MyHealthAvatar platform: matching real life patients with the generated virtual profiles from *in silico* clinical trials

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Objectives: MyHealthAvatar (MHA) platform aims towards a collaborative partnership among patients and healthcare providers [1]. Nowadays, in silico clinical trials (ISCTs), population pharmacokinetics, pharmacogenomics and information communication technologies have provided several tools towards stratified and personalized medicine approaches [2-4]. In this work a methodology of potential fitting of results generated through ISCTs with real life patients through virtual profiles of MHA is presented. To this respect, we use a simple example of discontinuation of warfarin administration during pre-operative period for a 55 year's old male patient with a MHA profile.

http://myhealthavatar.org/mha/

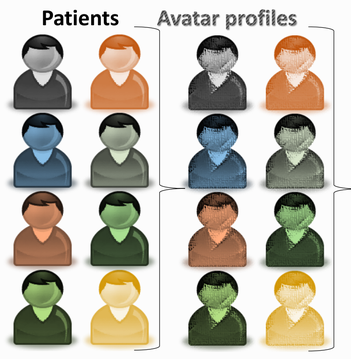


Table 1. Virtual cohort through patients' MHA profiles.
Bold & red circle indicate the 55 year old of this example

Demographic data						Physiology data			Genotype/Phenotype data (metabolic enzymes)		
Gender	Age (Years)	Weight (kg)	Height (m)	BSA (m^2)	BMI (kg/m^2)	Haematocrit (%)	Serum Creatinine (μmol/L)	Renal function	CYP2C9	CYP2C19	CYP2D6
M	57	82	1.76	1.99	26.48	40	47.50	Normal	*1/*2	EM	EM
M	53	85	1.75	2.01	27.88	42	84.70	Normal	*1/*2	EM	EM
M	**55**	**103**	**1.87**	**2.28**	**29.27**	**46**	**75.43**	**Normal**	***1/*1**	**EM**	**EM**
M	51	74	1.69	1.84	26.06	44	62.52	Normal	*1/*1	EM	EM
M	56	95	1.86	2.20	27.38	46	64.29	Normal	*1/*1	EM	PM
M	59	100	1.76	2.16	32.17	45	79.92	Normal	*1/*3	EM	EM
M	54	53	1.62	1.56	20.24	46	76.14	Normal	*1/*3	EM	EM
M	50	76	1.78	1.94	23.77	38	80.03	Normal	*1/*2	EM	EM

Facts of anticoagulating/anti-platelet therapies

- *Anti-platelet therapy may lead in appearance of bleeding in the postoperative period*
- *Therapeutic drug monitoring & personalized medicine tools are necessary for this group of medicines*
- *Large inter-subject variability in PK/PD due to genetic and epigenetic factors (i.e. metabolizing enzymes)*
- *Clinical trials regarding discontinuation of therapy in patients for pre-operative period are limited*

Methods: MHA's architecture is based on integration of multiscale data gained from several sources (i.e. demographic, biomedical, genomics, lifestyle) and transform them into a representation of health status as a "virtual twin" or avatar [1]. The integration of these information from different avatars can lead in a creation of a virtual population profile (i.e. patients follow anti-coagulating treatment). The population pharmacokinetics in this example are based on the results from simulation of S-warfarin administration in a virtual population through Simcyp® population based simulator [5].

Table 2. Example of data output for a virtual population from Simcyp® platform

Demographic data						Physiology data						Genotype/Phenotype data (metabolic enzymes)		
Sex	Age (Years)	Weight (kg)	Height (cm)	BSA (m^2)	BMI (kg/m^2)	Cardiac Output (L/h)	Haematocrit (%)	HSA (g/L)	AGP (g/L)	Serum Creatinine (μmol/L)	GFR (mL/min)	Renal Function	CYP2C9	CYP2C19	CYP2D6
M	39	86	179	2.05	26.88	345.49	43.63	53.12	0.93	71.35	126.60	1.05	*1/*1	EM	EM
F	42	74	158	1.76	29.34	293.39	38.20	44.24	0.72	61.75	120.66	0.93	*1/*2	PM	EM
F	39	67	151	1.63	29.03	274.71	37.59	49.11	0.60	60.45	123.61	0.95	*1/*1	IM	EM
F	48	66	168	1.75	23.52	285.95	39.16	48.58	0.86	68.53	91.69	0.71	*1/*1	IM	EM
M	33	106	184	2.28	31.21	393.24	41.98	39.79	0.79	80.52	130.80	1.09	*1/*1	UM	EM
M	38	75	175	1.91	24.77	322.67	41.06	42.26	1.14	71.93	119.76	1.00	*2/*3	EM	IM
M	42	66	170	1.76	22.55	293.61	47.12	52.21	0.85	70.25	109.63	0.91	*1/*1	IM	PM
F	38	71	167	1.80	25.55	304.14	35.42	41.13	0.63	49.01	149.24	1.15	*1/*1	UM	EM
F	38	45	150	1.36	19.94	230.52	38.91	53.51	0.75	62.62	96.13	0.74	*1/*1	EM	EM
M	54	76	169	1.86	26.37	297.66	44.61	46.85	0.68	85.53	86.89	0.72	*1/*1	UM	EM
M	41	91	180	2.11	28.20	352.71	40.39	41.88	1.07	87.46	104.18	0.87	*1/*1	UM	PM

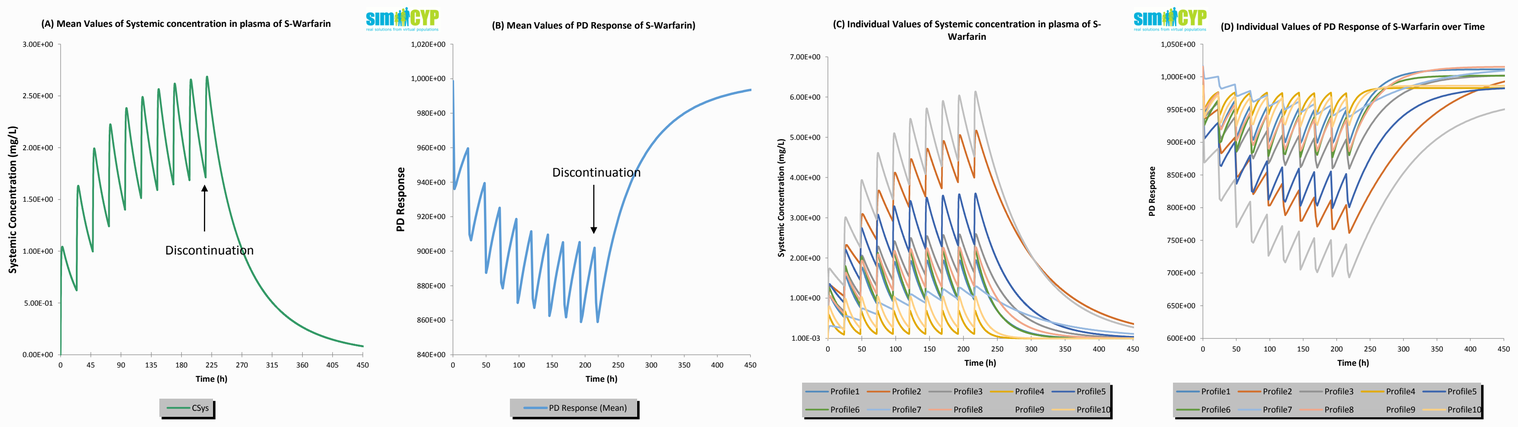


Figure 1. Simulated concentration time profiles and pharmacodynamic responses of S-warfarin up to 20 days with administration for 10 days in a virtual population with characteristics of the virtual cohort from MHA platform (A) Mean C-t profiles (B) Mean PD profiles (C) individual profiles (D) individual PD profiles for the virtual population

Results: The results from the Simcyp® simulations generated a PK/PD profile of S-warfarin during and after the discontinuation of the treatment in a virtual population with different characteristics regarding demographic, physiology and genomic data. The data output from MHA platform allow also the generation of a virtual cohort with characteristics regarding demographic, physiology and pharmacogenomics (i.e. CYP2C9 polymorphism). To this respect, the best fit of data between these two virtual profiles, e.g. based on patient's demographics and genomic information, finally leads in generation of information regarding our real-life patient (in this example, the 55 years old male) serving as additional information tool regarding the schedule of the operation

Table 3. Data output of the simulated clinical trial in a virtual population with similar characteristics from the cohort of MHA profiles. The red circles indicate the two virtual profiles that could best fit with the patient based on demographic and pharmacogenomic data

Demographic data						Physiology data							Genotype/Phenotype data (metabolic enzymes)		
Gender	Age (Years)	Weight (kg)	Height (cm)	BSA (m^2)	BMI (kg/m^2)	Cardiac Output (L/h)	Hct (%)	HSA (g/L)	AGP (g/L)	Serum Creatinine (μmol/L)	GFR (mL/min)	Renal Function	CYP2C9	CYP2C19	CYP2D6
M	57	72	180	1,91	22,34	301,53	44,83	38,87	0,88	76,88	86,68	0,72	*1/*1	EM	PM
M	62	72	168	1,82	25,66	281,01	40,45	40,46	0,86	69,42	94,94	0,79	*1/*1	EM	EM
M	57	82	176	1,99	26,48	313,16	40,35	50,69	0,95	47,50	153,26	1,28	*1/*2	EM	EM
M	53	85	175	2,01	27,88	321,55	42,21	42,12	0,73	84,70	92,68	0,77	*1/*2	EM	EM
M	55	93	188	2,28	26,57	363,58	47,29	37,13	0,75	75,43	108,07	0,90	*1/*1	EM	EM
M	51	74	169	1,84	26,06	297,32	44,30	46,81	0,92	62,52	121,46	1,01	*1/*1	EM	EM
M	56	95	186	2,20	27,38	348,49	46,18	50,98	0,85	64,29	120,15	1,00	*1/*1	EM	PM
M	59	100	176	2,16	32,17	337,90	45,28	45,38	0,72	79,92	99,60	0,83	*1/*3	EM	EM
M	55	53	162	1,56	20,24	251,16	46,30	44,61	0,84	76,14	84,34	0,70	*1/*3	EM	EM
M	50	76	178	1,94	23,77	313,82	38,82	45,20	0,73	80,03	93,22	0,78	*1/*2	EM	EM

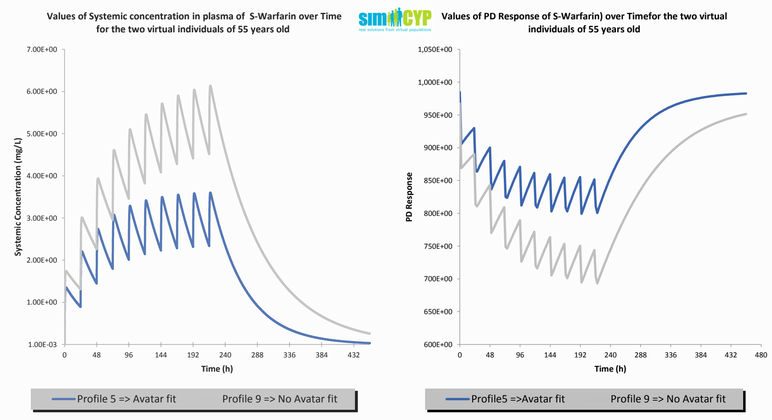


Figure 2. Simulated concentration time profiles (I) and pharmacodynamic responses (II) of S-warfarin for the two virtual profiles with similar characteristics with those of the patient in this use-case. The differences are attributed in the differences in physiology and genomic data and the optimum fit could be introduced as additional information in patient's MHA avatar profile matching the in silico results with the clinical case (Picture below)

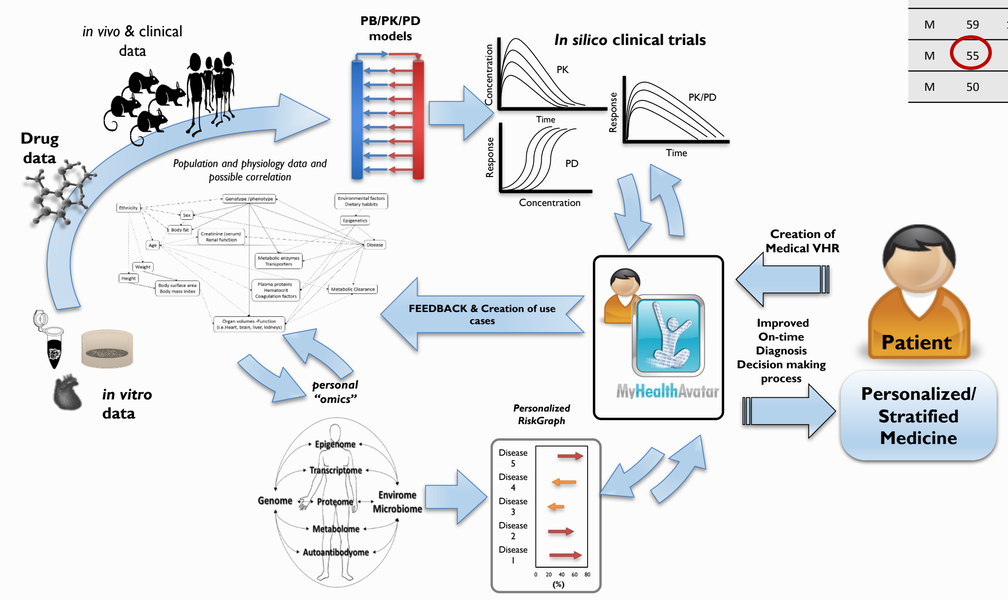
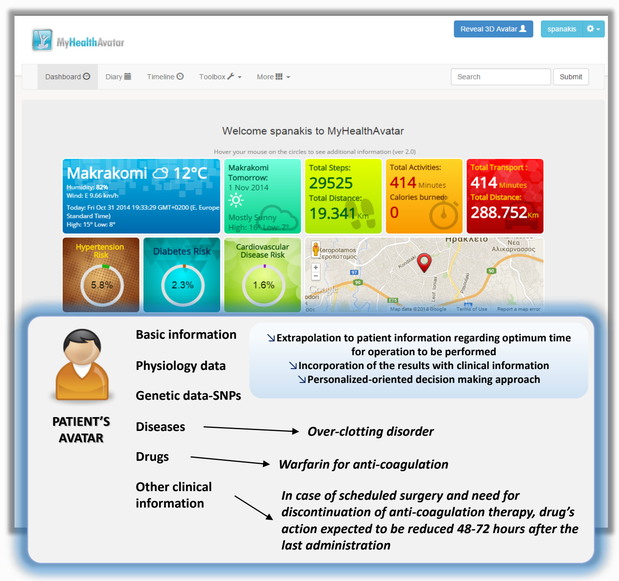


Figure 3. The virtual representation of physiology as it is developed through MHA platform could serve as a connection point between scientific disciplines towards personalized/stratified medicine approaches exploiting data from different scientific disciplines into clinical profiles (adopted from [7])

Conclusions: MHA aims to serve as an innovative representation of the health status for citizens whereas for clinicians MHA potentially could support clinical decisions by extrapolating and/or fitting profiles with simulation models (i.e. population pharmacokinetics) and visual analytics [6]. The potential interconnection with in silico tools can provide novel approaches towards implementation of stratified and/or personalized medicine [7].



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