EasyAP: a Web-Based Simulation and Analysis Tool for High-Throughput Ion-Channel Screening Data

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Importance of cardiac safety in drug market

Cardiac toxicity is a leading cause of **attrition** in clinical studies and **post-marketing withdrawal**.

Phase	Nonclinical	Phase I	Phase I-III	Phase III/ Marketing	Marketing	Marketing
Information	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint® (2006)	Budnitz et al. (2006)	Stevens & Baker (2008)
Sample size	88 CDs stopped	1,015 subjects	82 CDs stopped	1,138 drugs	21,298 patients	47 drugs
Cardiovascular	27%	9%	21%	36%	15%	40%
Nervous system	14%	28%	21%	65%	39%	2%
Respiratory	2%	0%	0%	32%	8%	2%
Gastrointestinal	3%	23%	5%	67%	14%	2%
Renal	2%	0%	9%	19%	2%	0%
Hepatotoxicity	8%	7%	33%	13%	0%	23%
Reprotox	13%	0%	1%	11%	0%	2%
Genetic tox	5%	0%	0%	0%	0%	0%
Carcinogenicity	3%	0%	0%	0%	0%	0%
Haematology/BM	7%	2%	4%	16%	10%	9%
Musculoskeletal	4%	0%	1%	?	3%	2%
Immunotox; photosensitivity	7%	16%	11%	5%(+)	34%	2%
Other	0%	0%	4%	?	2%	2%

0% 1-10% 10-20% >20%

Drug-induced **QT prolongation**, in a very small % of people, leads to a potentially fatal arrhythmia: **Torsades de Pointes**. A substantial number of drugs have been withdrawn from sale due to QT interval prolongation and Torsades de Pointes.

As **an FDA requirement**, all candidate drugs must be screened for activity against the **hERG** potassium channel. However, measurement of hERG activity is not sufficient to accurately predict cardiac toxicity[6]. Physiomics' EasyAP™ takes into account activity against **hERG and two additional ion channels** (hNav1.5 and hCav1.2) to deliver **action potential time courses and duration calculations** based on several literature models.

Current models available on EasyAP

EasyAP currently provides simulations for 5 action potential models from literature:

- **3 Human models[1, 2, 3]**
- **1 Rabbit model[4]**
- **1 Dog model[5]**

These models have been adapted to integrate the agonistic or antagonistic effect of a drug on the three ion channels. In the future more models will be added (*e.g.* guinea pig).

1. Grandi, E., Pasqualini, F.S., and Bers, D.M. (2010). A novel computational model of the human ventricular action potential and Ca transient. *J. Mol. Cell. Cardiol.* 48, 112–121.

2. ten Tusscher, K.H.W.J., Noble, D., Noble, P.J., and Panfilov, A.V. (2004). A model for human ventricular tissue. *Am. J. Physiol. Heart Circ. Physiol.* 286, H1573–1589.

3. O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Computational Biology.* 2011;7(5)e1002061.

4. T.R. Shannon, F. Wang, J. Puglisi, C. Weber, D.M. Bers. A mathematical treatment of integrated Ca dynamics within the ventricular myocyte. *Biophys. J.*, 87 (2004), pp. 3351–3371.

5. Benson AP, Aslanidi OV, Zhang H, Holden AV. The canine virtual ventricular wall: a platform for dissecting pharmacological effects on propagation and arrhythmogenesis. *Prog Biophys Mol Biol.* 2008 Jan-Apr;96(1-3):187-208. This model is a modification of the model published in Hund TJ, Rudy Y. Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. *Circulation.* 2004 Nov 16;110(20):4008-74.

6. Mirams GR, Cui Y, Sher A, Fink M, Cooper J, Heath BM, *et al.* Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk. *Cardiovasc Res.* 2011;91:53–61.

Benefits and features of EasyAP

EasyAP™ provides **action potential time course simulations** to facilitate the **prediction of cardiac toxicity** and **compound de-risking**.

EasyAP

www.easyap.co.uk

- **Simulate action potential time courses based on hNav1.5, hCav1.2 and hERG ion channel drug agonistic or antagonistic effects**
- **De-risking by comparing the effect of blocking multiple ion channels vs hERG alone**
- **Calculate AP Duration and Upstroke values for a dose range**
- **Compare multiple AP models in parallel**
- **Compare multiple compound AP profiles**
- **Import compound data from files**
- **Automatic reporting - data and figures**
- **Affordable fee-per-compound analysis or site licensing**

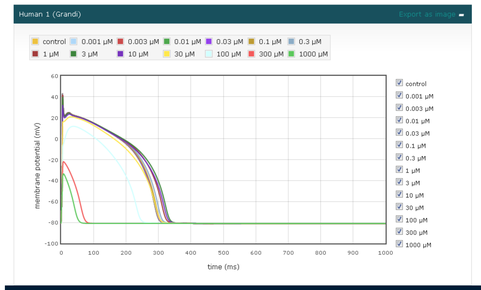
Convenient web interface

- **Dynamic control panels**
- **Organise your compounds in project folders**
- **Import and export compound and simulation data**
- **Easy to use**

Select	Name	Added (d/m/y)	$hNa_v1.5$			$hCa_v1.2$			hERG			Status
			Type	I/EC50 (µM)	Emax (fold)	Type	I/EC50 (µM)	Emax (fold)	Type	I/EC50 (µM)	Emax (fold)	
☐	ajmaline	25/09/2014	AN	8.2	None	AN	71.0	None	AN	1.04	None	DONE
☐	↳ ajmaline (hERG only)	25/09/2014	NO	None	None	NO	None	None	AN	1.04	None	DONE
☐	chlorpromazine	25/09/2014	AN	4.3	None	NO	None	None	AN	1.47	None	DONE
☐	↳ chlorpromazine (hERG only)	25/09/2014	NO	None	None	NO	None	None	AN	1.47	None	DONE
☐	dofetilide	25/09/2014	AN	300.0	None	AN	60.0	None	AN	0.005	None	DONE
☐	↳ dofetilide (hERG only)	25/09/2014	NO	None	None	NO	None	None	AN	0.005	None	DONE

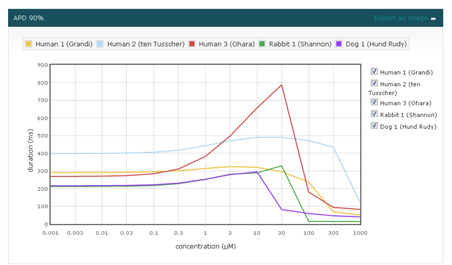
Action potential time course simulations

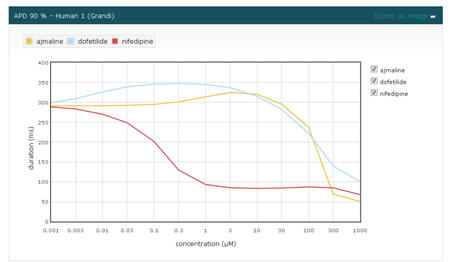
- **Dose-range profiles for each model**
- **Single compound analysis and multiple compound comparison**
- **SVG dynamic plots**
- **Export graphs as images and values in spreadsheet for convenient reporting**

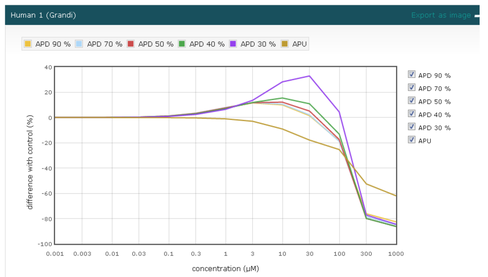


Action potential durations and upstroke

- **APD values at 90, 70, 50, 40 and 30% and APU**
- **Simple and multiple compound comparison**
- **Multiple model comparison**
- **Display numerical results as raw or percentage of control: all calculations are done for you!**







	0	0.001	0.003	0.01	0.03	0.1	0.3	1	3	10	30	100	300	1000
APD 90 %	0.0	0.0	0.0	0.1	0.4	1.3	3.4	7.8	11.5	10.0	1.5	-18.5	-76.2	-82.6
APD 70 %	0.0	0.0	0.0	0.1	0.4	1.3	3.5	8.0	11.8	10.6	2.1	-18.9	-78.5	-85.0
APD 50 %	0.0	0.0	0.0	0.1	0.4	1.2	3.3	7.7	11.8	12.2	5.1	-17.4	-79.9	-86.2
APD 40 %	0.0	0.0	0.0	0.1	0.3	1.1	3.0	7.1	11.9	15.5	10.9	-13.1	-79.9	-86.3
APD 30 %	0.0	0.0	0.0	0.1	0.3	0.9	2.5	6.5	13.7	28.3	32.9	4.4	-77.2	-84.5
APU	0.0	0.0	-0.0	-0.0	-0.0	-0.1	-0.3	-1.0	-3.0	-9.1	-17.8	-25.4	-52.5	-62.0

De-risking

- **Compare QT prolongation risk for hERG alone vs all 3 ion channel effects**
- **Example of ajmaline: using the 3 channel inhibition values, the Human 1 model (based on Grandi *et al.*) predicts more significant duration changes at concentrations higher than 3 µM than with hERG alone.**