CHIC (Computational Horizons in Cancer) - Perspective from the clinical side

Norbert Graf on behalf of the CHIC Consortium

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement No 600841

I have nothing to disclose

The CHIC Project

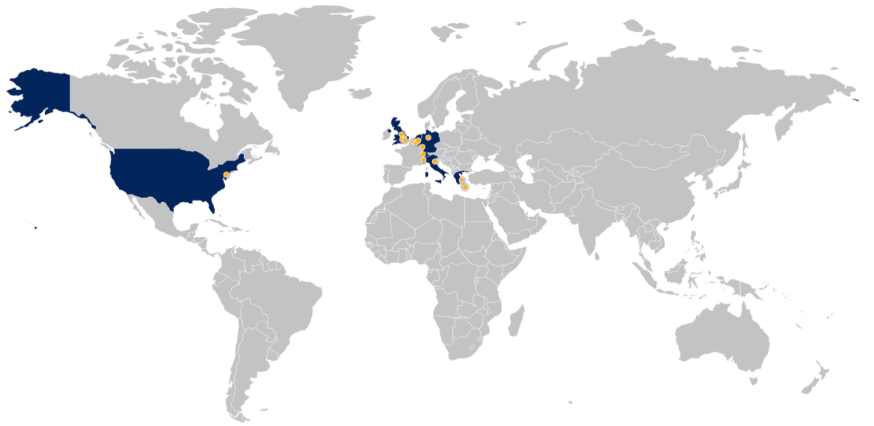
http://chic-vph.eu/

Project Summary

- **Duration**
  - 48 months
    - Start date: April 2013
- **Project funding**
  - 10.582.000,00 €
    - from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement No 600841
- **Full title:**
  - Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology
- **Coordinator**
  - Professor Dr. Georgios Stamatakos
    - Institute of Communication and Computer Systems
      National Technical University of Athens
      In Silico Oncology Group

Consortium

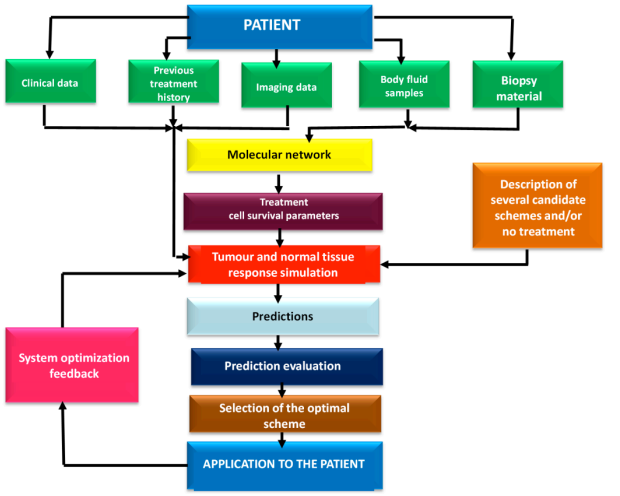
Consortium



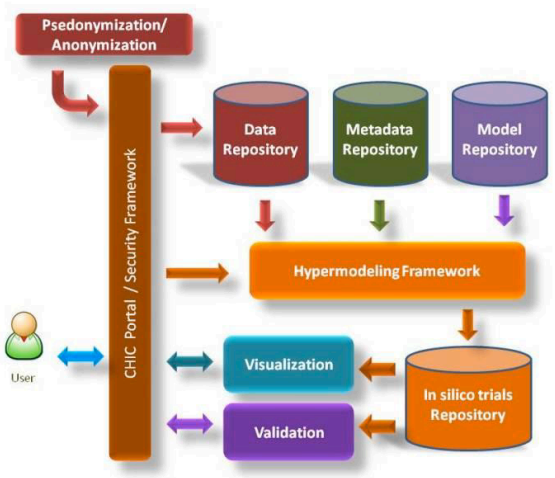
Objectives

- Development of clinical driven tools within a secure infrastructure to support the creation of multiscale cancer hyper-models

Hypermodel based Oncosimulator



Components of CHIC

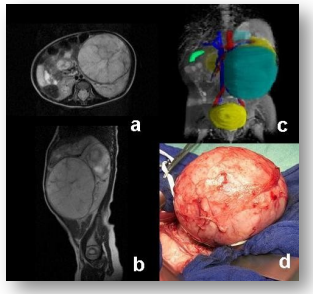


Clinical questions to be answered

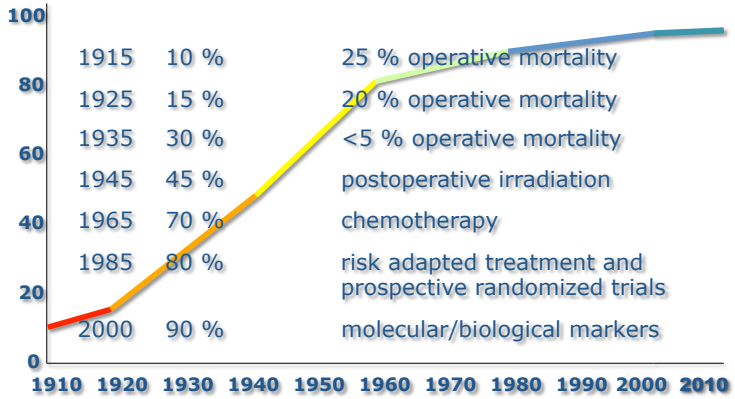
- **Nephroblastoma:**
  - Will a WT respond to preoperative chemotherapy?
- **Glioblastoma:**
  - Will a specific patient benefit from adding Dendritic Cell vaccination (DC vaccination) to the standard treatment for glioblastoma?
- **NSCLC:**
  - Will genetics facilitate the therapy-related clinical decisions
- **Prostate Cancer:**
  - Which patient needs what kind of therapy at what time?

Nephroblastoma

- Most common childhood renal tumour
- Excellent prognosis (> 90% overall survival)
- Rare disease
  - Incidence: 7/1.000.000 children < 15 y
  - 15% metastatic disease
  - 5% bilateral disease
  - Different histological types
  - Heterogeneity of molecular biology



Outcome



SIOP

- Preoperative Chemotherapy
  - Stage
  - Histology
  - Tumor volume (500 ml, GPOH)
  - Response to treatment
  - Age (<6m, >16y)
  - **Blastemal Subtype**

COG

- Primary Surgery
  - Stage
  - Histology
  - Tumor weight (550g)
  - Response to treatment (Stage IV)
  - Age (2y)
  - **LOH 1p & 16q**

Blastemal Subtype (5 - 10%) poor EFS

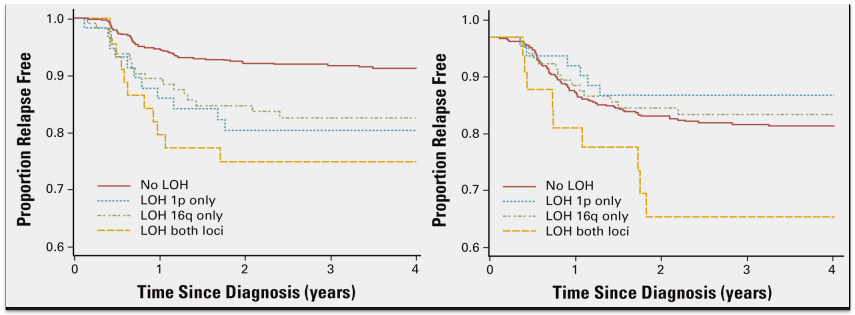
Both groups do need additional molecular markers for a better risk stratification

LOH 1p and 16q (5%) poor EFS

Number of relapses by prior treatment group (SIOP WT 2001)

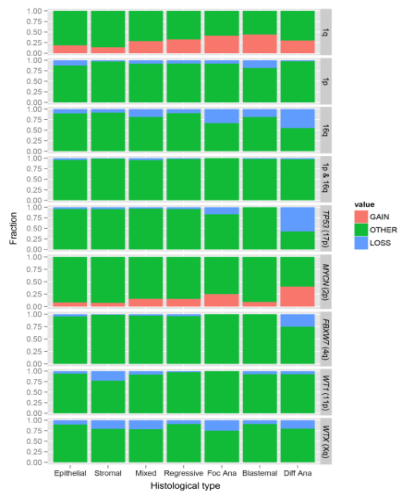
Treatment	No. patients (2yr ~EFS)	No. relapse	% all relapse	No. deaths	% all deaths
VA only	1,785 (90%)	127	38%	16	14%
VA+RT/AVD	603 (88%)	60	18%	13	11%
4 drug arm	225 (75%)	47	14%	29	25%
Stage IV	474 (74%)	103	30%	57	50%
Total	**3,087 (87%)**	337	100%	115	100%

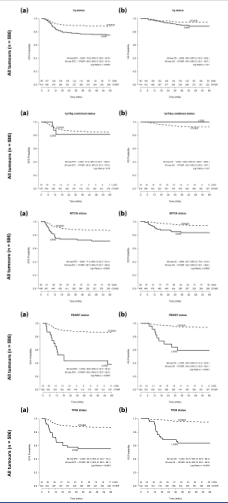
LOH (COG Data)



Paul Grundy et al., JCO 2015

Molecular Biology



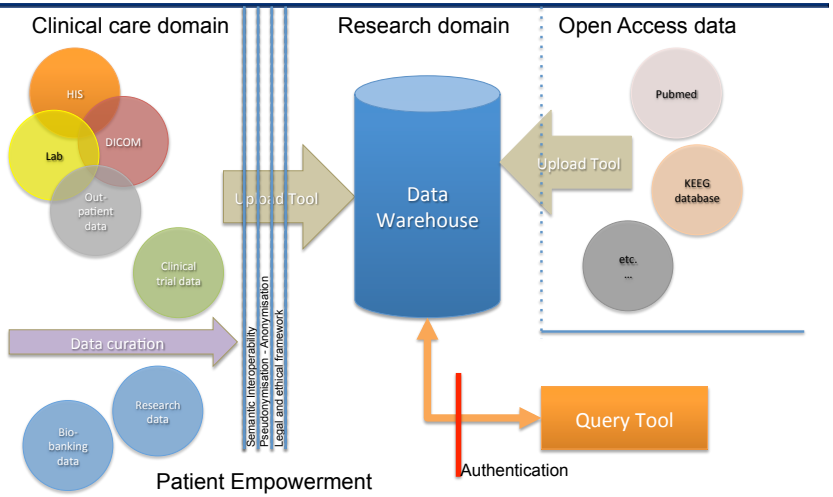


Chagtai T et al.: Gain of 1q as a prognostic biomarker in Wilms tumours treated with pre-operative chemotherapy in the SIOP WT 2001 trial: A SIOP Renal Tumours Biology Consortium Study. JCO, published online, 2016

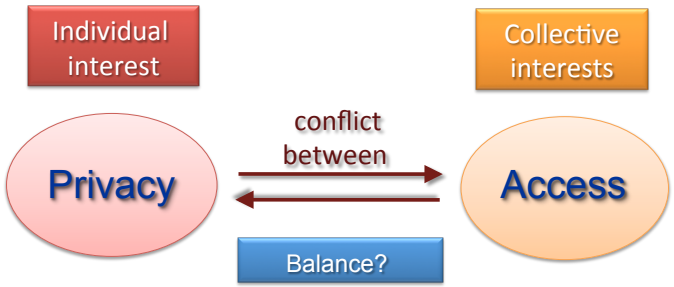
Specific objectives

- **Stakeholders**
  - Clinicians, Patients, Basic Scientists, Bio-informaticians, software developers, data managers...
- **A common security framework**
  - To cater for users Authentication, Authorization, Access control, etc. and support the (pseudo) anonymisation of sensitive patient data
- **Common ontology and semantics mechanisms**
  - For the annotation, publication, discovery of data and the semantic based interoperability and integration),
- **An assortment of new or externally available tools**
  - For visualization, predictive modeling, and knowledge discovery integrated or linked with an IT-infrastructure platform
- **Services for patient empowerment**
  - e.g. for informed consent and linking to biobanks

Data usage for research

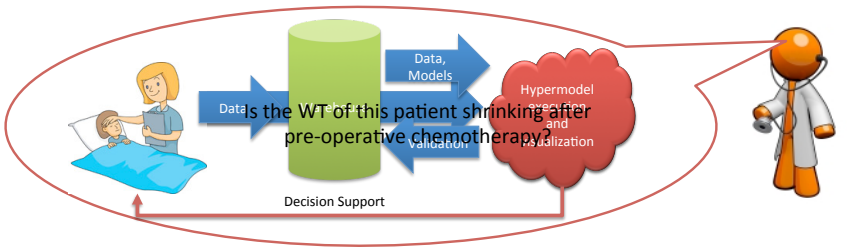


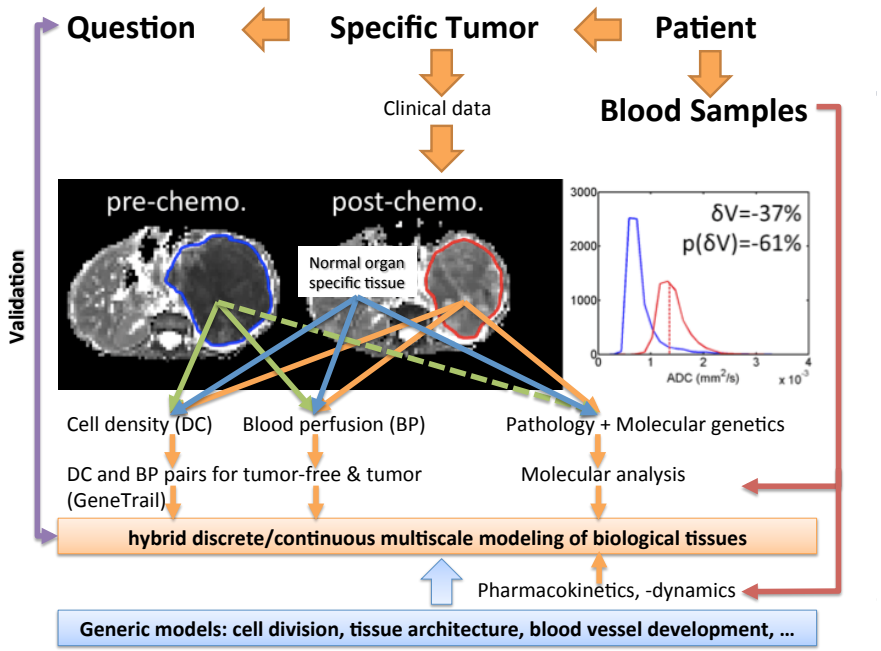
Value conflicts



Clinical perspective

- Two important areas:
  - **Data management** (pre- and post-processing, upload, pseudo/anonymization, storage, …)
  - **Execution of the hypermodel(s)**





Two Hypermodels are developed

- Phenomenological Hypermodel
- Multimodeler Hypermodel

WT Phenomenological Hypermodel

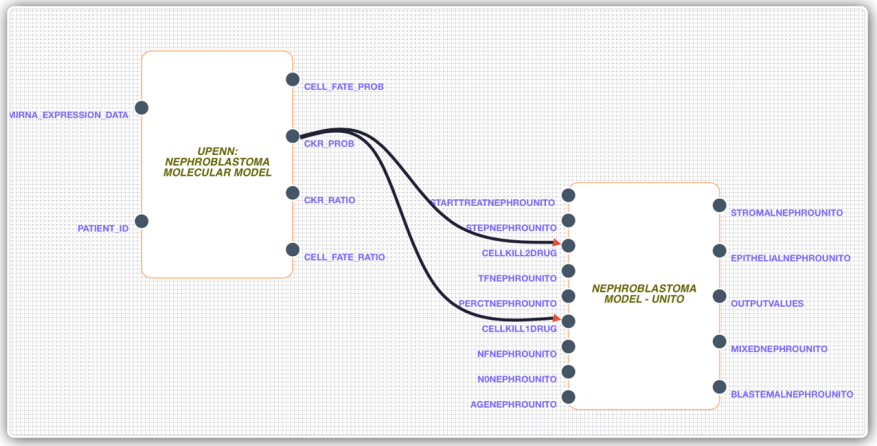
The Phenomenological Universalities (PUN) approach describes growth of a tumour with the following equation:

$$\begin{cases} \dfrac{dN(t)}{dt} = c(t)N(t) \\ \dfrac{dc(t)}{dt} = \displaystyle\sum_{i=0}^{n} \beta_i c^i \end{cases}$$

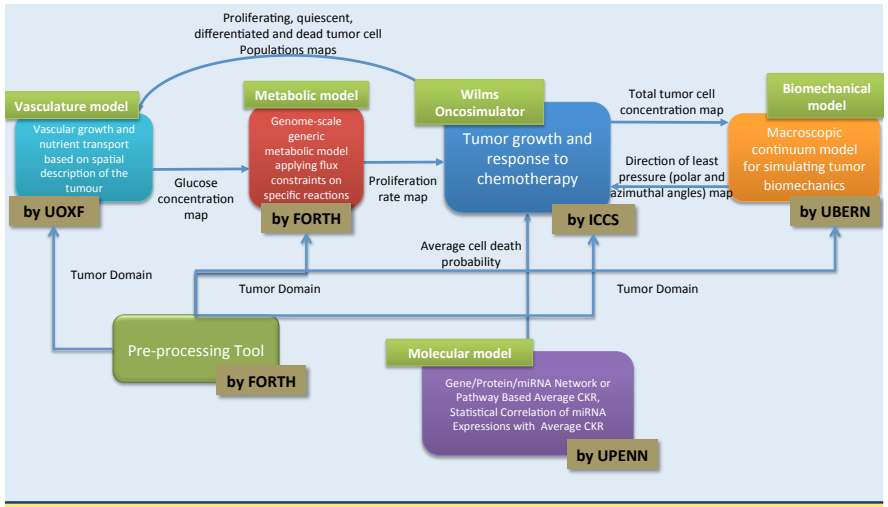
- *k(t) N(t)*

Time , modality and drug –dependent kill rate

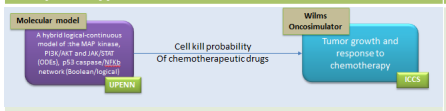
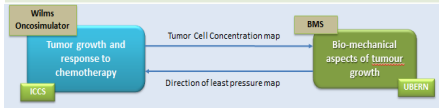
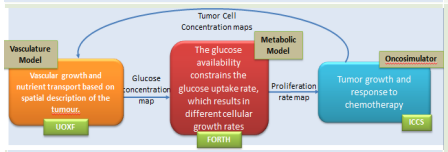
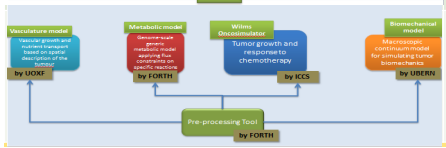
WT Phenomenological Hypermodel



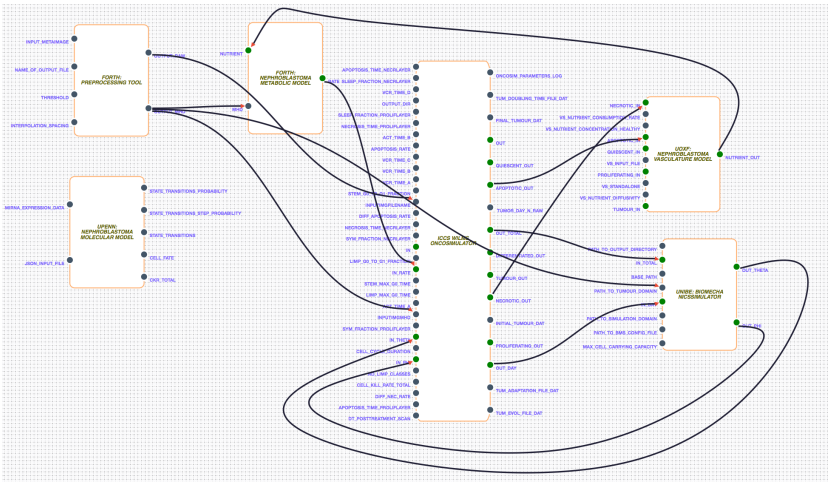
WT Multimodeler Hypermodel



Hypomodels' Coupling

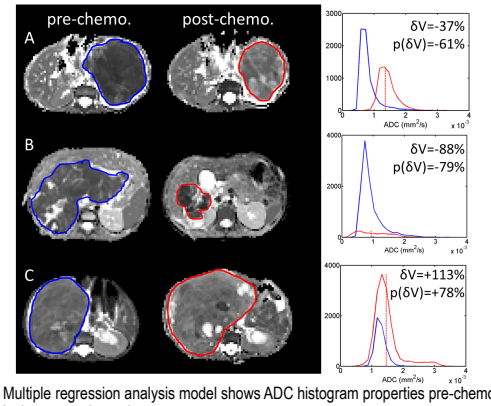
Coupled Hypomodels	Communication
	Molecular Model -> Oncosimulator Parameter Exchanged: Cell kill probability of chemotherapeutic drugs (ACT+VCR) Type: Sequential coupling
	Oncosimulator -> Biomechanics Parameter Exchanged: Tumor Cell Concentration Maps Biomechanics->Oncosimulator Parameter Exchanged: Direction of least pressure maps Type: Iterative coupling (step: 10 sim days)
	Vasculature->Metabolic Parameter Exchanged: Glucose Concentration Map Metabolic->Oncosimulator Parameter Exchanged: Proliferation Rate Map Oncosimulator->Vasculature Parameter Exchanged: Tumor Cell Populations Map TypeIterative coupling (step 10 sim days)
	Preprocessing Tool->Oncosimulator ->Vasculature ->Metabolic ->Biomechanics Parameter Exchanged : Metaimages of tumor area (mhd, raw) Type: : Sequential coupling

WT Multimodeler Hypermodel



CT-response in WT by DWI

- Diffusivity of water molecules (ADC) is a biomarker of cellular density
- ADC histograms measured in 22 Wilms' lesions, before and after chemotherapy
- Chemotherapy-induced response varies across the cohort…



Chemo. induced response

Volume ↓, ADC ↑

Volume ↓, ADC —

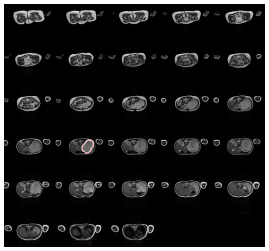
Volume ↑, ADC ↑

Multiple regression analysis model shows ADC histogram properties pre-chemo. may predict change in cellularity and volume of lesions post-chemotherapy.

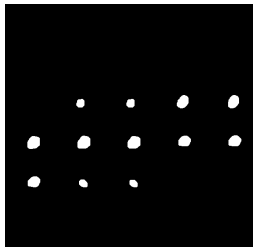
Presented at the annual meeting of the British Chapter of the ISMRM, September 2012, provided by Prof. Kathy Pritchard-Jones

Segmentation of the Complete Tumor boundary

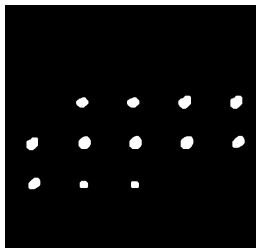
- The graph cut algorithm, which includes a kernel induced segmentation functional is used to extract the complete boundary of the tumor in a 3D image data.



Input image with user selected ROI in red



Segmented tumor boundaries

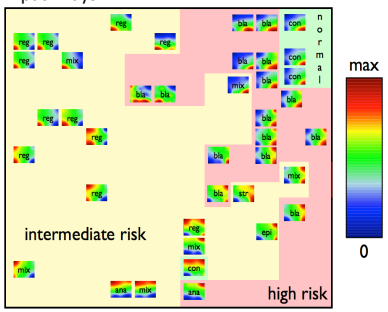


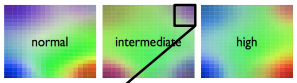
Manually Segmented tumor boundaries

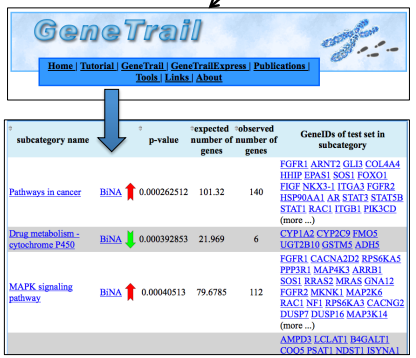
SOMs: miRNA landscape in WT

Self **O**rganizing **M**aps:

- expression data of 1204 miRNAs merged to 400 „meta"-miRNAs
- visualization of different expression profiles in WT subtypes
- *in silico* pathway analysis to identify underlying cancer pathways







20 most significant miRNA in blood of WT before treatment

MiRNA	Log median Wilms	Log median Control	Log difference	Fold	Ttest	Ttest adj	AUC
hsa-miR-20a	10.124	12.929	-2.805	-6.988	7.01E-012	5.94E-009	0.977
hsa-miR-20b	10.057	12.410	-2.353	-5.108	2.49E-011	1.05E-008	0.984
hsa-miR-766	10.079	8.494	1.585	3.000	2.63E-009	3.29E-007	0.033
hsa-miR-144*	7.994	9.524	-1.531	-2.889	2.40E-009	3.29E-007	0.953
hsa-miR-144	8.967	11.506	-2.540	-5.815	2.71E-009	3.29E-007	0.954
hsa-miR-106a	11.506	13.639	-2.132	-4.385	2.14E-009	3.29E-007	0.950
hsa-miR-1246	6.007	2.737	3.270	9.649	1.36E-009	3.29E-007	0.059
hsa-miR-197	11.205	8.888	2.317	4.984	4.33E-009	4.59E-007	0.055
hsa-miR-224	6.403	3.745	2.658	6.310	5.20E-009	4.90E-007	0.043
hsa-miR-18a	9.168	11.205	-2.037	-4.104	6.75E-009	5.72E-007	0.962
hsa-miR-93	10.830	12.766	-1.936	-3.825	8.50E-009	6.55E-007	0.935
hsa-miR-17	11.839	13.273	-1.434	-2.702	1.20E-008	8.48E-007	0.962
hsa-miR-18b	7.044	8.901	-1.856	-3.621	2.02E-008	1.32E-006	0.982
hsa-miR-126	8.320	11.425	-3.104	-8.601	3.38E-008	2.05E-006	0.944
hsa-miR-520d-3p	4.497	2.134	2.363	5.145	4.13E-008	2.33E-006	0.061
hsa-miR-1305	4.877	6.898	-2.021	-4.058	5.14E-008	2.60E-006	0.966
hsa-miR-373	4.819	1.976	2.843	7.173	5.22E-008	2.60E-006	0.064
hsa-miR-106b	13.004	14.104	-1.100	-2.143	6.24E-008	2.94E-006	0.938
hsa-miR-1204	5.360	3.048	2.312	4.967	1.21E-007	5.42E-006	0.078
hsa-miR-374a	6.473	8.483	-2.010	-4.029	1.39E-007	5.91E-006	0.934

The 20 most significant miRNAs when comparing Wilms patients before therapy to healthy controls. Down-regulated fold-change is indicated by negative values, up-regulated fold-change is indicated by positive values.

Schmitt J et al.: Treatment-independent miRNA signature in blood of Wilms tumor patients. BMC Genomics 2012, 13:379

Nephroblastoma Demonstrator Specifics

Model Inputs:

$$D\nabla^2 c - \lambda P c + \rho V(c_n - c) = 0$$

Glucose Diffusivity
Literature [1]

Glucose Consumption Rate
Modifiable by User/
Default Literature Value [1]:
vs_nutrient_consumption_rate

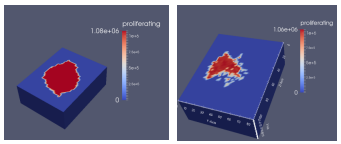
Vascular Delivery Efficiency
User Chosen/Fit to Data

Glucose Concentration in Well Perfused Tissue
Value Used In Metabolic Model

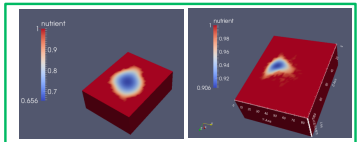
Model Output:
Normalized glucose concentration $^{c}/_{c_n}$

[1] T. Roose et al. (2007), SIAM Review, 49.

Spatial Distribution of Cells
From Growth Hypomodel



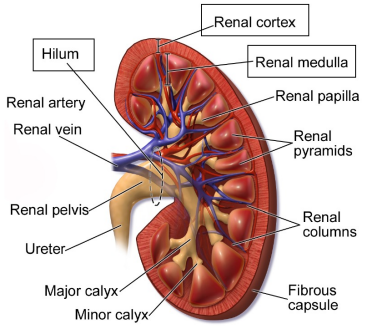
Hypermodel output: 3d slice through the tumour region (red)



Application to Nephroblastoma

Kidney – mechanical properties

	E [kPa]	v
Renal Cortex	4.7	0.45
Renal medulla	7.7	0.45
Renal Hilum	3.4	0.45



Simulation assumptions

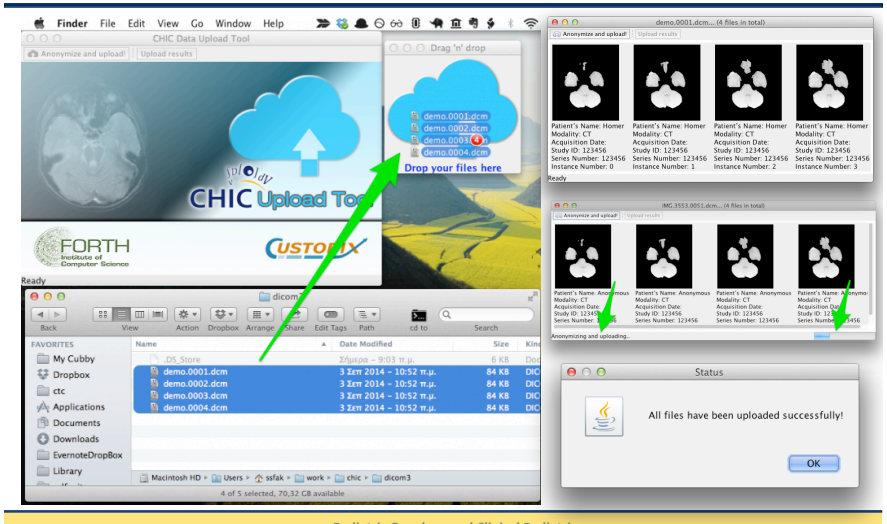
- Mechanical Tissue Properties:

	E [kPa]	v
Healthy kidney (avg)	5.3	0.45
Nephroblastoma	20.0	0.45
Spine	10000.0	0.3
Other tissue	5.0	0.45

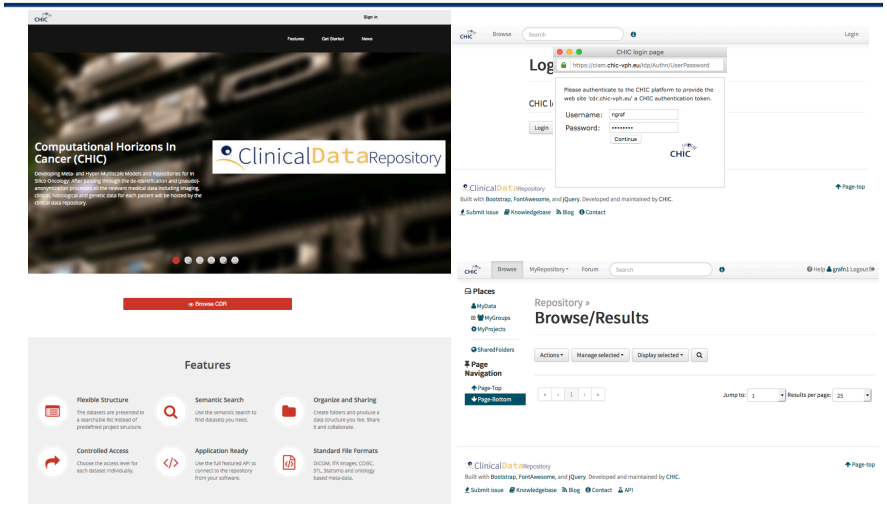
- Boundary Conditions:
  - Nodal positions of domain boundary fixed

[domain boundary = margin of 'other tissue' surrounding kidney & tumour]

Data Upload Tool

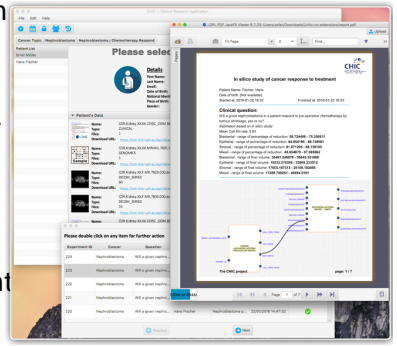


https://cdr.chic-vph.eu/

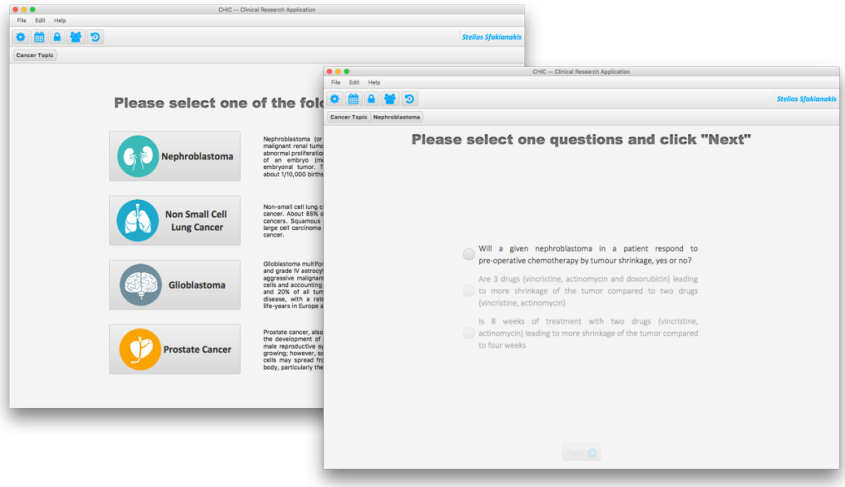


Clinical Research Application Framework (CRAF)

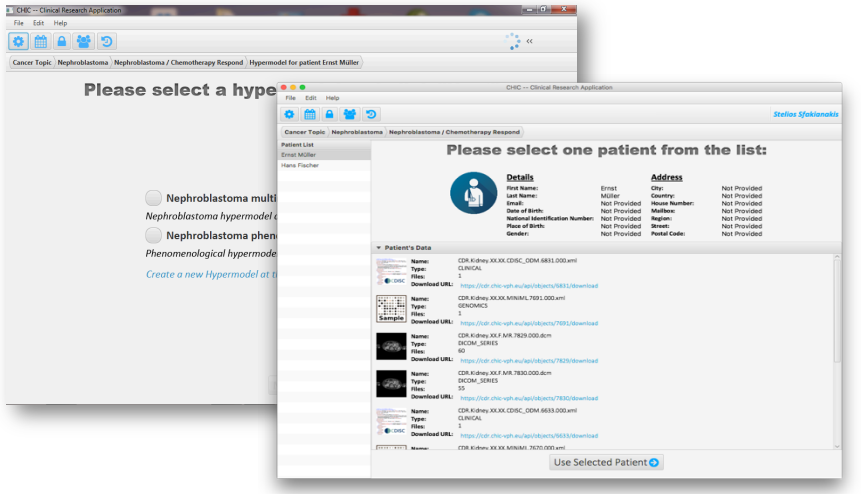
- The Clinical Research Application Framework ("CRAF") is the central component to support the clinicians to perform CHIC-enabled clinical research in their premises
- CRAF coordinates the functionality of other CHIC components, such as the Data Upload tool for uploading patient data to the CHIC cloud, and the Visualization and image processing tools



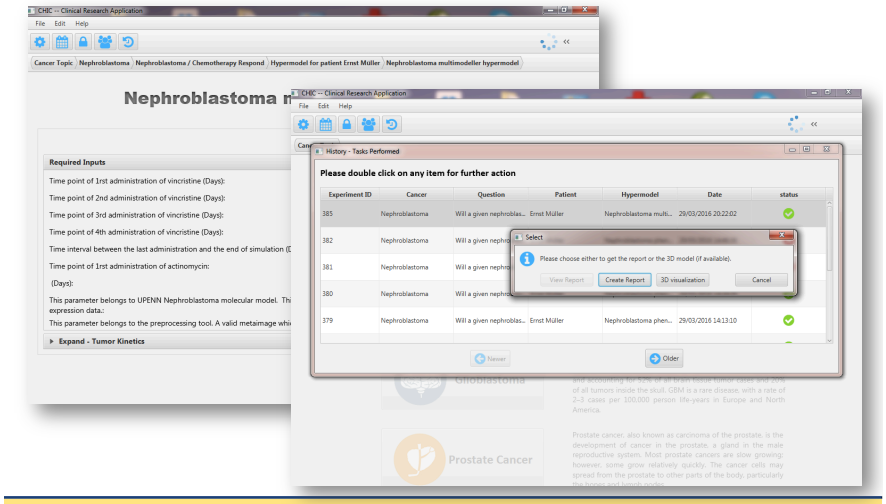
CRAF



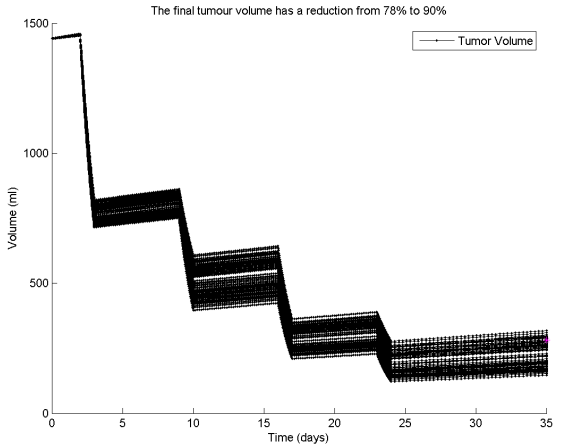
CRAF



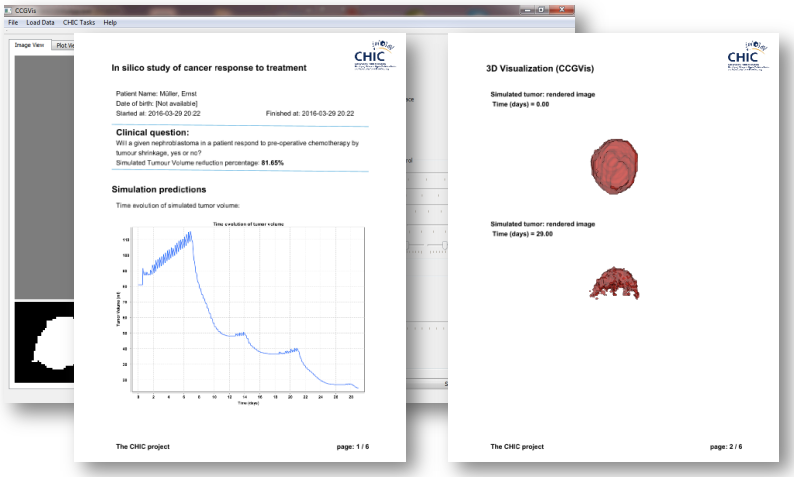
CRAF



WT Phenomenological hypermodel



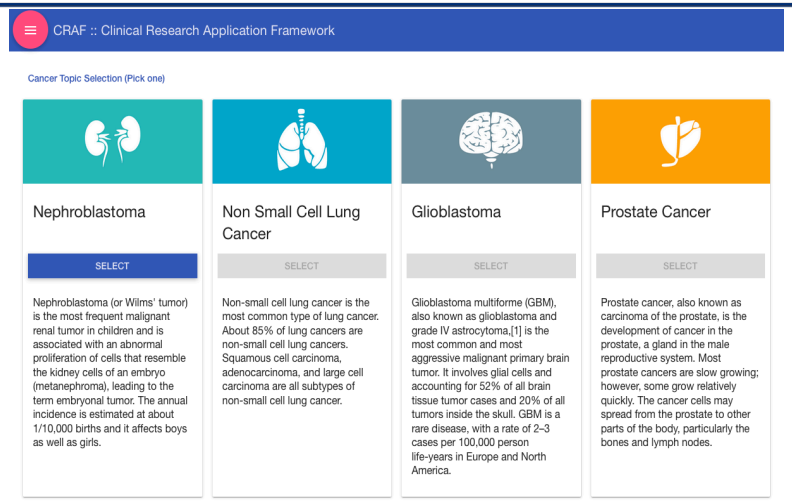
WT Multimodeller Hypermodel



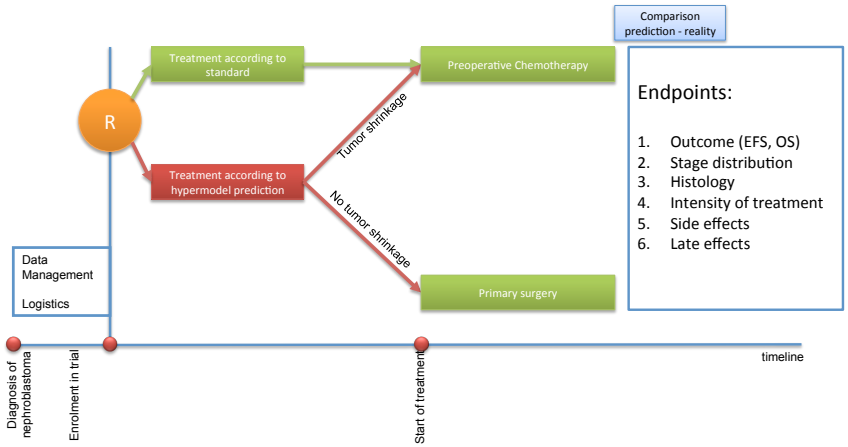
Perspectives

- Retrospective Evaluation
  - 100 Patients from GPOH with WT to compare prediction with the reality and refine the hypermodels using machine learning
- Prospective Evaluation
  - New patients entered in UMBRELLA to compare prediction with reality and fine tune the hypermodels

CRAF



Designing a randomized clinical trial with ethical approval



Tools and Evaluation

Evaluation