Integrative Biomedical Research
Design Patterns, HPC, Semantic Interoperability and Grid

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Biomedical Informatics Consortia
What are these guys up to anyway?
Example: caBIG Organization Structure

caBIG Oversight

General Contractor

Clinical Trials
Integrative Cancer Research
Tissue Banks & Pathology Tools
Imaging

Architecture

Vocabulary & Common Data Elements

Open to all, not just funded participants.
190 institutions, 2000 people involved thus far.

Strategic Working Groups
“Big” Design Patterns for Translational Research

- Deep Integrative Analyses
- Multiscale Investigations that encompass genomics, epigenetics, (micro)anatomic structure and function
The Reynolds Study

- Prospective clinical research study – Deep Integrative Clinical Analysis
- Large subject cohort (~ 1,200) at high risk for sudden cardiac death
- All have:
  - CAD
  - LV dysfunction
  - received ICD placement
- Multi-scale data from each patient
- Challenge – discover biomarkers predictive of high risk
- Test biomarkers on novel (currently ~500) subject population
Data Analysis and Exploration: Multi-Scale Cardiovascular Data

- Investigate genotype-phenotype characteristics among a subset of patients in the Reynolds study
- Combine features across different levels of biological organization
  - SNP
  - mRNA
  - Protein
  - Imaging
  - Electrophysiology (ECG)
  - Clinical

- Analyze data
- Filter and integrate different data types
CVRG: Primary Aims

- Support collaborative cardiovascular research
  - Integrative data analysis using heterogeneous, distributed resources
  - Securely share data and analysis methods with collaborators
  - Establish common set of services, data sources, vocabulary and common data elements for cardiovascular research community
  - Leverage caGrid, caBIG™, BIRN
  - Initial driving application is the Reynolds study -- an example of deep integrative clinical analysis
  - PI – Rai Winslow PhD, Center spans Hopkins, Emory, UCSD, Ohio State
Biomedical Informatics Services

- Security
- Semantic interoperability
- Data structure interoperability
- Interoperability with existing standards (e.g. HL-7, DICOM)
- Ability to compose services to create application
- Ability to efficiently invoke HPC services
- Efficient and expressive federated query
Image Management Workflow

(Virtual) PACS → Functional Image Analysis

AIM Annotation Database
CT Cardiac Shape Analysis Workflow

Heart Images (Human CT) → Isotropic preprocessing and segmentation to isolate left ventricle. → Affine Registration

- Isolating left ventricle
- Generating representative shape model (ES & ED)
- Registering heart images to the representative shape model.
- Statistical analysis of transformation vector fields using:
  - Principal Component Analysis (PCA)
  - Hotelling T-square

Generate Templates for end-systole and end-diastole phases → Register Heart Images to template and perform LDDMM mapping → Statistical Analysis (Principal Component Analysis)
Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular analysis
I SPY TRIAL Design

Neoadjuvant Chemotherapy  →  Surgery

Serial Core Biopsies  Serial MR Imaging

Outcomes
• Residual Disease
• Recurrence
Surgery RT
Anthracycline & Taxane
Clinical Study
Tam if ER+

Classification of Morphologic Pattern/Volume Response
Tissue: Core or Surgical

Serum markers, proteomics

Expression Array
H&E, IHC, FISH

Genome location
1p 1q 3 5 7 9 11 13 15 17 19 21 X

CGH

Fig. 1. Proteomic spectra. Representative expression and copy number abundance (in blue).

Gene expression

Pathology Coordinated Review

Multiheaded Microscope
cAMicroscope

National Heart Lung and Blood Institute

CVRG
Computer-assisted Histopathology

- Analyze images by computer
- Analyze the whole tissue, several slides
- Provide quantitative information to the pathologist
- Reduce inter- and intra-reader variability

Morphological characterization of tissue used for prognosis

Neuroblastoma – Shimada Classification (Gurcan-OSU, Shimada – LA Children’s)
caMicroscope parallel processing
caGrid/caOS/DataCutter

Whole-slide image

Image tiles (40X magnification)

Parallel Classification

Processor 1

Processor N

Assign classification labels

- Label 1
- Label 2
- background
- undetermined

Hiro Shimada CHLA, Metin Gurcan OSU
Example Algorithm Results:
Neuroblastoma Grade of Differentiation

UD: Undifferentiating
PD: Partially differentiating
D: Differentiating
Design Pattern Driven Requirements

- **Semantics**: Design template involves deep integration of many types of information to synthesize knowledge
- **Interoperability**: Information drawn from commercial/enterprise systems e.g. health information records, PACS, Lab information systems, as well as genetic, genomic, epigenetic, microscopy databases
- **HPC requirements arise from many sources**: natural language processing, whole genome analyses, coordinated analysis of multiple types of molecular, image data
Design Pattern Driven Requirements

- Composition of computationally modest and HPC services – caGrid, caOS, DataCutter
- Composition of services written in multiple languages running in varied environments – Wings/Pegasus/Taverna/Introduce/gRAVI
- Workflow engines capable of efficient inter-service large scale data transfer, security delegation – New caOS Workflow Engine
- Libraries of optimized components/services – GPU/Cell DataCutter libraries for image analysis
- Integrated analysis/human review may require soft real time response
Design Pattern Driven Requirements

- **Flexibility**: ability to accommodate different data formats, different semantic classifications
- **Interoperability**: composition of caGrid, myGrid, BIRN, CVRG and unaffiliated web services
- **Goal of caGrid Roadmap** – plug and play workflow scripting environment, service level execution environment, fine grained execution environment
  - e.g. Taverna, caGrid, caOS, DataCutter;
  - Wings, Pegasus, Condor, DataCutter;
  - WEEP, caGRID, MPI
“Big” Design Patterns for Translational Research

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Tumor Microenvironment

- Cancer is a complex phenomenon
- A tumor is an organ
- Structural and functional differentiation within tumor
- Molecular pathways are time and space dependent
- “Field effects” – gradient of genetic, epigenetic changes
- *Experiments to elucidate integrate microscopy, high throughput genetic, genomic, epigenetic studies, flow cytometry, microCT, nanotechnologies …*
- *Simulation is next frontier*

Tumors are organs consisting of many interdependent cell types

- *From John E. Niederhuber, M.D. Director National Cancer Institute, NIH*
Tumor Microenvironment

Slide Scanning

The ScanScope T108 Slide Scanning System. An entire microscope slide is rapidly scanned by the ScanScope®, creating a virtual slide that is viewed on a display monitor. The ScanScope® computer controls the ScanScope® using Aperio’s console software.

Ducts

Imaging Team led by Raghu Marchiraj
Kun Huang OSU
“GIS type service”: Semantic Annotation and Spatial Reasoning

Ontology
- Endothelial cells touch blood vessel lumen
- Protein C is expressed only in endothelial cells

Instance Data
- Region A is a cell (from image analysis)
- Region A expresses protein C (from molecular assay)
- Region B (from expert markup)

Spatial Rule
- touches(Region B, Region A) – algorithmically evaluates to true

Spatial and Ontological Inference
- Region A is an endothelial cell
- Region B is a blood vessel
Extra-embryonic function of Rb is essential for embryonic development and viability

Lizhao Wu¹, Alain de Bruin¹, Harold I. Saavedra¹, Maja Starovic², Anthony Trimboli¹, Ying Yang³, Jana Opavska¹, Pamela Wilson¹,⁴, John C. Thompson⁴, Michael C. Ostrowski⁴,⁵, Thomas J. Rosol⁵,⁶, Laura A. Woollett⁷, Michael Weinstein⁴,⁵, James C. Cross², Michael L. Robinson³,⁵,⁸ and Gustavo Leone¹,⁴,⁵

The retinoblastoma (Rb) gene was the first tumour suppressor identified¹. Inactivation of Rb in mice results in unscheduled cell proliferation, apoptosis and widespread developmental defects, leading to embryonic death by day 14.5 (refs 2–4). However, the actual cause of the embryonic lethality has not been fully investigated. Here we show that loss of Rb leads to excessive proliferation of trophoblast cells and a severe disruption of the normal labyrinth architecture in the placenta. This is accompanied by a decrease in vascularization and a reduction in placental transport function. We used two complementary techniques—tetraploid aggregation and conditional knockout strategies—to demonstrate that Rb-deficient embryos supplied with a wild-type placenta can be carried to term, but die soon after birth. Most of the neurological and erythroid abnormalities thought to be responsible for the embryonic lethality of Rb-null animals were virtually absent in rescued Rb-null pups. These findings identify and define a key function of Rb in extra-embryonic cell lineages that is required for embryonic development and viability, and provide a mechanism for the cell autonomous versus non-cell autonomous roles of Rb in development.
Wild vs Mutant

Wild type - Labyrinth neat, well-ordered, maternal blood sinusoids and trophoblasts evenly dispersed among fetal blood cells.

Mutant - Trophoblasts grow wildly, clump together and disrupt fetal and maternal cells layers necessary for proper embryonic growth.
Wild Type vs Mutant: Analysis of Entire Placenta

3-D Reconstruction

Quantitative tissue analysis

![Images of 3-D reconstructions showing differences between Wildtype (Rb\textsuperscript{+/4}) and Mutant (Rb\textsuperscript{-/-}) placenta.]

![Bar chart showing intravascular fraction comparison between Wildtype and Mutant littermates.]

- Intravascular Fraction
  - Littermate 1: Wildtype 31.86%, Mutant 21.99%
  - Littermate 2: Wildtype 20.22%, Mutant 12.01%
  - Littermate 3: Wildtype 23.01%, Mutant 16.68%
Design Pattern Driven Requirements for Multiscale

- Complex, hierarchical annotation of microanatomic structures; molecular composition: “ducts, a specific duct, epithelial cells surrounding a specific duct, a particular epithelial cell in the neighborhood of a particular duct, the nucleus of a specific epithelial cell in the neighborhood of a particular duct …”
- Spatial/semantic queries: What is the morphological/molecular effect on cell type 1 if we make a genetic change in cell type 2
- Algorithm annotation and composition: Interoperability critically dependent on semantic modeling of application domain
- Interplay between spatial and molecular data underlies increasing fraction of biomedical research studies – “GIS type” service
When are we going to get serious about simulation?
Data and Analytic Services – Present and Future

- Easy integration of existing database systems, High-performance Grid Nodes, multi-core systems, on-demand computing, data intensive computing, parallel database and file systems.

Workflows and Orchestration

- Interoperability between different workflow execution environments; hierarchical workflow systems; HPC and large scale data support

Federated Query

- Semantic, federated, spatial query support

Semantic Infrastructure

- Semantic annotations for services, relationship between semantics and data structures, systematic curation vs community freedom, semantic query support.

Security

- Security middleware support for complex organizations, complex workflows. Compliance with regulatory guidelines
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