PHY138Y – Nuclear and Radiation Section

Supplementary Notes V

Radioisotopes in Medicine

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References.

- 1. P.P. Dendy and B. Heaton, Physics for Radiologists (Blackwell, 1987).
- 2. Russell K. Hobbie, Intermediate Physics for Medicine and Biology (3rd ed., Wiley, 1978)
- 3. R.D. Badawi, *Nuclear Medicine*, Physics Education 36, 452-459 (2001): see the *Reference* section of the N&R Web page.
- 4. D.E.S. McNeill and K.G. McNeill, Notes for PHY238Y (Kishmul Resources, 2002).
- 5. P.Savaria, Notes for PHY238Y (unpublished, 2002).
- 6. The Knight text, §42.7 (p.1374), has a brief discussion of medical uses of radiation, and a nice picture of a PET scan of the brain on p.1187.
- The Globe and Mail (<u>http://www.theglobeandmail.com/</u>) have several good articles on tracers, prompted by the crisis in production caused by an aging reactor. Search their archives for "isotopes" – the December 7, 2007 article is particularly detailed.

5.1 Introduction

Radioisotopes have a multitude of uses in both diagnosis and therapy. This is a *huge* subject, and these notes will touch on only a few of the interesting topics.

For diagnosis, a selected radioisotope is introduced into the body; its subsequent distribution can be observed by detecting the emitted radiation. In this case, the radioisotope acts as a tracer for a specific physiological process.

Radiation therapy falls into two types: **teletherapy**, where the radiation from a radioisotope is directed into the body from the outside, and **brachytherapy** (the root comes from Greek, meaning short distance), in which the radioisotope is placed close to the site of the cancerous tissue.

5.2 Radioisotopes for Diagnosis

For diagnostic use, radioisotopes are attached to a drug or a pharmaceutical that is known to target a specific organ. The pharmaceutical is then introduced into the patient by injection, inhalation, or ingestion, and its future is watched with interest by a variety of sophisticated detectors. The resultant data is analyzed using equally sophisticated software. Diagnostic nuclear medicine examinations are used to identify abnormalities in the brain, thyroid, heart, lung, kidney, liver, spleen, and bone.

5.2.1 Tracers

A compound that concentrates in the organ of interest is tagged by attaching a known radioisotope. Technetium (^{99m}Tc) is one of the most commonly used in scans of many different organs. It combines with many chemical compounds, and its half-life of 6 hours is short enough to keep the long-term dose low, but long enough to allow adequate time for a good signal. I've listed some other commonly used radioisotopes in the table. Typical tracer activities are around 0.1 mCi.

Radio isotope	Half-life	Decay Mode	Organ to be scanned	
¹²³ I	13 hours	EC , γ	Thyroid	
¹³¹ I	8 days	β ⁻ , γ	Thyroid	
¹⁹⁸ Au	2.7 days	β ⁻ , γ	Liver	
²⁰¹ Tl	3.0 days	EC, y	Heart	
^{111m} In	2.8 days	IT, γ	Blood	
⁸⁵ Sr	65 days	EC, y	Bone	
EC: Floatnon Cantuna IT: Isomonia Transition				

EC: Electron Capture. IT: Isomeric Transition

Many radioisotopes – including almost two-thirds of the world's supply of 99m Tc – are produced at the reactors of the Chalk River Laboratories in Ontario (Atomic Energy of Canada Limited, AECL).

The figure (Ref.3, figure 1) shows posterior and anterior wholebody scans of a patient who has ingested ^{99m}Tc. The 'hot spots' indicate disease in the bone. The difference in intensity of the hot spots is due to the attenuation of the radiation in the patient's bone and tissues.



5.2.2 Single Photon Emission Computed Tomography (SPECT)

Here the gamma radiation from a radioisotope in the patient's body is detected at a variety of angles around the patient, and the results used to reconstruct slices through the patient using a process similar to that used for CT scans. The dose absorbed by the patient is greater than that absorbed during a single planar view, due to the longer time required for a SPECT scan.

5.2.3 Positron Emission Tomography (PET)

PET uses the pair production that occurs after a positron, emitted from an ingested radiopharmaceutical, annihilates with an electron. The positron emerges from the decay and slows down in tissue within a few millimeters; when it is virtually at rest, it annihilates with a local electron. The resultant 511 keV gamma rays (the electron and positron have the same mass of 511 keV/c^2), conserving momentum, travel in directly opposite directions out of the patient's body. Simultaneous (coincident) detection of the two gamma rays gives a precise line along which the radionuclide must lie. If the detectors can also measure the difference between the times of arrival of the two photons, the position along this line can be identified. The detection of many such coincident events at different angles allows the area where the radiopharmaceutical has concentrated to be precisely located. The experimental set-up is similar to that used for CT scans discussed in SNII.

Some of the radionuclides available for PET are listed in the table. All are all very short lived, so an on-site cyclotron is a necessity for all but ¹⁸F, the most widely used.

Radioisotope	Half-life	Max. β+ Energy
	(min)	(MeV)
¹¹ C	20	0.96
¹³ N	10	1.19
¹⁵ O	2	1.70
¹⁸ F	110	0.64
⁸² Rb	1	3.15

Fluoro-deoxyglucose (FDG), in which the ¹⁸F has been incorporated, is absorbed into cells that have a high glucose metabolic rate – such as tumours. Once it is in the cell it does not further metabolize, so it accumulates in tumours where it serves as an excellent marker. This type of tomography is particularly valuable for **functional analyses** – i.e. investigations in which biological functions can be studied as they happen.

The figure (Ref.3, figure 7) shows a schematic of the detector array and indicates how the coincident signals are used to remove background noise.



5.2.4 Isotopic Dilution

Radioactive tracers can be used to determine the mass or volume of a fluid in the body. A radiopharmaceutical with a known activity, R, is introduced to the body. Once the radioisotope has dispersed throughout the bodily fluid, of total volume, V, a small volume, v, of fluid is extracted. Its activity, r, is then measured. The total volume of the fluid that received the radiopharmaceutical is then given by V = v R/r. This calculation assumes that the isotope has been thoroughly mixed in the fluid, and that there has been no dilution by nuclear or biological excretion (see §5.4.2).

Similarly, dilution techniques can measure the amount of what is called the **exchangeable pool** of a given element in the body; this is that part of the element being measured that exchanges with the environment through ingestion and excretion. For example, the exchangeable calcium in the body can be measured by dilution techniques; obviously the calcium deposited in the bones is not part of this exchangeable pool.

5.3 Radioisotopes for Therapy

In teletherapy, high activity isotopes can provide intense high energy gamma ray beams that are directed at diseased areas in a similar way to X-ray or electron beams. In brachytherapy, high activity radioisotopes are introduced into the body by ingestion or implantation, where the emitted radiation attacks a localized tumour.

5.3.1 Teletherapy

The most common radioisotope used in teletherapy is 60 Co, made by neutron activation of 59 Co, via 59 Co + n $\rightarrow {}^{60}$ Co, using neutrons from a nuclear reactor. Much of the world's supply of this isotope is made at the Chalk River Laboratories (AECL), and the first Cobalt therapy unit was brought into operation in London, Ontario, by Harold Johns, a professor at the University of Toronto, in 1951.

The advantages of Cobalt 'bomb' units include their compact size, the high energy and intensity of the gamma rays, and their relatively low cost; many clinicians prefer them for treatment of head, neck and breast cancer. However they cannot be switched off, so require great care in shielding medical personnel, and the source must be replaced every 3 to 5 years (the half life is 5.26 years); they are gradually being replaced by the more expensive and bulky linear accelerators. The effective energy of radiation from an X-ray machine is approximately one third of the maximum energy of the X-rays. ⁶⁰Co produces gamma rays of energies 1.17 and 1.33 Mev, with an average energy of about 1.25 MeV. Thus, approximately, the Cobalt machine radiation is as penetrating as that from a 3 MV X-ray machine. A typical ⁶⁰Co radiation unit uses a source of up to 100TBq (terra Bq = 10^{12} Bq).

 137 Cs, another previously popular isotope obtained from the fission products of a nuclear reactor, is no longer being produced for teletherapy; the gamma rays (662 keV) do not penetrate sufficiently to treat deep seated tumours, and the **specific activity** (the activity per gram) of 137 Cs is not so high as that of 60 Co.

5.3.2 Brachytherapy

Brachytherapy has a long history; Radium was used to treat cancer within five years of its discovery, by placing tubes or needles of the radioisotope in or on tumours. In Quebec and French speaking countries it is called Curietherapie in honour of you-know-who. Often beta emitters are preferred, due to the short range of beta particles in tissue, which ensures that the damage caused by the radiation is limited to the organ being targeted. Therapeutic radioisotopes should also have short half lives to reduce unwanted long-term effects. Some common diseases treated by brachytherapy are discussed below.

The thyroid gland accumulates Iodine. If the gland becomes cancerous, a dose of radioactive iodine, administered orally, can attack the cancerous cells. Since iodine does not accumulate in other parts of the body, the damage to healthy organs is limited. Several iodine isotopes are in common use (e.g. ^{123}I , ^{131}I) depending on the therapeutic requirements.

Another cancer often treated with brachytherapy is prostate cancer, the third cause of death by cancer of males in Canada; approximately 1 in 8 males will contract prostate cancer. Titanium catheters containing a suitable radioisotope (e.g. ¹²⁵I with a half life, $T_{\frac{1}{2}}$, of 60 days, or ¹⁰³Pd with $T_{\frac{1}{2}}$ = 17 days) are prepared and inserted through the perineum, guided by ultrasound images in real time. For aggressive cancers, temporary implants of high activity are used; for lower risk cancers, permanent low activity implants are used. The latter method of treatment has been found to be as efficacious as chemotherapy or surgery, with a much shorter hospital stay (usually one day) and less severe side effects.

Breast cancer is a leading cause of death in women; about 1 woman in 9 will develop breast cancer, or around 22,000 annually in Canada. Recently (2004), brachytherapy has been used in an experimental programme as a post-operative treatment for breast cancer in women. A selected group of patients at Toronto's Sunnybrook hospital have been treated by inserting 60 to 90 radioactive ¹⁰³Pd beads around the scar left after a surgical removal of a cancerous tumour in the breast (lumpectomy). The Palladium releases continuous low doses of radiation, replacing the conventional treatment of from two to seven months of daily radiation (of the order of 50 Gy delivered in 25 fractions) that requires regular hospital visits and often produces unpleasant side effects.

5.4 Radiometry

Teams of radiation physicists spend their lives calculating the most effective doses for different situations and calculating and refining methods of delivering them. In order to give you some insight into the basic concepts, this section presents some of the simpler considerations in the calculation of the dose received when radioisotopes are administered internally for diagnostic or therapeutic purposes.

5.4.1 Committed Dose

Let's consider the ingestion or implantation of a radioisotope into an organ of the body for therapeutic purposes. The total absorbed dose expected over the lifetime of the radioactivity in the body is called the **committed dose**.

First, consider the case where the radioisotope remains in the body, essentially for infinite time. In this case, the committed dose, denoted by $D_m (0 \rightarrow \infty)$ is just equal to the total number of radioactive nuclei that have decayed from the time the radioisotope was introduced, multiplied by the energy deposited by the products of each nuclear disintegration, e_n , divided by the mass of the organ in which the radiation is deposited.

That is,

$$D_m (0 \to \infty) = e_n N(0)/m,$$

where N(0) is the number of radioactive isotopes introduced into the organ at time t = 0, and *m* is the mass of the organ. N(0) is given by the usual formula:

$$N(0) = R(0)/\lambda$$

where λ is the disintegration constant. Thus the absorbed dose is

$$D_m(0\rightarrow\infty) = e_n R(0) / (\lambda m).$$

This can also be written as

$$D_m(0 \rightarrow \infty) = D_m(0)/\lambda$$

where the initial dose rate is written as

$$D_m(0) = [dD_m(t)/dt]_{t=0} = e_n R(0) /m.$$

As expected, the committed dose is proportional to the activity of the radioisotope, its energy and its half-life, and inversely proportional to the mass of the organ.

In many cases the implanted radioisotope is removed after a certain time, in order to ensure the delivery of the correct dose required for treatment. In this case, the calculation can be treated as a special case of the result calculated in the next section.

5.4.2 Biological Excretion

Of course, the natural decay of the radioisotope may not be the only mechanism whereby the radioactive nuclei disappear from the body or from an organ into which they have been introduced. Sometimes the introduced radioisotope is removed after some time by a medical procedure. Also, in all realistic cases, the biological processes of excretion must also be taken into account. The situation can be complicated – e.g. if the radioisotope is stored in the gut or bladder. However, for simplicity of calculation, it is usual to assume that the disappearance of an isotope from a particular organ caused by biological processes follows an exponential law.

Let us generalize the result in §5.4.1 to consider the case in which a radioisotope is introduced into an organ at time t = 0 and is removed after a time t = T, during which biological excretion operates. Assume that all of the energy from those nuclei that decay in the organ contribute to the absorbed dose in the organ; let each decay deposit energy e_n . Use the suffixes 'n' to denote nuclear decay, and 'be' to denote biological excretion. Remember that , for any number, N(t), of radioactive nuclei at time t, the activity – the number of <u>radioactive</u> decays per second – is given by $\lambda_n N(t)$. Here we must use the 'n' suffix.

(11)

At time *t*, the number of nuclei that decay in the organ in an interval of time d*t* due to nuclear decay can thus be written: where λ_n is the usual nuclear decay constant. $dN_n(t) = -\lambda_n N(t) dt$, (1)

Similarly, the number of nuclei that disappear from the organ in time dt due to biological excretion can be written: $dN_{be}(t) = -\lambda_{be}N(t) dt$, (2) where λ_{be} is called the **biological decay constant.** These are the fundamental equations.

First we use them to derive a couple of useful results. The total number of radioactive nuclei that disappear from the body in dt, at time t is the sum of the numbers above:

$$dN(t) = dN_n(t) + dN_{be}(t)$$

= $-\lambda_n N(t) dt - \lambda_{be} N(t) dt$
= $-(\lambda_n + \lambda_{be}) N(t) dt$
= $-\lambda_{eff} N(t) dt$ (3)

with $\lambda_{eff} = \lambda_n + \lambda_{be}$, is called the 'effective' decay constant. The solution of equation (3) (see §2.5 and §3.2) yields an expression for the number of nuclei remaining in the organ at time t:

$$N(t) = N(0) \exp(-\lambda_{eff} t)$$
(4)

As usual, N(0) is the number of radioactive isotopes introduced into the organ at t = 0.

Similarly, rearranging (1) above, we can calculate the decay rate at time *t* to be: $R(t) = |dN_n(t)/dt| = \lambda_n N(t)$ (6)

(Of course, this is obvious from the definition of these quantities, but is nice to see it also makes sense within the present formalism!)

Of course, only a fraction of the total number, N(t), of nuclei in the organ at time t, actually contribute to the absorbed dose in the organ by decaying; the rest are excreted before they deposit any energy. From (1) and (2) this fraction is:

$$f = dN_n(t)/dN(t) = \lambda_n / \lambda_{eff}$$
(5)

Since *f* is independent of the time, it must be the same fraction for any time interval – including the one from t = 0 to t = T. (Note to the mathematically fastidious – this is a ratio of two quantities, NOT a differential coefficient!).

We can now proceed to calculate the dose delivered to the organ. The number of nuclei disappearing from the organ – by decay or biological excretion – is the difference between the number of nuclei at time t = 0 and the number remaining at t = T:

$$(N(0) - N(T)) = N(0)\{1 - exp(-\lambda_{eff} T)\}$$
from equation (4)
(7)

The fraction of these nuclei that deposited their energy in the organ is f. Thus the energy deposited by these decays from t = 0 to t = T is

$$E_m(0 \rightarrow T) = e_n f(N(0) - N(T)) = e_n f N(0) \{1 - exp(-\lambda_{eff} T)\}$$
Substituting for *f* from equation (5), yields
$$(8)$$

$$E_m(0 \to T) = e_n \left(\lambda_n / \lambda_{eff}\right) N(0) \{1 - exp(-\lambda_{eff} T)\}, \qquad (9)$$

and for N(0) from equation (6), we obtain $F_{-}(0 \rightarrow T) = e_{-} R(0) (1 - e_{-}rn(-\lambda - \pi T)) (\lambda - \pi T) (10)$

$$E_m(0 \rightarrow T) = e_n R(0) \{ T - exp(-\lambda_{eff} T) \} / \lambda_{eff}$$
(10)
Thus, finally, the dose delivered in this time interval T is

$$D_m(0 \to T) = E_m(0 \to T)/m$$

= $e_n R(0) \{1 - exp(-\lambda_{eff} t) \}/(m \lambda_{eff})$

A more elegant derivation of this formulae is given in Appendix 5-A.

If the radioisotope is not removed from the organ, the dose to infinity, obtained by allowing $T \rightarrow \infty$, is thus $D_m(0 \rightarrow \infty) = e_n R(0) / (m \lambda_{eff})$, as we might expect by comparing to the formula in §5.4.1 above.

These calculations assume that the biological 'uptake' time is instantaneous. Appendix 5-B gives the result when the time for the organ to absorb the radioisotope cannot be neglected.

5.4.3 Exposure from a Beam of Particles

To calculate the dose from beam of photons, electrons, etc, directed into the body, we need to know the energy and type of the radiation emitted by the radioisotope being used and the fraction of that energy that remains in the irradiated organ. Tables exist to provide these numbers.

5.5 Generation of Radioisotopes

Most radioisotopes are created artificially by bombarding stable nuclides with beams from particle accelerators or by neutrons from nuclear reactors. Fission products from reactors are also a rich source of radioisotopes. Many modern medical facilities have onsite cyclotrons to produce their own radioisotopes. Chalk River Laboratories in Ontario are a leading player in this industry.

The fourth section in Ref.3, entitled 'Generation of Radiotracers' discusses the use of generators to produce radioisotopes for medicine. Here, I expand on the method of production for the commonly used radioisotope, technetium, ^{99m}Tc.

Consider a radioactive decay chain, in which a parent radioisotope decays to a daughter. Let $N_1(t)$ be the number of nuclides of the parent at time t, with half-life T_1 ; $N_2(t)$ is the number of daughter nuclides at time t, with half-life T_2 . Then the rate of change of the daughter can be written as:

 $(dN_2(t)/dt) = (\text{rate of formation of } N_2) - (\text{rate of decay of } N_2)$ = (rate of decay of N_1) - (rate of decay of N_2) = $\lambda_1 N_1(t) - \lambda_2 N_2(t)$

Substitute $N_1(t) = N_1(0)exp(-\lambda_1 t)$ and the equation can be solved (see Appendix 5-C) to give an expression for the activity of the daughter, $R_2(t)$, in terms of that of the parent,

$$R_1(t): \qquad R_2(t) = \lambda_2 N_2 = \lambda_1 N_1 \left\{ \frac{\lambda_2}{\lambda_2 - \lambda_1} \right\} \left\{ 1 - \exp[-(\lambda_2 - \lambda_1)t] \right\} \\ = R_1(t) \left\{ \frac{\lambda_2}{\lambda_2 - \lambda_1} \right\} \left\{ 1 - \exp[-(\lambda_2 - \lambda_1)t] \right\}$$

An interesting situation arises when the parent has a half-life that is much greater than that of the daughter: $T_1 >> T_2$, or $\lambda_1 << \lambda_2$. In that case, $R_2(t) = R_1(t)\{1 - exp(-\lambda_2 t)\}$. This function is plotted in the figure opposite. At times long compared to T_2 , the activity of the daughter becomes equal to the activity of the parent: $R_2(t) = \lambda_2 N_2 = \lambda_1 N_1 = R_1(t)$. This is called '**secular equilibrium**'.



For the production of ^{99m}Tc, the parent is ⁹⁹Mo (molybdenum-99). A simplified version of the relevant decay chain is sketched opposite. The half-lives of ⁹⁹Mo and ^{99m}Tc are about 2.5 days and 6 hours respectively.



The ⁹⁹Mo, produced as a fission product or by neutron bombardment of ⁹⁸Mo, is absorbed on alumina. Assuming that all of the ⁹⁸Mo decays to ^{99m}Tc, the latter accumulates according to the equation above: $R_2(t) = R_1(t) \{\lambda_2/(\lambda_2 - \lambda_1)\}\{1 - exp[-(\lambda_2 - \lambda_1)t]\}\}^*$ At regular intervals the column is flushed with a saline solution, which dissolves the ^{99m}Tc, leaving the Mo behind to generate more of it. In this way the ⁹⁹Mo acts as a 'cow' that can be 'milked' (the fancy word is 'eluted') of the more useful ^{99m}Tc.

The activities of the two radioisotopes are shown in the figure opposite, when the Mo cow is milked every day. Note that both parent and daughter decay, and that about a day (approximately 4 half-lives) is required for the ^{99m}Tc to reach its (approximately) maximum activity after milking. When that happens, **'transient equilibrium'** is said to have been reached.



^{*} In fact, since only 0.88 of the ⁹⁹Mo decays to ^{99m}Tc, $R_2(t)$ has to be multiplied by this fraction for this particular decay.

Appendix 5-A. Alternative Derivation of Committed Dose with Biological Excretion

If e_n is the energy deposited by each nuclear disintegration in the organ of mass *m*, then the incremental dose at time *t* in an interval d*t*, is given by the number of contributing decays in time d*t* multiplied by the energy per kg contributed by each:

 $dD_m(t \rightarrow t + dt) = |(e_n/m)dN_n(t)| = (e_n/m)\lambda_nN(t) dt = (e_n/m)R(t)dt$ $= (e_n/m)R(0)exp(-\lambda_{eff}t)dt.$

The total dose is the integral of $dD_m(t)$ from t = 0 to t = T is thus just the integral:

$$D_m(0 \to T) = \int_0^T dD_m(t) = (e_n/m)R(0)\int_0^T exp(-\lambda_{eff} t) dt = (e_n/m)R(0)\{1 - exp(-\lambda_{eff} T)\}/\lambda_{eff}$$

This can also be written as $D_m(0 \rightarrow T) = 1.44 \ e_n R(0) \ T_{eff} \{1 - exp(-\lambda_{eff} T)\}/m$.

Appendix 5-B. Committed Dose with Biological Uptake

If the time required for an organ to absorb an ingested radioisotope is comparable to the nuclear or biological half-life, the calculation given in §5.4.2 overestimates the committed dose. The calculation is complicated, depending on the precise assumptions made, and I quote only the result. If the uptake can be assumed to be exponential with a half-life of T_{bu} , the total absorbed dose in the organ is given by:

 $D_m (0 \to \infty) = (1.44 \ e_n R(0) \ T_{eff}/m)(1 - T_{up}/T_{eff})$, where $1/T_{up} = 1/T_{eff} + 1/T_{bu}$.

Appendix 5-C. Calculation of Parent Daughter Generation

Now search for a solution – try $N_2(t) = K(e^{-\lambda_1 t} - e^{-\lambda_2 t})$, where K is a constant. This satisfies the requirement that $N_2(t) = 0$, when t = 0 and $t = \infty$.

Inserting this trial solution into the equation yields LHS = $K(-\lambda_1 e^{-\lambda_1 t} + \lambda_2 e^{-\lambda_2 t}) = -K \lambda_1 e^{-\lambda_1 t} + K \lambda_2 e^{-\lambda_2 t}$ RHS = $\lambda_1 N_1(0) e^{-\lambda_1 t} - \lambda_2 K(e^{-\lambda_1 t} - e^{-\lambda_2 t}) = \lambda_1 N_1(0) e^{-\lambda_1 t} - \lambda_2 K e^{-\lambda_1 t} + K \lambda_2 e^{-\lambda_2 t}$

Equating yields:
$$-K \lambda_{1} e^{-\lambda_{1} t} = \lambda_{1} N_{1}(0) e^{-\lambda_{1} t} - \lambda_{2} K e^{-\lambda_{1} t}$$

Or $K = \{\lambda_{1}/(\lambda_{2} - \lambda_{1})\} N_{1}(0)$.
So $N_{2}(t) = K\{e^{-\lambda_{1} t} - e^{-\lambda_{2} t}\} = \{\lambda_{1}/(\lambda_{2} - \lambda_{1})\} N_{1}(0) \{e^{-\lambda_{1} t} - e^{-\lambda_{2} t}\}$
 $= \{\lambda_{1} N_{1}(0) e^{-\lambda_{1} t} / (\lambda_{2} - \lambda_{1})\} \{1 - e^{-(\lambda_{2} - \lambda_{1}) t}\}$
 $= \{R_{1}(t) / (\lambda_{2} - \lambda_{1})\} \{1 - e^{-(\lambda_{2} - \lambda_{1}) t}\}$

Finally $R_2(t) = \lambda_2 N_2(t) = \{R_1(t) \ \lambda_2 / (\lambda_2 - \lambda_1)\} \{I - e^{-(\lambda_2 - \lambda_1)t}\}$

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