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Simcyp

The development of an Immunogenicity Simulator through a quantitative systems pharmacology consortium approach

Piet van der Graaf & Andrzej Kierzek

Certara QSP

Workshop Predictive Immunogenicity for Better Clinical Outcomes, FDA, 3rd October 2018

Problem statement

- **Biologicals:**
  - ~30% of new drug approvals (12/46 FDA 2017)
  - $445 billion sales projected 2019

- **Immunogenicity (IG):**
  - 89% incidence; 49% efficacy impacted

→*Management of IG will be a significant and recurring topic in interactions between sponsors and regulatory agencies*

Wang et al., AAPS J. 18: 395 (2016)

Highly variable

Strand et al., BioDrugs 31: 299 (2017)

Table 3 Summary of ADAb formation rates for individual biologic/biosimilar by chronic inflammatory disease

Biologic	Frequency of ADAb formation, % (no. of studies[a])							
	RA	PsA	JIA	AS	Ps	CD	UC	Range
ABA	2–20 (7)		2–11 (2)					2–20 (9)
ADA	0–51 (33)	0–54 (8)	6–33 (6)	8–39 (9)	0–51 (12)	0–35 (13)	3–5 (3)	0–54 (80)
CZP	2.8–37 (7)				21 (1)	3–25 (6)		3–37 (14)
ETN	0–13 (25)	0 (3)	0–6 (2)	0 (4)	2–5 (5)			0–13 (37)
GLM	2–10 (11)	6 (1)		0–6.4 (2)			0–19 (8)	0–19 (22)
INF	8–62 (48)	15–33 (3)	26–42 (2)	6.1–69 (10)	0–41 (12)	3–83 (29)	6–46 (10)	0–83 (110)
RTX	0–21 (8)							0–21 (8)
SEC		0–0.1 (3)		0–0.3 (3)	0–1 (8)			0–1 (14)
TCZ	0–16 (14)		1–8 (3)					0–16 (17)
UST		8–11 (3)			4–8.6 (10)	0–1 (2)		1–11 (15)
CT-P13	26–52 (2)			27 (1)		21 (1)	24 (1)	21–52 (5)

- **Compound**
- **Dose and administration**
- **Patient population**
- **Disease state**
- **Co-medication**
- **Other**

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IG QSP Consortium: rationale

- Management of IG in a diverse patient population is a complex, multifactorial problem

- The use of mechanistic models is well-precedented in such circumstances (i.e. PBPK)
  - Increased regulatory focus on utilizing in-silico models for decision making

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

In silico clinical trials use computer models and simulations to develop and evaluate devices and drugs. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. FDA's efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of these state-of-the-art technologies.

FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. We'll be putting out additional, updated guidance on how aspects of these in silico tools can be advanced and incorporated into different aspects of drug development.

→The Consortium aims to develop the industry-standard quantitative systems pharmacology (QSP) model, coupled to a robust IT platform, to predict and manage IG and guide decision making in drug development

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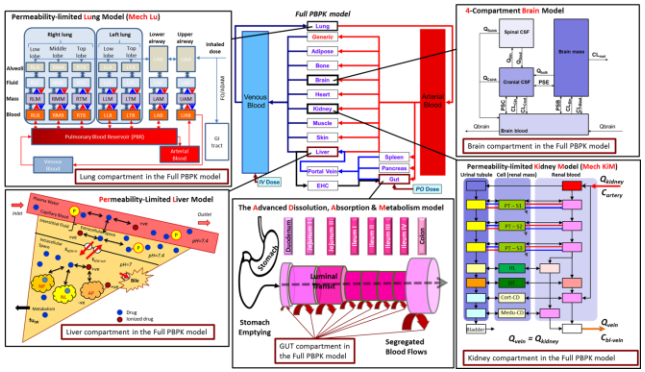
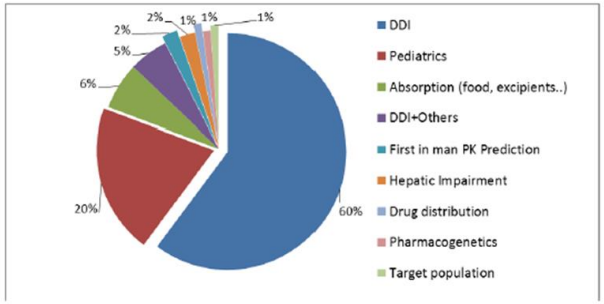
Physiologically-based pharmacokinetics (PBPK)

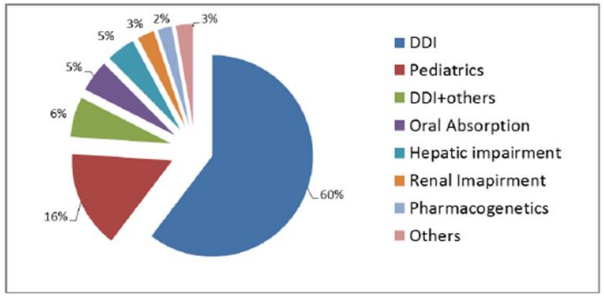


FDA submissions using PBPK modelling



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

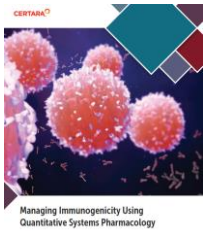
41 Labels with *in-silico* substitutes for clinical data informed by Simcyp

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 (Selexipeg) 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 Alunbrig (Brigatinib)	**Ariad** Erleada (Apalutamide)	**Janssen**	**Helsinn** Akynzeo	**AkaRx** Doptelet	

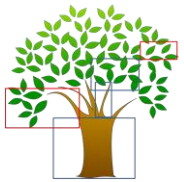
Consortium approach

Building the industry standard IG Simulator:

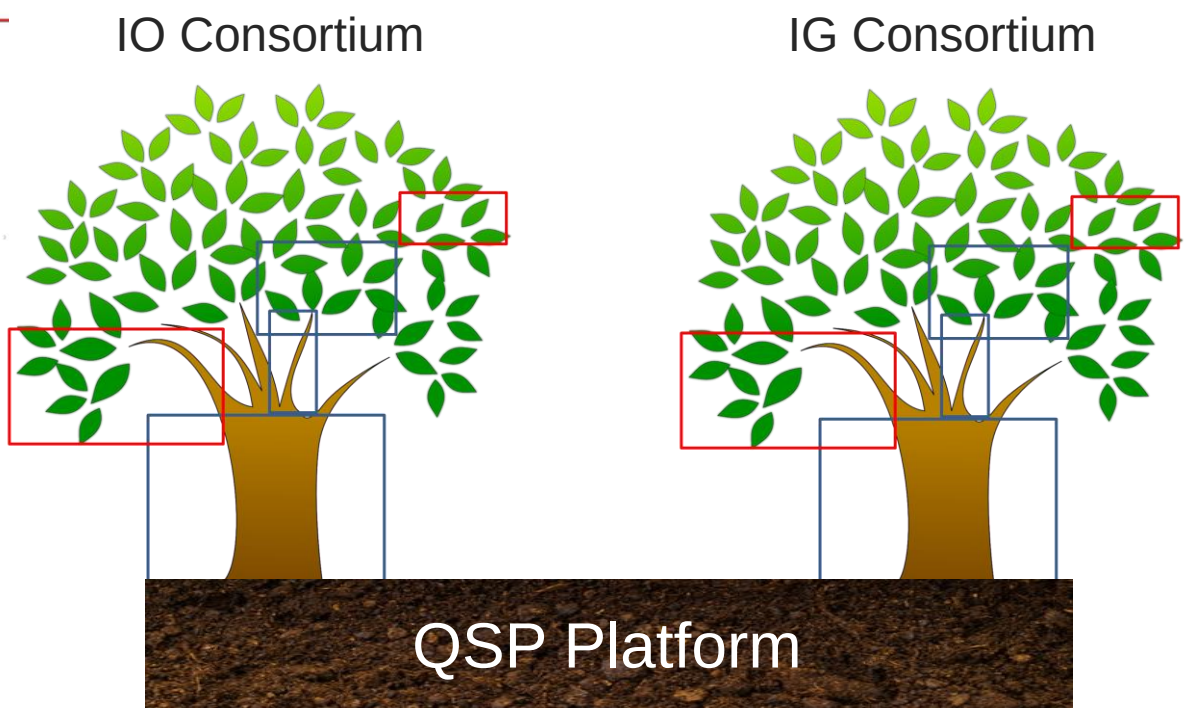
- Sharing knowledge/resources/data
- Consensus on science and common tools/standards
- Engaging academics and regulators through publication & education *(a.o. upcoming British Pharmacological Society, ASCPT and European Immunogenicity Platform conferences)*



- Rigorous approach to IT and QA: interoperable, future proof and meeting regulatory requirements
- Ability for individual members to integrate confidential data/knowledge/models on a continuous and seamless manner



Certara's QSP Platform



Each QSP Consortium is a tree, where trunk represents biology common to all applications, while branches and leaves represent target specific mechanisms. Consortia are rooted in QSP Platform.

IG QSP Consortium: Facts and Figures

- Launched January 2017
- Six member companies
- Initial duration 3 years
- Monthly Webinar meetings
- Annual Face-Face
- Supported by ~10 Certara staff (QSP, IT, Operations)
- *G: Certara - QSP - IG Consortium*
  - Multi-disciplinary team of ~50 experts
  - 2 Sub-teams: In Vitro Assays and IT

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The IG QSP Consortium model and simulator

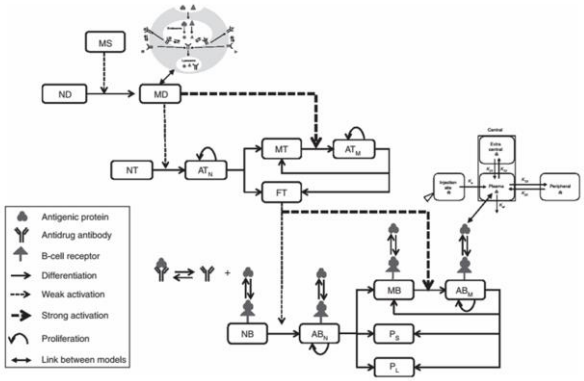
Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134; doi:10.1038/psp.2014.31

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]

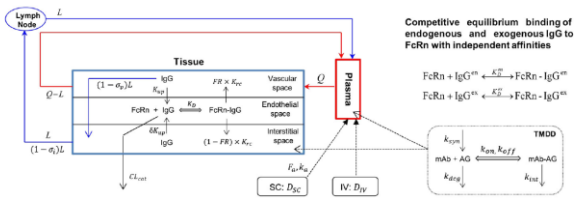


The AAPS Journal, Vol. 16, No. 5, September 2014 (© 2014)
DOI: 10.1208/s12248-014-9640-5

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 v7

IG Simulator v2

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

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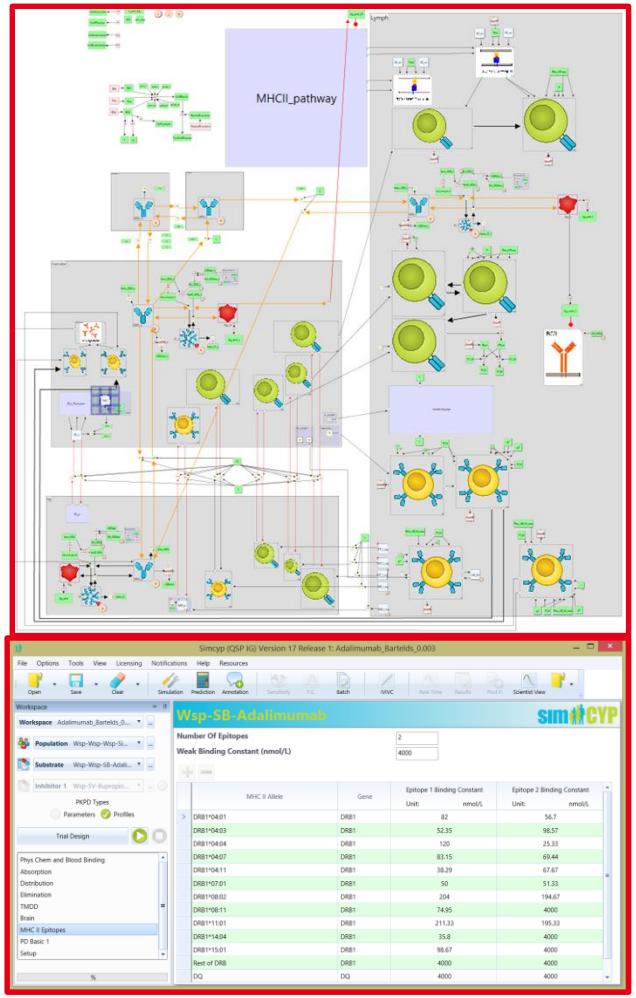
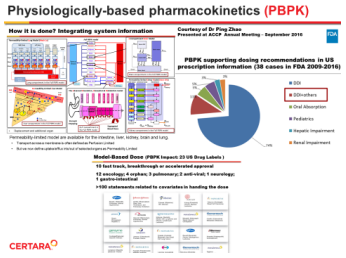
Application



- 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



Case study: PCSK9

Genentech
A Member of the Roche Group

Kapil Gadkar & Jennifer Rohrs

Bio-informatics analysis alone does not predict clinical ADA response

Antibody Drug	# Binding peptides*	# MHC II alleles	% ADA+ Patients
Bococizumab (Pfizer)	2	12	68% (Ridker, 2017)
Alirocumab (Regeneron)	1	1	5.1% (Roth, 2017)
Evolocumab (Amgen)	0	0	0.1% (Henry, 2016)
GNE anti-PCSK9 (Genentech)	2	8	4% (GENE data*)

** Based on Phase II clinical study with ~200 subjects*

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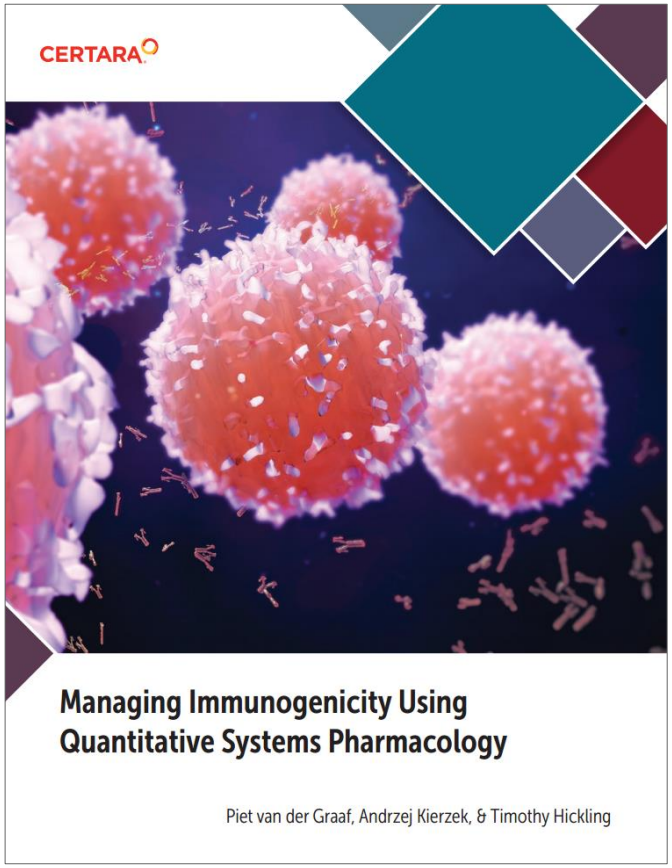
IG QSP White Paper



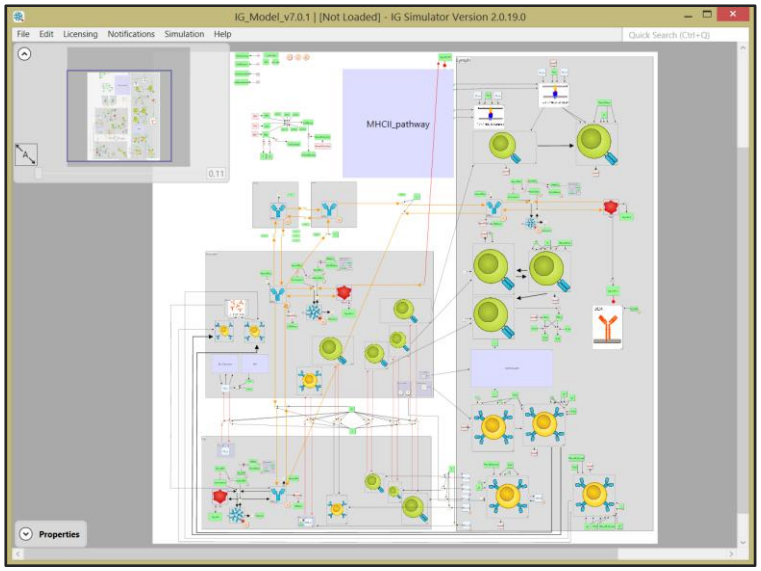
- Review on biologics drug development using MIDD approaches and managing immunogenicity with the IG Simulator
- Available for download on the Certara Quantitative Systems Pharmacology web site

https://www.certara.com/consulting/systems-pharmacology/?ap%5B0%5D=CSC&ap%5B1%5D=CSC

piet@certara.com

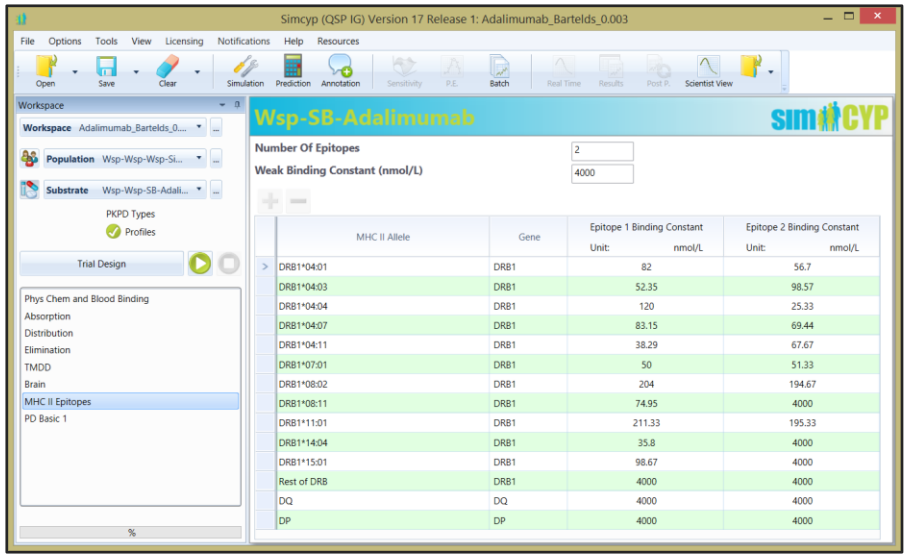
Overview of IG Simulator

Biological Process Map interface



Read workspace file.

Simcyp simulator



Export IG Model code.

Write IG Model

Read IG Model and augment ODEs

Simulate virtual trial and output results.

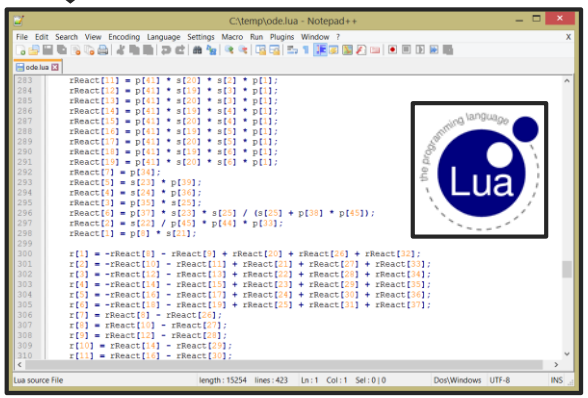
Matlab code

R code

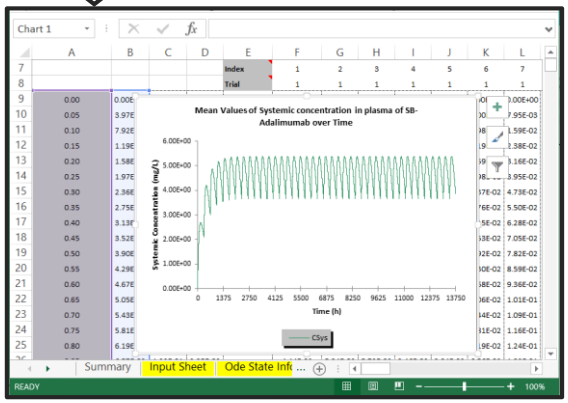
R code with equation in C

Excel file with documentation of variables, equations and parameters

IG Model code and documentation



IG Model code and PBPK variable connections in Lua



Virtual trial results in Simcyp formatted Excel file

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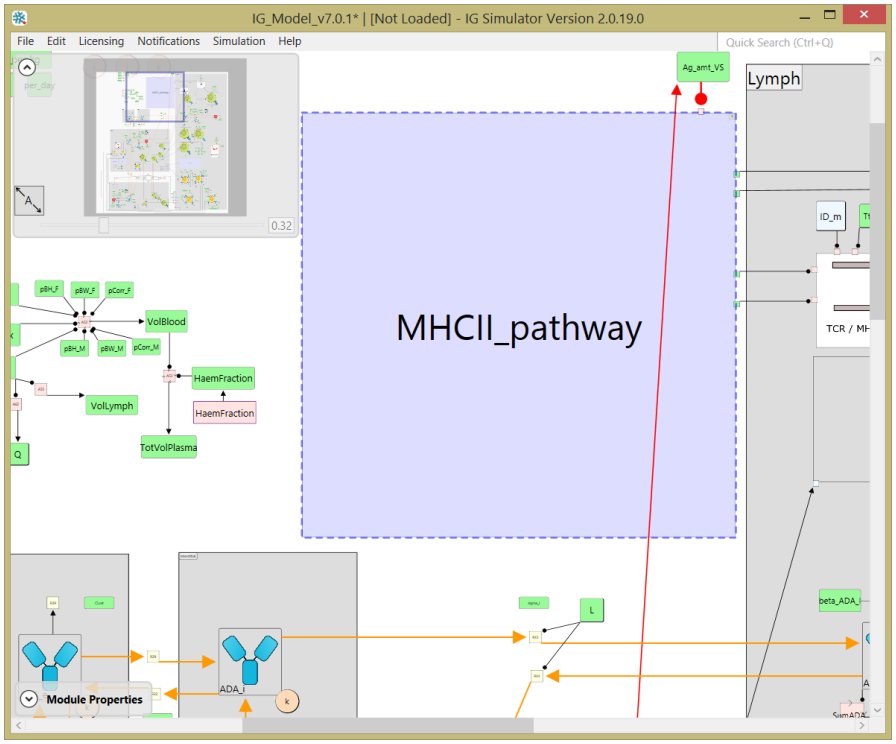
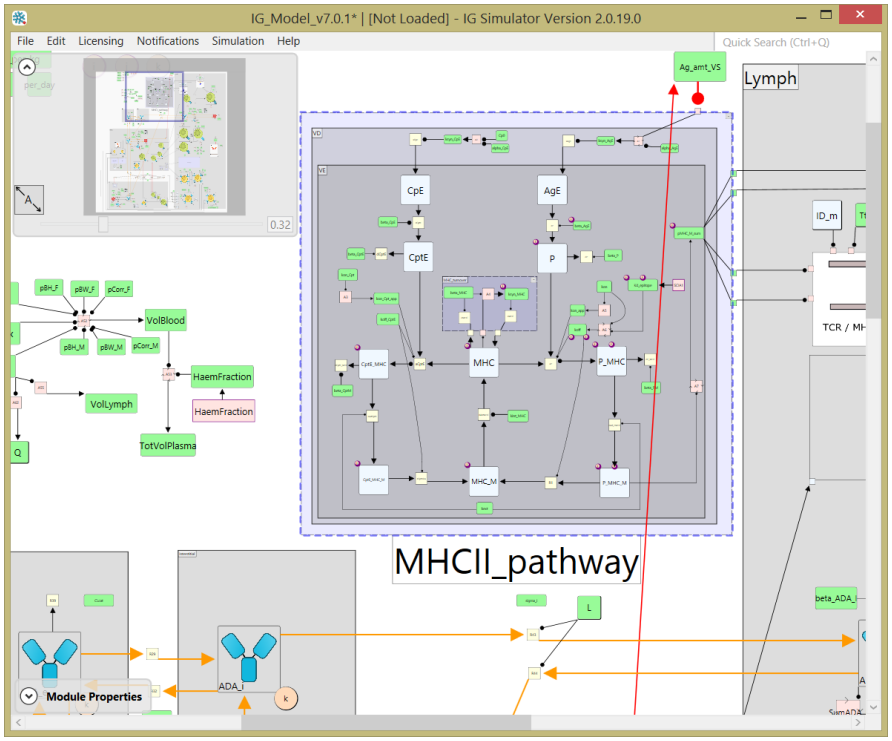
Modular Biological Process Map interface





Modules encapsulate complex mechanisms which are connected to the model through well defined interfaces. This facilitates both visualisation and consortium team development of multiscale mechanistic models.

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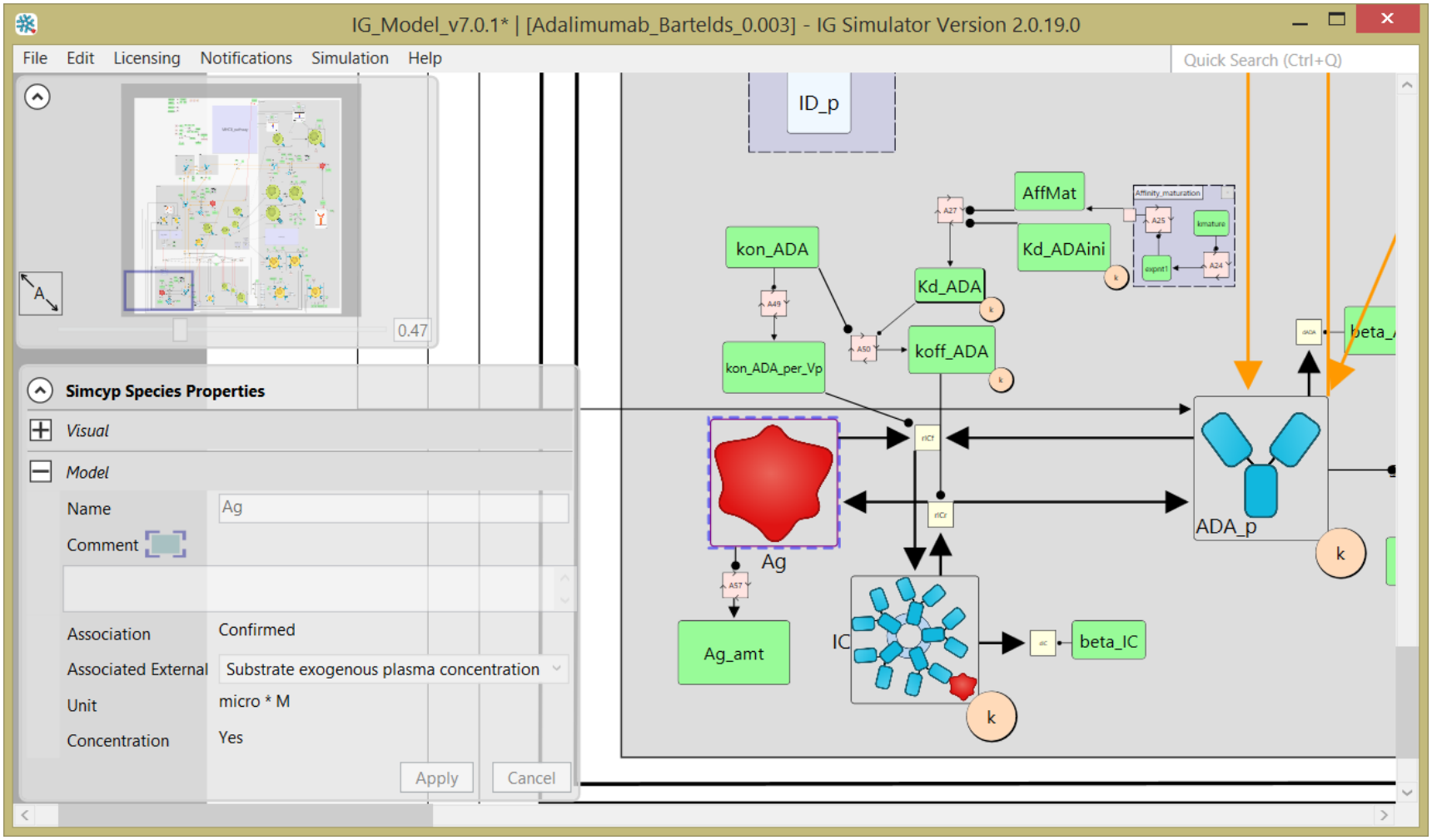
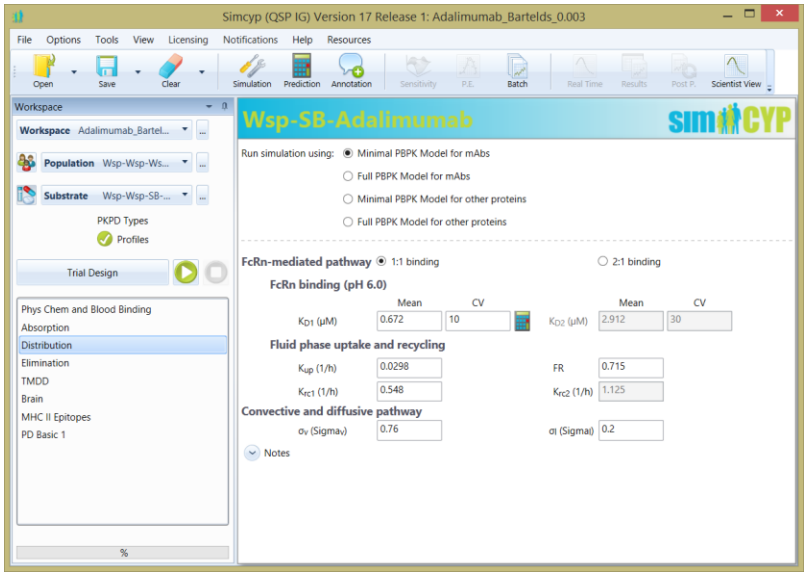
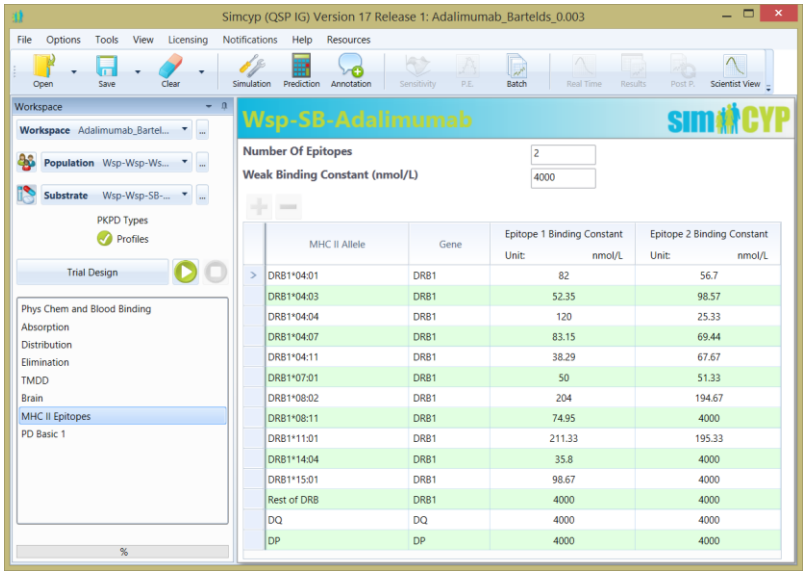
Connection to Simcyp PBPK model



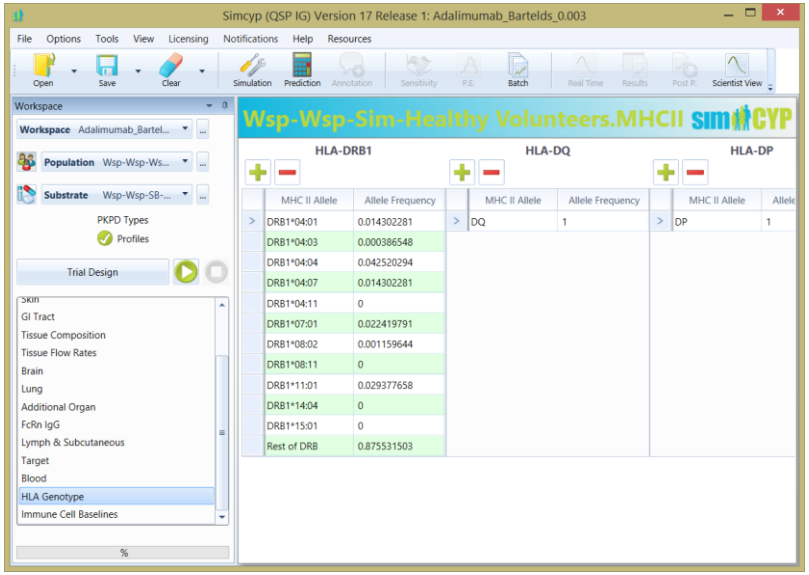
Specie "Ag" in biological process map is merged with variable "Substrate exogenous plasma concentration" in Simcyp PBPK. The ODE for Simcyp variable is augmented by rate laws of ADA binding and Immune Complex dissociation.

Simcyp simulator with Immunogenicity screens

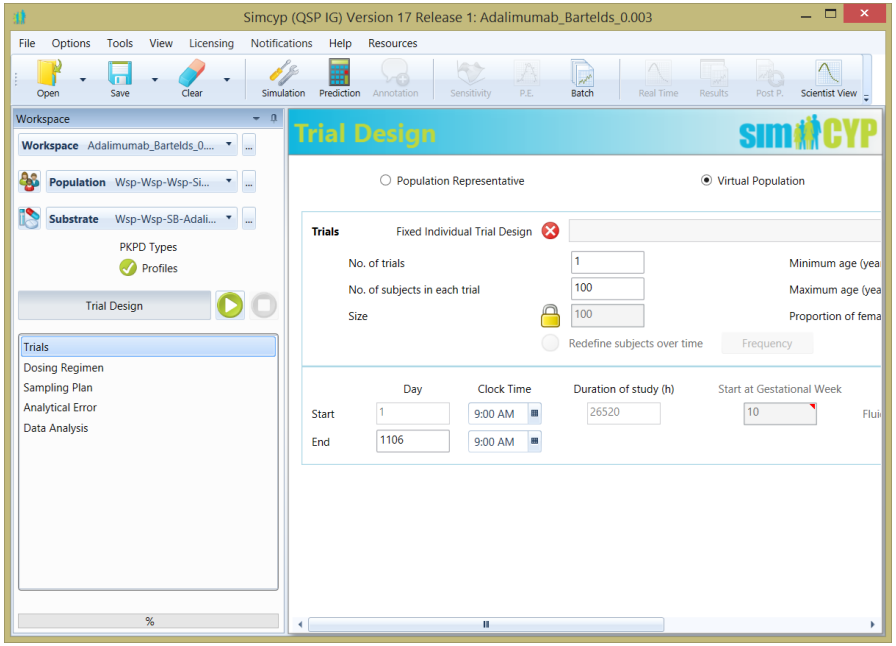


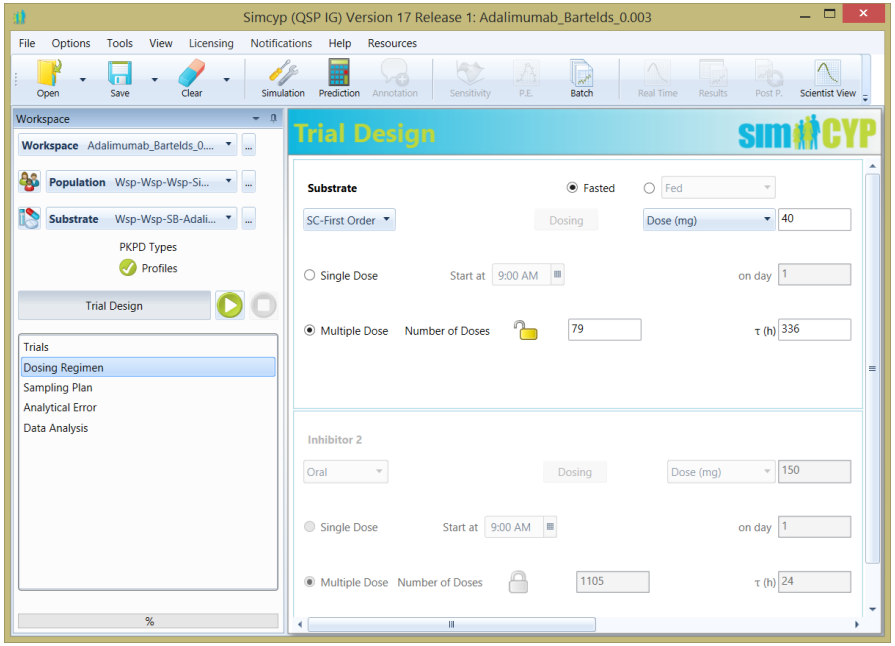


- The compound section of Simcyp biologics model has been expanded to allow input of antigenic peptide binding constants.
- Population section of Simcyp has been expanded
- Allele frequencies are used to generate MHC II binding constants for individual subject Correlated Monte Carlo simulation of a clinical trial.



Trial design





Simcyp simulator is modularised into System, Compound, Population and Trial design. Trial screens specify number of subjects from target Population and dosing regime of the Compound. Virtual trial is then simulated with Correlated Monte Carlo approach. In IG Simulator, Compound and Population files include IG specific parameters and simulation is run with multiscale model integrating PBPK and Immune response parts.

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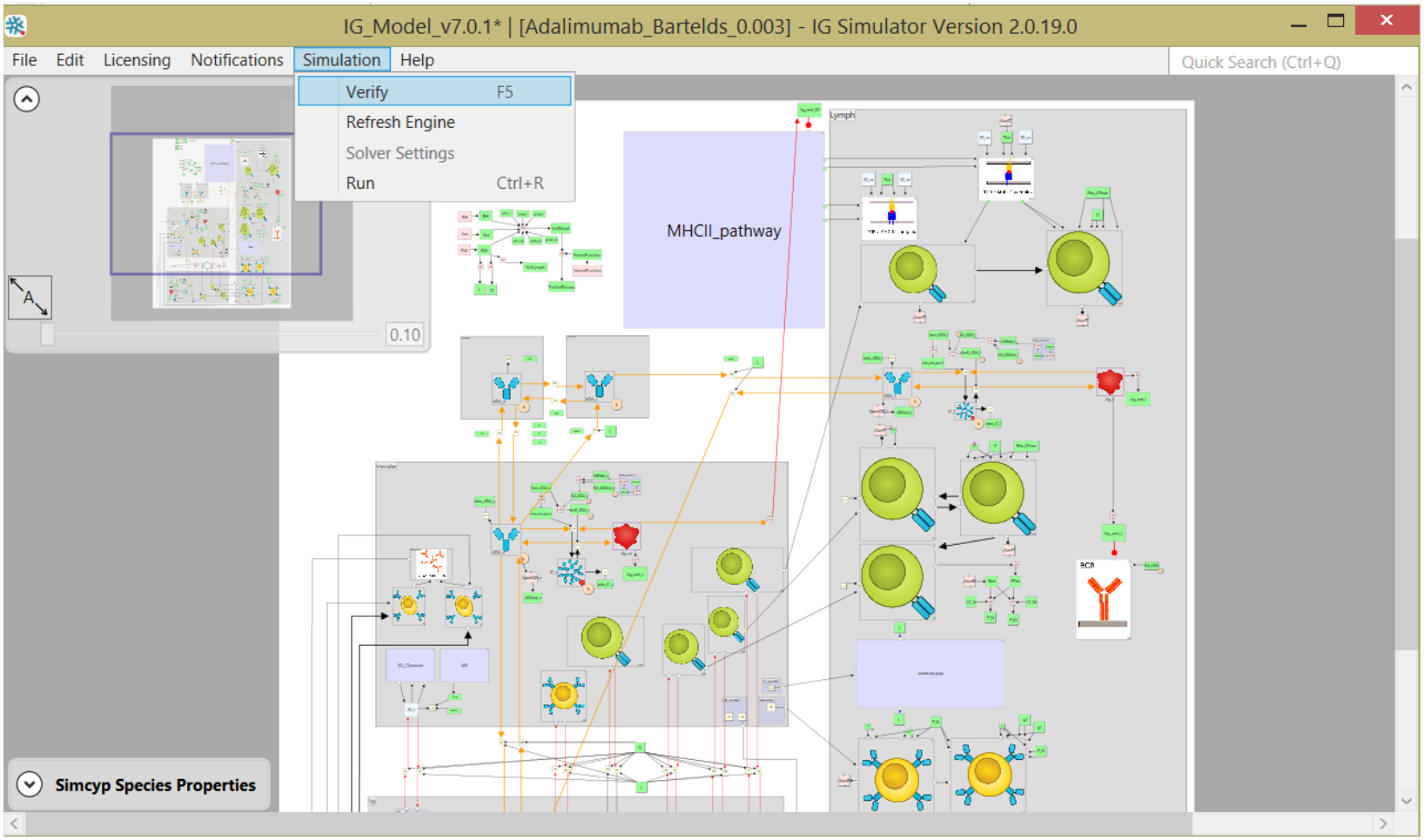
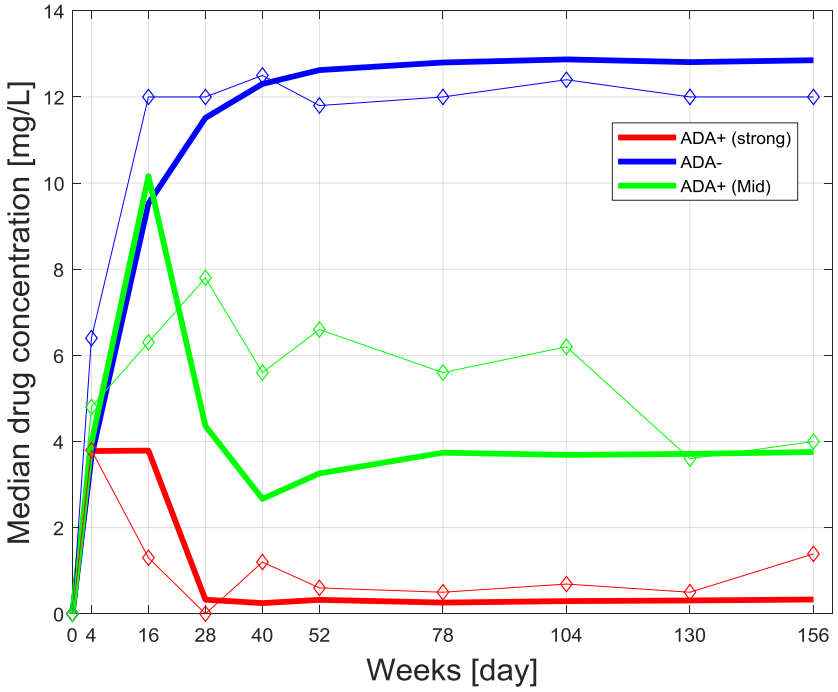
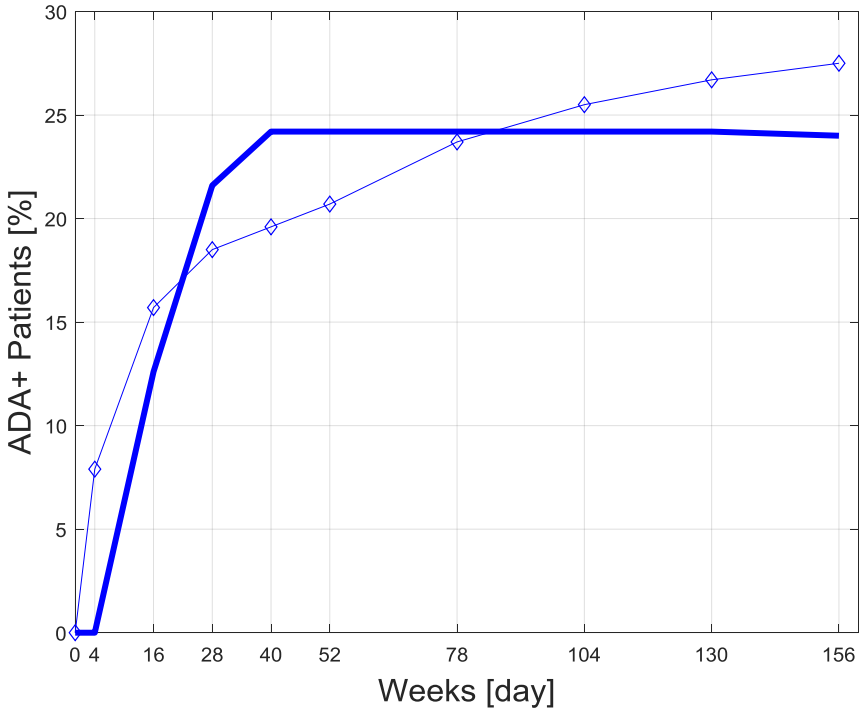
Running simulation



Before simulation is run the model is verified. This includes unit dimensionality verification as well as unit conversion.

Clinical trial simulation: output





Simulation of Adalimumab clinical trial of Bartelds et al (JAMA. 2011;305(14):1460-1468). Simulated time profiles were analysed following patient classification criteria used by authors allowing direct comparison with clinical data. The threshold for weak ADA+ (green) group has been modified, but our simulation predicted existence of distinct group. **We find different ADA reporting methods to be major challenge in development of predictive models**. Mechanistic model simulating both compound and ADA dynamics allows integration of studies using different reporting criteria and will facilitate harmonisation.

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Acknowledgements

- Abbvie
- Astellas
- BMS
- Genentech/Roche
- Lilly
- Pfizer

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