

3rd Annual Predictive Toxicology
half day interactive pre-conference workshop

Tox IVIVE - inter-individual variability matters!

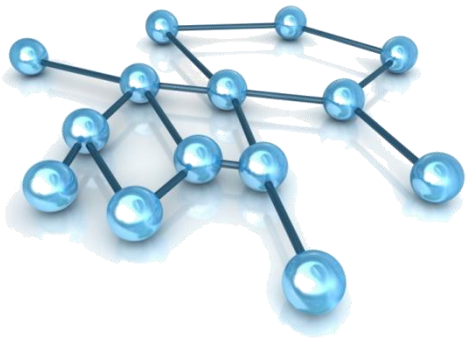
ToxComp platform

Sebastian Polak



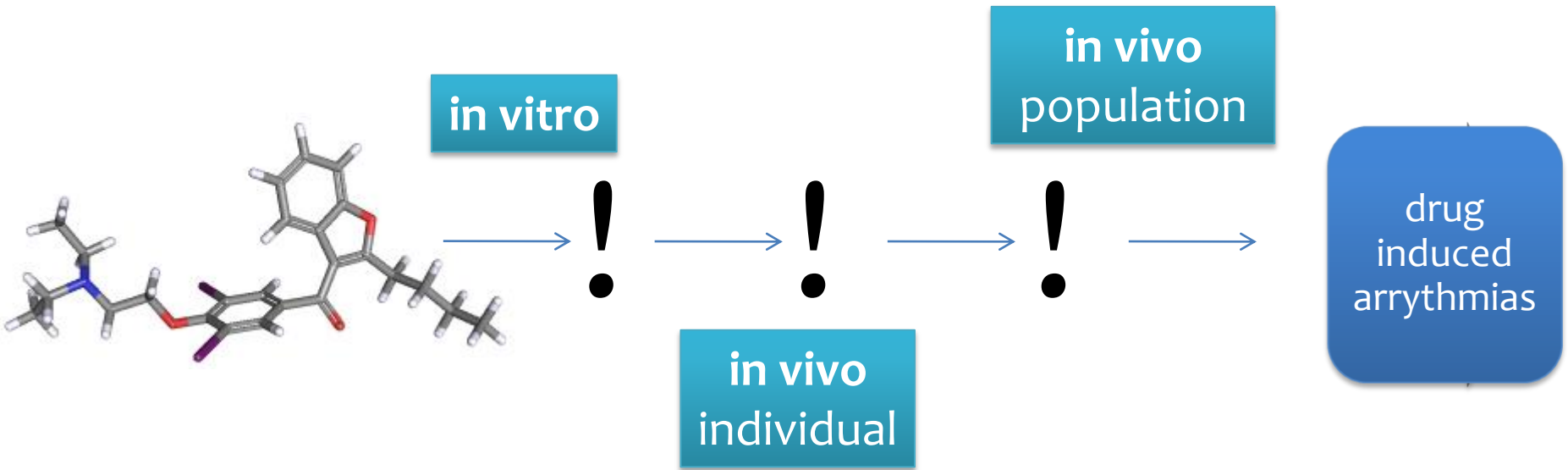
Unit of Pharmacoepidemiology and
Pharmacoeconomics
Jagiellonian University Medical College

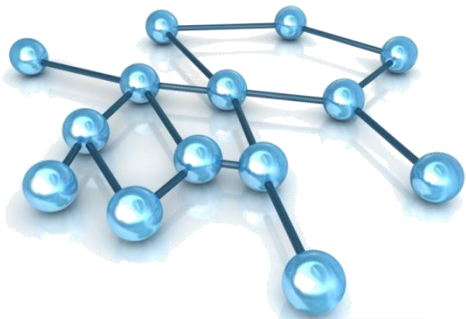




proarrhythmic potency assessment

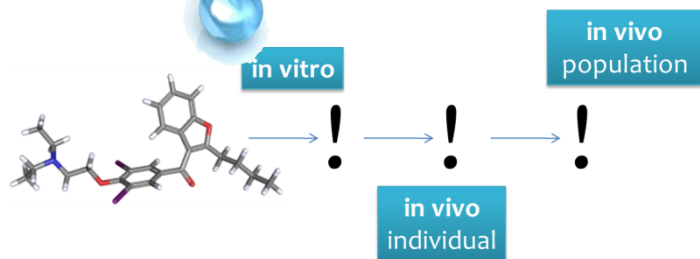
in silico – in vitro – in vivo extrapolation





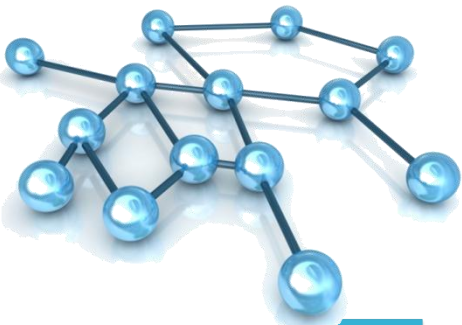
proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation



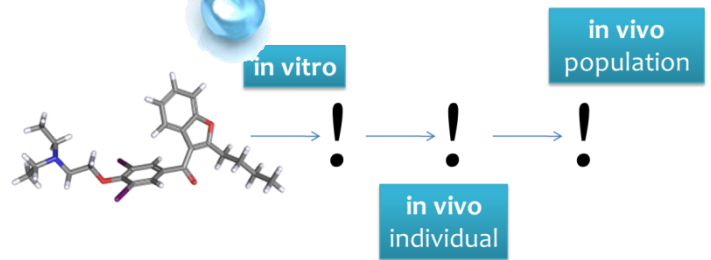
project financed by the Polish National Center for Research and Development LIDER project number LIDER/02/187/L-1/09





proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation



MODULE 4
ADME IVIVE

MODULE 1

hERG in vitro

hERG in silico

MODULE 2

other ion channels in vitro

other ion channels in silico

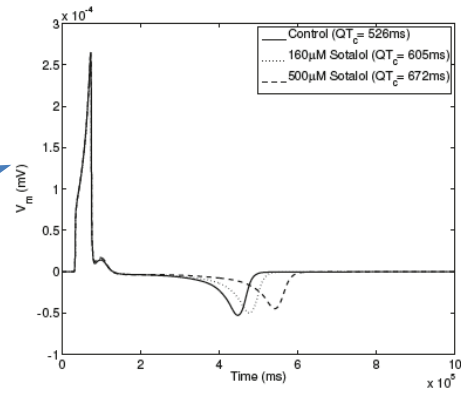
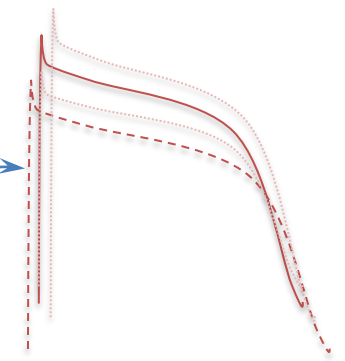
MODULE 3
HEART VENTRICULAR CELL MODEL

DEMOGRAPHIC & PHYSIOLOGICAL & GENETIC DATA

MODULE 3
HEART VENTRICULAR CELL MODEL

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HEART VENTRICULAR CELL MODEL

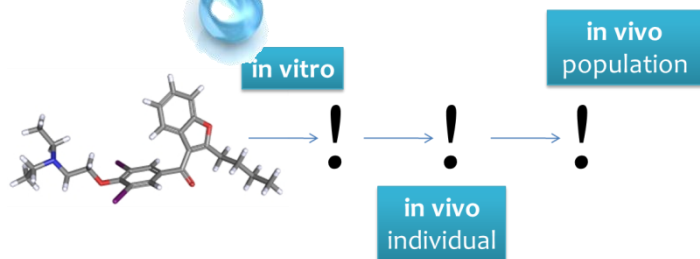
MODULE 3
HEART VENTRICULAR CELL MODEL





proarrhythmic potency assessment

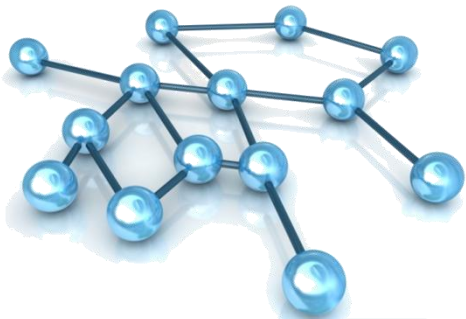
in silico – in vitro – in vivo extrapolation



- **ASSUMPTIONS - meritorious**

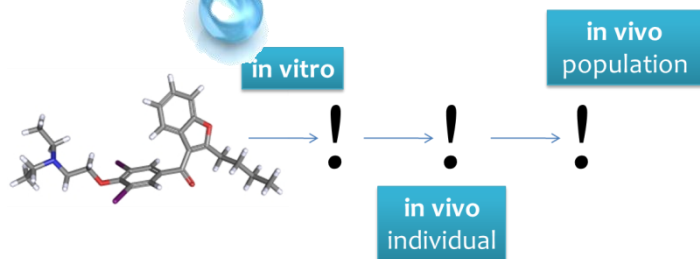
- in vitro – in vivo extrapolation of the cardiotoxic effect
- inter-individual variability matters! - population
- system designed for screening applications
- APD / pseudoQTc as the endpoints
- based on best, well know and accepted models
- new approaches and techniques proposed





proarrhythmic potency assessment

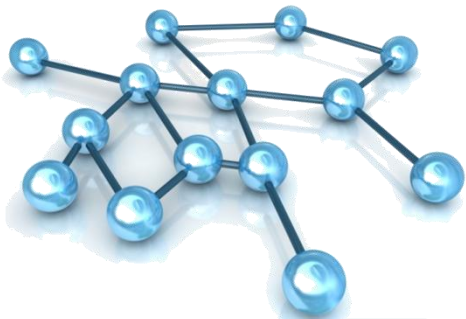
in silico – in vitro – in vivo extrapolation



- **ASSUMPTIONS - administrative**

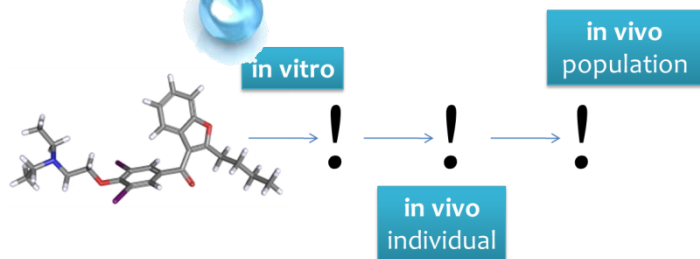
- freely available at all times
- OpenSource (GPLv3)
- all data sets, models, assumptions, equations freely available
- on-line and off-line versions available
- manual available
- stable version 1.0





proarrhythmic potency assessment

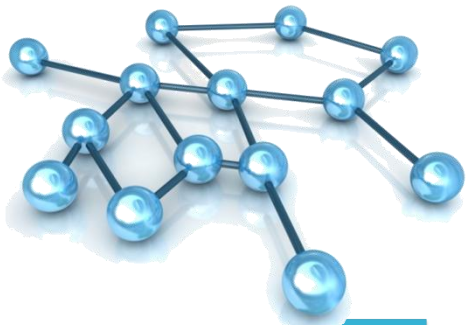
in silico – in vitro – in vivo extrapolation



- **ASSUMPTIONS - technical**

- written in Java – OS transparent (most Linux flavours, all MS, Mac OS X tested)
- free JavaFX installation needed for the on-line version (GUI); no such need for the off-line version
- data security matters – no client-server architecture, no data transfer; all calculations made on local machine
- new features will be published on a regular basis





proarrhythmic potency assessment in silico – in vitro – in vivo extrapolation

in vitro

in vivo
population

ToxComp
system

File Edit View History Bookmarks Tools Help

http://tox-portal.net/index.html

Toxportal - toxicity prediction for drug ...

Tox-Portal.net
toxicity prediction for drug discovery

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Welcome

Welcome to the website of the Computational Toxicology Group. Here we publish the results of our research, offer free access to the toxicological databases and on-line toxicity prediction algorithms developed by the Group members.
Website is divided into two parts - open and accessible for registered users. To log in please create an account choosing Register new account link on your left hand side. Once the account is created we are starting the opening procedure which can take maximum few days. After that user has FULL, FREE access to the whole tox-portal.net content.

Conference presentation

8/23/11

We will be presenting our results during the [3rd Annual Predictive Toxicology Conference](#); 14-16 Sep 2011, Berlin, Germany.

Beta version of the ToxComp platform goes on-line

6/12/11

It is our great pleasure to announce that the beta version of the Tox-Comp platform goes live. Tox-Comp specialize in in vitro - in vivo extrapolation of the cardiotoxic effect.

To run the system please log-in and navigate to the *ToxComp* bookmark available in menu. Detailed manual is accessible from the Repository. We look forward to hear all your comments and queries!

Done zotero



proarrhythmic potency assessment

in silico – in vitro – in vivo extrapolation

in vitro

in vivo
population

ToxComp
system

Tox-Comp.net

file parameters help

ionic channels

drug concentration

cardiomyocytes

populations

settings

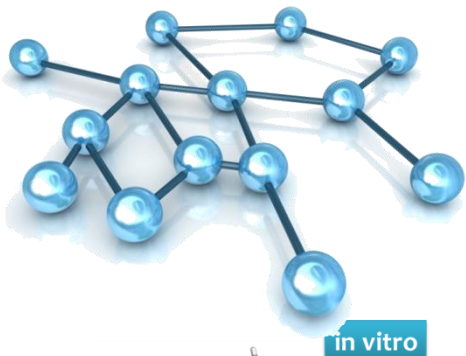
results

Tox-Comp.net

[2011.09.06 13:41:03]: ToxComp started

Start simulation

save log clear log

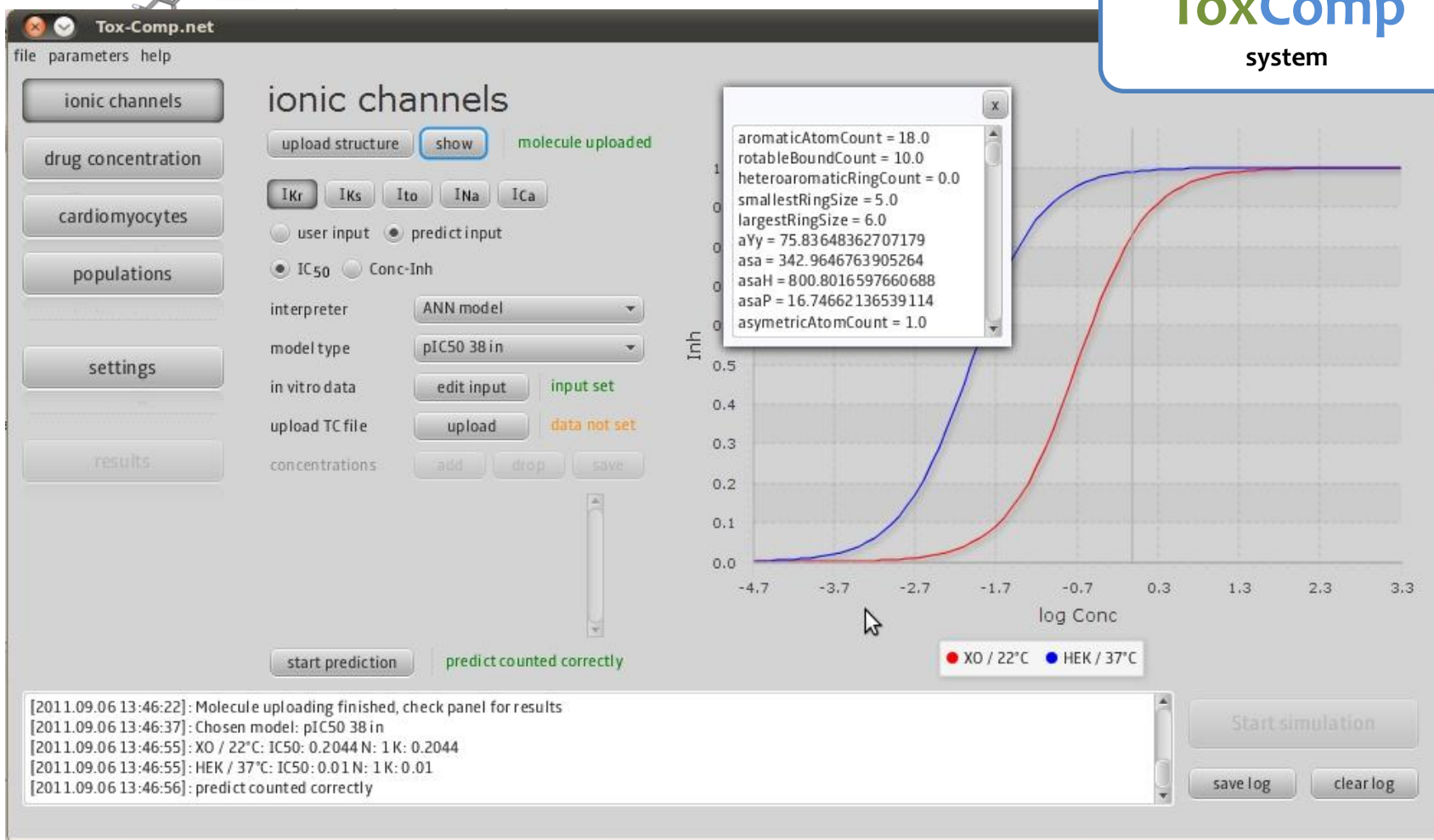


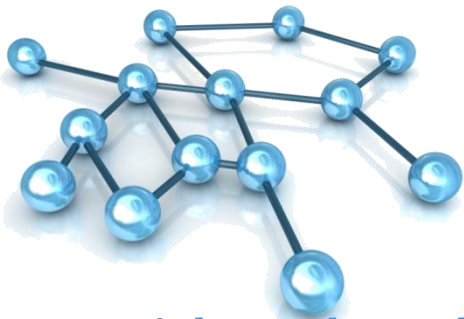
proarrhythmic potency assessment in silico – in vitro – in vivo extrapolation

in vitro

in vivo
population

ToxComp
system



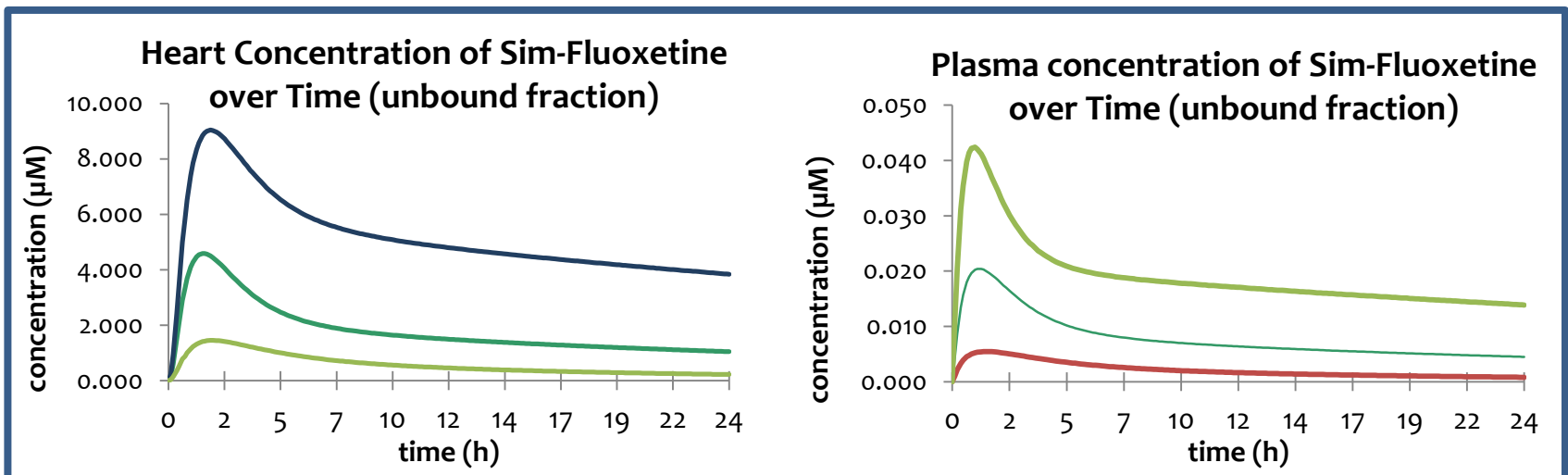


proarrhythmic potency assessment

in silico - in vitro – in vivo extrapolation

Materials and methods Simcyp® 10.20 PBPK module was used to simulate fluoxetine concentration changes in plasma and heart tissue after oral administration.

Simulation settings were as follows: single 40mg dose, first order absorption ($f_a = 1$, $CV = 30\%$; $k_a = 0.97 [h^{-1}]$, $CV = 30\%$), full PBPK disposition distribution - heart tissue-to-plasma partition coefficient was calculated to be 18.29, North European Caucasian – 10 studies á 10 individuals (age 18-65), to assess inter-individual variability in PK.





proarrhythmic potency assessment

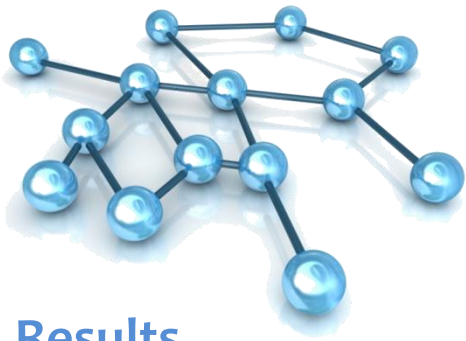
in silico - in vitro – in vivo extrapolation

Materials and methods ToxComp version 1.0 was utilized.

Simulation settings were as follows: *North European Caucasian* – 10 studies á 10 individuals (age 18-65), to assess inter-individual variability.

I_{onnic} channels inhibition data were derived from the literature.

		Simulated Concentration (µM)					
		Plasma			Heart		
		C _{min}	C _{max}	C _{mean}	C _{min}	C _{max}	C _{mean}
		0.0054	0.0424	0.0204	1.4537	9.0425	4.589
Inhibition [%]	I _{Kr}	1	6	3	68	93	87
	I _{Ca}	0	0	0	19	64	46

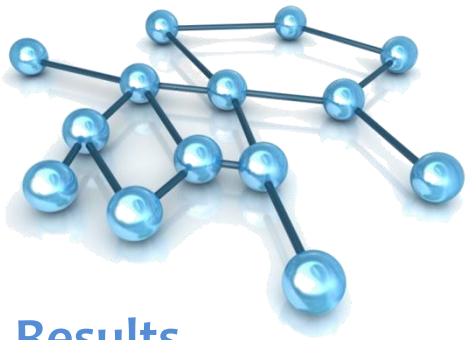


proarrhythmic potency assessment

in silico - in vitro – in vivo extrapolation

Results

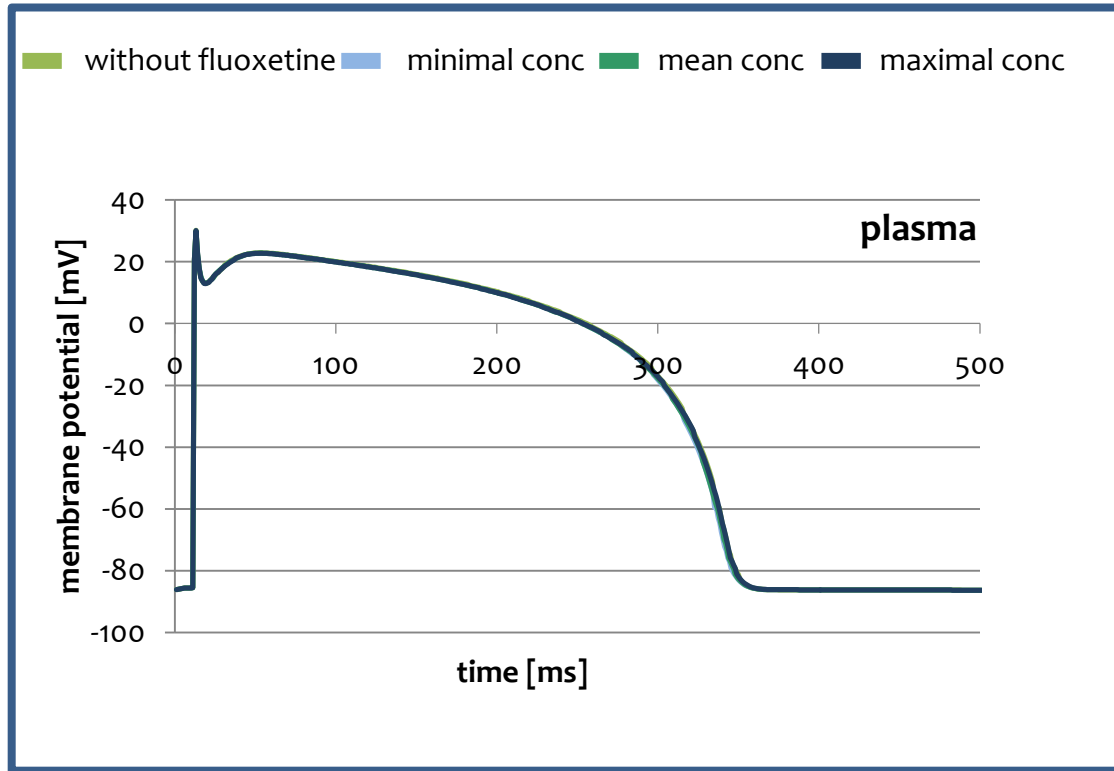
Group		Index	mean	SD
		Age (years)	28.97	8.54
APD ₉₀ [ms]	Heart tissue	Without fluoxetine	342.50	0.84
		With fluoxetine	327.78	0.54
		Difference	14.73	0.98
		Change compared to native [%]	-4.28	0.06
	Plasma	Without fluoxetine	342.50	0.84
		With fluoxetine	344.17	0.86
		Difference	1.67	1.17
		Change compared to native [%]	0.49	0.07



proarrhythmic potency assessment

in silico - in vitro – in vivo extrapolation

Results

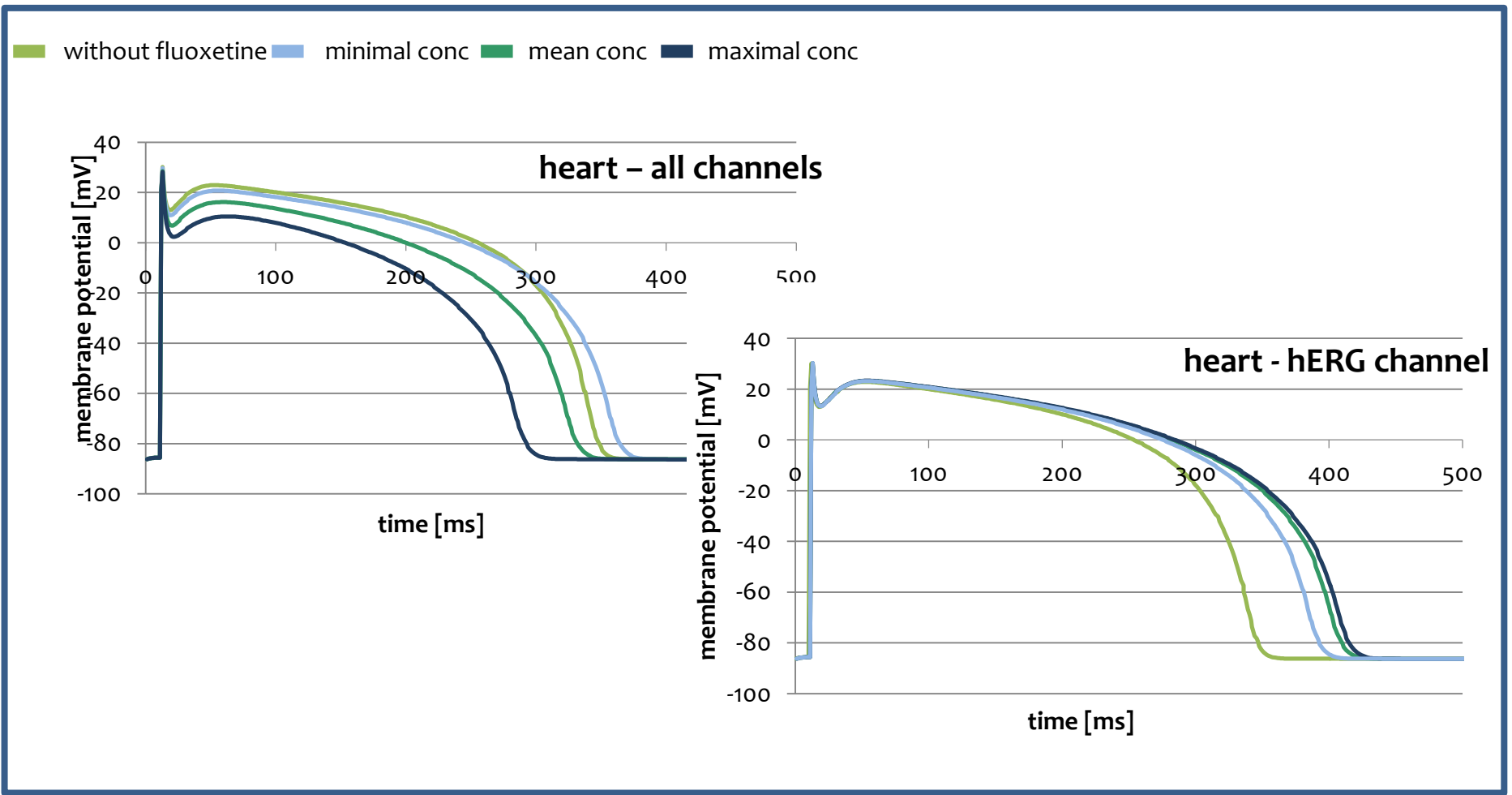


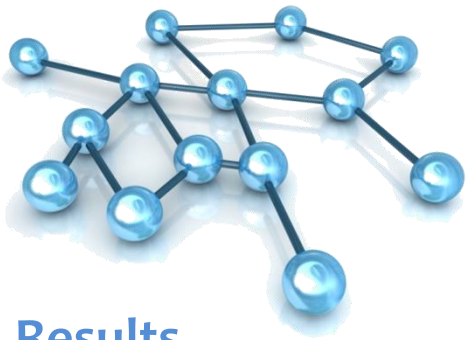


proarrhythmic potency assessment

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Results

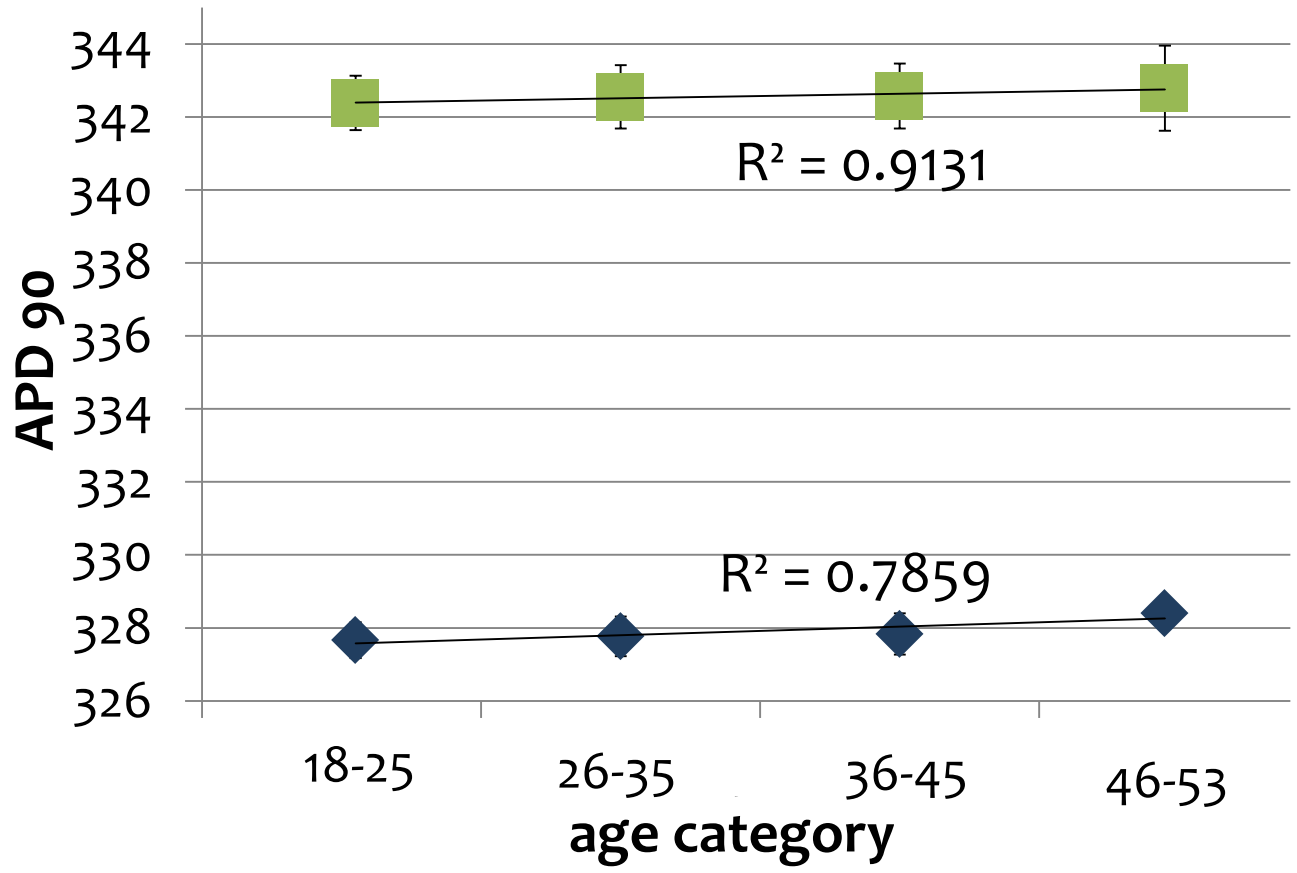


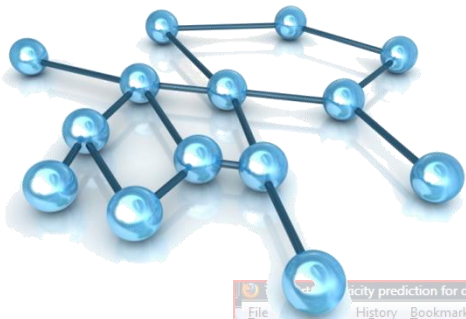


proarrhythmic potency assessment

in silico - in vitro – in vivo extrapolation

Results





proarrhythmic potency *in silico*

ToxComp.net

- P
- A
- S
-
-
-

1st CONFERENCE 06/05/09

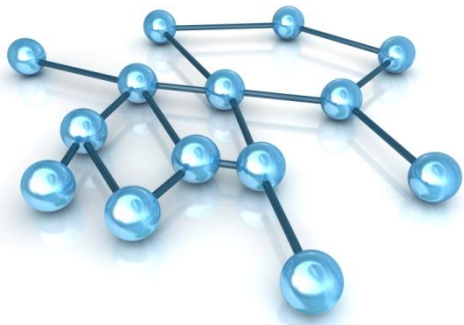
2nd CONFERENCE 28/06/09

New data files in the repository 11/08/09

Tox-Portal.net © 2009 | toxicity prediction for drug discovery

more information can be found at the

www.tox-portal.net



acknowledgements

team

Barbara Wiśniowska PhD

Aleksander Mendyk PhD

Miłosz Polak

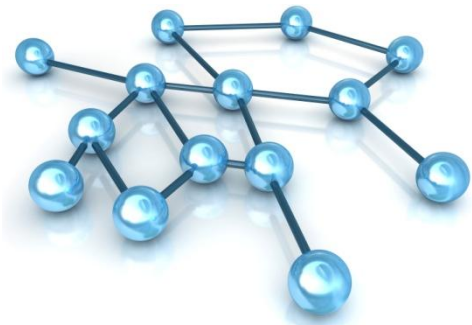
Kamil Fijorek

Anna Glinka

Małgorzata Kozłowska



project financed by the **Polish National Center for Research and Development LIDER** project number LIDER/02/187/L-1/09



THANK YOU



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Pharmacoeconomics
Jagiellonian University Medical College

