The ^{99}Mo Supply Chain for Nuclear Medicine

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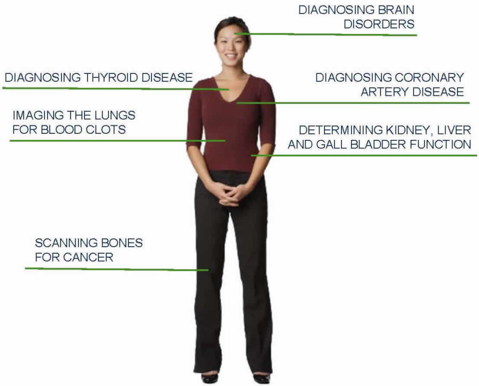
Nuclear Medicine:
Meeting Patient Needs with ^{99}Mo



Worldwide: ~30 Million* Tc 99m Procedures
Europe: ~10 Million* Tc 99m Procedures

*:"Radiosotopes in Medicine" http://www.world-nuclear.org/infomap.aspx (updated 16 April 2010)

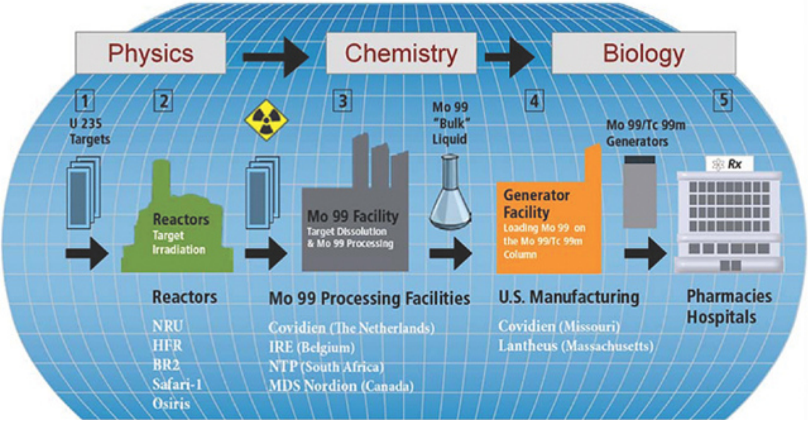
Background and Motivation

Study of Nuclear Medicine Supply Chains is a combination of

- Physics
- Chemistry
- Biology
- Operations Research

with some *Biomedical Engineering* thrown in at each step!

Background and Motivation



Medical Nuclear Supply Chains

Medical nuclear supply chains are essential supply chains in healthcare and provide the conduits for products used in nuclear medical imaging, which is routinely utilized by physicians for diagnostic analysis for both cancer and cardiac problems.

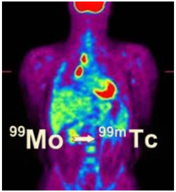
Such supply chains have unique features and characteristics due to the products' time-sensitivity, along with their hazardous nature.

Salient Features:

- complexity
- economic aspects
- underlying physics of radioactive decay
- importance of considering waste management.

Nuclear Medicine

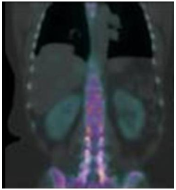
To create an image for medical diagnostic purposes, a radioactive isotope is bound to a pharmaceutical that is injected into the patient and travels to the site or organ of interest.



The gamma rays emitted by the radioactive decay of the isotope are then used to create an image of that site or organ.

Nuclear Medicine

Technetium, ^{99m}Tc, a decay product of Molybdenum, ^{99}Mo, is the most commonly used medical radioisotope, accounting for over 80% of the radioisotope injections and representing over 30 million procedures worldwide each year.



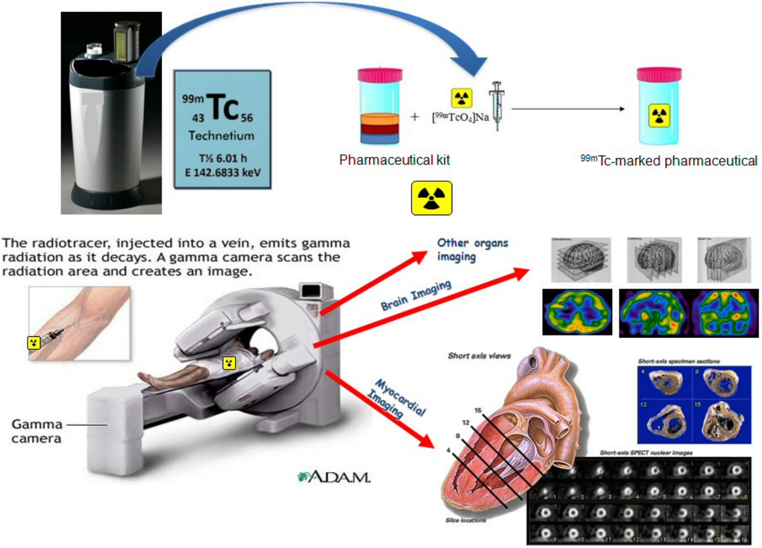
Nuclear Medicine

Over 100,000 hospitals in the world use radioisotopes (World Nuclear Association (2011)).

In 2008, over 18.5 million doses of ^{99m}Tc were injected in the US with 2/3 of them used for cardiac exams

It is estimated that the global market for medical isotopes is 3.7 billion US$ per year (Kahn (2008)).

Nuclear Medicine



Challenges

Reactors are old nearing their end of life.

Planned and unplanned shutdowns have created spot shortages.

Result is Nuclear Medical Procedures are delayed.

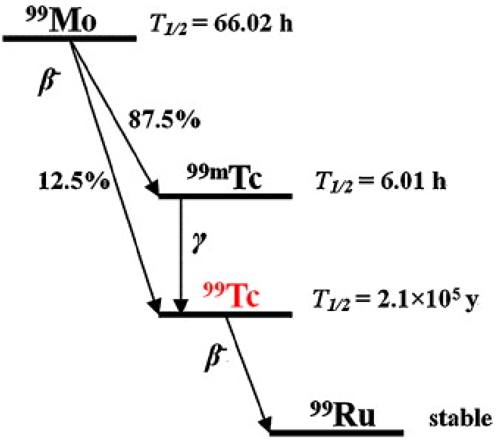
UPDATED MAY 2010							JUNE 2010						
S	M	T	W	T	F	S	S	M	T	W	T	F	S
						1			X	X	3	X	X
2	3	X	X	6	X	8	6	7	8	9	10	11	12
9	10	11	X	X	X	15	13	14	15	16	17	18	19
16	X	X	X	20	21	22	20	21	22	23	24	25	26
23	X	X	X	X	28	29	27	28	29	30			
30	31												

	Generator standing orders met with some extra
	Majority of generator standing orders met but no extra
	Generator standing order shortage resulting in size reductions, Tc 99m shortage
	Significant shortage to generator standing orders, severe Tc 99m shortage
X	No Mo99 supply expected. Generator production canceled.

Frequently updated calendars depicting available supply

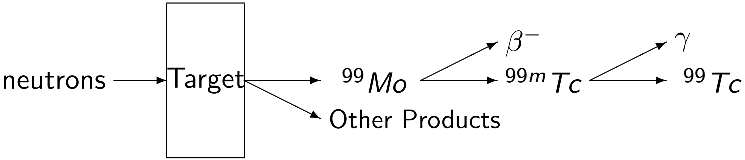
Nuclear Physics Background

^{99m}Tc comes from the decay of ^{99}Mo



Physics Background

To create ^{99m}Tc, an enriched Uranium target is irradiated with neutrons in a reactor. After irradiation, the ^{99}Mo product is separated from the other products and purified.



The ^{99}Mo decays by emitting a β^- to create ^{99m}Tc with a $t_{1/2}$ of 66.7 hours.

The ^{99m}Tc decays by emitting a γ to create ^{99}Tc with a $t_{1/2}$ of 6 hours.

It is the γ emitted from the ^{99m}Tc decay that creates the image.

Targets HEU vs LEU

Most targets currently used are Highly Enriched Uranium (HEU) which can possibly be diverted for military uses.
Can convert to Lightly Enriched Uranium (LEU) targets, but requires significant investment in the reactors and processing plants. — New Reactors use LEU targets.

Radioactive Decay

The activity of a radioisotope (in disintegrations per unit time) is proportional to the quantity of that isotope, i.e.,

$$\frac{dN}{dt} \propto N$$

where $N = N(t) =$ the quantity of a radioisotope.
The radioactive decay multiplier $\alpha_{d\,a}$ for a link a as

$$\alpha_{d\,a} = e^{-\lambda t_a}$$

and t_a is the time spent on link a. The decay constant, λ, can be conveniently represented by the half-life $t_{1/2}$, where

$$t_{1/2} = \frac{\ln 2}{\lambda}.$$

We can write $\alpha_{d\,a}$ as

$$\alpha_{d\,a} = e^{-\lambda t_a} = e^{-\ln 2 \frac{t_a}{t_{1/2}}} = 2^{-\frac{t_a}{t_{1/2}}}.$$

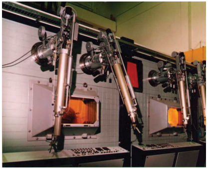
6 Day Curies

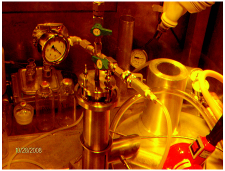
The value of $t_{1/2}$ for *Mo* is 66.7 hours.
Since it takes several days to process and ship the *Mo*, we usually normalize our amounts to what is referred to as a 6 Day Curie, i.e., the amount irradiated/sipped,etc so that a Curie would be left after 6 days.
Since $2^{-\frac{6 days}{66.7 hours}} \approx .28.$ we need to irradiate roughly 4 times as much as we need.
Or, in other words, 75% is lost in processing/shipping.

Physics Background

The irradiated targets are highly radioactive and must be handled and shipped with extreme caution.
The only shipping method that is allowed is via truck.

At the processing plant the ^{99}Mo is separated and purified.



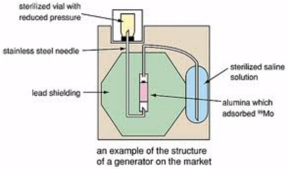


The purified *Mo* is shipped to generator manufacturers, where it is packaged in generators, which are then shipped to hospitals and medical imaging facilities worldwide.

Multiple modes of transportation can be used at this stage.

^{99m}Tc Generators

Inside a generator, the ^{99}Mo and the ^{99m}Tc are in an ion column. A saline solution is used to elute the ^{99m}Tc, which is then prepared for injection into the patient.



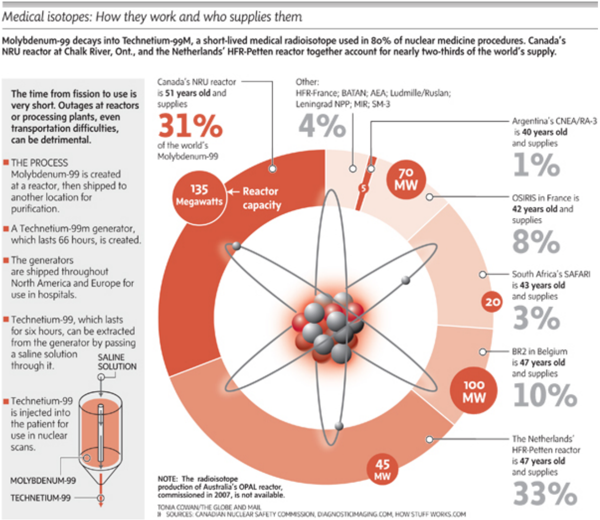
The Production of ^{99}Mo

The production of ^{99}Mo occurs at only nine reactors in the world.

Reactor name	Location	Annual operating days	Normal production per week[a]	Weekly % of world demand	Fuel/targets[b]	Date of first commissioning
BR-2	Belgium	140	5 200[c]	25-65	HEU/HEU	1961
HFR	Netherlands	300	4 680	35-70	LEU/HEU	1961
LVR-15[d]	Czech Rep.	–	>600	–	HEU[e]/HEU	1957
MARIA[d]	Poland	–	700-1 500	–	HEU/HEU	1974
NRU	Canada	300	4 680	35-70	LEU/HEU	1957
OPAL	Australia	290	1 000-1 500	–[f]	LEU/LEU	2007
OSIRIS	France	180	1 200	10-20	LEU/HEU	1966
SAFARI-1	South Africa	305	2 500	10-30	LEU/HEU[g]	1965
RA-3	Argentina	230	200	< 2	LEU/LEU	1967

From: The Supply of Medical Radioisotopes: An Economic Study of the Molybdenum-99 Supply Chain, OECD (2010)

Worldwide Production of ^{99}Mo - ^{99m}Tc


Medical isotopes: How they work and who supplies them
Molybdenum-99 decays into Technetium-99M, a short-lived medical radioisotope used in 80% of nuclear medicine procedures. Canada's NRU reactor at Chalk River, Ont., and the Netherlands' HFR-Petten reactor together account for nearly two-thirds of the world's supply.
The time from fission to use is very short. Outages at reactors or processing plants, even transportation difficulties, can be detrimental.
THE PROCESS Molybdenum-99 is created at a reactor, then shipped to another location for purification.
A Technetium-99m generator, which lasts 66 hours, is created.
The generators are shipped throughout North America and Europe for use in hospitals.
Technetium-99, which lasts for six hours, can be extracted from the generator by passing a saline solution through it.
SALINE SOLUTION
Technetium-99 is injected into the patient for use in nuclear scans.
MOLYBDENUM-99
TECHNETIUM-99
Canada's NRU reactor is 51 years old and supplies
31%
of the world's Molybdenum-99
135 Megawatts
Reactor capacity
Other: HFR-France; BATAN; AEA; Ludmille/Ruslan; Leningrad NPP; MIR; SM-3
4%
5
70 MW
Argentina's CNEA/RA-3 is 40 years old and supplies
1%
OSIRIS in France is 42 years old and supplies
8%
South Africa's SAFARI is 43 years old and supplies
3%
20
BR2 in Belgium is 47 years old and supplies
10%
100 MW
45 MW
The Netherlands' HFR-Petten reactor is 47 years old and supplies
33%
NOTE: The radioisotope production of Australia's OPAL reactor, commissioned in 2007, is not available.
TONIA COWAN/THE GLOBE AND MAIL
SOURCES: CANADIAN NUCLEAR SAFETY COMMISSION, DIAGNOSTICIMAGING.COM, HOW STUFF WORKS.COM

Supply Chain Challenges

Supply Chain Challenges

With a 5% annual growth rate for imaging, the demand will exceed the supply by the end of the decade.

This assumes that all reactors are capable of irradiating the targets at all times.

With routine maintenance, unexpected maintenance, and shutdowns due to safety concerns, there have been severe disruptions over the past several years.

In 2009, the demand exceeded the supply and created a worldwide shortage of ^{99}Mo.

Supply Chain Challenges

Several of the reactors are reaching the end of their lifetimes, since they are 40 to over 50 years old.

Between 2000 and 2010, there were six unexpected shutdowns of reactors used for medical imaging products due to safety concerns with the Canadian one shut down in May 2009 due to a leak in the reactor with its return to service more than a year later in August 2010.

There are only four bulk ^{99}Mo processors that supply the global market, located in: Canada, Belgium, The Netherlands, and South Africa.

Australia and Argentina produce bulk ^{99}Mo for their domestic markets but are expected to export small amounts in the future.

Supply Chain Challenges

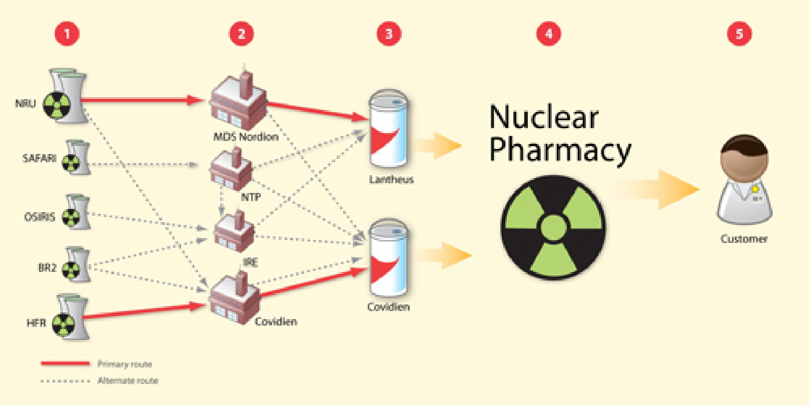
There are parts of the world in which there are no processing facilities for ^{99}Mo, including the United States, parts of South America, and Japan.

Such limitations in processing capabilities limit the ability to produce the medical radioisotopes from regional reactors since long-distance transportation of the *Mo* targets raises safety and security risks, and also results in greater decay of the product.

The number of generator manufacturers with substantial processing capabilities is under a dozen.

In 2015, the Canadian reactor is scheduled for complete shutdown, raising critical questions for supply chain network redesign, since its processing facility will also need to be shut down.

^{99}Mo Supply Chain for the US



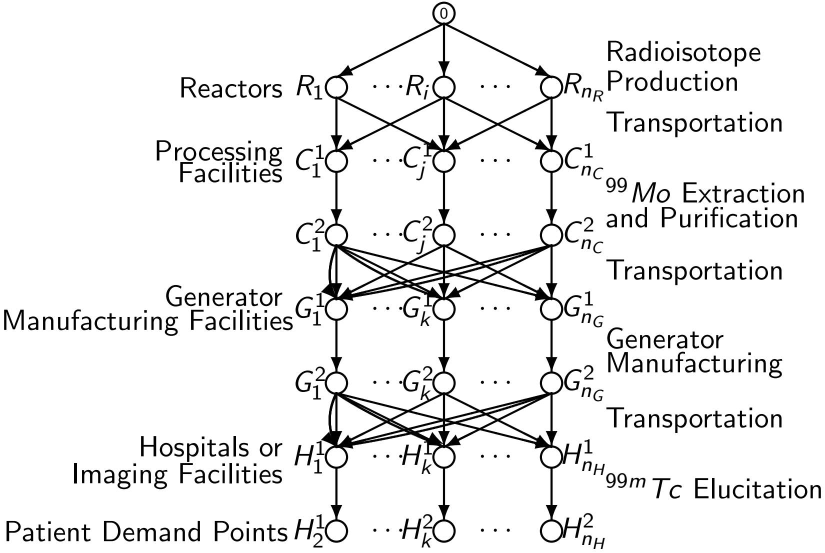
The Medical Nuclear Supply Chain
Network Design Model

The Medical Nuclear Supply Chain Network Design Model

We consider a possible network topology of the medical nuclear supply chain.
We assume that in the initial supply chain network topology, there exists at least one path joining node 0 with each destination node: $H_1^2, \ldots, H_{n_H}^2$.
This assumption guarantees that the demand at each demand point will be met.

The initial template should include both existing facilities (nodes) and processes (links) as well as prospective new ones that are to be quantifiably evaluated and selected from.

The Medical Nuclear Supply Chain Network Topology



The possible supply chain network topology, as depicted in Figure 1, is represented by $\mathcal{G} = [N, L]$, where N and L denote the sets of nodes and links, respectively. The ultimate solution of the complete model will yield the optimal capacity modifications on the various links of the network as well as the optimal flows.

Let d_k denote the demand for the radioisotope at the demand point H_k^2; $k = 1, \ldots, n_H$.

The Link Operational Costs

With each link of the network, we associate a unit operational cost function that reflects the cost of operating the particular supply chain activity.

The unit operational cost on link a is denoted by c_a and is a function of flow on that link, f_a. The *total* operational cost on link a is denoted by $\hat{c}_a$, and is constructed as:

Capturing the Underlying Physics Through Link and Path Multipliers

We associate with every link a in the network, a multiplier α_a, which corresponds to the percentage of decay and additional loss over that link.

This multiplier lies in the range (0,1], for the network activities, where $\alpha_a = 1$ means that 100% of the initial flow on link a reaches the successor node of that link, reflecting that there is no decay/waste/loss on that link.

The multiplier α_a can be modeled as the product of two terms, a radioactive decay multiplier α_{d_a} and a processing loss multiplier α_{l_a}.

Radioactive Decay Multiplier

The activity of a radioisotope (in disintegrations per unit time) is proportional to the quantity of that isotope, i.e.,

$$\frac{dN}{dt} \propto N, \tag{2}$$

where $N = N(t) =$ the quantity of a radioisotope.
We can represent the radioactive decay multiplier $\alpha_{d\,a}$ for link a as

$$\alpha_{d\,a} = e^{-\lambda t_a}, \tag{4}$$

and t_a is the time spent on link a. The decay constant, λ, in turn, can be conveniently represented by the half-life $t_{1/2}$, where

$$t_{1/2} = \frac{\ln 2}{\lambda}. \tag{5}$$

We can write $\alpha_{d\,a}$ as

$$\alpha_{d\,a} = e^{-\lambda t_a} = e^{-\ln 2 \frac{t_a}{t_{1/2}}} = 2^{-\frac{t_a}{t_{1/2}}}. \tag{6}$$

The processing loss multiplier α_{l_a} for link a is a factor in the range (0,1] that quantifies for the losses that occur during processing. Different processing links may have different values for this parameter.

For transportation links there is no loss beyond that due to radioactive decay; therefore, $\alpha_{l_a} = 1$ for such links. For the top-most manufacturing links $\alpha_a = 1$.

The organization is also responsible for disposing the waste which is hazardous.

The Link Discarding Costs

Since α_a is constant, and known apriori, a total discarding cost function, $\hat{z}_a$, can be defined accordingly, which is a function of the flow, f_a, is assumed to be given by:

$$\hat{z}_a = \hat{z}_a(f_a), \qquad \forall a \in L. \tag{8}$$

Note that, in processing/producing an amount of radioisotope f_a, one knows from the physics the amount of hazardous waste and, hence, a discarding function of the form (8) is appropriate.

The Organization's Objectives

The organization wishes to determine which facilities should operate and at what level, and is also is interested in possibly redesigning the existing capacities with the demand being satisfied, and the total cost being minimized.

The Link Investment / Reduction Costs

Let $\bar{u}_a$ denote the nonnegative existing capacity on link $a, \forall a \in L$.
The organization can enhance/reduce the capacity of link a by $u_a, \forall a \in L$.
The total investment cost of adding capacity u_a on link a, or contrarily, the induced cost of lowering the capacity by u_a, is denoted by $\hat{\pi}_a$, and is a function of the change in capacity:

$$\hat{\pi}_a = \hat{\pi}_a(u_a), \qquad \forall a \in L. \tag{14}$$

The Total Cost Minimization Problem

The total cost minimization objective faced by the organization includes the total cost of operating the various links, the total discarding cost of waste/loss over the links, and the total cost of capacity modification. This optimization problem can be expressed as:

$$\text{Minimize} \quad \sum_{a \in L} \hat{c}_a(f_a) + \sum_{a \in L} \hat{z}_a(f_a) + \sum_{a \in L} \hat{\pi}_a(u_a) \tag{15}$$

subject to: constraints (9), (11), and (13), and

$$f_a \leq \bar{u}_a + u_a, \qquad \forall a \in L, \tag{16}$$

$$-\bar{u}_a \leq u_a, \qquad \forall a \in L. \tag{17}$$

If $\bar{u}_a = 0$, $\forall a \in L$, then the redesign model converts to a *design from scratch* model.

Case Study: North America

Highlights of a Case Study

We considered the Molybdenum-99 supply chain in North America with the focus on the Canadian reactor, the Canadian processing facility, and the two US generator manufacturing facilities.

This reactor (and associated processing facility) is scheduled to be decommissioned around 2016.

Highlights of a Case Study

The NRU reactor is located in Chalk River, Ontario.

The AECL-MDS Nordion processing facility is located in Ottawa.

Transportation of the irradiated targets from NRU to AECL - MDS Nordion takes place by truck.

Two generator manufacturers in the United States (and none in Canada), Lantheus in Billerica, Massachusetts and Covidien, outside of St. Louis, Missouri.

We considered the supply chain network design problem from scratch, assuming that the $\bar{u}_a = 0.00$, for all links.

Highlights of a Case Study

We calculated the values of the arc multipliers α_{da}, for all links $a = 1, \ldots, 20$, using data in the OECD (2010a) report and in the National Research Council (2009) report, which included the approximate times associated with the various links in the supply chain network.

According to OECD (2010a), we may assume that there is no loss a_{la} on each link a for $a = 1, \ldots, 20$, except for processing link 3; hence, $\alpha_{la} = 1$ for all the former links; therefore, $\alpha_a = \alpha_{da}$ for all those links, as reported in Table 1. In the case of link 3, $\alpha_{la} = .8$ and $\alpha_{da} = .883$; therefore, $\alpha_3 = .706$.

All capacities and flows are reported in Curies.

Highlights of a Case Study

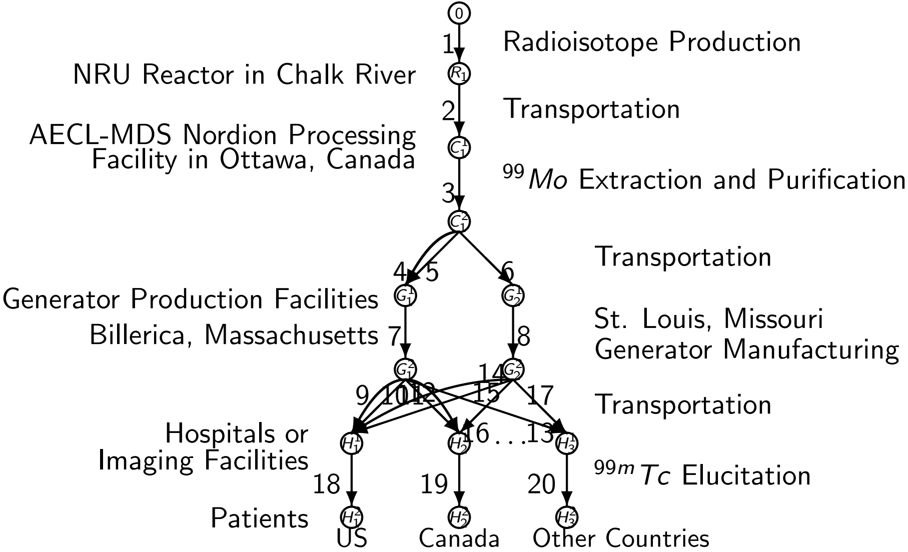
Capital and operating cost data were taken from OECD (2010b) and converted to per Curie processed or generated. As noted by the National Research Council (2009), the US generator prices are proprietary, but could be estimated from a functional form derived from publicly available prices for Australian generators coupled with several spot prices for US made generators.

We assumed three demand points corresponding, respectively, to the collective demands in the US, in Canada, and in other countries (such as Mexico, and the Caribbean Islands).

We are using 3 demand points, as approximations, in order to be able to report the input and output data.

The demands were as follows: $d_1 = 3,600$, $d_2 = 1,800$, and $d_3 = 1,000$ and these denote the demands, in Curies, per week. These values were obtained by using the daily number of procedures in the US and extrapolating for the others. The units for the path and link flows are also Curies.

North America Supply Chain Topology



Input Data and Optimal Link Flow and Capacity Solution

	Loss	Operating Cost	Discarding Cost	Investment Cost	Initial Capacity	Flow	Capacity
Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	$\bar{u}_a$	f_a^*	u_a^*
1	1.00	$2f_1^2 + 25.6f_1$	0.00	$u_1^2 + 743u_1$	0.00	$15,034$	15,034
2	.969	$f_2^2 + 5f_2$	0.00	$.5u_2^2 + u_2$	0.00	$15,034$	15,034
3	.706	$5f_3^2 + 192f_3$	$5f_3^2 + 80f_3$	$.5u_3^2 + 289u_3$	0.00	$14,568$	14,568
4	.920	$2f_4^2 + 4f_4$	0.00	$.5u_4^2 + 4u_4$	0.00	$4,254$	4,253
5	.901	$f_5^2 + f_5$	0.00	$2.5u_5^2 + 2u_5$	0.00	$1,286$	1,286
6	.915	$f_6^2 + 2f_6$	0.00	$.5u_6^2 + u_6$	0.00	$4,744$	4,744
7	.804	$f_7^2 + 166f_7$	$2f_7^2 + 7f_7$	$.5u_7^2 + 289u_7$	0.00	$5,072$	5,072
8	.804	$f_8^2 + 166f_8$	$2f_7^2 + 7f_7$	$.5u_8^2 + 279u_8$	0.00	$4,341$	4,341
9	.779	$2f_9^2 + 4f_9$	0.00	$.5u_3^2 + 3u_9$	0.00	0.00	0.00
10	.883	$f_{10}^2 + 1f_{10}$	0.00	$.5u_{10}^2 + 5u_{10}$	0.00	2,039	2,039
11	.883	$2f_{11}^2 + 4f_{11}$	0.00	$.5u_{11}^2 + 3u_{11}$	0.00	2,039	2,039
12	.688	$f_{12}^2 + 2f_{12}$	0.00	$.5u_{12}^2 + f_{12}$	0.00	0.00	0.00
13	.688	$2.5f_{13}^2 + 2f_{13}$	0.00	$.5f_{13}^2 + u_{13}$	0.00	0.00	0.00
14	.779	$2f_{14}^2 + 2f_{14}$	0.00	$u_{14}^2 + uf_{14}$	0.00	0.00	0.00
15	.883	$f_{15}^2 + 7f_{15}$	0.00	$2u_{15}^2 + 5u_{15}$	0.00	2,037	2,037
16	.688	$2f_{16}^2 + 4f_{16}$	0.00	$.5u_{16}^2 + u_{16}$	0.00	0.00	0.00
17	.688	$2f_{17}^2 + 6f_{17}$	0.00	$u_{17}^2 + u_{17}$	0.00	1,453	1,453
18	1.00	$2f_{18}^2 + 800f_{18}$	$4f_{18}^2 + 80f_{18}$	$.5u_{18}^2 + 10u_{18}$	0.00	3,600	3,600
19	1.00	$f_{19}^2 + 600f_{19}$	$1f_{19}^2 + 60f_{19}$	$.5u_{19}^2 + 5u_{19}$	0.00	1,800	1,800
20	1.00	$f_{20}^2 + 300f_{20}$	$1f_{20}^2 + 30f_{20}$	$.5u_{20}^2 + 2u_{20}$	0.00	1,000	1,000

Highlights of a Case Study

The total cost associated with this supply chain network design was: 2,976,125,952.00.

The computed capacity at the Canadian reactor is 33,535, whereas the computed capacity at the processor is 32,154. Hence, one can infer from the above analysis that both of these are operating with excess capacity, which has been noted in the literature.

The case study demonstrates how data can be acquired and the relevance of the output results. With our model, a cognizant organization can then investigate the costs associated with new supply chain networks for a radioisotope used in medical imaging and diagnostics.

Summary and Suggestions for Future Research

Summary and Suggestions for Future Research

Here, we developed a rigorous framework for the design and redesign of medical nuclear supply chains.

We focused on the most widely used radioisotope, Molybdenum, ^{99}Mo, which is used in medical diagnostics for cancer and cardiac problems. *Nuclear supply chains have numerous challenging features, including: time-sensitivity of the product, which is subject to radioactive decay, the hazardous nature of production and transportation as well as waste disposal.*

Radioisotopes are produced globally in only a handful of reactors and the same holds for their processing.

The nuclear reactors where they are produced are aging and have been subject to failures creating shortages of this critical healthcare product.

The contributions in the paper can serve as *foundation for the investigation of other medical nuclear product supply chains*.

The framework can serve as the basis for *exploration of alternative behaviors among the various stakeholders, including competition*.

It can be used to *the vulnerability of medical nuclear supply chains* and to explore alternative topologies and the associated costs.

Future Challenges
What needs to be done? — What can be done?

Alternative Reactors — .

Alternative methods of Irradiation —.

New Technologies —

Small B&W Reactor

Diversifying Mo 99 Supply: Medium Term

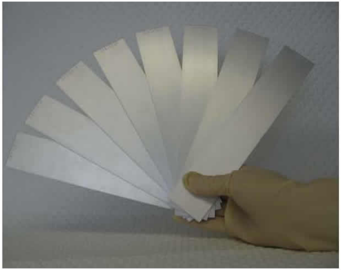
- Development work began in 1/26/09
- Dedicated isotope production facility
- Low Enriched Uranium (LEU) fueled Aqueous Homogeneous Reactor
- Significant joint investment: $80-110M over life of project
- Target capacity is 4,400 Curies per week
- Fuel is recycled after Mo 99 is removed, minimizing radioactive waste and uranium usage
- First installation designed to meet majority of Covidien U.S. demand - completion in 2014
- Additional Installations elsewhere in world

B&W Solution-Based Reactor
4 ft. tall, 22" diameter

HEU / LEU considerations

- Current target technology

- Target design & Manufacturing
  - Yield (R&D)
  - Safety (Licensing)
- Transport of targets to reactor
  - Container design
  - Storage at reactor sites
- Reactor irradiation (licenses)
  - (Reactor safety Cie)
  - Available irradiation 'space'
- Transport of irradiated targets to Mo-99 processing facility
  - Container design & license



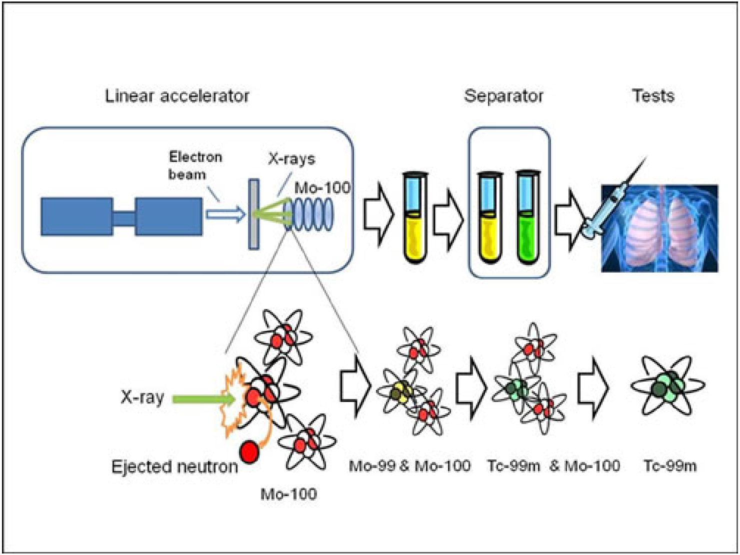
HEU / LEU considerations

- Current target technology

- Mo-99 processing
  - Process design
  - Waste treatments (gas, liquid, solid)
  - (Chemical) yield
  - Impurities
  - DMF
- Generator validation
  - FDA, Health Canada
  - European competent authorities

Image from Covidien

Linear Accelerator



THANK YOU!

This presentation is based on the papers,
Medical Nuclear Supply Chain Design: A Tractable Network Model and Computational Approach, Anna Nagurney and Ladimer S. Nagurney, *International Journal of Production Economics* 140(2): (2012) pp 865-874,
Securing the Sustainability of Global Medical Nuclear Supply Chains Through Economic Cost Recovery, Risk Management, and Optimization Anna Nagurney, Ladimer S. Nagurney, and Dong Li, to appear in the *International Journal of Sustainable Transportation*,
and the book,
Networks Against Time: Supply Chain Analytics for Perishable Products, Anna Nagurney, Min Yu, Amir H. Masoumi, and Ladimer S. Nagurney, Springer, available January 2013