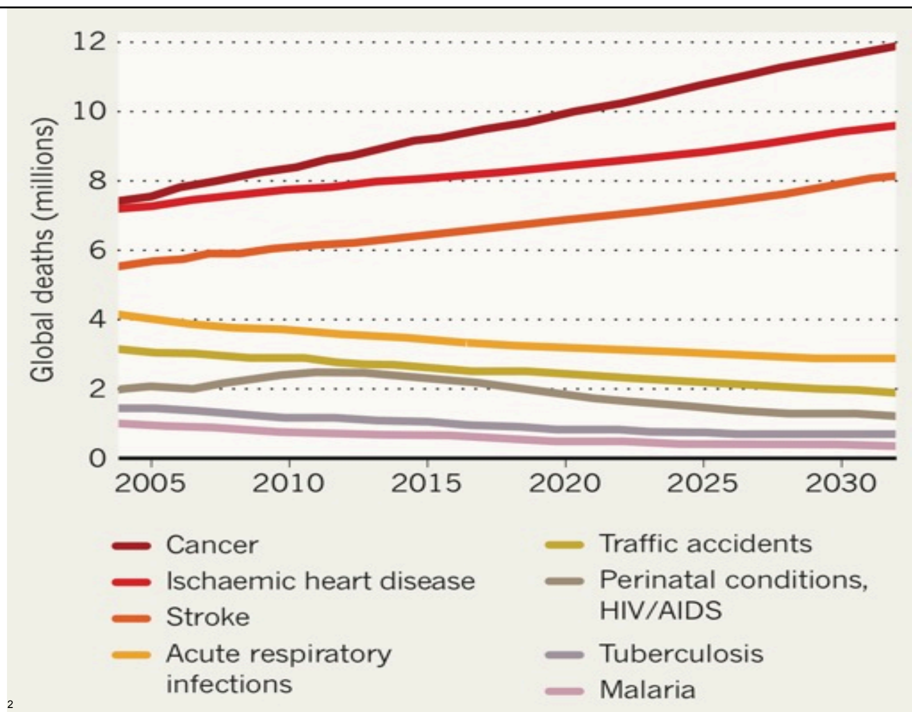
Sani Nassif
IBM Research – Austin

From Circuits to Cancer



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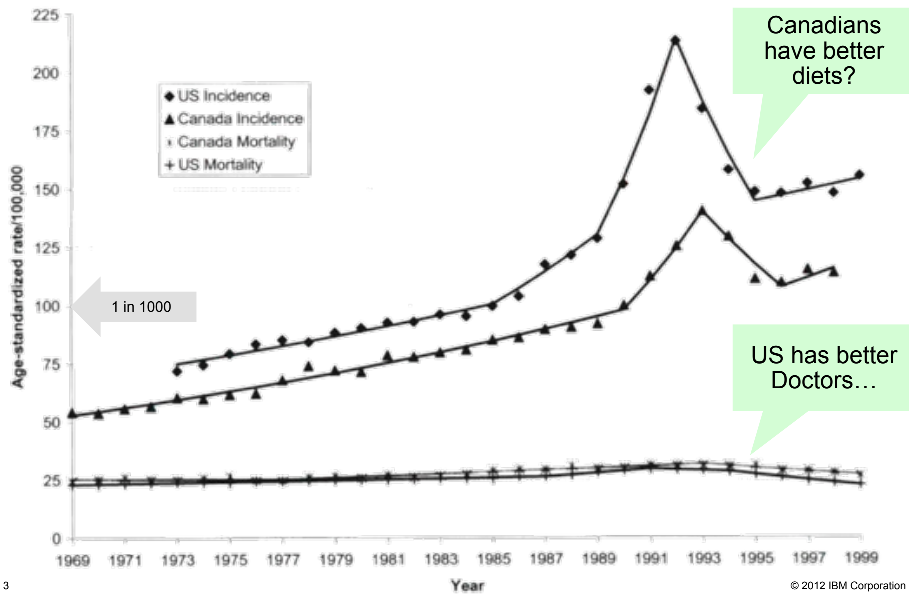
Prostate Cancer Rates in the US & Canada



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Key Statistics about Prostate Cancer

- Other than skin cancer, most common cancer in American men.
  – Second leading cause of cancer death in American men (behind Lung cancer).
- In 2012 estimates are that:
  – **241,000** new cases will be diagnosed.
  – **28,000** men will die.
- About 1 man in 6 will be diagnosed with prostate cancer in his lifetime.
- Two thirds of diagnosis are in men aged 65 and older.
- But… modern medicine “miracles” mean that only a small proportion of men diagnosed with prostate cancer die from that cancer.

http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics

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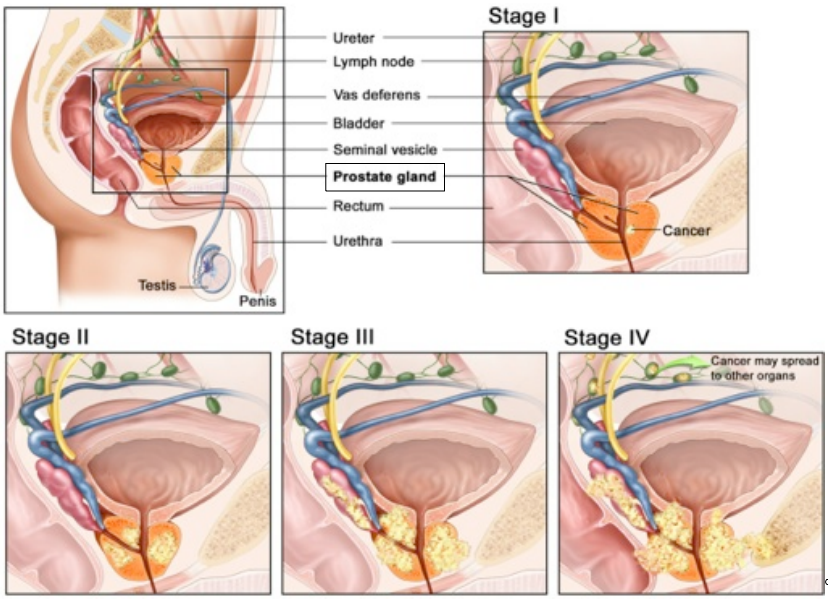
The Prostate…

The prostate is close to many "important" parts of a man's body!



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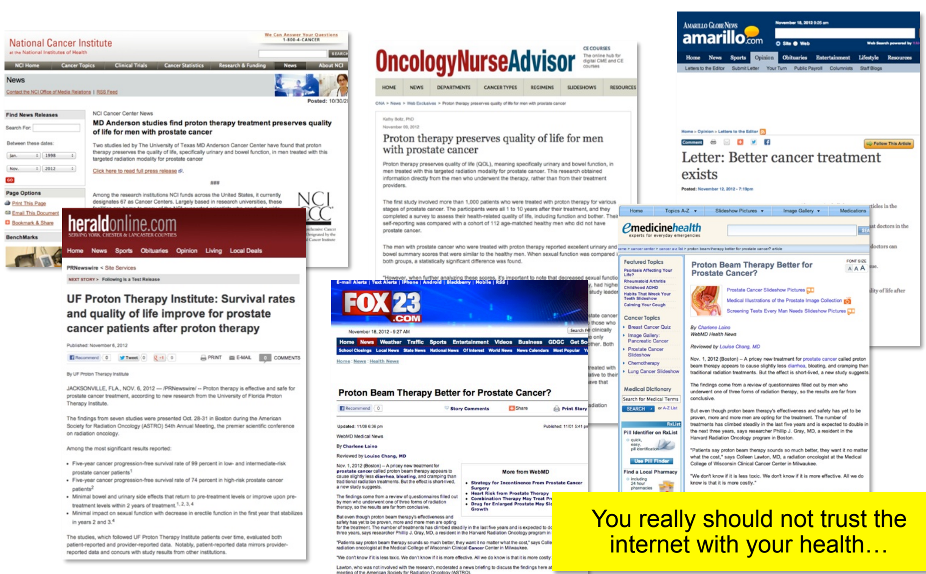
Treatment of Choice: Proton Radiation Therapy



You really should not trust the internet with your health…

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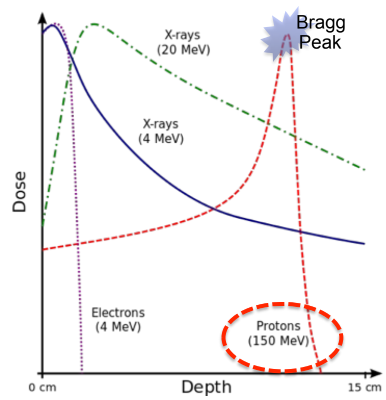
Radiation and the Human Body

- Radiation deposits energy in the atoms that make up a cell, and results in disruption of the DNA. Cells stop reproducing and eventually die…
- A number of alternative types.
  - Used in about 60% of cancer treatments.
- Energetic Protons interact with solids in an interesting way:
  - Energetic means ~200MeV (½ c).
  - The "interaction cross-section" is small for high speeds, and large for low speeds.
  - Result: energy loss rate = dE/dx ~ 1/E
- Leads to a strongly localized peak in energy deposited vs. depth.
  - Ideal for treating tumors deep in the body (like the Prostate, **+ many others**)!



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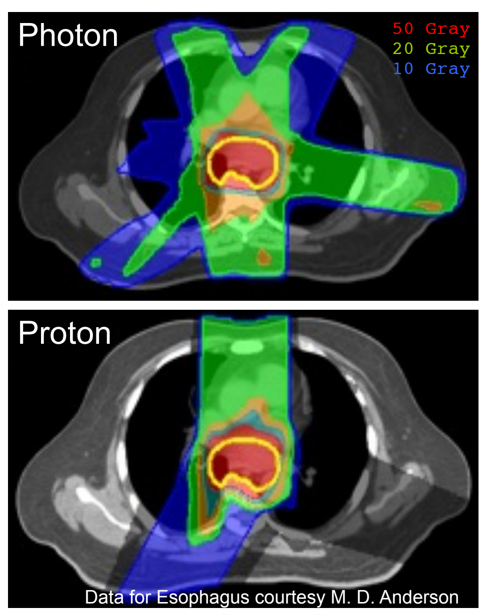
Proton vs. Photon (X-Ray)

- Because of higher selectivity Proton beam therapy can achieve the same dose delivery with far less damaging radiation to surrounding tissue.
- Cancer cells are more sensitive to radiation because of their higher rates of reproduction.
  - And…
- Normal cells can recover from small doses, but can also be permanently damaged by higher radiation doses.



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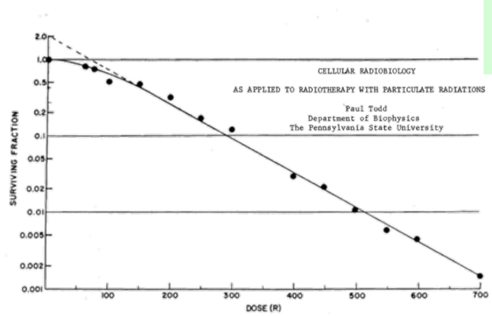
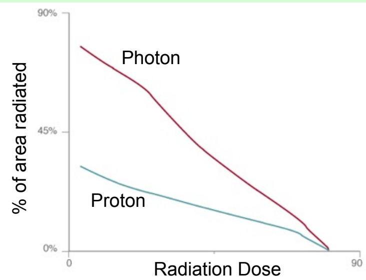
Impact on Cells

- Higher levels of radiation reduce cell survival rates.
  - At lower levels, cells can repair themselves.
  - This is why a typical treatment is delivered over many "fractions" (~30 days).
- But… Higher levels of radiation also increase risk of secondary cancer.
  - This is one of the major strengths of Proton Therapy (selectivity).

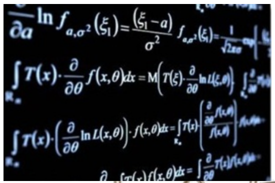


Symposium On Pion And Proton Radiotherapy
1971, Batavia, Illinois

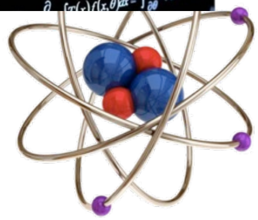
Quantitative comparison between Photon and Proton therapy for Prostate Cancer.



Protons, Electrons, Photons and "Circuits"?



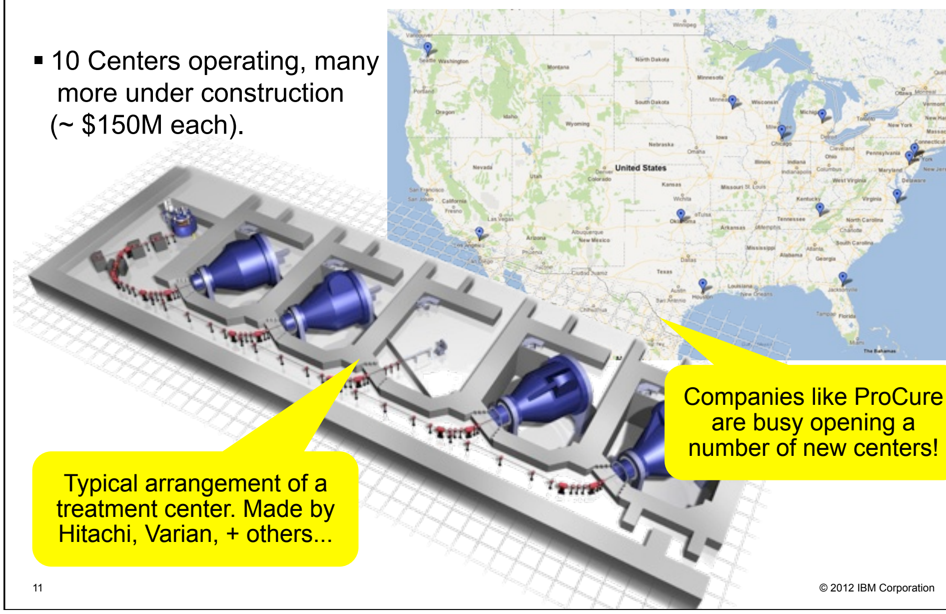
- How does Radiation Therapy relate to Computers and Circuits?
- Observation: VLSI researchers often have strong skills in and links to mathematics and physics.
  - As well as software, algorithms, modeling, etc…
  - We deal well with complexity.
  - And are accustomed to working on large-scale problems.



- These foundational skills are <u>highly portable</u> to other areas.
- Requirements: partnership and perseverance!
  - More on this later.

Radiation Treatment Centers (in the US)

- 10 Centers operating, many more under construction (~ $150M each).



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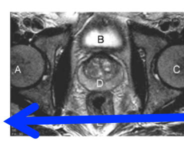
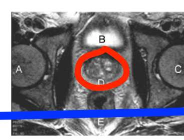
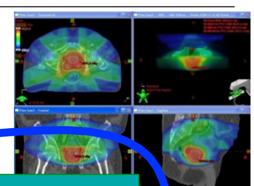
Radiation Treatment Process





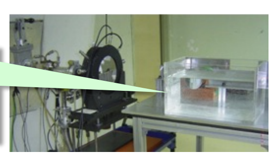


- Patient gets MRI or CT scan.
- Scan + Lab results used to locate tumor
- Treatment plan manually developed
- Treatment plan is "reviewed"
- Treatment plan is verified
- Patient receives treatment(s)

Subsequent Fractions

Delay: ~5 Days!

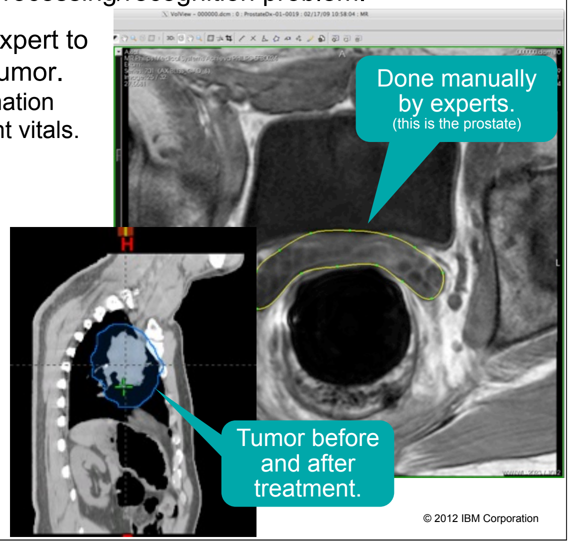
Verification is done by applying treatment to a box of water.



60% of cost is in "staff" because treatment requires Oncologists + PhD Physicists!

First Challenge: Find the Malignancy

- A hard data mining + image processing/recognition problem.
- Currently requires a human expert to determine location/extent of tumor.
  - While integrating other information like lab test results and patient vitals.
- Two instances:
  - Initial tumor identification. (quite hard?)
  - Subsequent identification, e.g. during or after treatment. (possibly easier?)
- A lot of work is needed in this area!
  - Example: respiration-caused movement…



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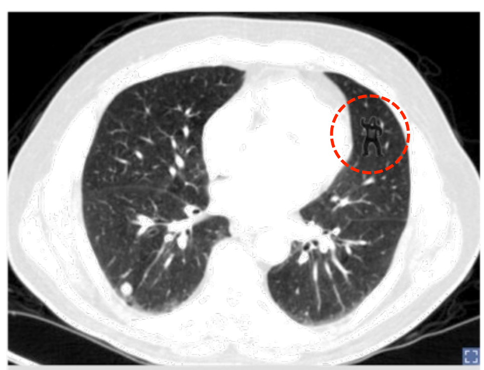
Is this a Hard Problem?

- Apparently even for experts!
  - This is a well studied area?
  - Image segmentation, registration, and so on.
- Goal: apply data mining methods to this problem.
  - Many issues need to be resolved.

Why Even Radiologists Can Miss A Gorilla Hiding In Plain Sight

by ALIX SPIEGEL

February 11, 2013 3:33 AM



Notice anything unusual about this lung scan? Harvard researchers found that 83 percent of radiologists didn't notice the gorilla in the top right portion of this image.

- Intermediate goal: focus on one body region only…
  - Develop specific features manually and use for mining.
  - Example: Prostate.

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Second Challenge: Predict Efficacy

- To determine impact of a beam of particular energy and shape coming from a specified direction, current state of the art is to use either:

  1. Physics-based Monte-Carlo.
  2. Simple analytical models.

- Very slow (~many hours / beam) with tools like Geant4 and MCNPX.

– or –

- Very inaccurate, especially for heterogeneous case (e.g. soft tissue + bone + air +…).

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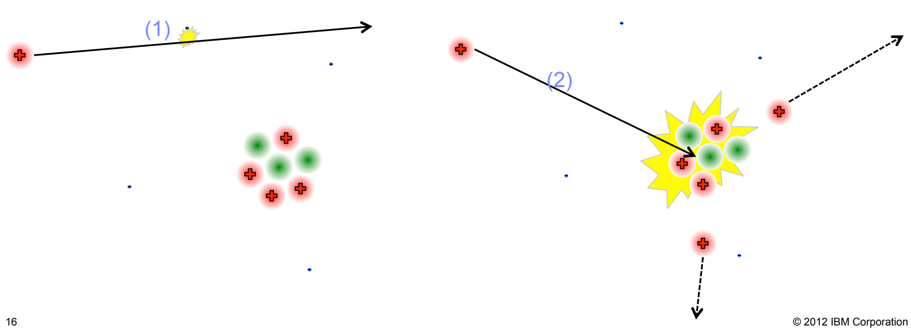
Protons in Matter

- Protons slow down because of interactions with:
  1. Electron cloud: frequent, small energy loss.
  2. Nuclei: rare, large energy loss, new particles generated.
- Existing simulators perform a Monte-Carlo simulation of a large number of protons, and track the spatial distribution of deposited energy.



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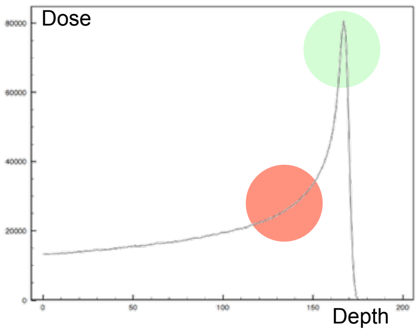
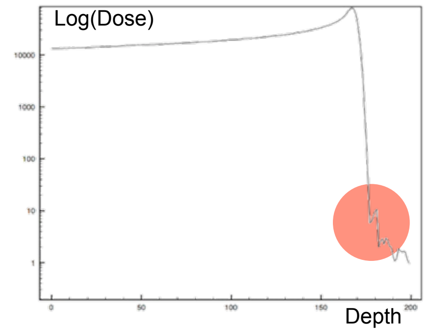
Deposited Energy (Dose)

Need to accurately predict in a 3-dimensional space:

- The areas with high values of deposited energy, since they are the target of the treatment (the tumor, "Planning Target Volume").
- The adjacent areas, with smaller values of deposited energy, where we want to insure a good estimate of the dose delivered to healthy tissue!





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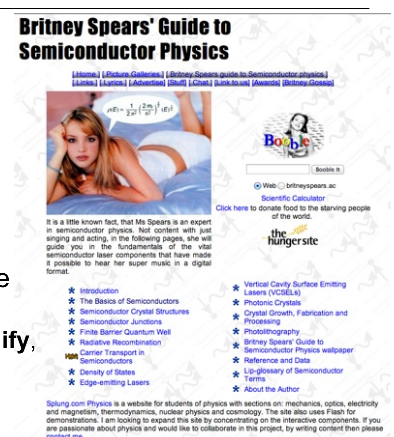
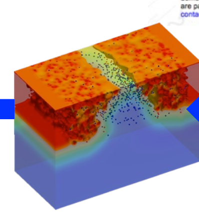
A Lesson from VLSI



- We all studied semiconductor physics.
- And we know devices are very very complicated…
  - So much that we need help from Ms. Spears!
- But that does not stop up from predicting the performance of a Billion-Transistor chip!
  - We have had to learn how to **abstract**, **simplify**, while retaining essential characteristics and preserving predictability.



$$\begin{cases} -\mathrm{div}(\lambda^2 \nabla \varphi) = p - n + D, \\ -\delta_n^2 \Delta\sqrt{n} + \sqrt{n}(\varphi_n - \varphi + \ln(n)) = 0, \\ \quad G_n = \varphi_n - \varphi + \ln(n), \\ -\delta_p^2 \Delta\sqrt{p} + \sqrt{p}(-\varphi_p + \varphi + \ln(p)) = 0, \\ \quad G_p = \varphi_p - \varphi - \ln(p), \\ -\mathrm{div}(\mu_n(\nabla n - n\nabla(\varphi + G_n))) = -U, \\ -\mathrm{div}(\mu_p(\nabla p + p\nabla(\varphi + G_p))) = -U. \end{cases}$$

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Computational Cost and Speedup

- There are a number of existing high-accuracy Particle Monte-Carlo codes.
  – Geant4, MCNPX, …
- Typical high-accuracy computational cost: ~10msec / particle.
  – On one core of a modern workstation.
  – With some compromises (grid size, step size, etc…) can be 5X faster.
- Typical simulation run *(to insure good Monte-Carlo convergence)*: 20M.
  – Two days for most accuracy. Few hours with some compromise.
  – Significant speedup possible by using parallel computation but still not enough for "interactive" use.
- Compact models + modern implementation have already achieved **1000X** (10μsec/particle) speedup on identical hardware.
  – GPU version provides additional ~**30X**.
  – FPGA version currently being developed.
- Fast enough to be used for treatment planning!

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Third Challenge: Create A Treatment Plan

- Many degrees of freedom available for treatment.
  – Beam Energy.
  – Direction.
  – Treatment Time.
  – Beam Shape …
- A very large search space with millions of options & constraints.
  – Impact of each beam requires a large Monte-Carlo to evaluate.
- Typical computational cost for optimization only: 3 days.
  – Experts "gave up".

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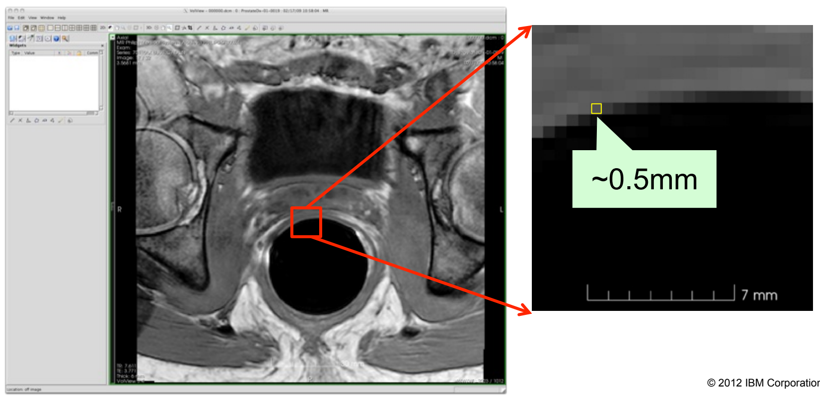
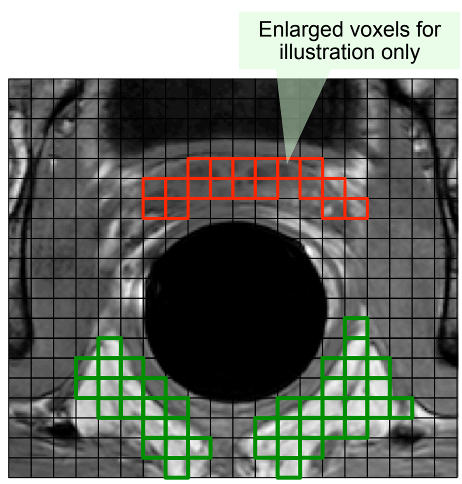
Formulating the Problem

- The physical domain is naturally discretized because scan data has limited resolution, so…
  - We consider a discrete version of the problem working on each individual “voxel” in the region of interest.
  - We rely on EDA’s long history of tackling large-scale optimization problems.



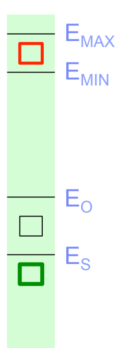
Voxels and Constraints



Voxels can be classified as:

- Part of the tumor (□).
- Part of a “sensitive area” (□).
- Other…

100x100x100 ~ 1M voxels.



Dose constraints:

- Tumor: $E_{MIN} \le E_{\square} \le E_{MAX}$
- Sensitive: $E_{\square} \le E_S$
- Other: $E_{\square} \le E_O$

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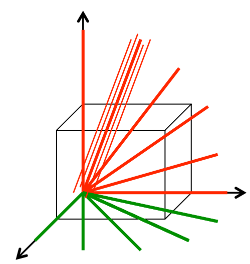
Treatment Planning as a Large Scale Linear Program

- Beam settings are discretized to a finite number of choices.
  - Consistent with the finite tolerances of positioning apparatus.
  - Free variable: beam weight (equivalent to beam use time)!
- For each beam, we can compute its contribution to each voxel (B_N(i,j,k)).
  - This is done via a lengthy Monte-Carlo…
- Dose at a voxel is a weighted sum of all beam contributions, weight = beam time.
  - $E_{\square}$ = Dose(i,j,k) = $\Sigma\ \alpha_N\ B_N$(i,j,k)
- Resulting raw linear program:
  - Minimize: $\Sigma\ \alpha_N$
  - Subject to:
    - $E_{MIN} \le E_{\square} \le E_{MAX}$
    - $E_{\square} \le E_S$
    - $E_{\square} \le E_O$

1M variables.
1M constraints.
~20% sparsity.
1.6TB Matrix!



- **Solve time (with many innovations): ~5min on a large P server.**

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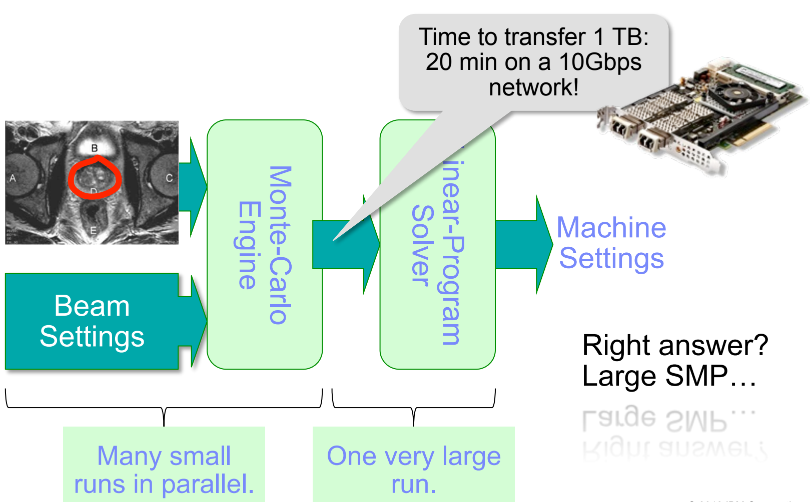
Treatment Planning Hardware

- Computational requirements drive a very specific type of architecture!



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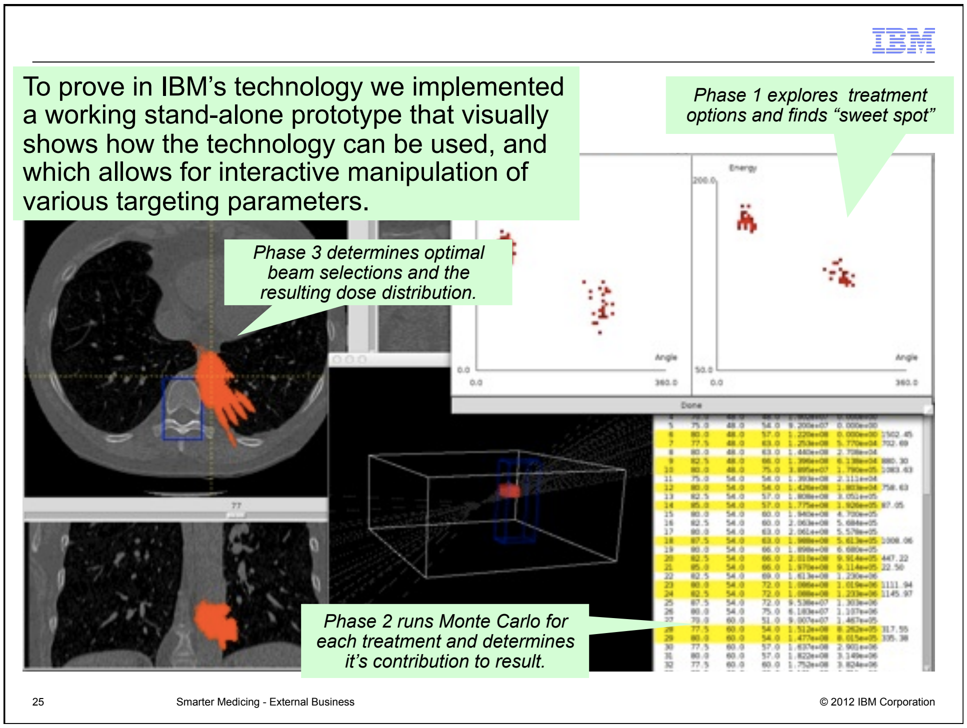
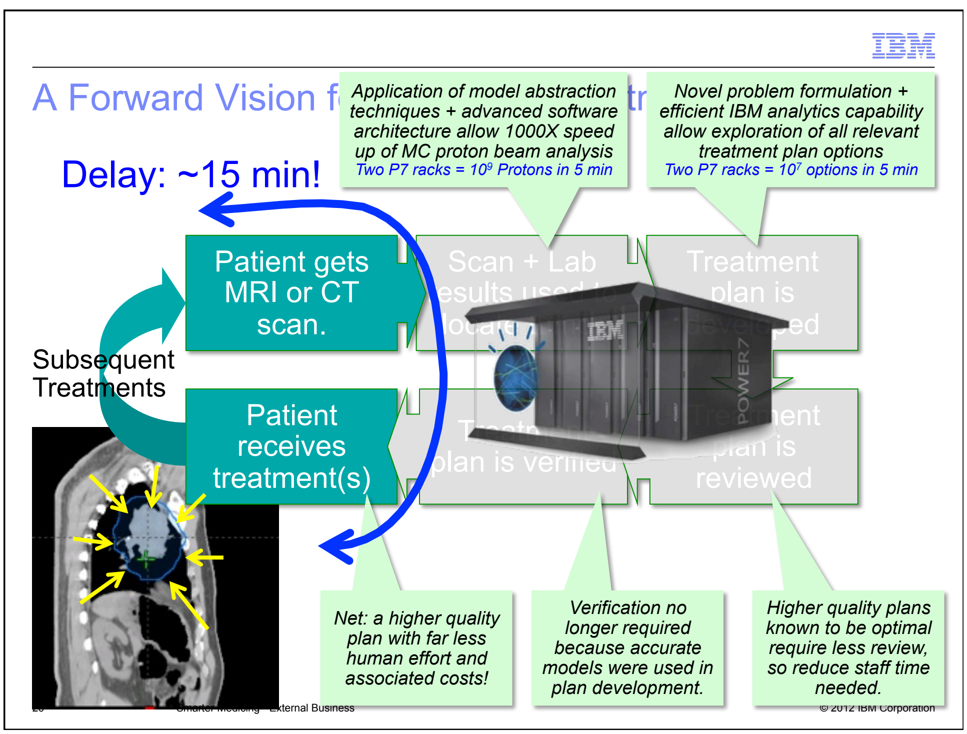

To prove in IBM's technology we implemented a working stand-alone prototype that visually shows how the technology can be used, and which allows for interactive manipulation of various targeting parameters.
Phase 1 explores treatment options and finds "sweet spot"
Phase 3 determines optimal beam selections and the resulting dose distribution.
Phase 2 runs Monte Carlo for each treatment and determines it's contribution to result.
Energy
Angle
25
Smarter Medicing - External Business
© 2012 IBM Corporation


A Forward Vision f
Delay: ~15 min!
Application of model abstraction techniques + advanced software architecture allow 1000X speed up of MC proton beam analysis
Two P7 racks = 10⁹ Protons in 5 min
Novel problem formulation + efficient IBM analytics capability allow exploration of all relevant treatment plan options
Two P7 racks = 10⁷ options in 5 min
Patient gets MRI or CT scan.
Scan + Lab
Treatment plan is
Subsequent Treatments
Patient receives treatment(s)
plan is verified
plan is reviewed
POWER7
Net: a higher quality plan with far less human effort and associated costs!
Verification no longer required because accurate models were used in plan development.
Higher quality plans known to be optimal require less review, so reduce staff time needed.

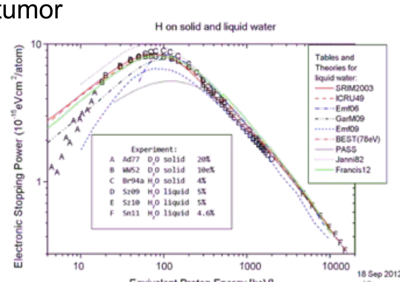
The Future of Cancer Therapy

- Companies like Mevion are developing treatment machines that are much less expensive than current generation.
- As the hardware becomes more available proton radiation therapy will become far more pervasive.
  - Example: studies underway for application to early stage breast cancer!
- Positive feedback cycle, market will broaden, costs will need to drop…
- Automation will be crucial to enabling this technology.

Many Many Many Other Challenges

The major challenge: Uncertainty!

- Location of tumor (next gen machines integrate imaging + treatment).
- Spatial discretization of treatment region.
- Limited precision in simulation (number of MC runs).
- Variability in cell response to dose.
- Stopping power of tissue in and around tumor (for Proton simulation).
- + …
- A number of good research topics.



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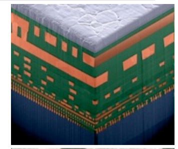
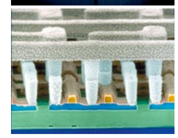
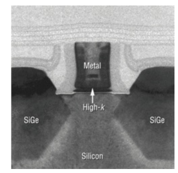
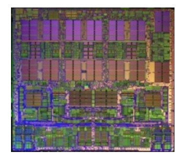
From Circuits to Cancer?

- I began my EE education in 1976, and have worked in the area of Design Automation for VLSI since that time.
- I am tired of having to explain what I do to people.
- IBM is encouraging researchers to apply themselves in related/adjacent areas, referred to as the "Smarter Planet" initiative.
- With some hard work, and an open and collaborative attitude, it is possible to make contributions to other areas!
- VLSI and Design Automation are quite broad subjects, good preparation for working on other problems.
- I can even explain what I do to my Mother now!



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Acknowledgements

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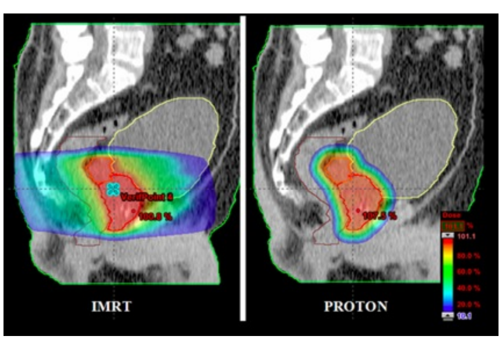
- M. D. Anderson Cancer Research Center.
- Mass General Cancer Research Center.



I guess this work will eventually make the real time radiotherapy planning, and intervention realistic. ***We probably can change the current practice of radiotherapy***.

Xiaodong Zhang, Ph.D.
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History