This is a repository copy of *Generation of digital patients for the simulation of tuberculosis with UISS-TB*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/213564/

Version: Accepted Version

Generation of digital patients for the simulation of tuberculosis with UISS-TB

Marzio Pennisi‡,Miguel A. Juárez∗,Giulia Russo†,Marco Viceconti§,Francesco Pappalardo†

∗ *School of Mathematics and Statistics*
University of Sheffield
S3 7RH, Sheffield, UK
Email: m.juarez@sheffield.ac.uk
† *Department of Drug Sciences,*
University of Catania,
Catania, Italy
{giulia.russo;francesco.pappalardo}@unict.it
‡*Department of Mathematics and Computer Science,*
University of Catania,
Catania, Italy
mpennisi@dmi.unict.it
§*Department of Industrial Engineering,*
University of Bologna,
Bologna, Italy
marco.viceconti@unibo.it

Abstract—**EC funded STriTuVaD project aims to test, through a phase IIb clinical trial, two of the most advanced therapeutic vaccines against tuberculosis. In parallel, we have extended the Universal Immune System Simulator to include all relevant determinants of such clinical trial, to establish its predictive accuracy against the individual patients recruited in the trial, to use it to generate digital patients and predict their response to the HRT being tested, and to combine them to the observations made on physical patients using a new in silico-augmented clinical trial approach that uses a Bayesian adaptive design. This approach, where found effective could drastically reduce the cost of innovation in this critical sector of public healthcare. One of the most challenging task is to develop a methodology to reproduce biological diversity of the subjects that have to be simulated, i.e., provide an appropriate strategy for the generation of libraries of digital patients. This has been achieved through the the creation of the initial immune system repertoire in a stochastic way, and though the identification of a "vector of features" that combines both biological and pathophysiological parameters that personalize the digital patient to reproduce the physiology and the pathophysiology of the subject.**

1. Introduction

Tuberculosis (TB) represents one of the world's deadliest diseases: one third of the world's population, mostly in developing countries, is infected with TB. But TB is becoming again very dangerous also for developed countries, due to the increased mobility of the world population, and the appearance of several new bacterial strains that are multi-drug resistant (MDR). There is now a growing awareness that TB can be effectively fought only working globally, starting from countries like India, where the infection is endemic.

Once a person presents the active disease the most critical issue is the current duration of the therapy, because of the high costs it involves, the increased chances of non-compliance (which increase the probability of developing an MDR strain), and the time the patient is still infectious to others. One exciting possibility to shorten the duration of the therapy is represented by new host-reaction therapies (HRT) as a coadjuvant of the antibiotic therapy. The end-points in the clinical trials for HRTs are time to sputum culture conversion, and incidence of recurrence. While for the first it is in some cases possible to have a statistically powered evidence for efficacy in a phase II clinical trial, recurrence almost always requires a phase III clinical trial with thousands of patients involved, and huge costs.

In the STriTuVaD multidisciplinary consortium we are going to test, through a phase IIb clinical trial, two of the most advanced therapeutic vaccines against drug sensistive tuberculosis (DS-TB) and multi-drug resistant tuberculosis (MDR-TB) i.e., RUTI vaccine, provided by Archivel Farma S.L (Spain) and ID93+GLA-SE vaccine, provided by Infectious Disease Research Institute (US).

In parallel we extend the Universal Immune System Simulator to include all relevant determinants of such clinical trial, establish its predictive accuracy against the individual

patients recruited in the trial, use it to generate digital patients and predict their response to the HRT being tested, and combine them to the observations made on physical patients using a new in silico-augmented clinical trial approach that uses a Bayesian adaptive design. This approach, where found effective could drastically reduce the cost of innovation in this critical sector of public healthcare.

To reproduce biological diversity of the subjects that have to be simulated, an appropriate strategy for the generation of libraries of digital patients has been developed. This has been achieved through the identification of a "vector of features" that combines both biological and pathophysiological parameters that personalize the digital patient.

In this paper, after a brief recall about UISS and its extension to tuberculosis (sect. 2), we sketch the strategy we adopt to generate the cohort of digital patients(sect. 3), and we show some preliminary results about the dynamics of MTB on a subset of these patients. (sect. 4).

2. Extension of the UISS computational framework to reproduce TB

We will briefly describe here the UISS computational framwork and its extension to model tuberculosis, UISS-TB. The interested reader can find more details about UISS-TB in [1].

2.1. Introduction to the UISS modeling framwork

UISS is a multi-agent framework for the simulation of the immune system dynamics that can be extended to reproduce specific diseases and related treatments. Differently from classical top-down approaches, in which mean behaviors are studied by means of differential equations as presented in [2], [3], [4], in agent based models and multi-agent systems entities are followed individually, and global nonlinear behaviors arise as the sum of individual behaviors. UISS has been developed as a multi-scale computer simulator of the immune system, as it takes into account both cellular and molecular entities and processes.

UISS has a long track record of successful stories that include, among others, its use for modelling the effects of a vaccine against the onset of mammary carcinoma [5], [6] and consequent lung metastases [7], for the initial stages of atherosclerosis [8], for melanoma [9], and more recently, for the study of Multiple Sclerosis [10], [11] and for testing the efficacy of citrus-derived adjuvants for influenza vaccines and human papilloma virus [12], [13].

We then extended UISS to include all the MTB dynamics along with the artificial immunity induced by vaccination strategies as presented in [1].

Finally, to depict individual diversity, a vector of features has been identified. It combines both biological and pathophysiological parameters that personalize the digital patient to reproduce the physiology and the pathophysiology of the subject. In particular, the digital patient model defines a specific patient through 26 features: Drug Sensitive

Feature Description	Type and Range
Drug Sensitive status	Y/N (MDR otherwise)
Bacterial load in the sputum	[50-400] CFU (D)
MTB virulence	[0-1] (Adimemsional) (C)
CD4 T cell type 1	approx.1370 cells/μL (D)
CD4 T cell type 2	approx.1370 cells/μL (D)
Specific IgG titers	[2-8] IgG titer (C)
CD8 T cell	approx.560 cells/μL (D)
Interleukin 1	[0-10000] pg/mL (C)
Interleukin 2	[50-1000] pg/mL (C)
Interleukin 10	[5-16] pg/mL (C)
Interleukin 12	[3-300] pg/mL (C)
Interleukin 17	[0-1000] pg/mL (C)
Interleukin 23	[0-1000] pg/mL (C)
Type 1 Interferon	[0-11000] pg/mL (C)
Interferon-γ	[[6-19] pg/mL (C)
TNF-α	[4-40] pg/mL (C)
TFG-β	[2-8] pg/mL (C)
LXA4	[0-3] ng/mL (C)
PGE2	[0-2.2]ng/mL (C)
General chemokine	[0-20] ng/mL (C)
Vitamin D	[0-100] ng/mL (C)
HLA-class 1	[$0 - 2^{\text{NBITSTR}-1}$] (Adimemsional) (D)
HLA-class 2	[$0 - 2^{\text{NBITSTR}-1}$] (Adimemsional) (D)
FoxP3 cells	approx.60 cells/μL (D)
Age	[0-90] years (D)
Body Mass Index	[16-41] Kg/m^2 (C)

TABLE 1. VECTOR OF FEATURES AND RELATIVE RANGE USED TO IDENTIFY AND DEFINE DIGITAL PATIENTS. (D) STANDS FOR DISCRETE VARIABLE; (C) STANDS FOR CONTINUOUS VARIABLE.

(DS)/Multi-drug resistant (MDR); Bacteria Load (BL) in the sputum; MTB strain; CD4 Th1; CD4 Th2; IgG titers; CD8 T cells; IL-1; IL-2; IL-10; IL-12; IL-17; IL-23; IFN Type I: IFNγ; TNFα; TGFβ; LXA4; PGE2; Chemokines; Vitamin D; HLA-1; HLA-2; FoxP3; Age; BMI. The list of parameters, together with the relative range, is presented in table 1.

3. Generation of Digital Patients: a Bayesian approach

3.1. The UISS-TB input vector

The UISS-TB model defines a specific patient through a vector of 26 features as described in section **??**:

In order to create an *in silico* patient, one needs to provide a single value for each one of 1–26. These values could be taken from individual physical patients; however, if a cohort of digital patients is to be produced, one should have a mechanism for producing as many different input vectors as needed, that are biological/physiological plausible. Formally, this requires the characterisation of the joint distribution of the inputs in the population. We have compiled typical values and standard deviations for each feature, providing a way to generate plausible values for each component at a time. Proceeding in this way would neglect the biological correlations between features and thus

would not guarantee a physiologically plausible input vector. Hence, we must take into account these correlations. Given that we have 25 numerical input variables (DS/MDR is a factor), we should specify $25 \times 24/2 = 300$ correlations. Using relevant literature and expert opinion, we have qualified these correlations, determining that all correlations are positive, but the correlation of IL-10 with the rest of the features.

3.2. Formalising *in silico* profile generation

In theory, one could elicit the joint distribution of the 25 features, i.e. describe mathematically how each feature relate to each other in a space of 25 dimensions; but this would be not only extremely difficult, but also time consuming and data demanding. Our approach is to rely on current mathematical biology consensus and use a Gaussian to represent the population distribution. The additional advantage of using this approach will be discussed in the next section.

Formally, we say that the vector $\boldsymbol{x} = \{x_1, \ldots, x_d\}$ follows a d-variate Gaussian distribution with joint probability density function (pdf)

$$N_d(\boldsymbol{x} \mid \boldsymbol{\mu}, \Sigma) = (2\pi)^{-d/2} |\Sigma|^{-1/2} \times$$
$$\exp\left[-\frac{1}{2}(\boldsymbol{x} - \boldsymbol{\mu})'\Sigma^{-1}(\boldsymbol{x} - \boldsymbol{\mu})\right],$$

with mean $\boldsymbol{\mu} = \{\mu_1, \ldots, \mu_d\}$ and covariance matrix,

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \ldots & \sigma_{1d} \\ \sigma_{21} & \sigma_2^2 & \ldots & \sigma_{2d} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{d1} & \sigma_{d2} & \ldots & \sigma_d^2 \end{pmatrix}$$

where,

$$\mathrm{Cov}(x_i, x_j) = \sigma_{ij}$$

related to the correlations by

$$\mathrm{Cor}(x_i, x_j) = \rho_{ij} = \frac{\sigma_{ij}}{\sqrt{\sigma_i^2 \sigma_j^2}}$$

So, if we are able to elicit a measure of correlation between two inputs, we can calculate their covariance.

The elements in the diagonal, σ_i^2 are the marginal variances of each element, x_i, and μ_i the corresponding marginal mean. As mentioned above, we already have compiled a list with these values, so we have elicited values for $\boldsymbol{\mu}$ and the diagonal elements of Σ, σ_i^2.

3.3. Cohort generation

Once $\boldsymbol{\mu}$ and Σ have been elicited, generating an *in silico* profile is a relatively trivial task: one must sample a point in the 25-dimensional space, consistent with $N_d(\boldsymbol{x} \mid \boldsymbol{\mu}, \Sigma)$. But we can exploit the properties of the Gaussian distribution to produce a cohort consistent with some specific characteristics. Say, for instance, that our target population has a particular range of BL, we would like then to produce digital

patients consistent with that specific profile. Formally, let x_1 represent BL and $\boldsymbol{x}_{-1} = \{x_2, \ldots, x_{18}\}$, the rest of the features; we would like to sample from

$$N_d(\boldsymbol{x}_{-1} \mid x_1, \boldsymbol{\mu}, \Sigma)$$

i.e. the conditional distribution of the rest of the features, given that BL has a specific value. This is a standard procedure, which can be readily implemented. We can go even further and sort the list of features according to either their importance in determining the profile of a patient, or to the precision of their elicited mean, variance and covariance, and then proceed to sample from the conditional distributions, one at a time.

4. Preliminary results

To test the approach presented in sect. 3 we created an R script for the generation of digital patents. In table 2 we report 30 generated digital patients using the aforementioned approach. All the patients have been then simulated using UISS-TB.

In the following figures we show the typical UISS-TB simulation framework when applied to the sample set of digital in silico patients depicted in table 2. We show, for each biological entity, both the mean behavior (according to the entities the color line may vary) and the +/- SD (blue lines). We run a total of 30 simulations for untreated digital in silico patients. In figure 1 it is depicted the dynamics of alveolar macrophages during two phases. The first one is during the active TB phase where both necrotic and MTB-infected populations increase. After the active phase, a latent phase is established, and necrotic alveolar macrophages contribute to typical granuloma formation.

5. Conclusions and future work

The set up an "in silico" trial requires that the involved computational model is able to coherently reproduce the disease dynamics on different individuals. As a consequence of that, it is important to establish a rigorous strategy for the definition of a credible cohort of digital patients. To this end, we presented an approach for creating a set of digital patients whose features can be in line with those of the real population.

Preliminary results about the execution of UISS-TB on the cohort of digital patients show that the simulator is able to capture the dynamics of this pathology.

The next step will be focused on the generation of reference digital populations to be used as part of the technical validation of UISS-TB. Once the data from the clinical trials will be available, we will regenerate the digital cohorts, and we will use a Bayesian statistical model approach to explore specific use cases, such as that of in silico-augmented clinical trials, where digital and physical patients are combined.

N.Ag	strain	Th1	Th2	IgG	TC	IL1	IL2	IL10	IL12	IL17	IL23	IFN1	IFNG	TNF	TGFB	LXA4	PGE2	Chem	VD	MHC1	MHC2	Treg	Age	BMI
189	0.7064	43	46	4.53	50	5061.45	555.26	14.4	166.02	534.23	516.91	5534.17	21.86	13.02	7.53	2.96	0.89	9.15	47.43	2029	2077	57	39	30.72
249	0.4037	49	52	4.91	52	5074.84	532.75	14.95	186.13	515.34	510.78	5443.04	18.69	17.89	3.82	2.61	0.82	11.88	55.15	2047	2061	56	46	32.57
187	0.5344	63	53	7.09	51	4993.29	514.32	15.59	158.93	510.4	522.28	5499.65	20.16	19.5	6.83	2.92	748	11.78	51.74	2067	2036	51	47	32.34
253	0.1497	54	62	4.72	44	4986.72	515.62	18.74	138.36	524.74	512.97	5445.44	20.26	10.84	8.1	1.98	0.3	7.01	50.09	2021	2014	47	47	28.52
175	0.2359	51	43	4.74	51	4925.43	509.98	18.89	140.16	500.57	475.85	5514.87	20.29	11.76	5.66	2.45	0.41	12.16	43.49	2077	2047	50	47	27.82
229	0.8574	56	43	6.64	48	4954.02	538.34	17.48	151.19	495.06	484.93	5484.89	21.54	13.91	3.02	2.27	0.34	8.61	49.42	2072	2044	46	47	27.29
221	0.7262	51	54	4.92	46	4975.01	507.1	16.17	154.19	512.23	485.33	5477.36	18.61	15.8	5.49	2.41	0.35	8.4	48.88	2034	1990	42	49	29.29
199	0.2529	47	56	3.67	54	5019.55	515.44	17.39	150.84	502.38	460.19	5430.43	19.5	9.6	5.44	2.37	1.07	10.53	45	2069	2029	46	36	30.09
158	0.341	44	53	4.05	59	5007.74	542.11	20.79	145.03	498.41	479.92	5460.33	20.79	12.38	6.77	2.68	0.71	9.75	51.58	2066	1992	52	42	29.61
191	0.2069	40	45	3.64	43	4981.71	519.91	18.01	138.63	494.85	503.23	5395.49	21.54	7.92	5.73	2	0.64	8.36	41.33	2024	2076	37	41	26.83
328	0.56	48	40	4.32	50	5018.13	513.28	17.84	144.18	501.32	505.75	5519.12	20.22	12.06	5.87	2.24	0.53	7.9	58.25	2033	2065	40	46	25.81
252	0.5409	35	53	5.44	43	4973.13	496.53	18.62	143.75	478.83	500.98	5493.01	21.74	12.08	6.12	2.09	0.9	8.26	52.65	1991	2041	49	38	29.29
261	0.496	54	56	6.2	56	4946.85	525.38	17.88	153.03	502.42	502.62	5587.85	22.67	13.08	4.13	3.22	1.03	9.73	59.39	2077	2109	51	55	29.8
273	0.8468	52	49	7.31	54	5035.47	550.42	16.67	173.35	505.56	504.44	5510.07	21.51	13.46	6.78	3.05	1.4	12.71	51.72	2103	2107	59	54	32.99
300	0.7984	42	47	6.02	50	4956.64	500.79	16.64	146.57	508.83	507.02	5487.82	21.76	12.29	1.78	3.09	1.08	11.7	46.76	2036	2037	55	44	25.03
245	0.3408	49	43	5.74	50	4916.78	522.15	21.1	134.55	481.55	497.47	5430.43	20.29	15.08	6.08	2.94	1.03	8.74	57.86	2031	2057	38	42	31.76
221	0.6764	53	50	6.75	45	4958.18	484.49	18.45	153.83	487.77	476.68	5491.86	21.47	13.64	3.73	2.33	1.02	8.93	53.04	2059	2032	51	36	29.9
122	0.8234	54	45	6.14	51	4911.57	520.65	17.55	163.81	499.58	504.62	5599.99	22.12	14.77	2.50	2.24	987	9.99	44.99	2039	2064	53	38	27.25
242	0.816	42	51	4.21	51	4983.22	527.73	17.32	147.31	494.85	491.66	5440.64	19.32	12.34	5.17	2.62	0.78	9.300	53.42	2041	2088	48	47	30.6
313	0.5595	43	51	6.19	55	5001.22	514.22	17.19	155.13	499.22	488.78	5537.17	20.38	12.86	3.14	2.27	0.33	5.61	50.71	1992	2071	47	42	27.05
179	2.63E-2	42	44	6.79	43	5070.49	520.66	21.95	170.17	525.5	525.2	5458.13	19.68	13.22	2.63	2.17	1.110	11.05	45.17	2020	2020	50	36	32.617
345	0.3713	52	44	6.2	48	4975.01	541.12	17.48	155.88	507.21	502.65	5467.4	21.17	13.29	6.82	2.76	0.87	14.8	49.63	2024	2112	55	56	34.29
245	0.6411	51	52	5.82	57	4992.59	551.01	15.56	173.09	518.22	514.61	5569.51	22.26	13.26	8.31	2.65	1.15	13	51.33	2064	2059	54	49	29.1
251	0.5810	51	51	2.99	49	4988.39	521.97	20.7	127.72	489.56	484.17	5438.56	18.89	12.88	3.99	2.46	0.19	5.27	53.35	2054	2069	42	38	24.82
234	0.2243	46	42	4.40	57	5003.68	551.15	20.72	154.75	501.44	519.77	5515.5	20.75	14.23	4.11	2.2	0.49	10.25	44.46	2021	2017	45	44	26.95
186	0.4632	50	47	4.36	47	4869.57	551.46	20.02	138.66	496.34	500.4	5476.01	20.67	12.43	4.49	3.1	0.74	6.99	47.49	2080	2045	56	45	30.6
154	0.3493	54	49	6.01	44	5014.58	515.5	18.26	152.16	502.53	482.3	5576.32	20.55	13.9	5.67	2.68	0.99	10.35	56.32	2011	2028	54	41	27.18
239	0.7161	58	56	6.29	48	4961.32	548.38	17.89	141.16	520.83	487.15	5519.7	20.38	12.25	3.23	2.44	1.17	12.23	45.65	2057	2048	54	45	28.06
208	0.498	46	54	4.65	52	5064.60	539.2	19.04	160.08	494.1	520.26	5638.14	21.84	14.05	4.08	2.86	0.96	6.37	56.91	2062	2026	45	51	26.84
209	0.5812	47	57	3.77	53	5118.04	530.24	17.28	149.22	501.75	492.45	5513.76	21.82	11.72	7.06	2.69	0.4	8.76	47.44	2043	2043	51	44	32.81

TABLE 2. VECTOR OF FEATURES FOR 30 DIGITAL PATIENTS GENERATED ACCORDING THE APPROACH DESCRIBED IN SECTION 3. THE COLUMN FOR DS/MDR STATUS IS NOT REPORTED IN TABLE.

Acknowledgments

References

[1] M. Pennisi, G. Russo, G. Sgroi, A. Bonaccorso, G. A. Parasiliti Palumbo, D. K. Mitra, K. B. Walker, P.-J. Cardona, M. Amat, M. Viceconti, and F. Pappalardo, "Predicting the artificial immunity induced by RUTI vaccine against tuberculosis using universal immune system simulator (UISS)," *BMC Bioinformatics*, vol. doi:10.1186/s12859-019-3045-5, 2019.

[2] M. A. Ragusa and G. Russo, "ODEs approaches in modeling fibrosis: Comment on "Towards a unified approach in the modeling of fibrosis: A review with research perspectives" by Martine Ben Amar and Carlo Bianca," *Phys Life Rev*, vol. 17, pp. 112–113, Jul 2016.

[3] F. Castiglione, F. Pappalardo, C. Bianca, G. Russo, and S. Motta, "Modeling Biology Spanning Different Scales: An Open Challenge," *BioMed Research International*, pp. 1–9, jan.

[4] F. Pappalardo, M. Pennisi, A. Ricupito, F. Topputo, and M. Bellone, "Induction of T-cell memory by a dendritic cell vaccine: a computational model," *Bioinformatics*, no. 13, pp. 1884–1891, jul.

[5] F. Pappalardo, S. Motta, P.-L. Lollini, and E. Mastriani, "Analysis of vaccine's schedules using models," *Cellular Immunology*, no. 2, pp. 137–140, dec.

[6] A. Palladini, G. Nicoletti, F. Pappalardo, A. Murgo, V. Grosso, V. Stivani, M. L. Ianzano, A. Antognoli, S. Croci, L. Landuzzi, C. De Giovanni, P. Nanni, S. Motta, and P.-L. Lollini, "In silico modeling and in vivo efficacy of cancer-preventive vaccinations." *Cancer research*, no. 20, pp. 7755–63, oct.

[7] M. Pennisi, F. Pappalardo, A. Palladini, G. Nicoletti, P. Nanni, P.-L. Lollini, and S. Motta, "Modeling the competition between lung metastases and the immune system using agents," *BMC Bioinformatics*, no. Suppl 7, p. S13, jan.

[8] F. Pappalardo, S. Musumeci, and S. Motta, "Modeling immune system control of atherogenesis," *Bioinformatics*, no. 15, pp. 1715–1721, aug.

[9] F. Pappalardo, I. M. Forero, M. Pennisi, A. Palazon, I. Melero, and S. Motta, "SimB16: Modeling Induced Immune System Response against B16-Melanoma," *PLoS ONE*, no. 10, p. e26523, oct.

[10] M. Pennisi, G. Russo, S. Motta, and F. Pappalardo, "Agent based modeling of the effects of potential treatments over the blood–brain barrier in multiple sclerosis," *Journal of Immunological Methods*, pp. 6–12, dec.

[11] F. Pappalardo, G. Russo, D. Maimone, M. Pennisi, G. Sgroi, G. Alessandro, F. Pappalardo, G. Russo, M. Pennisi, G. Sgroi, G. Alessandro, P. Palumbo, S. Motta, and D. Maimone, "Agent based modeling of relapsing multiple sclerosis : a possible approach to predict treatment outcome," *2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pp. 1380–1385, 2018.

[12] F. Pappalardo, E. Fichera, N. Paparone, A. Lombardo, M. Pennisi, G. Russo, M. Leotta, F. Pappalardo, A. Pedretti, F. De Fiore, and S. Motta, "A computational model to predict the immune system activation by citrus-derived vaccine adjuvants," *Bioinformatics*, no. 17, pp. 2672–2680, sep.

[13] M. Pennisi, G. Russo, S. Ravalli, and F. Pappalardo, "Combining agent based-models and virtual screening techniques to predict the best citrus-derived vaccine adjuvants against human papilloma virus," *BMC Bioinformatics*, no. S16, p. 544, dec.

Figure 1. Total (red lines), Dead (yellow lines) Infected (green lines) and Necrotic (dark green lines) Alveolar Macrophages mean behavior for a simulation time of 2 years computed over the 30 random digital patients in table 2 absence of treatment. Blue lines represent mean +/- SD