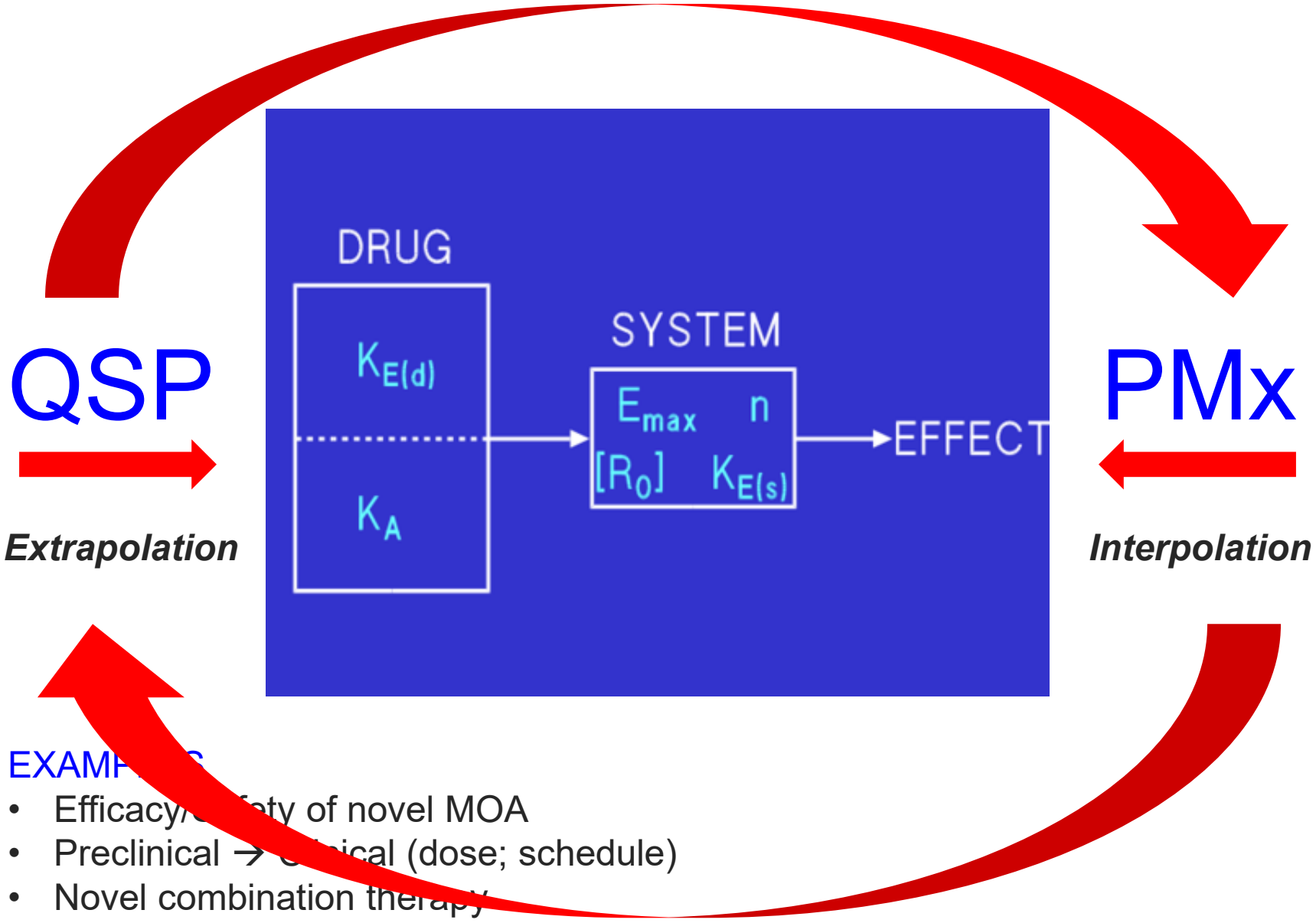
Systems Pharmacology for Drug Discovery and Development: Paradigm Shift or Flash in the Pan?

P Vicini[1] and PH van der Graaf[2,3]

Systems pharmacology is an emerging approach that sets out to use quantitative concepts rooted in the synergy between modeling and simulation on one hand and large-scale data collection and analysis on the other to investigate biological systems and design therapeutic interventions. Interest in this field has recently increased substantially, but so have perceived challenges and misunderstandings, especially related to implementation. This Commentary explores the opportunities and challenges in the rapidly evolving area of systems pharmacology from a drug discovery and development perspective.

tistical regression techniques teach us that the more components a model has, the greater its explanatory power will be; however, the individual contributions of those components will become more and more difficult to discern. Systems-pharmacology models attempt to inject biological realism early in the process—not necessarily with the intent to build a "bulldozer out of quarks"[3] but, rather, to bring molecular or cellular detail closer to high-level, functional behavior.

Systems pharmacology was defined in a recent white paper by the National Institutes of Health (NIH) Quantitative Systems Pharmacology (QSP) workshop group[4] as "an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs [with the aim of] determining mechanisms of action of new and existing drugs in preclinical and animal models and in patients."



EXAMPLES

- Efficacy/safety of novel MOA
- Preclinical → clinical (dose; schedule)
- Novel combination therapy
- Biomarker identification
- Novel patient populations
- Novel indications

QSP case study: Immunogenicity (IG)

The IG QSP Consortium

abbvie Pfizer Lilly astellas Bristol-Myers Squibb Roche Genentech CERTARA

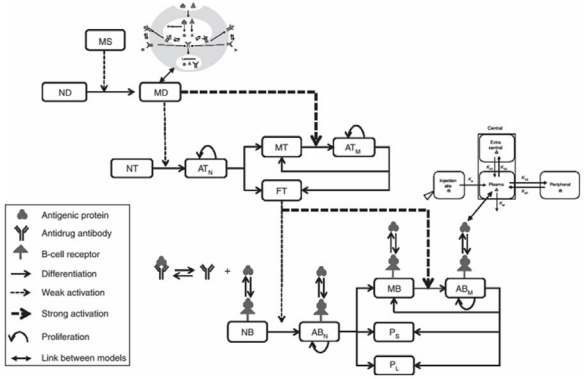
Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31

www.nature.com/psp

ORIGINAL ARTICLE

A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 2—Model Applications

X Chen[1], TP Hickling[2] and P Vicini[3]

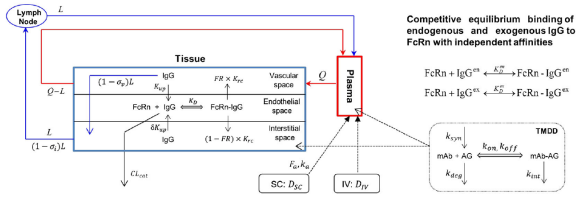


The AAPS Journal, Vol. 16, No. 5, September 2014 (© 2014)
DOI: 10.1208/s12248-014-9640-5

Research Article

Simulation of Monoclonal Antibody Pharmacokinetics in Humans Using a Minimal Physiologically Based Model

Linzhong Li,[1,3] Iain Gardner,[1] Miroslav Dostalek,[2] and Masoud Jamei[1]



IG Model

IG Simulator

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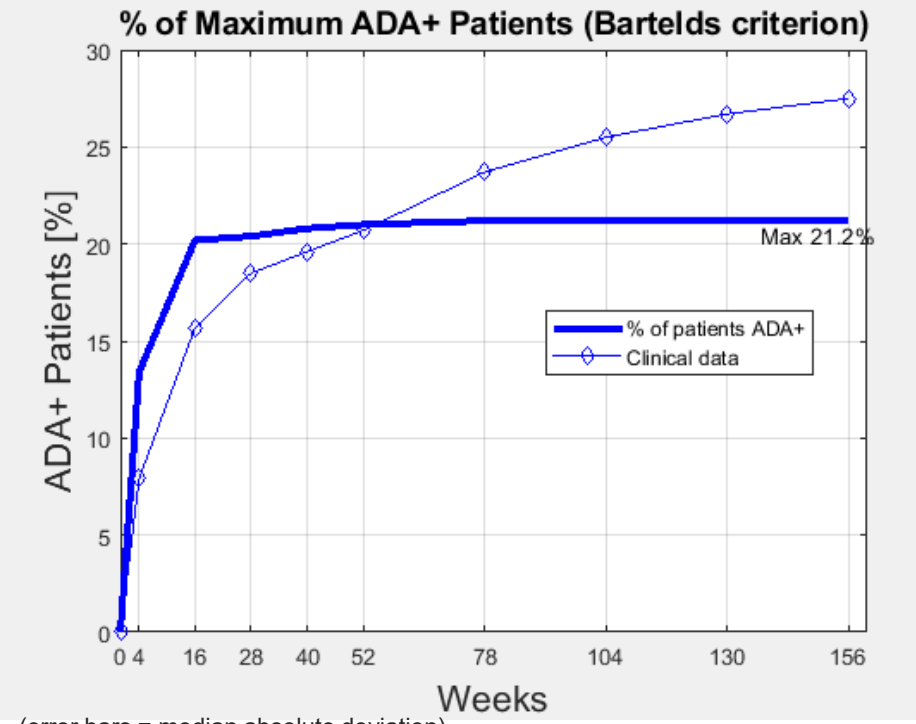
Bioinformatics predictions

Number of epitopes = 2

MHC Class II allele	Allele frequency (North American population)	Epitope 1 binding affinity (include BC loop region)	Epitope 2 binding affinity (include FG loop loop region)
DPA1*01:03/DPB1*02:01	0.5200	203	4000
DPA1*01/DPB1*04:01	0.2364	426	4000
DRB1*03:01	0.0689	472	4000
DRB1*11:01	0.0472	278	4000
DRB1*15:01	0.0696	447	218
DRB1*04:05	0.0231	4000	118
DRB1*07:01	0.0872	4000	161
DRB1*08:02	0.0742	4000	854
DRB1*13:02	0.0394	4000	168

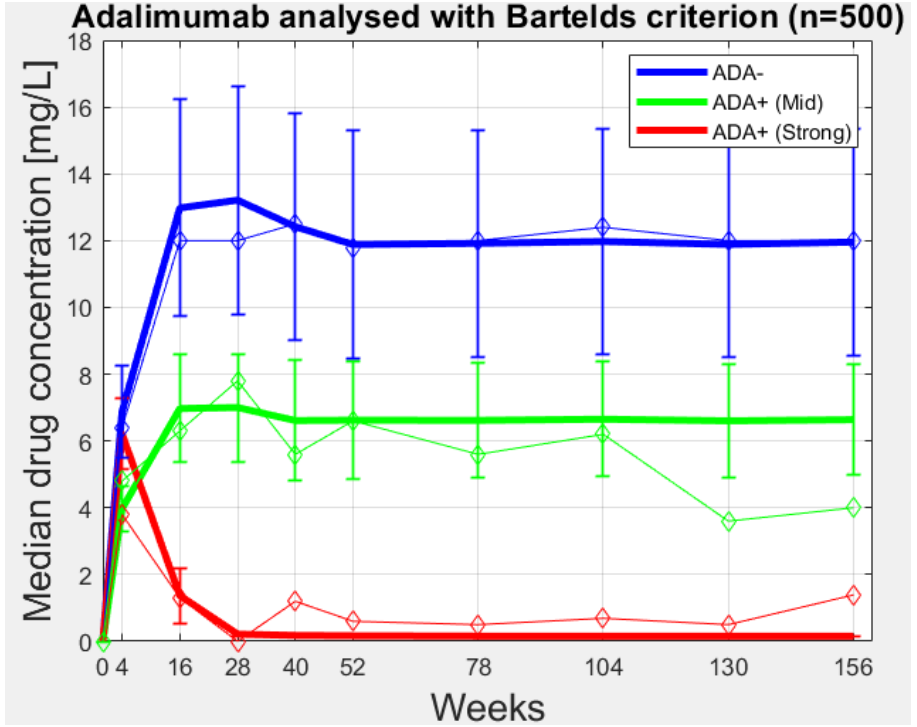
Example: Adalimumab

ADA response



(error bars = median absolute deviation)

Pharmacokinetics



ADA+ Cohort	Model	Data
ADA+ 12-100AU/ml	60%	59%
Strong ADA+ >100AU/ml	40%	41%

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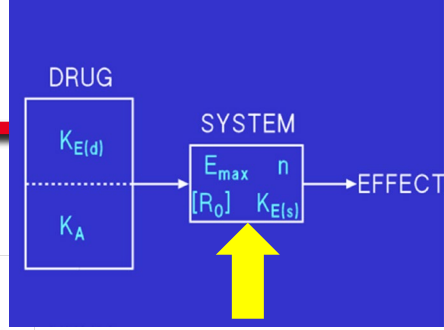
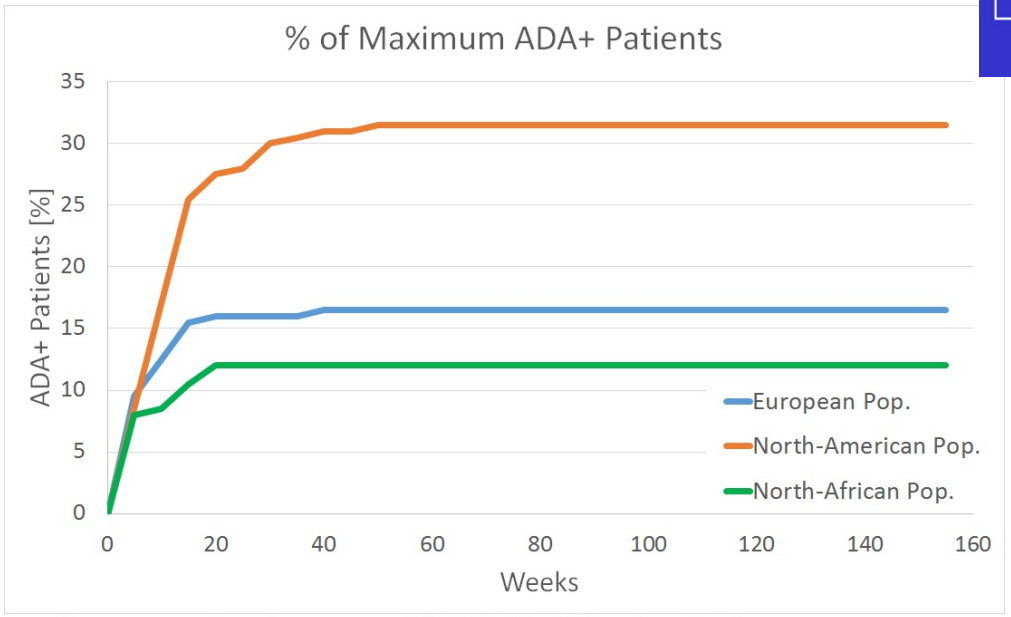
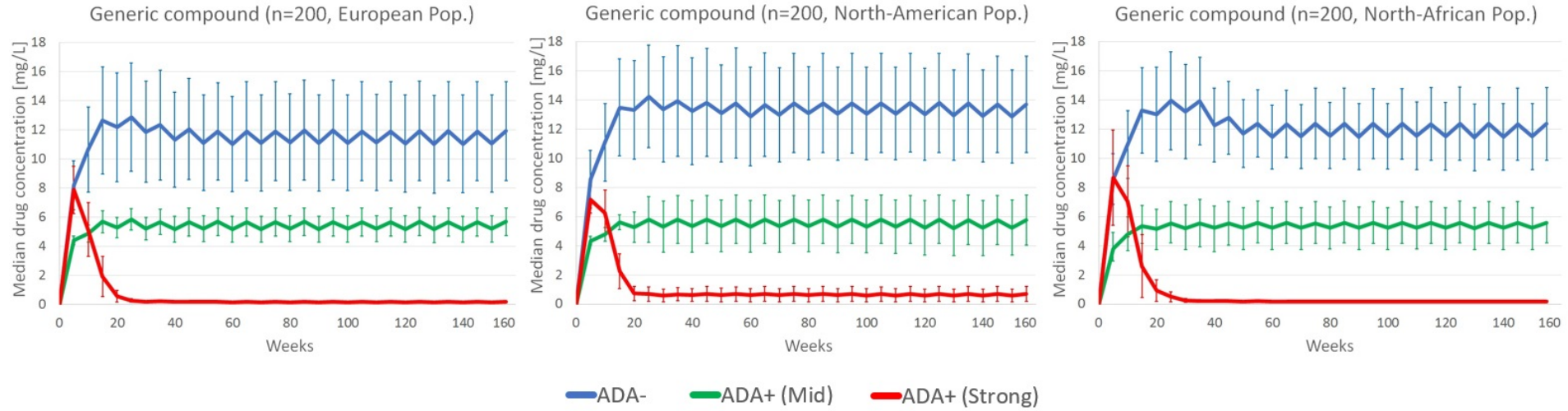
Bartelds et al., doi:10.1001/jama.2011.406

Change System

Compound X (adalimumab-like)







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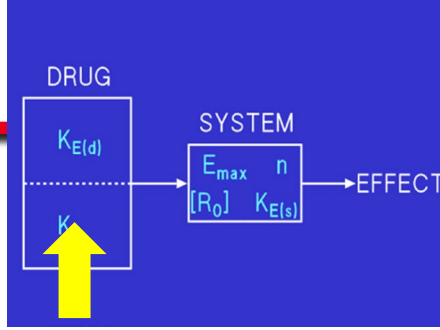
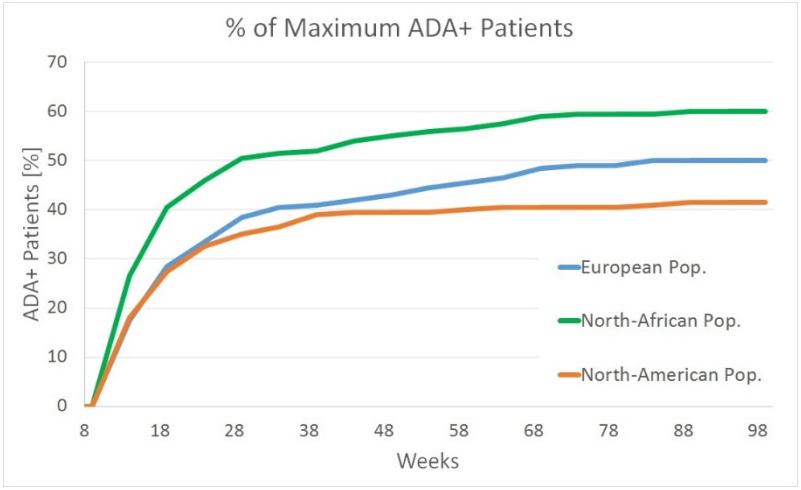
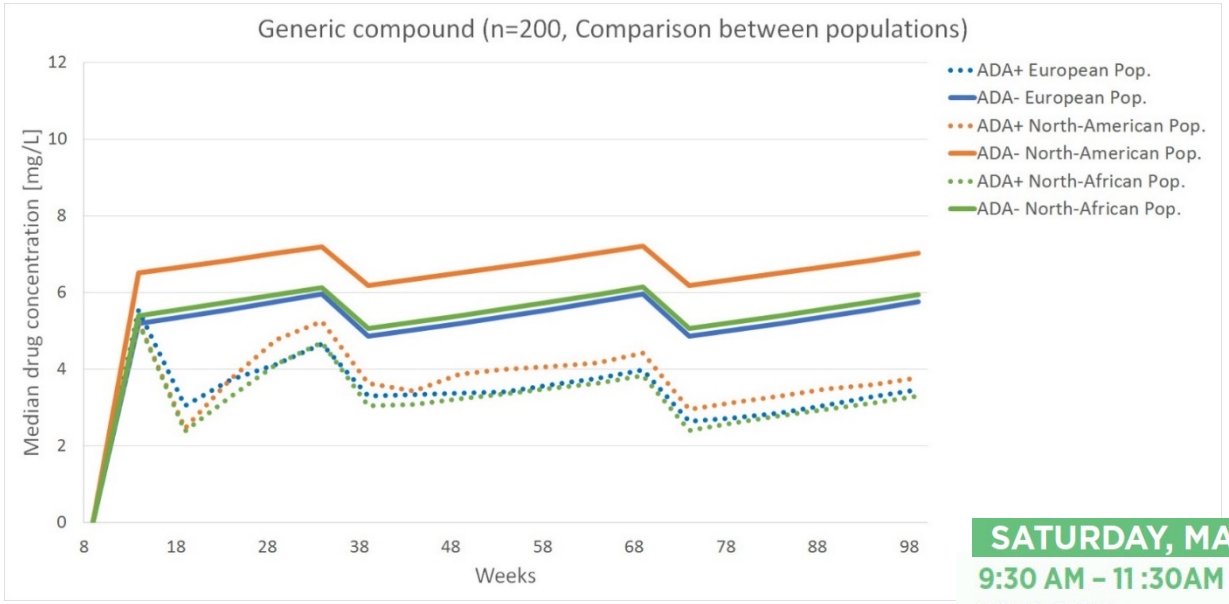
Change Compound



Compound Y





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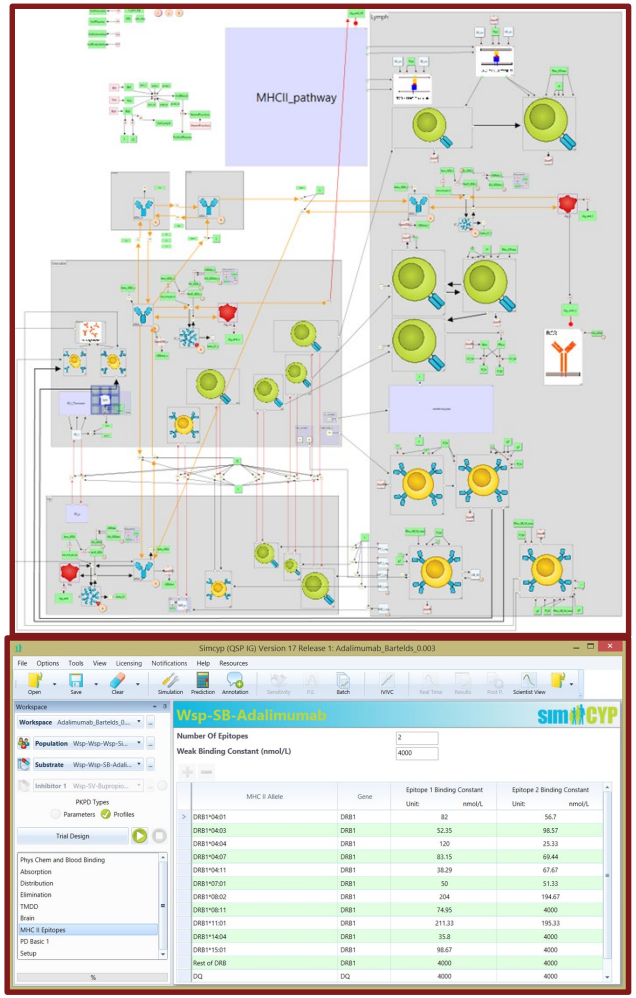
Applications: Extrapolation



Extrapolation to population with different HLA allele frequencies.

Personalised & Precision medicine: Prediction of PK and IG for genotyped individual.

Extrapolation to larger populations. (Phase III, IV)

IG Management: Extrapolation to different dosing regimes.

Extrapolation to paediatric population or individual children.

Extrapolation to disease population.

Extrapolation to age group.

Prediction of the effect of co-therapy

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Some additional Points for Consideration

- Open Source?
- Experimentation?
- Pharmacometrics ←→ QSP?
- …..

Open Source?

Reproducibility of Quantitative Systems Pharmacology (QSP) Models: Current Challenges and Future Opportunities

Daniel C. Kirouac[1,3,*], Brian Cicali[2,3] and Stephan Schmidt[2,3]

ABSTRACT

Provision of model code is required for publication in *CPT:PSP*, enabling QSP model *availability*. A searchable repository of published QSP models would enhance model *accessibility*. We assess the feasibility of establishing such a resource, based on 18 QSP models published in this journal. However, due to the diversity of software platforms (9), file formats and functionality, such a resource is pre-mature. We evaluated 12 of the models (those coded in R, PK-Sim/MOBI and Matlab) for functionality. Of the 12, only 4 were executable, in that figures from the associated manuscript could be generated via a 'run' script. Many researchers are aware of the challenges involved in re-purposing published models. We offer some ideas to enable model sharing going forward, including annotation guidelines, standardized formats, and inclusion of 'run' scripts. If practitioners can agree to some minimum standards for provision of model code, this would accelerate model re-use and extension.

Open Science

- Sharing knowledge/resources/data
- Consensus on science and common tools/standards
- Engaging pharma, academics and regulators through publication & education
- Rigorous approach to IT and QA: interoperable, future proof and meeting regulatory requirements
- Ability to integrate confidential data/knowledge/models in a seamless and incremental manner

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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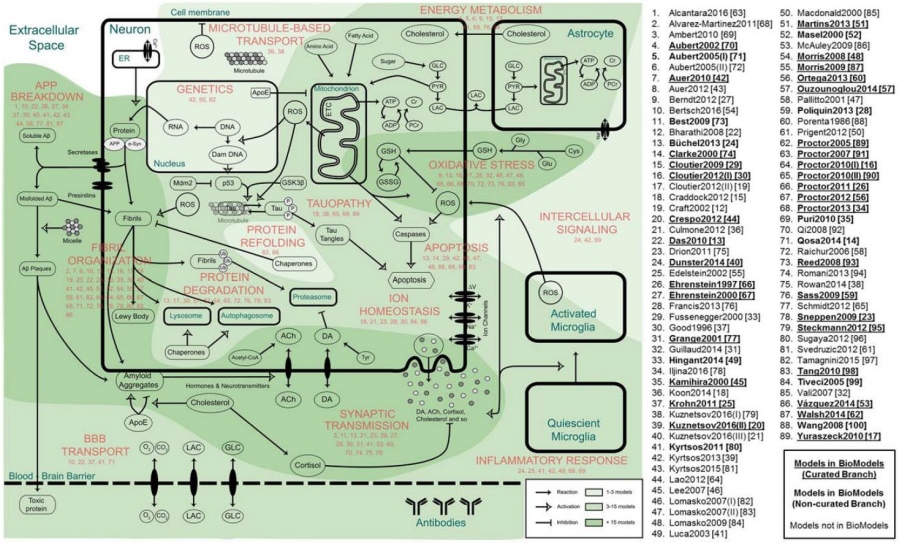
Open Science example: literature mining

Neurodegeneration



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73. **Reed2008 [93]**
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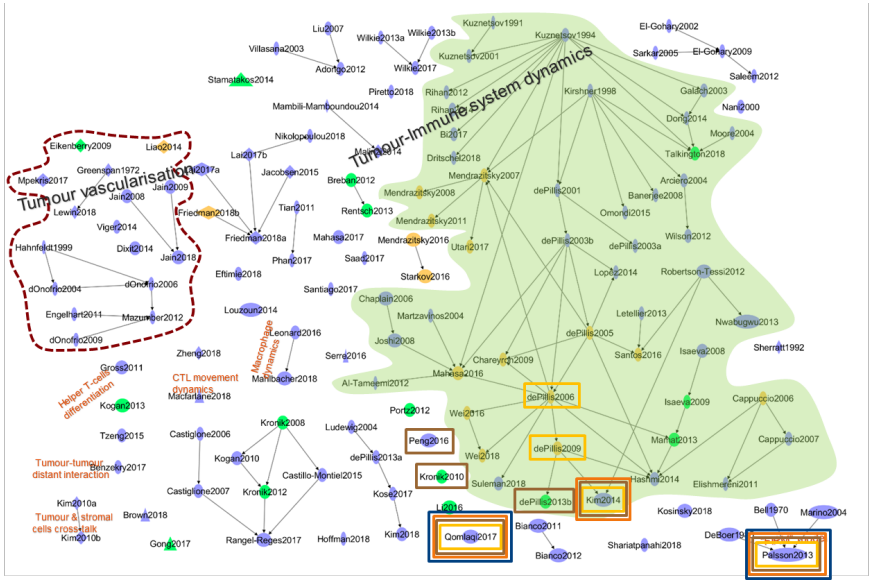
85. Vali2007 [32]
86. **Vázquez2014 [53]**
87. **Walsh2014 [62]**
88. **Wang2008 [100]**
89. **Yuraszeck2010 [17]**

Models in BioModels (Curated Branch)

Models in BioModels (Non-curated Branch)

Models not in BioModels

Immuno-Oncology



REVIEW

The Impact of Mathematical Modeling in Understanding the Mechanisms Underlying Neurodegeneration: Evolving Dimensions and Future Directions

A Lloret-Villas[1], TM Varusai[1], N Juty[1], C Laibe[1], N Le Novère[2], H Hermjakob[1] and V Chelliah[1]*

PAGE 2019

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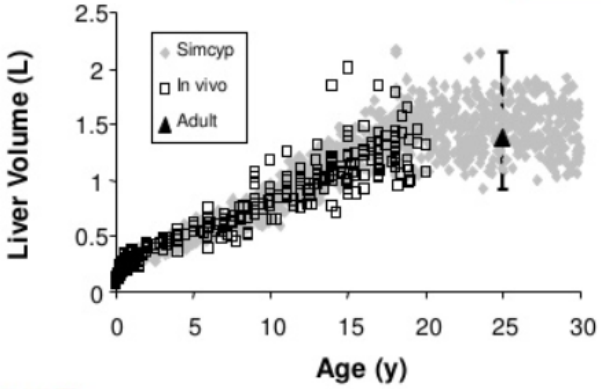
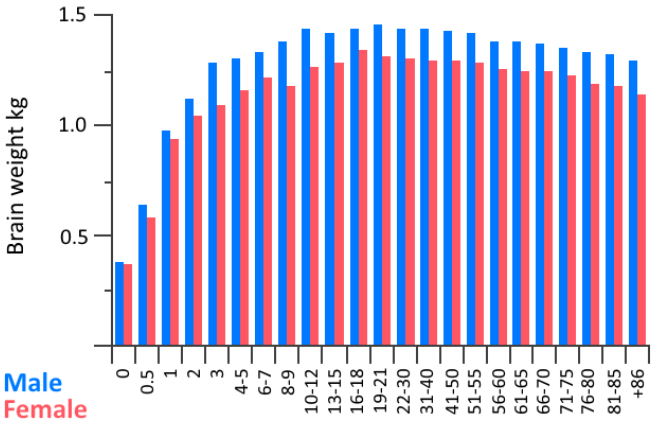
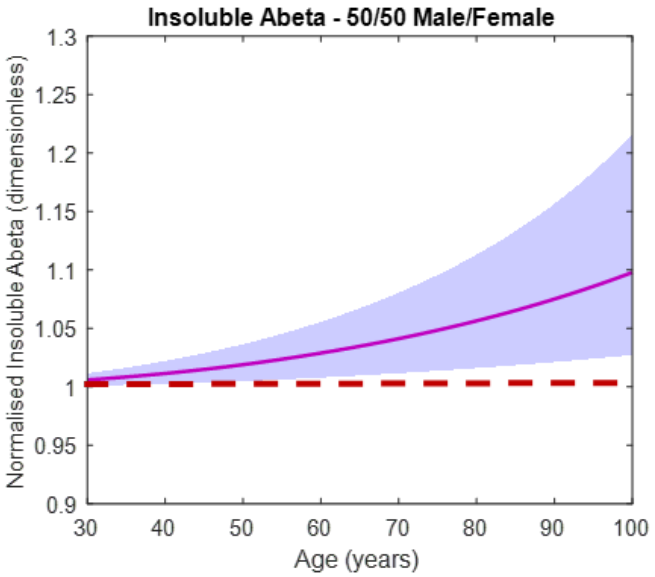
Open Science example: organ size

- Impact of variable organ size (age, gender etc.) well-established in PBPK
- Similar scholarship needs to be developed for QSP
- Example: Brain volume in models of AD







Open Science example: target expression

PRP Pharmacology Research & Perspectives
Open Access

ORIGINAL ARTICLE

Application of a systems pharmacology model for translational prediction of hERG-mediated QTc prolongation

Verena Gotta[1,2], Zhiyi Yu[3], Frank Cools[4], Karel van Ammel[4], David J. Gallacher[4], Sandra A. G. Visser[5], Frederick Sannajust[6], Pierre Morissette[6], Meindert Danhof[1] & Piet H. van der Graaf[1,7]

1.2. External evaluation of translational predictions *(sotalol & moxifloxacin)*

Good clinical predictions in adults and children were obtained (*<5-10 ms prediction discrepancy from clinical regression model until ΔQTc of 35 ms*). However, QTc- effects in neonates were under-predicted (*>20 ms prediction discrepancy*).

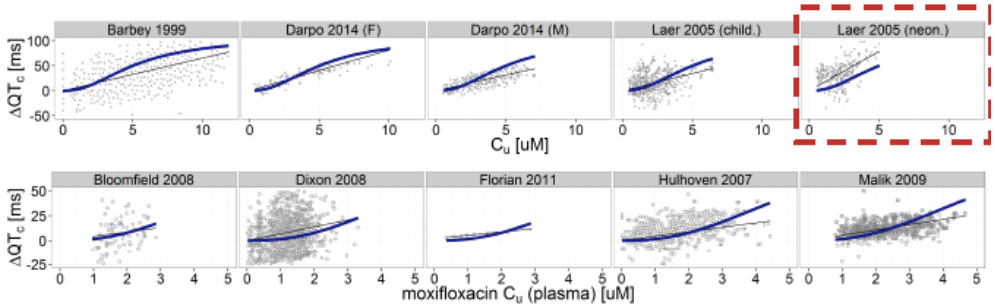


Fig.2: Translational predictions from preclinical data and system-specific scaling parameters only *(blue lines)* are contrasted with reported clinical ΔQTc from indicated references (*grey dots:* digitized observations. *black lines:* predictions from respective clinical regression model).

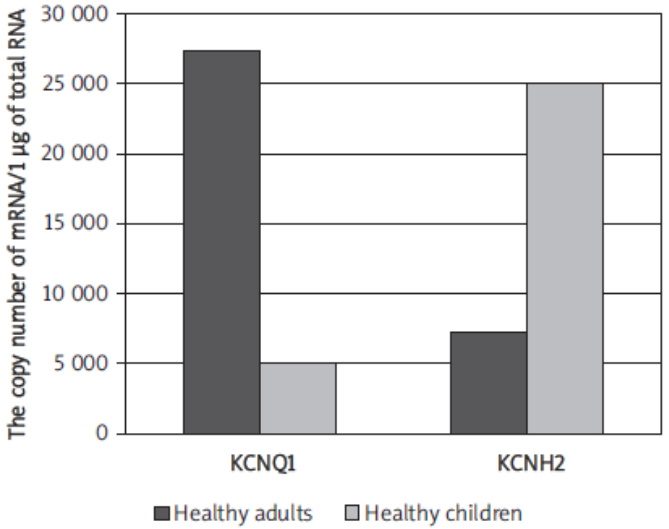


Figure 3. Comparison of KCNQ1 and KCNH2 mRNA levels between healthy adults and healthy children. Results are expressed as copy numbers per 1 µg of total RNA

Arch Med Sci 2011; 7, 6: 941-947
DOI: 10.5114/AOMS.2011.26604

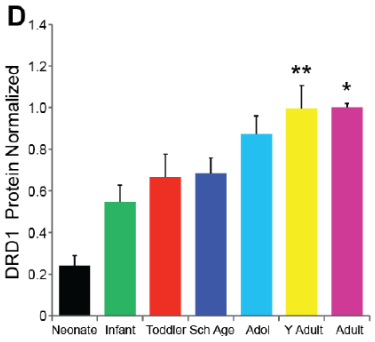
Rothmond *et al. BMC Neuroscience* 2012, **13**:18
http://www.biomedcentral.com/1471-2202/13/18

BMC Neuroscience

RESEARCH ARTICLE Open Access

Developmental changes in human dopamine neurotransmission: cortical receptors and terminators

Debora A Rothmond[1,2,3*], Cynthia S Weickert[1,2,3] and Maree J Webster [4]



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Experimentation?

Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms

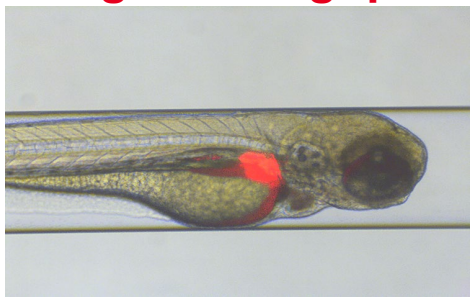
An NIH White Paper by the QSP Workshop Group – October, 2011

Definitions: QSP is defined as an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs. QSP will provide an integrated "systems-level" approach to determining mechanisms of action of new and existing drugs in preclinical and animal models and in patients. QSP will create the knowledge needed to change complex cellular networks in a specified way with mono or combination therapy, alter the pathophysiology of disease so as to maximize therapeutic benefit and minimize toxicity and implement a "precision medicine" approach to improving the health of individual patients.

Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape

This lack of dedicated experimental support is currently a gap within most companies and may hinder the successful implementation of QSP models, especially when such mod-

High Throughput



High Content

British Journal of Pharmacology (2018) •• ••–••

RESEARCH PAPER

Fingerprints of CNS drug effects: a plasma neuroendocrine reflection of D_2 receptor activation using multi-biomarker pharmacokinetic/pharmacodynamic modelling

Correspondence Elizabeth CM de Lange, Division of Systems Biomedicine and Pharmacology, Leiden Academic Center for Drug Research, Leiden University, Leiden, The Netherlands. E-mail: ecmdelange@lacdr.leidenuniv.nl

Received 2 January 2018; Revised 6 July 2018; Accepted 11 July 2018

Willem J van den Brink[1], Dirk-Jan van den Berg[1], Floor E M Bonsel[1], Robin Hartman[1], Yin-Cheong Wong[1], Piet H van der Graaf[1,2] and Elizabeth C M de Lange[1]

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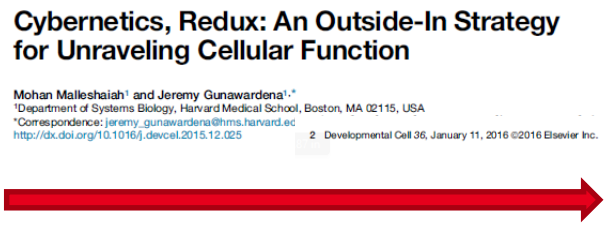
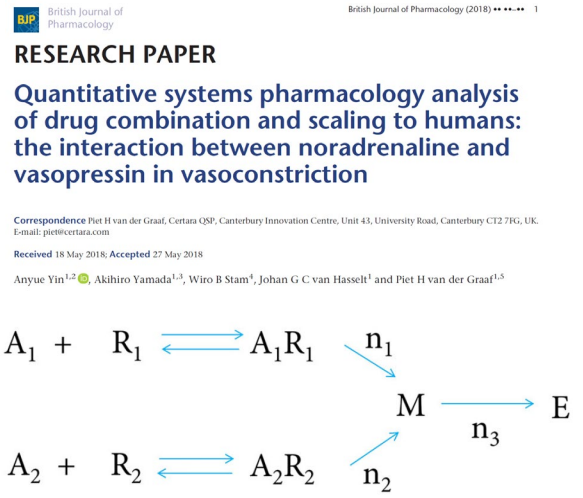
Cybernetics, Redux: An Outside-In Strategy for Unraveling Cellular Function



Mohan Malleshaiah[1] and Jeremy Gunawardena[1,*]
[1]Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: jeremy_gunawardena@hms.harvard.ed
http://dx.doi.org/10.1016/j.devcel.2015.12.025

2 Developmental Cell 36, January 11, 2016 ©2016 Elsevier Inc.



British Journal of Pharmacology (2018) •• ••–••

RESEARCH PAPER

Quantitative systems pharmacology analysis of drug combination and scaling to humans: the interaction between noradrenaline and vasopressin in vasoconstriction

Correspondence Piet H van der Graaf, Certara QSP, Canterbury Innovation Centre, Unit 43, University Road, Canterbury CT2 7FG, UK.
E-mail: piet@certara.com

Received 18 May 2018; Accepted 27 May 2018

Anyue Yin[1,2], Akihiro Yamada[1,3], Wiro B Stam[4], Johan G C van Hasselt[1] and Piet H van der Graaf[1,5]

$$A_1 + R_1 \rightleftharpoons A_1R_1 \xrightarrow{n_1} M$$
$$A_2 + R_2 \rightleftharpoons A_2R_2 \xrightarrow{n_2} M$$
$$M \xrightarrow{n_3} E$$

Slope	
N_H (observed)	2.3-2.7
N_1 & N_2	~0.5-0.7
N_3	4

Pharmacometrics ←→ QSP?

EDITORIAL

Pharmacometrics and/or Systems Pharmacology

Piet H. van der Graaf[1,2,*]

COMMENTARY

QSP Versus the Rest: Let the Competition Commence!

Hitesh B. Mistry[1,2]

PERSPECTIVE

Quantitative Systems Pharmacology and Empirical Models: Friends or Foes?

Neil Benson[1,*]

PERSPECTIVE

Benchmarking QSP Models Against Simple Models: A Path to Improved Comprehension and Predictive Performance

Andrew M. Stein[1,*] and Michael Looby[2]

My model is better than yours

Use of a Systems Pharmacology Model Based Approach Toward Dose Optimization of Parathyroid Hormone Therapy in Hypoparathyroidism

Manoj Khurana[1], Immo Zadezensky[2,*], Naomi Lowy[3], Dragos Roman[3], Jean-Marc Guettier[4,*], Liang Li[1], Jeffry Florian[3], Chandrahas G. Sahajwalla[1], Vikram Sinha[5,*] and Nitin Mehrotra[5,*]

pharmacodynamics (PDs) of PTH dose and dosing regimen. Although other modeling approaches may be feasible, in this specific case, QSP model-based simulations fulfilled the information gap to support recommendations of this postmarketing trial.

Pharmacometrics ←→ QSP?

Integrated Pharmacometrics and Systems Pharmacology (iPSP)

PERSPECTIVE

Perspective on the State of Pharmacometrics and Systems Pharmacology Integration

Mirjam N. Trame[1], Matthew Riggs[2], Konstantinos Biliouris[1], Dhananjay Marathe[3], Jerome Mettetal[4], Teun M. Post[5,6], Matthew L. Rizk[7], Sandra A. G. Visser[8] and Cynthia J. Musante[9]*

228 PSP papers 2012-2017:
19% iPSP

Linking QSP to Clinical Endpoints

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

www.nature.com/psp

Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis

MM Riggs[1], M Bennetts[2], PH van der Graaf[2] and SW Martin[3]

QSP meets MBMA

Model Reduction

Snowden et al. BMC Systems Biology (2017) 11:17
DOI 10.1186/s12918-017-0397-1

BMC Systems Biology

METHODOLOGY ARTICLE Open Access

A combined model reduction algorithm for controlled biochemical systems

Thomas J. Snowden[1,2], Piet H. van der Graaf[3,2] and Marcus J. Tindall[1,4*]

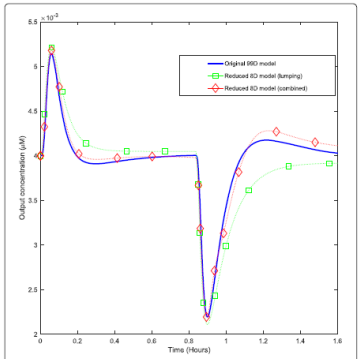


Fig. 6 Timecourses of the output from the original 99-dimensional and the reduced 8-dimensional systems. This plot emphasises the fact that the reduced model is designed to remain valid for any reasonable change in input. The system starts by being affected by an agonist that increases the rate of EGF binding by 25% for 50 minutes, at this point the input flips to an antagonist decreasing the rate of EGF binding by 50% and runs for the same time period. At any given time point the error between the original and reduced model exceeds no more than 5%

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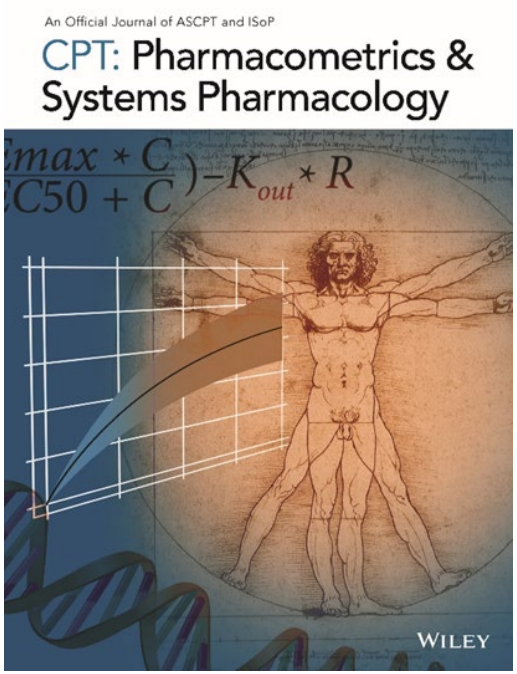
CPT: PSP 2.0



EDITORIAL

CPT: Pharmacometrics & Systems Pharmacology 2.0

France Mentré[1,*]

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Backups

PBPK guidelines a template for QSP?

EUROPEAN MEDICINES AGENCY
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13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Adobe Acrobat Document

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PBPK guidelines a template for QSP?

4. Reporting of PBPK modelling and simulation.....

4.1. Objective and regulatory purpose .....

4.2. Background information .....

4.3. Qualification .....

4.4. Model parameters.....

4.4.1. Assumptions .....

4.4.2. System-dependent parameters .....

4.4.3. Drug parameters and the drug model.....

4.5. Model development .....

4.6. Simulation of the intended scenario .....

4.7. Platform and drug model evaluation .....

4.7.1. Sensitivity analyses .....

4.7.2. Evaluation of the predictive performance of the drug model....

4.8. Results.....

4.9. Discussion of the regulatory application .....

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Model reduction

Snowden et al. BMC Systems Biology (2017) 11:17
DOI 10.1186/s12918-017-0397-1

BMC Systems Biology

METHODOLOGY ARTICLE Open Access

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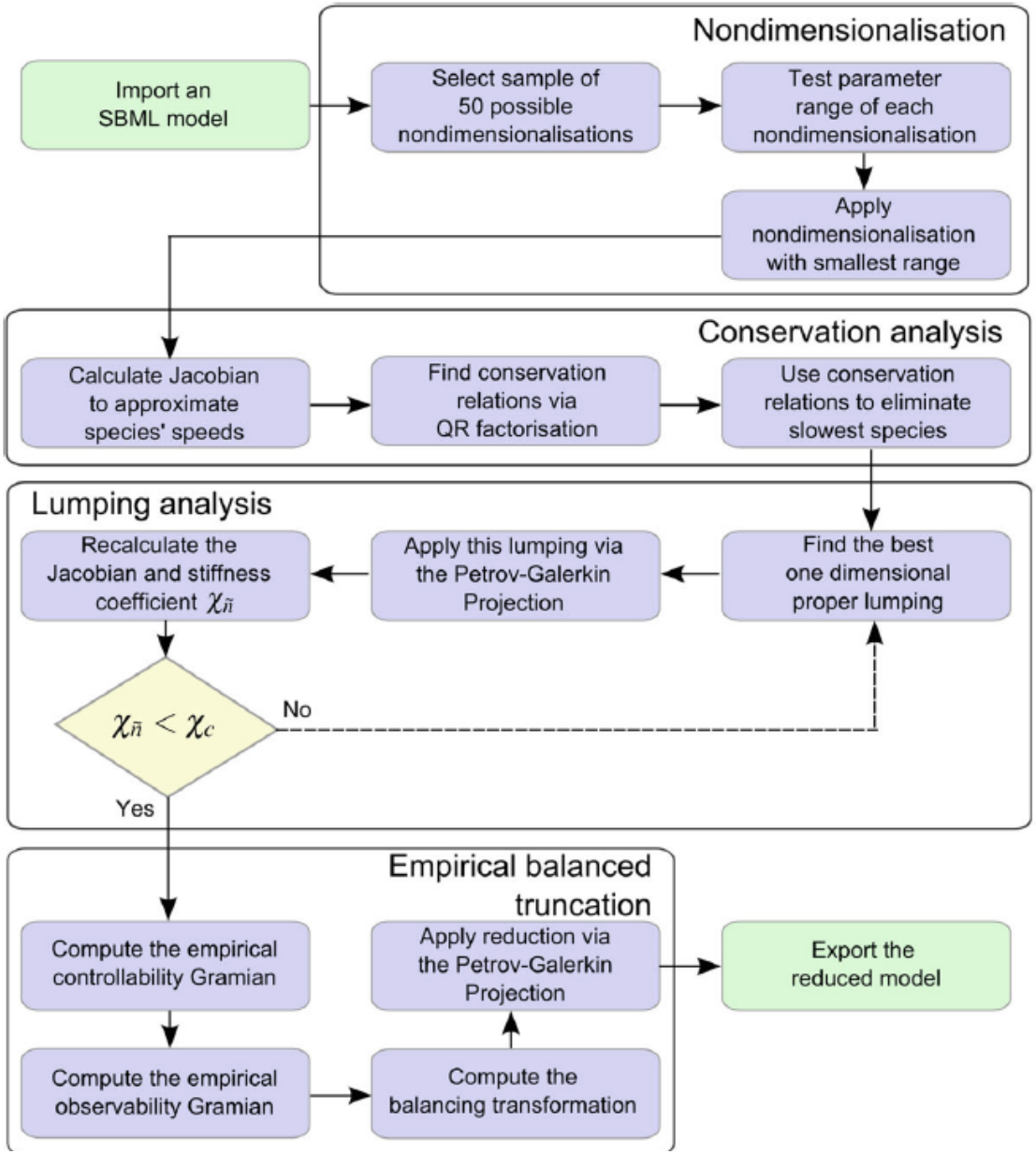
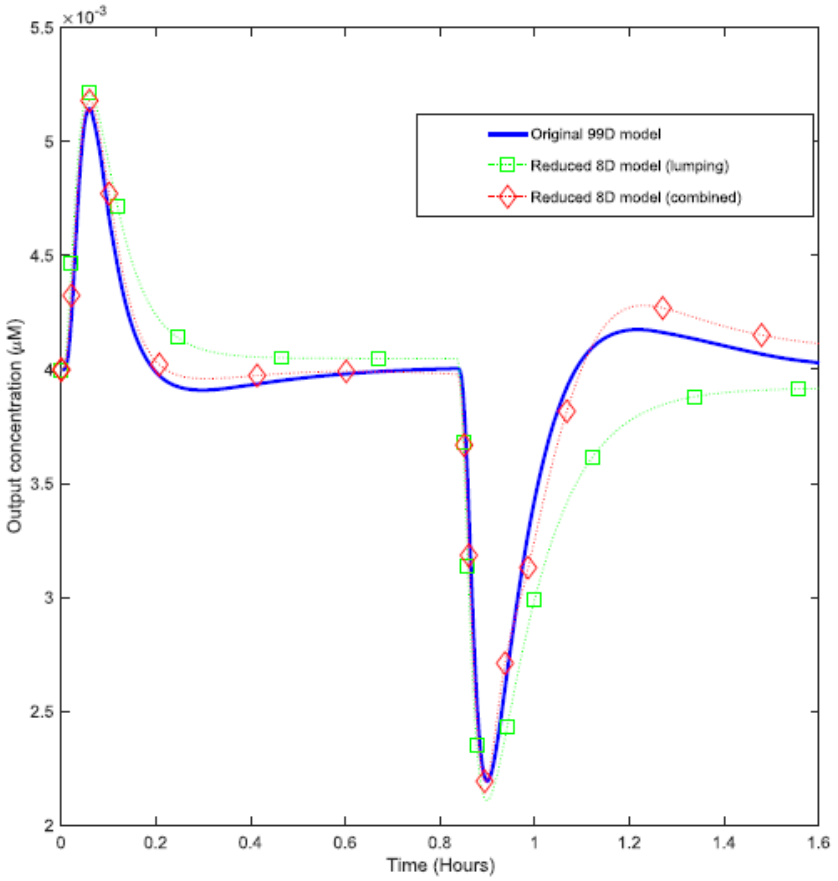


CERTARA

NGF model reduction



Dimension	EBT error	Lumping error	Stiffness	Combined error
75	0.76%	≈ 0%*	42658	—
50	#	0.01%	42633	—
25	#	0.52%	10664	—
15	#	1.26%	7934	—
14	#	2.21%	7934	—
13	#	2.29%	7934	—
12	#	1.21%	1591	—
11	#	3.07%	236	—
10	#	6.02%	264	2.84%
9	#	10.96%	211	4.02%
8	#	13.12%	43	4.32%
7	#	14.18%	42	4.77%
6	#	29.53%	44	13.08%
5	#	39.03%	45	20.81%
4	#	46.47%	212	31.09%
3	#	54.67%	42	34.58%
2	#	53.52%	18	41.10%
1	#	55.73%	1	50.46%

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