Ontologically Computing the Spread of Tumor Cells

Ira J. Kalet, Ph.D.
Professor Emeritus, Radiation Oncology
joint with Medical Education and Biomedical Informatics

University of Washington
Seattle, Washington USA

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Collaborators and Contributors

Cornelius Rosse	Professor, Biological Structure
Jim Brinkley	Professor, Biological Structure
Onard Mejino	Senior Scientist, Biological Structure
Matthew Lease	Computer Science and Engineering, BS, 1999
Jonn Wu	Radiation Oncology Fellow, 1999
Silvia Pessah	Biomedical and Health Informatics, MS, 2002
Jerry Barker	Radiation Oncology Resident, 2000-2002
Mary Austin-Seymour	Professor, Radiation Oncology
Mark Whipple	Assistant Professor, Otolaryngology
Noah Benson	Biomedical and Health Informatics, PhD student
Linda Shapiro	Professor, Computer Science and Engineering
Chia-Chi Teng	Electrical Engineering, PhD 2007
Vania Wang	Computer Science, undergrad student
Casey Overby	Biomedical and Health Informatics, PhD student

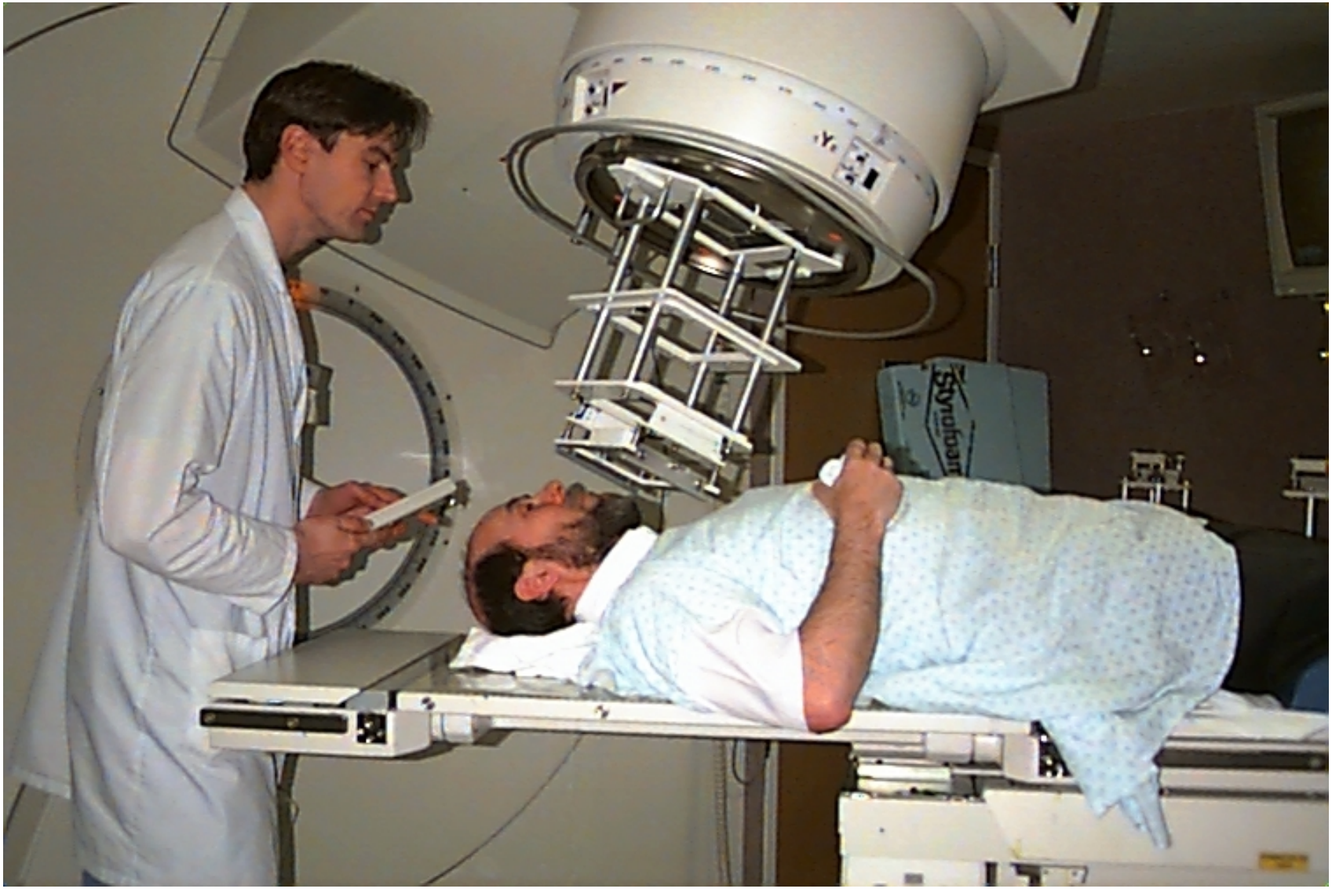
Overview

- The transformation of biology and medicine
- Radiotherapy Planning
- The Prism Project
- The Clinical Target Volume project
  - A theory of regional metastasis
  - The UW Foundational Model of Anatomy (FMA)
- A Model of Tumor Spread
  - Computational and Mathematical Model
  - Mapping an Atlas to Individuals

Biology and Medicine: a new era

- Biology is experiencing an explosion of data and chunks of knowledge.
- Medical practice is rapidly generating huge amounts of clinical data, laboratory data, images, and more.
- Three approaches to this are possible:
  1. organizing the data with tags and structure to make it widely accessible and enable integration (the Semantic Web),
  2. searching the data for patterns (data mining, knowledge discovery), and
  3. constructing computation based theories from what is known, to predict what is yet to be observed.

A typical radiotherapy machine setup



Radiation therapy planning

1. Gather clinical and physical data
2. Decide general approach
3. Select radiation type(s)
4. Use computer simulation to configure radiation beams
5. Verify feasibility

Repeat steps as necessary. . .

The Prism Project

Objectives:

- clinically useful 3-d treatment planning
- a base for research in treatment planning strategy
- a model of software engineering practice
  - rapid development
  - modularity
- a testbed for software research

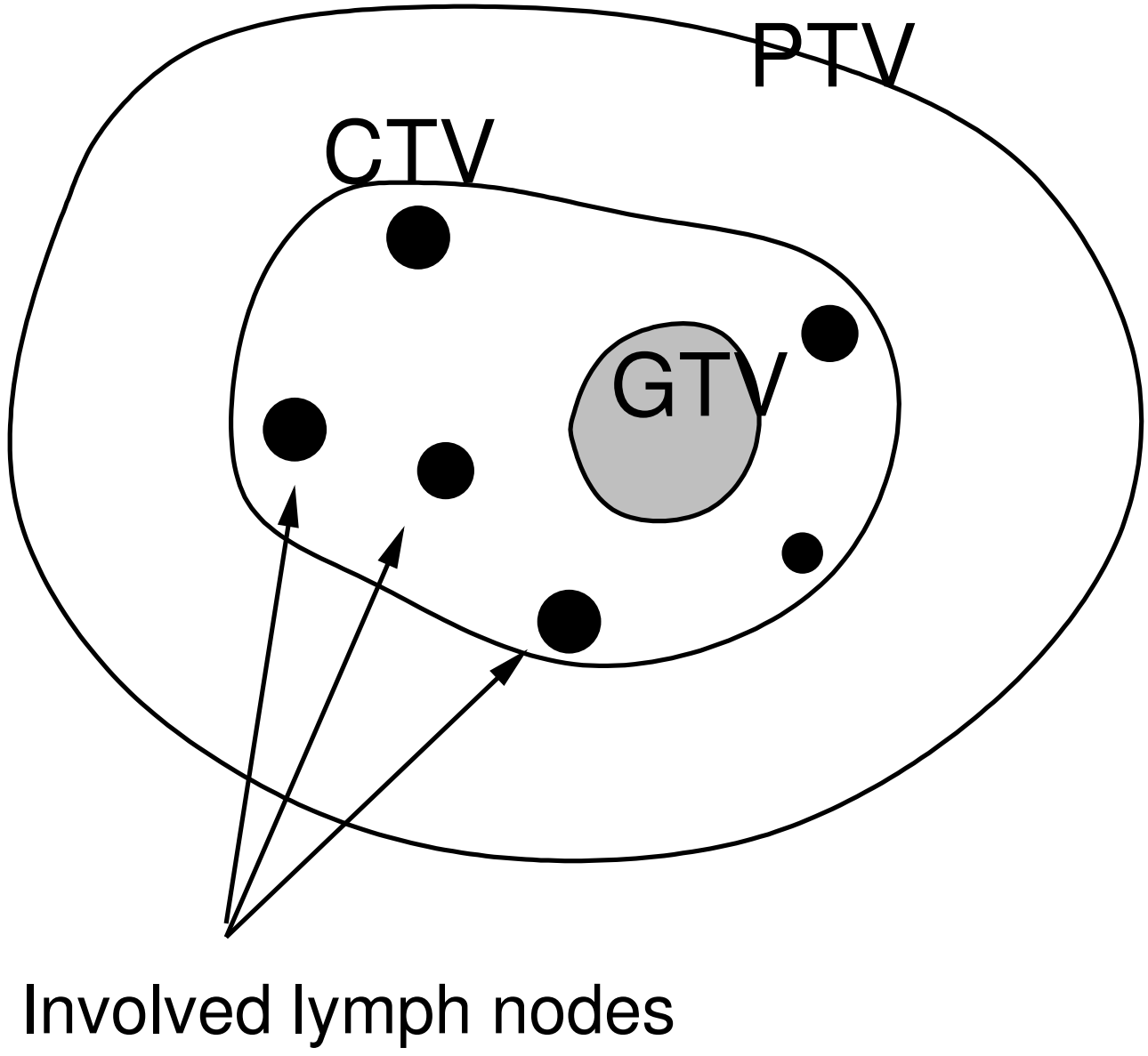
The Prism System

- is written in Common Lisp
- uses the X window system
- is independent of hardware and operating system platforms
- is available for research and experimentation

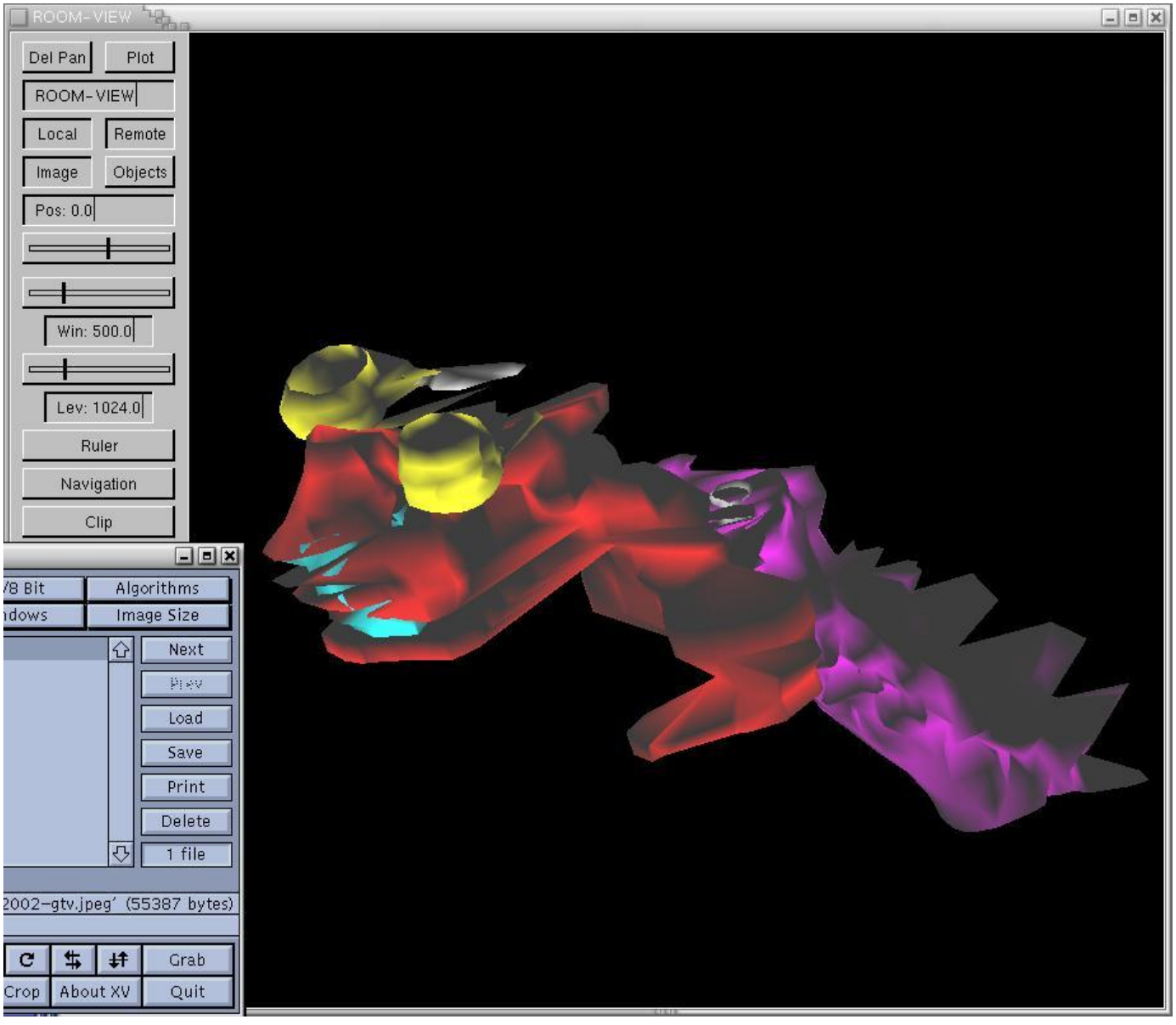
Contributors to the Prism Project (code and/or documentation)

- Jonathan Jacky, Jonathan Unger, Bob Giansiracusa, Mark Phillips, Paul Cho, Sharon Hummel, Juergen Meyer, Radiation Oncology
- David Notkin, Christine Sweeney, Brian Lockyear, Mark Niehaus, Witold Paluszynski, Craig Wilcox, Dat Nguyen, Kevin Sullivan, CSE
- John MacDonald, Statistics
- Lee Zeman, Jenny Sager, Matthew Lease, summer undergrad students
- Sharon Kromhout-Schiro, Gavin Young, Bioengineering
- Andrew Simms, Tung Le, Eric Webster, Biomedical and Health Informatics
- Drora Avitan, Ben-Gurion University, Israel

Defining the GTV, CTV and PTV



CTV defined from a CT image set



Predicting lymphatic spread of tumor cells

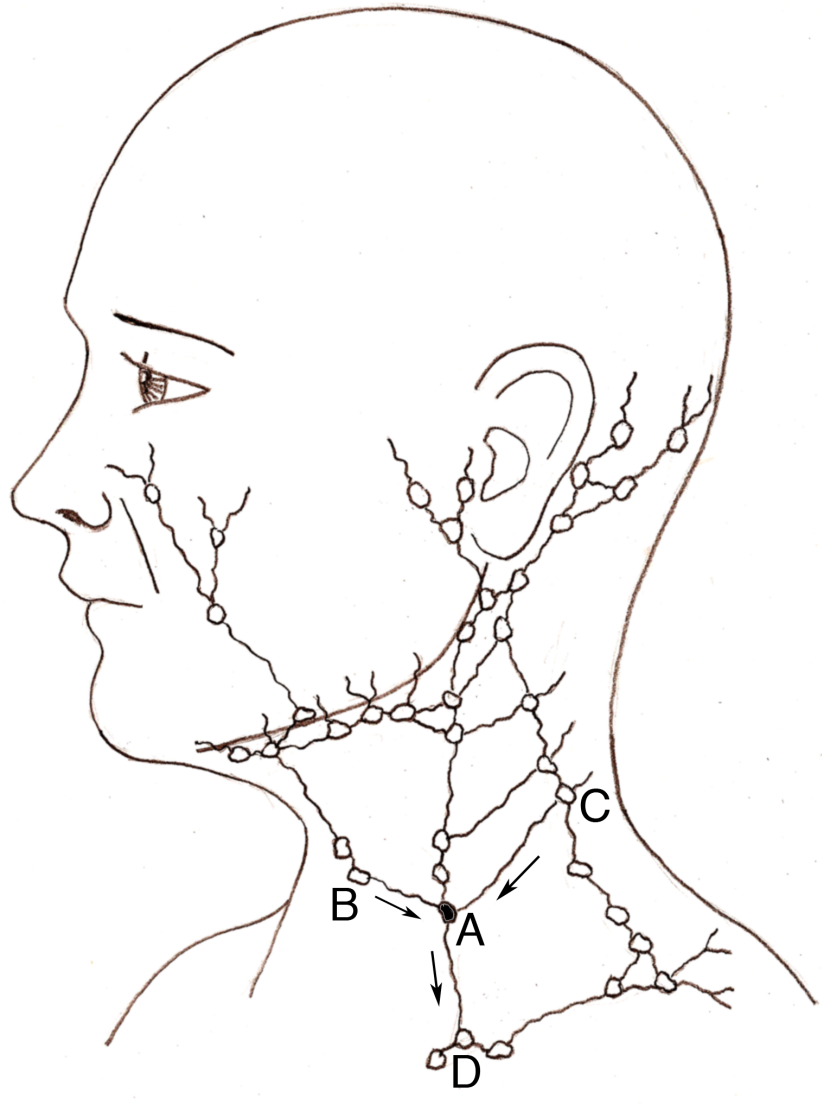
Case description: Adenoid cystic carcinoma in the nasal cavity, behind the nasal vestibule, between the left upper turbinate and the nasal bone.

Problem: Which lymph nodes are likely to have tumor cells? Where are they?

Problem: tumor cells migrate along nerves in this region, so we also need to include the nerves in the target, but they also cannot be seen on the patient's CT scan.

Can the Foundational Model of Anatomy (FMA) knowledge resource tell us which are the primary lymph nodes and nerve paths in this location, and then can we predict how far the cells will go?

Lymphatic chains and nodes in the head and neck



Ingredients of the CTV theory

The theory is tested by comparing its predictions with surgical data.

- Starting from tumor location, compute lymphatic drainage paths from the FMA.
- For each path, compute probabilities of downstream travel.
- For each lymph node group, compute the aggregate probability of metastasis according to the distance.

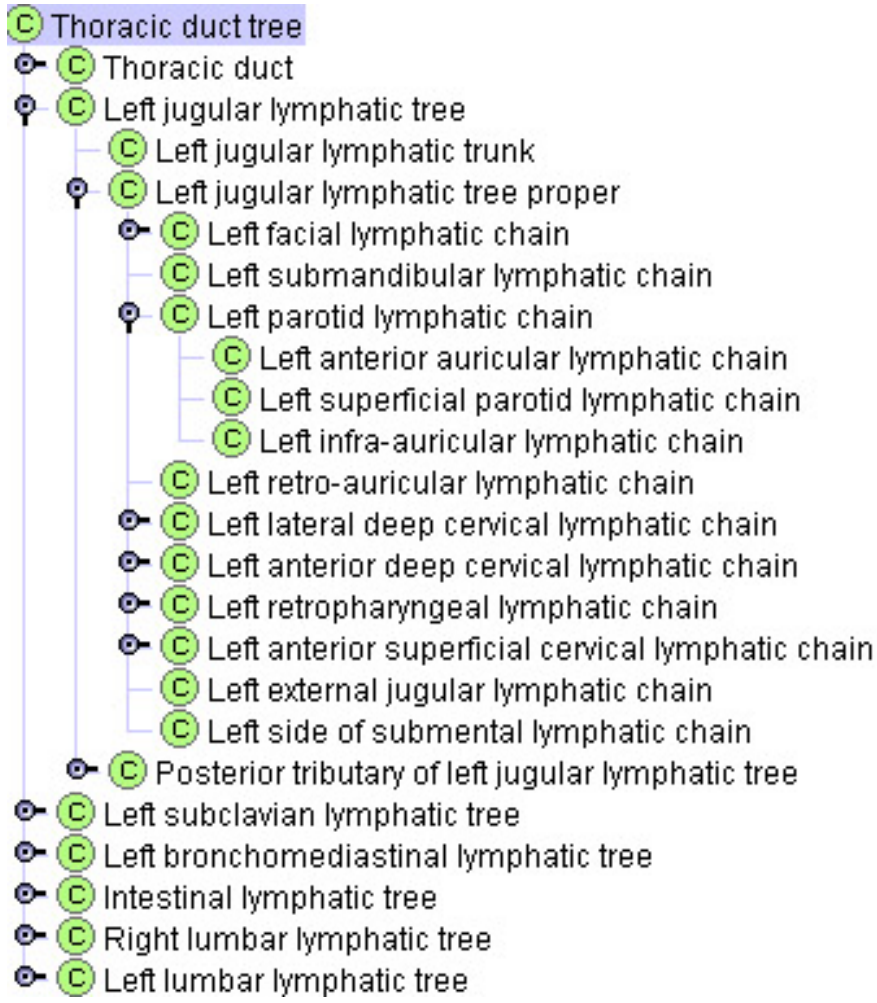
Conceptual Overview of the FMA

The FMA describes anatomical (structural) entities and relationships from subcelluar (macromolecular) structure to body parts and organ systems. Its components are:

- Anatomical taxonomy (At): classification hierarchy, with shared characteristics and distinctive ones
- Anatomical Structural Abstraction (ASA): part-whole and spatial relationships
- Anatomical Transformation Abstraction (ATA): morphological transformation during prenatal development and postnatal life cycle
- Metaknowledge (Mk): principles, rules and definitions

The lymphatics in the FMA

A Protégé class browser display shows the regional parts of a lymphatic tree, a subdivision of the lymphatic system.



Current Scale of the FMA

- 72,000 classes
- 115,000 terms
- 168 relationship types
- over 2.1 million relationship instances

The Foundational Model Server

implements a query facility with a Lisp-like syntax:

- `(fms-get-attribute <term> <attribute-name>)`
  Returns a single named attribute for the specified term.
- `(fms-get-attributes <term>)`
  Returns a list of all the attributes for the given term
- `(fms-get-children <term> <hierarchy>)`
  Returns a list contain all the immediate children in the specified hierarchy
- `(fms-get-parents <term> <hierarchy>)`
  (as for `fms-get-children`)

FMS Returns a List of Strings

```
> telnet fma.biostr.washington.edu 8098
Trying 128.95.10.191...
Connected to fma.biostr.washington.edu.
Escape character is '^]'.
connected
3
(fms-get-children "Heart" "part")
received
4
("Coronary sinus" "Great cardiac vein" "Left marginal vein"
 "Posterior vein of left ventricle"  "Middle cardiac vein"
 "Small cardiac vein"  "Oblique vein of left atrium"
 "Right marginal vein"  "Right atrium"  "Left atrium"
...
 "Cavity of right ventricle"  "Cavity of left atrium"
 "Cavity of left ventricle"  "Fibrous skeleton of heart"
 "Cavity of right atrium"  "Papillary muscle"
...
 "Mid zone of heart"  "Apical zone of heart")
3
```

The code for the metastatic path model

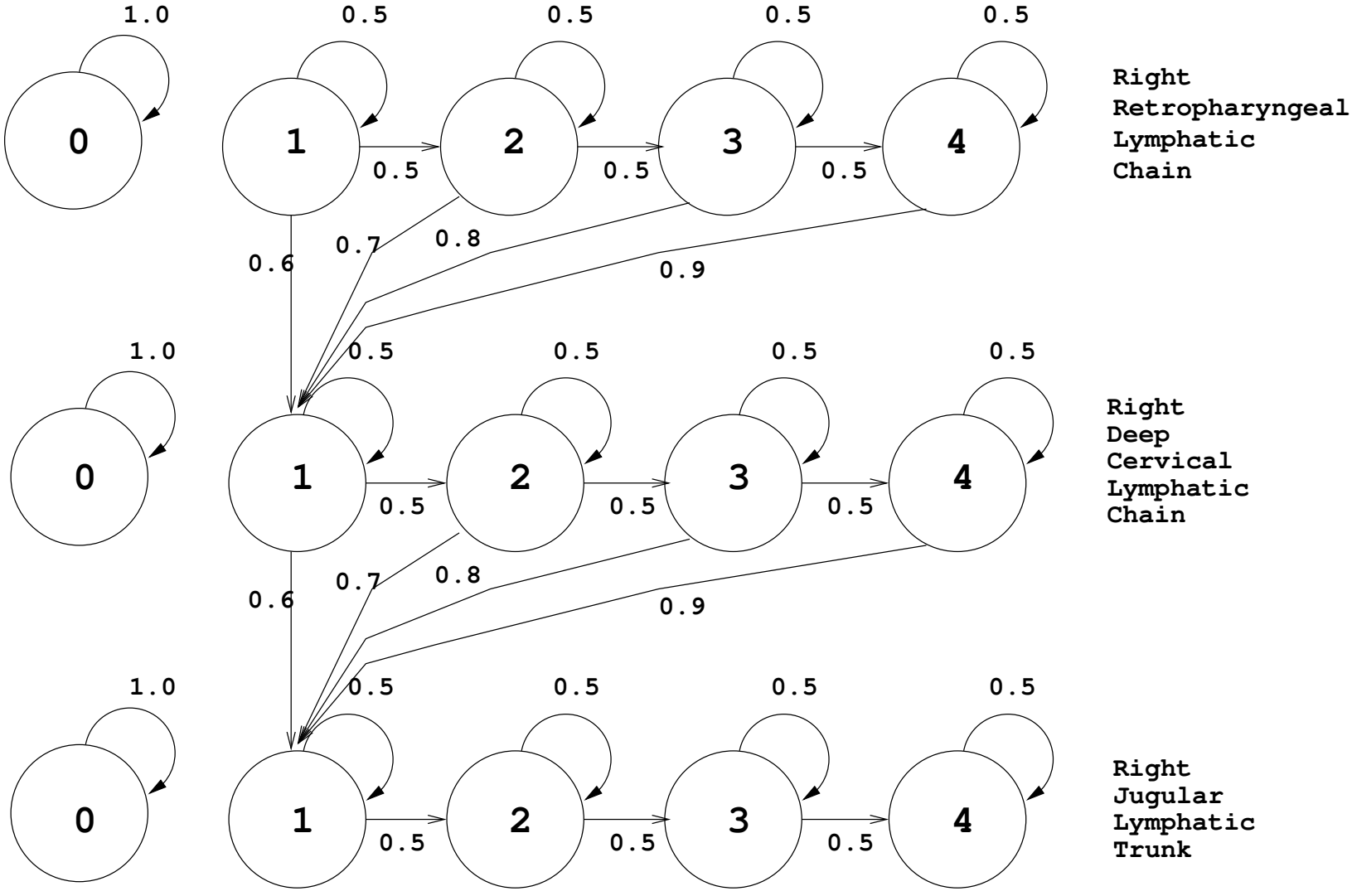
```
(defun find-all-paths (start)
  (labels ((successors (path)
             (get-children (first path) "efferent to")))
    (path-search start
                 #'(lambda (current) ;; stop when no more
                     (null (funcall successors current)))
                 nil ;; get all the paths
                 #'successors #'cons #'append)))

(defun lymphatic-paths (site)
  (apply #'append
         (mapcar #'(lambda (start)
                     (find-all-paths start))
                 (get-children site "lymphatic drainage"))))
```

Paths for the Soft Palate

```
> (fms-connect))
> (lymphatic-paths "Soft palate")
(("Jugular lymphatic trunk"
  "Inferior deep lateral cervical lymphatic chain"
  "Superior deep lateral cervical lymphatic chain")
...
 ("Right lymphatic duct" "Right jugular lymphatic trunk"
  "Right inferior deep lateral cervical lymphatic chain"
  "Right superior deep lateral cervical lymphatic chain"
  "Right retropharyngeal lymphatic chain")
...
 ("Thoracic duct" "Left jugular lymphatic trunk"
  "Left inferior deep lateral cervical lymphatic chain"
  "Left superior deep lateral cervical lymphatic chain"
  "Left retropharyngeal lymphatic chain")
 ("Thoracic duct" "Left jugular lymphatic trunk"
  "Left superior deep lateral cervical lymphatic chain"
  "Left retropharyngeal lymphatic chain"))
```

A Markov Model for Metastasis



The Transition Matrices

$$P_{chain} = \begin{pmatrix} 1.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.5 & 0.5 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.5 & 0.5 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.5 & 0.5 \\ 0.0 & 0.0 & 0.0 & 0.0 & 1.0 \end{pmatrix} \tag{1}$$

$$P_{tumor} = \begin{pmatrix} 1.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.9 & 0.1 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.9 & 0.1 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.9 & 0.1 \\ 0.0 & 0.0 & 0.0 & 0.0 & 1.0 \end{pmatrix} \tag{2}$$

Transition Formulas, Including Metastasis

For $k > 1$,

$$p(j, k, t+1) = \sum_{i=0}^{4} p(j, i, t) P(i, k) \tag{3}$$

and for $k = 0, 1$

$$p'(j, t+1) = \sum_{i=0}^{4} p(j-1, i, t) q(i) \tag{4}$$

$$p(j, 1, t+1) = \sum_{i=0}^{4} p(j, i, t) P(i, 1) + p'(j, t+1) p(j, 0, t) \tag{5}$$

$$p(j, 0, t+1) = \sum_{i=0}^{4} p(j, i, t) P(i, 1) - p'(j, t+1) p(j, 0, t) \tag{6}$$

Metastasis probabilities

$$q_{tumor} = \begin{pmatrix} 0.0 & 0.2 & 0.4 & 0.6 & 0.8 \end{pmatrix} \tag{7}$$

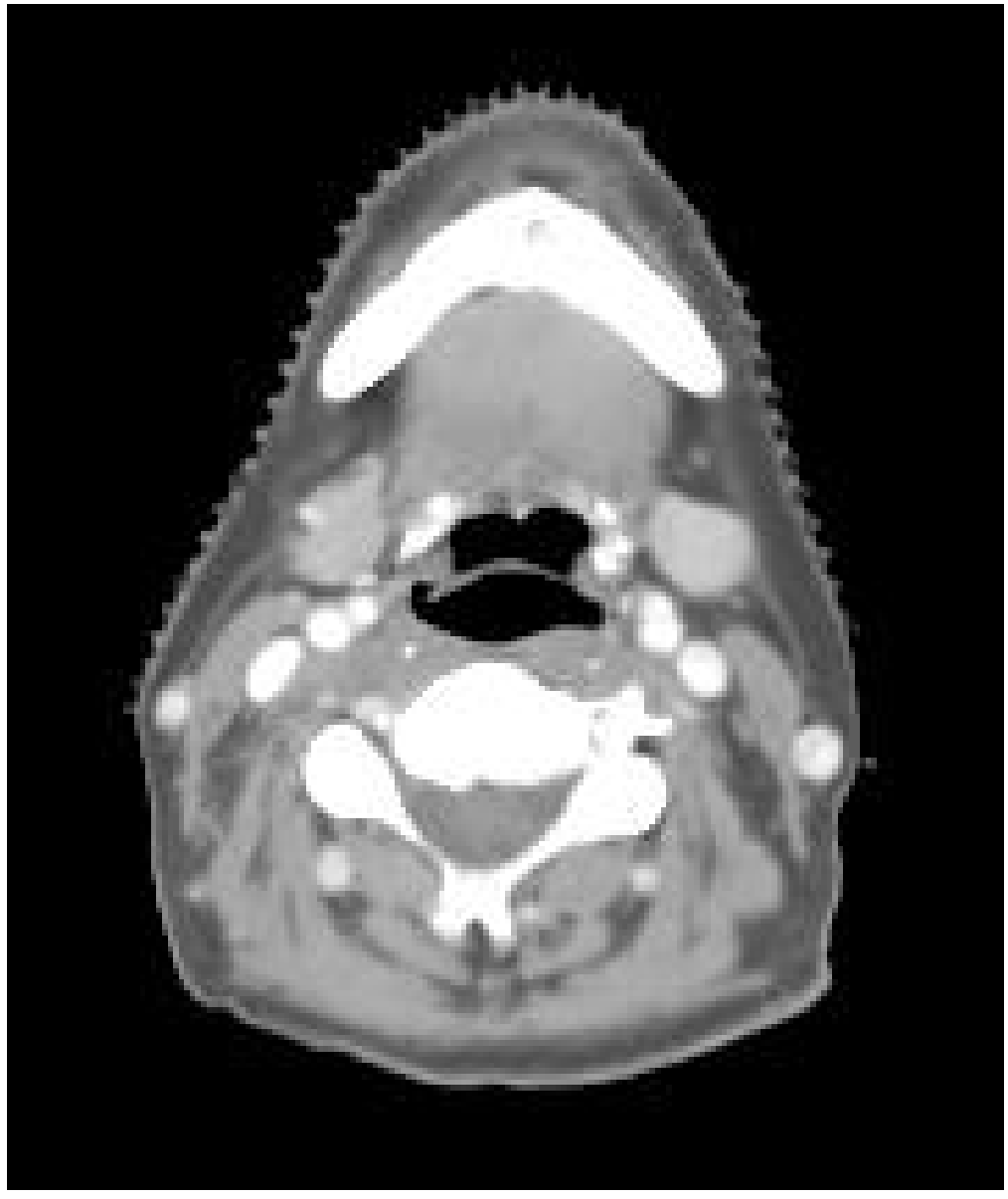
$$q_{chain} = \begin{pmatrix} 0.0 & 0.6 & 0.7 & 0.8 & 0.9 \end{pmatrix} \tag{8}$$

Converting Node Groups to Regions

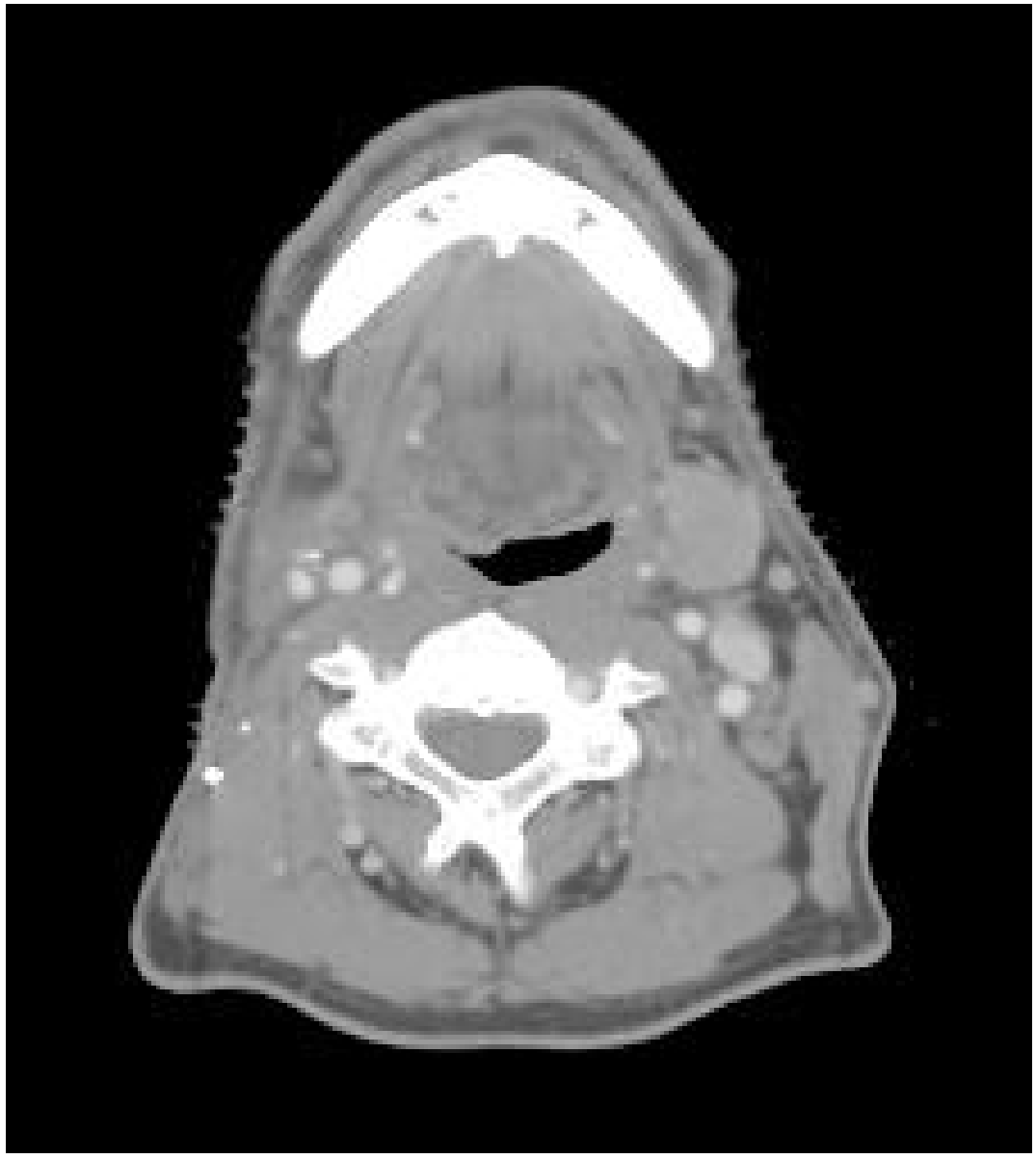
Radiologically (and/or surgically) defined regions and corresponding node groups

Level	Nodal Group
Ia	Submental
Ib	Submandibular
IIa	(Anterior) Upper Jugular
IIb	(Posterior) Upper Jugular
III	Middle Jugular
IV	Lower Jugular
Va	(Upper) Posterior Triangle
Vb	(Lower) Posterior Triangle
VI	Anterior Compartment
P	Parotid
B	Buccal
RP	Retropharyngeal

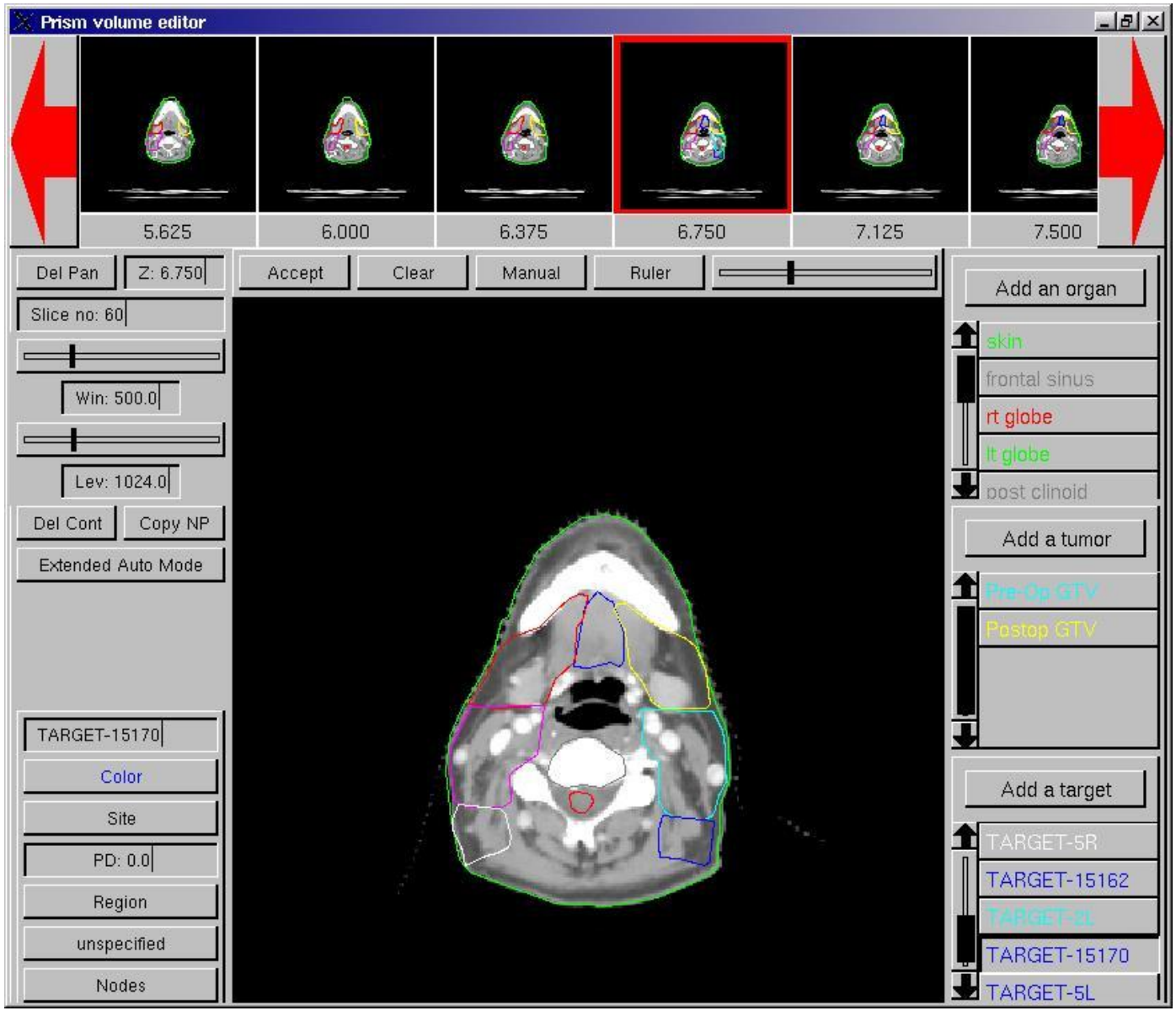
A sample cross section - what to treat?



A reference cross section



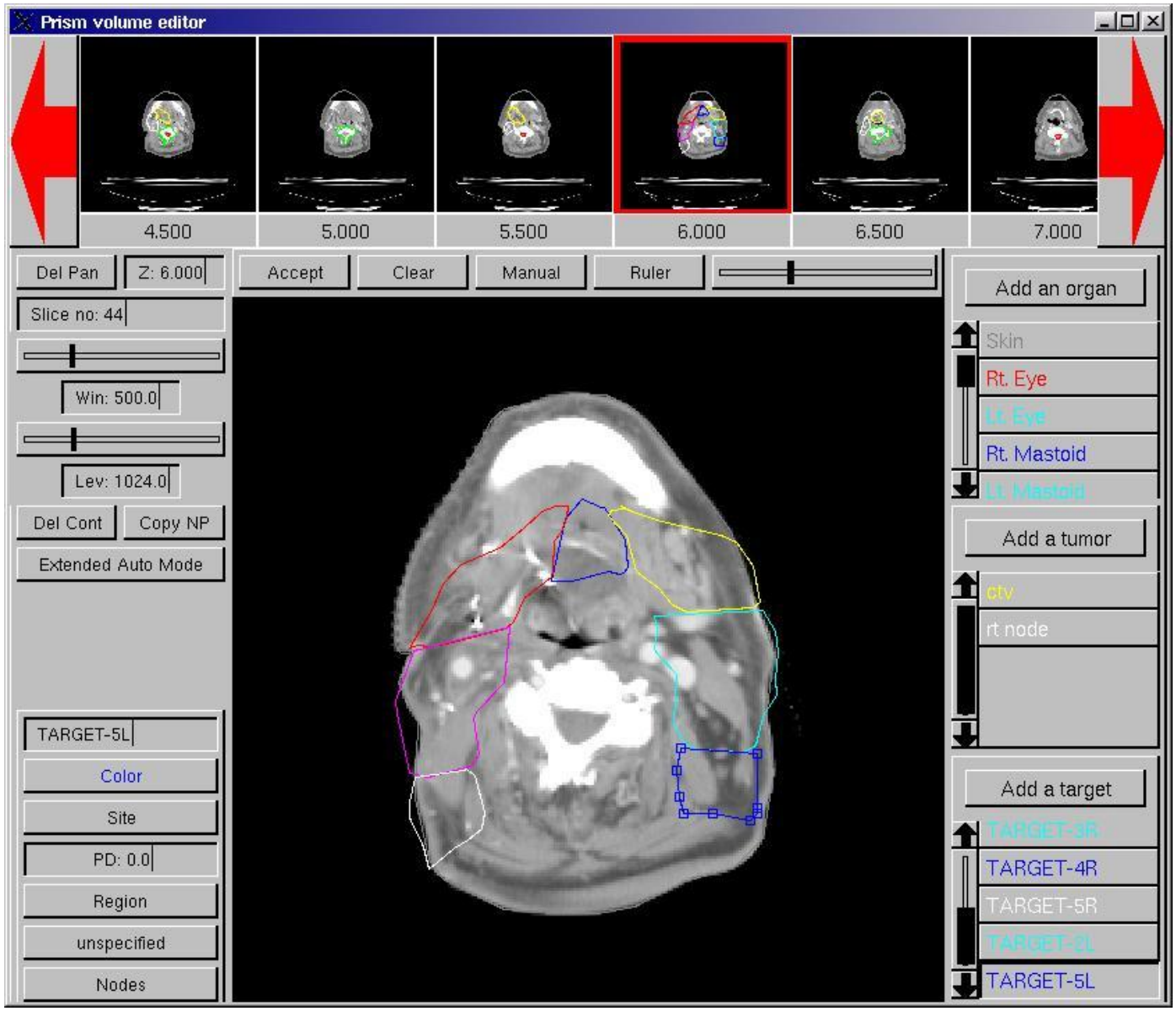
A reference cross section with nodal regions defined



Deformable Image Registration Using Maximum Entropy

- Initial transformation is rigid body
- Deformable registration uses “control points”
- We ran 12 cases against each other, with each playing the role of reference image or target image.
- Mmore recently we used landmarks (mandible and hyoid bone) to define the initial rigid body registration
- Results are promising but not yet adequate for clinical use

Matching standard regions to specific cases



Conclusions and Future Work

- A metastasis predictor based on lymphatic topology looks promising as a useful theory,
- Refining and testing the Markov model will require more surgical data,
- Extending the model to incorporate image data (to modify the initial state probabilities) is possible and interesting,
- Extending the model to incorporate pathologic and/or genomic data also would be interesting,
- Automated generation of the target volume needs somewhat better image mapping, and
- Finer granularity in defining target volumes may be possible.

Publications for more information

- Kalet, I.J., Whipple, M., Pessah, S., Barker, J., Austin-Seymour, M.M., Shapiro, L.G. A Rule-based Model for Local and Regional Tumor Spread. Proceedings of the American Medical Informatics Association (AMIA) Fall Symposium, pp. 360–364, Isaac S. Kohane, ed., Hanley & Belfus, Inc., 2002.
- Benson, N., Whipple, M. and Kalet, I.J. A Markov Model Approach to Predicting Regional Tumor Spread in the Lymphatic System of the Head and Neck. Proceedings of the American Medical Informatics Association Fall Symposium, pp. 31–35, David W. Bates, John H. Holmes and Gilad Kuperman, Eds., American Medical Informatics Association, 2006.
- Kalet, I.J., Mejino, J.L. Wang, V., Whipple, M., Brinkley, J.F. Content-Specific Auditing of a Large Scale Anatomy Ontology. Journal of Biomedical Informatics, volume 42, number 3, pp. 540–549, June, 2009.
- Kalet, I.J. Principles of Biomedical Informatics. Academic Press (Elsevier), San Diego, CA, 2009. 475 pp.

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