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Reliability Analysis of Transfer Coefficients of an Iodine Biokinetic Model

Using Akaike Information Criterion

by

Pamela Bernadette P. Manglona

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Reliability Analysis of Transfer Coefficients of an Iodine Biokinetic Model Using Akaike Information Criterion

Thesis Abstract – Idaho State University (2020)

The ICRP 78 iodine model (base model) was assessed using the concepts of Akaike Information Criterion (AIC). AIC was used to identify transfer coefficients and compartments in the base model that are greatly affected by optimization and to evaluate the reliability of these model parameters. The initial assumption is that the base model is an adequate representation of iodine metabolism in the body. Optimizing the transfer coefficients should not cause large differences between the base and optimized transfer coefficient values. However, the study found that optimization causes large changes in the transfer coefficient values. The optimization of transfer rates describing iodine translocation from "rest of the body" to "blood", "blood" to "thyroid", "thyroid" to the "rest of the body", and "blood" to "urine" produced pseudo-models with weighted relative likelihoods consistently greater than the base model. There is weak evidence to support that the ICRP 78 iodine model is the best approximation of the iodine dataset used in the study. Further efforts in internal dosimetry modeling might benefit from looking at methods to identify transfer coefficients and compartments a priori to create more reliable models.

Key Words: AIC, iodine, compartmental biokinetic models, internal dosimetry, model assessment

Chapter 1:

INTRODUCTION

1.1. Statement of the Problem

Humans, animals, and other living things have always been constantly exposed to radiation. Sources of radiation and radioactive materials to which humans are exposed can be cosmogenic in nature, from terrestrial materials present since the formation of the earth, or from anthropogenic activities such as medical procedures, nuclear weapons testing or nuclear accidents. Internal radiation exposure from the uptake and translocation of radioactive material in the body may occur through various intake pathways such as inhalation, ingestion, injection, and absorption through skin or wounds. Biokinetic models are used in internal dosimetry to characterize the complex behavior of radioactive materials inside the body. These models define compartments and transfer coefficients to mathematically describe the translocation of radioactive material within the body, determine the initial intake, as well as provide an estimation of the internal doses received by an exposed individual.

The International Commission on Radiological Protection (ICRP) publishes documents providing information on different radionuclides, including element-specific biokinetic models used to calculate intakes and conduct internal dose assessment for occupational and environmental exposures. One such biokinetic model can be found in ICRP Publication 78 entitled "Individual Monitoring for Internal Exposure of Workers" (ICRP, 1997). Publication 78 describes an iodine biokinetic model with three compartments representing the blood, thyroid and a generalized compartment called the "rest of the body". Included in the model are five transfer coefficients characterizing iodine movement among these compartments. The ICRP released an updated iodine

biokinetic model for occupational intakes in Publication 137. This new model more than doubled the number of compartments and transfer coefficients describing iodine behavior in the human body. The additional compartments and subsystems in ICRP 137 were introduced with an apparent vision to provide more physiological basis for biokinetic modeling (Leggett 2010). The ICRP 137 biokinetic model was developed by consolidating various published models for extrathyroidal inorganic iodide, thyroidal iodine, and extrathyroidal organic iodine (Leggett 2010). The continuous development and expansion of compartmental biokinetic models in internal dosimetry poses the need for an approach to assess the strength of their predictive capability and the reliability of transfer coefficients used in these models.

1.2. Objectives of the Study

The study aims to assess the transfer coefficients of the ICRP 78 iodine biokinetic model using the concepts of Akaike Information Criterion (AIC). AIC is a statistical analysis technique mostly used in model selection. It evaluates the quality of statistical models by estimating the respective information lost by the models relative to each other, based on a given dataset.

The iodine biokinetic model described in ICRP 78 is investigated in the study because of its relatively simple but adequate structure that allows for a meaningful assessment of the importance of various compartments and transfer coefficients. The principles of AIC are applied to identify compartments and transfer coefficients greatly affected by model optimization. AIC is also used to determine the relative likelihood of models with optimized parameters compared to the ICRP 78 iodine biokinetic model, and to evaluate the reliability of transfer coefficients in the biokinetic model. The asymptotic equivalence of AIC to cross-validation allows for the analysis of the biokinetic model using a relatively small data set.

1.3. Hypothesis Testing

The study considers the following hypotheses:

$H_{0,1}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,1}$: The optimized "rest of the body" to blood, k(1,3), transfer coefficient improves the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,2}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,2}$: The optimized blood to thyroid, k(2,1), transfer coefficient improves the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,3}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,3}$: The optimized thyroid to "rest of the body", k(3,2), transfer coefficient improves the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,4}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,4}$: The optimized "rest of the body" to feces, k(4,3), transfer coefficient improves the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,5}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,5}$: The optimized blood to urine, k(5,1), transfer coefficient improves the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,6}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,6}$: The optimized k(2,1) and k(3,2) transfer coefficients improve the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,7}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,7}$: The optimized k(2,1) and k(5,1) transfer coefficients improve the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,8}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,8}$: The optimized k(3,2) and k(5,1) transfer coefficients improve the ICRP 78 iodine biokinetic model's representation of the given dataset.

$H_{0,9}$: The ICRP 78 iodine biokinetic model is an adequate model for the given dataset.

$H_{A,9}$: The optimized k(2,1), k(3,2) and k(5,1) transfer coefficients improve the ICRP 78 iodine biokinetic model's representation of the given dataset.

The null hypothesis, for each case, will not be rejected if the ICRP 78 iodine biokinetic model (base model) has a weighted relative likelihood or Akaike weight w_i of 1.0 to 0.5. This means that there is not enough evidence to support that a competing model is a more adequate representation of the dataset than the base model.

If the optimization of transfer coefficient(s) produces a model with a weighted relative likelihood or Akaike weight w_i greater than the base model (i.e. greater than 0.5), the null hypothesis will be rejected in favor of the alternative hypothesis. This would mean that there is sufficient evidence to support that a competing model provides a better representation of the given dataset than the base model.

Chapter 2:

LITERATURE REVIEW

2.1. Modeling

A model is used as a representation of a system or phenomena being investigated. Models provide descriptions that allow for better understanding of the nature of the system as well as its underlying mechanisms and processes. Models are developed from observations, assumptions, and experimentations in order to describe, explain, and predict the complex behavior of various systems or subjects in the physical world (Dym 2006). Mathematical terms are often used in modeling to define functional relationships, give quantifiable meaning to observed results, and enable model validation and verification.

2.1.1. Model Fitting Using Least Squares and Maximum Likelihood Estimation

Making sound inferences from observed data requires finding the best approximating model of the information in a dataset (Burnham and Anderson 2002). Two common methods to estimate model parameter values are the least squares (LS) approximation and maximum likelihood estimation (MLE). LS approximations estimate the value of model parameters by considering the differences or residuals between observed data and the model fit. The estimated parameters that minimize the sum of the squared residuals between known data points and the values from a fitted model is considered the best approximation of the given dataset.

Maximum likelihood estimation (MLE) determines the value of model parameters by maximizing the likelihood of producing the given dataset from the model. It may be useful to understand the distinction between probability and likelihood in order to better understand

likelihood estimation. Probability is concerned with quantifying the occurrences of an outcome. Given a model and model parameters, the probability distribution describes how likely a particular event would occur. Likelihood is a function of estimated parameters that describe the probability of obtaining the known data (Burnham and Anderson 2002). The likelihood function characterizes the confidence in the model for producing the observed data. Different likelihoods can be computed for various estimates of an unknown parameter p. The best estimated parameter $\hat{p}$ maximizes the likelihood function.

2.2. Akaike Information Criterion

The Akaike Information Criterion (AIC) provides a measure of parsimony or the balance between the goodness-of-fit of a model to a given dataset and model complexity (Aho, et al. 2014). AIC was first introduced by Hirotugu Akaike in order to develop an estimate of the probability distribution of a future observation (Akaike 1978). The criterion has been found to be asymptotically equivalent to cross-validation (Korner-Nievergelt 2015, Stone 1977), which means AIC is able to estimate out-of-sample prediction error and evaluate the predictive accuracy of a model (Gelman 2013). AIC does not assume there is a known correct or "true" model representing the data, instead it allows for a set of models to be tested relative to each other in order to find the "best" predictive model for the given dataset (Burnham and Anderson 2002). AIC can be generally expressed as:

$$AIC = -2\ln(\hat{L}) + 2\mathrm{K} \tag{2.1}$$

The variable $\hat{L}$ represents the maximum value of the likelihood function for the model being investigated, while K is the number of estimated model parameters. The first term of the equation accounts for goodness-of-fit where the "-2" factor suggests that a lower AIC means a better model

fit. The second part of the equation serves as a penalty term to account for complexity. The more parameters added to a model, the higher it is penalized.

AIC can be adjusted for small sample sizes by multiplying a correction factor to the penalty term (Burnham and Anderson 2002),

$$AIC_C = -2\ln(\hat{L}) + 2K\left(\frac{n}{n-K-1}\right) \tag{2.2}$$

which can be simplified as:

$$AIC_C = AIC + \frac{2K(K+1)}{n-K-1} \tag{2.3}$$

where AIC_c is the corrected AIC when the ratio of sample size n to the number of adjustable parameters K is small, about less than 40. However, individual AIC scores by themselves are not very useful when selecting the best model among a model set. The relative AIC scores of the models compared with each other provide more insight when ranking models. A quantity known as the AIC difference or ΔAIC is used to rank models in a model set,

$$\Delta AIC = AIC_i - AIC_{min} \tag{2.4}$$

where AIC_i is the AIC of model i, and AIC_{min} is the lowest AIC among the model set. AIC_{min} is the AIC value associated with the best model among the candidate models. The best model will therefore have a $\Delta AIC \geq 0$. A low ΔAIC value for model "i" indicates that the model has a comparable predictive power to the best model, while a high ΔAIC value suggests that there is little evidence to support model "i".

The quantity relative likelihood is proportional to the probability that a particular model describes a given dataset better than another model (Burnham and Anderson 2002). The relative likelihood is calculated using the AIC differences:

$$e^{-\frac{1}{2}(\mathrm{AIC}_i - \mathrm{AIC}_{min})} \quad \text{or} \quad e^{-\frac{1}{2}(\Delta\mathrm{AIC})} \tag{2.5}$$

where AIC_i can be greater than or equal to AIC_{min}. Burnham and Anderson in their book "Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach" (2002), further described the relative likelihood of a model by defining a normalized set of positive quantities called Akaike weights, w_i,

$$w_i = \frac{e^{-\frac{1}{2}(\Delta AIC_i)}}{\sum_{r=1}^{R} e^{-\frac{1}{2}(\Delta AIC_r)}} \tag{2.6}$$

The Akaike weight of a particular model "i" is found by dividing its relative likelihood by the sum of all the relative likelihoods in the model set R, wherein the calculated w_i for all models of interest must add to 1. An Akaike weight of 1 suggests that a particular model is about 100% more plausible to be the best approximating model for a given dataset compared to other candidate models. Likewise, an Akaike weight of 0.5 means that there is about 50% support for a particular model to be the best representation of the dataset when compared to other models in the model set. Therefore, the model with the largest Akaike weight is considered the best model among the model set.

2.3. Biokinetic Models in Internal Dosimetry

Internal dosimetry is a scientific technique that is used to calculate, investigate, and assess radiation inside the body (Li 2018). Deposition of radiation energy within the body can result to excitation and ionization of molecules and atoms in tissues and even directly in the DNA, which then can lead to various biological outcomes (Potter 2004). These biological effects depend on the amount of radioactive material deposited within the body, type and energy of radiation emitted, physical and biological half-life of the radionuclide, and the duration and location of retention within the body. The complex and dynamic behavior of radioactive material inside the body is characterized in internal dosimetry using biokinetic models.

A biokinetic model is a mathematical description of the time-dependent behavior of a substance that enters the body through various routes of intake such as ingestion, inhalation, injection, or absorption through skin or wounds (Leggett and Eckerman 1994). Biokinetic models are used to predict the distribution of internally deposited radioactive material in the body, as well as the rates and pathways at which radioactive material is eliminated from the body. These estimates of distribution and excretion are necessary for determining the individual doses received by different organs and tissues, as well as the effective dose received by the body as a whole.

Radiation protection programs commonly adopt biokinetic models published by the International Commission of Radiological Protection (ICRP) and the National Council of Radiation Protection and Measurements (NCRP). ICRP provides biokinetic models that are typically used for dose assessment due to intake via inhalation, ingestion, and intravenous injection (ICRP 1997, ICRP 2017). The NCRP developed a biokinetic model for radionuclide-contaminated wounds that has been used in many radiation protection and dose assessment scenarios (NCRP 2006). These biokinetic models consist of compartments representing the various organs and organ systems in the body and transfer coefficients describing the rates of the translocation of radioactive material within each compartment.

The ICRP biokinetic models can be broadly classified as either generic or systemic. Generic biokinetic models attempt to characterize radionuclide behavior after an intake and before uptake into the blood (Paquet 2019). ICRP has two recognized generic biokinetic models: human respiratory tract model and human alimentary or gastrointestinal tract model (ICRP 1997). Systemic models describe the translocation of radioactive material after it has been taken up into the blood (Pacquet 2019). Systemic biokinetic models are developed for individual elements.

Different radionuclides have specific biokinetic models that describe their respective behavior and translocation within the body (ICRP 1997, ICRP 2017).

Development of biokinetic models requires thorough investigation of the nature of radionuclides and the complex interactions they have within a human body. These models are created based on human and/or animal data from various sources such as clinical, experimental, and radiation incident studies (ICRP 2017). Internal dosimetry researchers continually examine biokinetic models and transfer coefficients and compartments often get revisited when new information or data become available or whenever an approach for model optimization is being tested.

2.4. Iodine

Iodine is a fundamental element for everyday life. Humans and animals need iodine in their bodies to produce thyroid hormones that are essential for growth and development. Iodine has numerous applications, ranging from disinfectant and coloring agents in industry to treatment of cancer in medicine. Non-radioactive (stable) iodine is generally found in nature in its inorganic form in sodium and potassium salts. Several radioisotopes of iodine are commonly produced in large quantities as fission products in nuclear reactors. Iodine radioisotopes with long enough half-lives may also be found in the environment due to fallout from nuclear weapons tests or nuclear accidents.

2.4.1 Physical and Chemical Properties of Iodine

Iodine, denoted by chemical symbol I with atomic number 53, is one of the nonmetallic elements classified as a halogen on the periodic table. Pure iodine, in its solid form at standard

temperature and pressure conditions, has a blueish-black crystalline appearance. It has a vapor pressure of 0.0413 kPa at 25°C, which is below its melting point of 113.6 °C. Due to this, iodine readily sublimes into a rich violet vapor consisting of diatomic iodine molecules (I_2) (L'Abbé 2003). Although iodine is the least reactive member of the halogen group, it can easily form compounds with various elements including organic materials and is typically found in nature in a combined state (ATSDR 2004).

There are 37 known isotopes of iodine, with atomic masses ranging from 108 to 144 and only one of which, ^{127}I, is stable (Baum, et al. 2009). Table 2.1 lists the properties of common iodine isotopes. Iodine isotopes with mass less than 127 are commonly generated in particle accelerators, while those with masses greater than 127 are typically produced as fission products in nuclear reactors and byproducts from nuclear weapons (ATSDR 2004). It is estimated that about 72% of uranium (U) and 75% of plutonium (Pu) fissions produce iodine isotopes either directly or as decay progenies following the isobaric transition of fission products (ATSDR 2004).

Table 2.1. Properties of common isotopes of iodine

Isotope	Half-life	Beta Energies, MeV (Yield, %)	Gamma Energies[a], keV (Yield, %)
^{123}I	13 hours	1.07 (97%)	159 (87%)
^{124}I	4.2 days	3.2[b] (24%)	602.7 (63%)
^{125}I	59 days	Auger electrons	35.5 (6.7%)
^{127}I	Stable	NA	NA
^{129}I	1.57×10^7 years	0.154[a]	39.6 (7.5%)
^{131}I	8 days	606.3 (89.9%)	364.5 (82%)

[a] highest yield
[b] maximum beta energy

The longest-lived radioisotope of iodine is ^{129}I with a half-life of about 15.7 million years (Baum, et al. 2009). Its slow decay rate makes it a less radiological concern compared to ^{131}I which

has a half-life of 8 days (Eisenbud and Gesell 1997). Iodine-131 is considered to be an important radioisotope of iodine due to its short half-life and because of its relatively high fission byproduct yield of 2.89% for ^{235}U and 3.86% for ^{239}Pu. It undergoes an isobaric transition to xenon-131 producing beta radiation with a maximum energy of 606 keV 89.9% of the time and a 364-keV photon with a yield of 81.7%, Iodine-131 is also commercially produced in nuclear reactors due to its valuable applications in diagnosis and cancer treatment in medicine as well as its uses as a radiotracer in industrial radiography (IAEA 2004).

2.4.2. Iodine Metabolism and Biokinetic Behavior

The main intake route for dietary iodine in humans is through ingestion (IOM 1999). Iodine in food and drink is commonly in the form of inorganic iodine (I_2). Once taken into the body, iodine is reduced to iodide (I^-) in the alimentary tract before its absorption into the bloodstream (Riggs 1952). The small intestine is considered the primary site for absorption although some may occur from the stomach and other sites of the gastrointestinal tract (Leggett 2010). Iodide absorbed in the bloodstream is rapidly distributed to the extracellular fluids (ECF) of tissues (Riggs 1952). The iodide ion is predominantly excluded from most cells but can freely traverse the red blood cell (RBC) membrane, which results in a rapid equilibrium of iodine concentration in the plasma and RBC water (Riggs 1952).

Circulating iodide is rapidly taken up by the thyroid gland and the kidneys (Leggett 2010). An iodine thyroidal uptake of 6% to 22% is estimated for euthyroid adults after 24 hours of intake (Kramer, et al. 2002). A protein molecule called sodium-iodide symporter (NIS) removes iodide in the plasma via active transport to the follicular cells of the thyroid gland. The thyroid gland plays a major role in iodine metabolism. It is composed of multiple spherical thyroid follicles that

are about a few hundredths of a millimeter in diameter (Leggett 2010). These follicles enclose a lumen filled with a viscous material primarily composed of thyroglobulin (Tg), which is a protein produced from the follicular cells and secreted into the lumen through exocytosis. The secreted thyroglobulin contains tyrosine chains that serve as the foundation for the synthesis of thyroid hormones (Leggett 2010). Iodide within the thyroid follicular cells enters the follicular lumen from the luminal membrane by a protein transporter called pendrin (Ahad and Ganie 2010). The iodide in the lumen is oxidized and converted to atomic iodine by the enzyme thyroid peroxidase (TPO). The resulting iodine attaches to the tyrosine chains of Tg in two possible configurations. A tyrosine chain may bind to a single iodine forming monoiodotyrosine (MIT) or to two iodine atoms forming diiodotyrosine (DIT) (Leggett 2010). MIT and DIT may couple to produce a molecule with three iodine atoms called triiodothyronine (T3), while two DIT molecules may also bind together to form a molecule with four iodine atoms called tetraiodothyronine or thyroxine (T4). The thyroglobulin with bounded T3 and T4 then reenters the follicular cell through endocytosis. Lysosomes in the follicular cells cause the T3 and T4 molecules to split from the Tg. They are then secreted into the bloodstream as free T3 and T4. Figure 2.1 illustrates these processes.

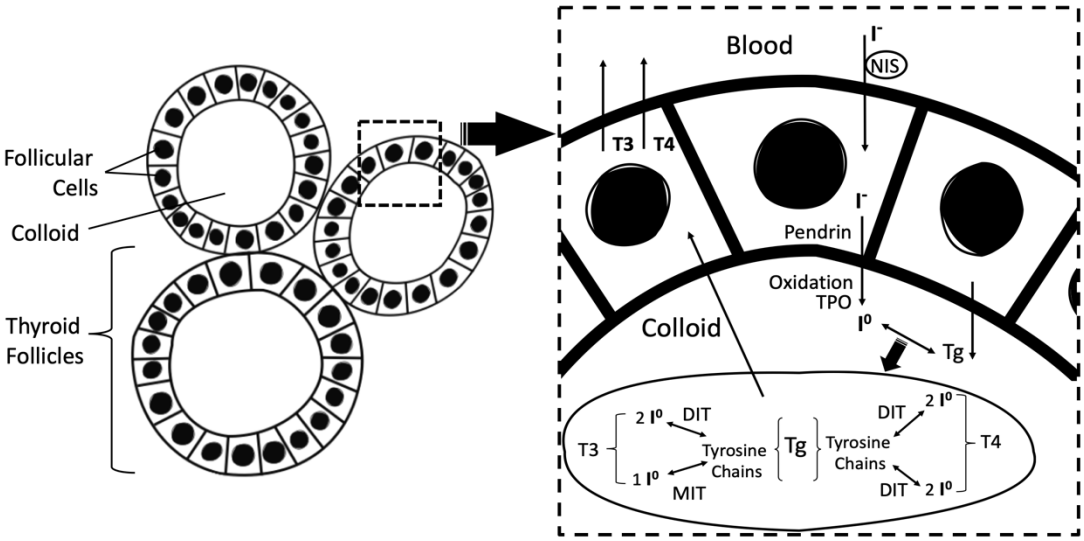


Figure 2.1. Illustration of thyroid follicles and synthesis thyroid hormones as described in section 2.4.2

Iodine is therefore removed from the thyroid in the form of the thyroid hormones, T3 and T4 (Ahad and Ganie 2010). T3 and T4 hormones that are released into the bloodstream may travel freely or bind with thyroid-binding proteins to reach target cells that will produce proteins necessary for promoting metabolism and growth.

The production and secretion of thyroid hormones are regulated by the pituitary gland through the feedback mechanism involving the thyroid-stimulating hormone (TSH) and the thyroid hormones (T3 and T4) plasma concentration levels (Leggett 2010). A decrease in T3 and T4 levels promotes the secretion of TSH, which stimulates the thyroid gland to release T3 and T4 into the bloodstream. Conversely, an increase in T3 and T4 plasma concentrations inhibit the secretion of TSH to maintain normal concentration of hormones in the blood (Leggett 2010). The thyroid typically secretes about 10 to 15 times more T4 hormones than T3. T4 is exclusively produced in the thyroid while only 20% of T3 hormones in the blood is secreted by the thyroid. The majority of T3 hormones are produced from the removal of an iodine atom from T4 in extrathyroidal tissues (Leggett 2010). T3 and T4 hormones are primarily metabolized in the liver where the hormones are deactivated by the removal of iodine. The liver releases about 80% of iodine back into the extracellular fluids while the rest is secreted into the bile for fecal excretion (Ahad and Ganie 2010).

Circulating iodide taken up by the kidneys are filtered as glomerular filtrate (Leggett 2010). An estimate of about 70% of filtered iodide is reabsorbed into the circulatory system while the rest is secreted to the urinary bladder contents to be excreted as urine (Leggett 2010). In general, more than 90% of iodine loss in the body is due to urine excretion of filtered blood iodide (Leggett 2010, Ahad and Ganie 2010).

2.5. ICRP Iodine Biokinetic Models

2.5.1. ICRP 78 Iodine Biokinetic Model

ICRP Publication 78 (1997) provides an iodine biokinetic model that was adapted from ICRP Publication 67, and initially introduced in ICRP Publication 30 (see Figure 2.2). The original model in ICRP 30 was essentially the model developed by Riggs (1952) describing a three-compartment model for iodine metabolism in an adult human (ICRP 2017). The three compartments represent iodine retention in blood, thyroid, and the "rest of the body". Older ICRP publications refer to the blood compartment as "all inorganic iodide in the body", the thyroid compartment as "organic iodine in thyroid", and "rest of the body" as "organic iodine in rest of the body" (ICRP 2017). Transfer coefficients were defined to describe the time-dependent translocation of iodine between the compartments. The transfer coefficient values (in day^{-1}) are determined by the fractional uptake to the compartments and the biological half-time of iodine in each compartment.

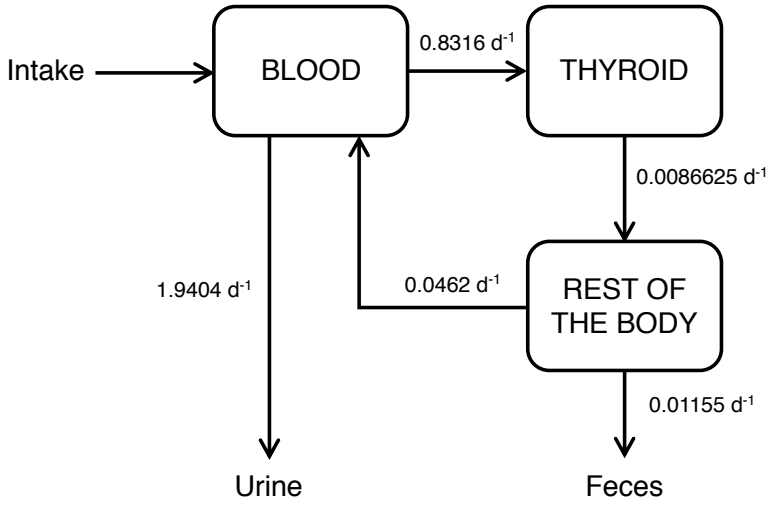


Figure 2.2. ICRP 78 Iodine Biokinetic Model

The ICRP 78 iodine model assumes that after absorption in the blood, a fraction of 0.3 of iodine in the blood is translocated to the thyroid while a fraction of 0.7 is directly excreted as urine (ICRP 1997). A biological half-time of 0.25 days for iodide in the blood is estimated for adults. Iodide transferred to the thyroid is used to synthesize thyroid hormones and is assigned a biological half-time of 0.25 days (ICRP 1997). Iodine in thyroid hormones released from the thyroid gland is metabolized in the tissues of the "rest of the body" where it can be retained with a biological half-time of 12 days (ICRP 1997). The model assumes that some iodine in the tissues may be recycled and return to the blood pool as inorganic iodide or be excreted in the feces. The ICRP model estimates that about 20% of iodine in fecal excretion for adults is due to the metabolism of thyroid hormones in the liver where iodine is removed and gets excreted into the bile.

ICRP acknowledges that there can be relatively large variations in the model depending on factors such as an individual's dietary stable iodine content and thyroid condition among other things (ICRP 1997). A low stable iodine content in the diet can result in an increased uptake of radioiodine by the thyroid gland (ICRP 2017). Conversely, a high dietary stable iodine content will decrease radioiodine accumulation and uptake by the thyroid.

Thyroid conditions may cause counter intuitive effects on doses delivered to the thyroid gland. A hypothyroid adult will have a lower thyroidal uptake of iodine but longer excretion period. This condition therefore leads to a higher dose to the thyroid gland than for an individual with normal thyroid condition (ICRP 1997). A hyperthyroid adult will have a shorter biological half-life for iodine in the thyroid resulting to a lower dose to the thyroid gland (ICRP 1997). ICRP encourages the use of individual parameter values in dose calculations when such conditions are suspected.

2.5.2. ICRP 137 Iodine Biokinetic Model

The ICRP released an updated iodine biokinetic model in Publication No. 137 (2017). The model used in the publication was an iodine model developed by Leggett in 2010 (ICRP 2017). The ICRP 137 iodine biokinetic model characterizes iodine in the body into three categories: circulating or extrathyroidal inorganic iodide, thyroidal iodine, and extrathyroidal organic iodine (ICRP 2017). The model was developed by consolidating various models describing these iodine subsystems (Leggett 2010, ICRP 2017). ICRP 137 also specified pathways to the alimentary tract compartments that were not present in the ICRP 78 iodine model. Figure 2.3 illustrates the ICRP 137 iodine model as it was presented in the publication with the transfer coefficients listed in Table 2.2.

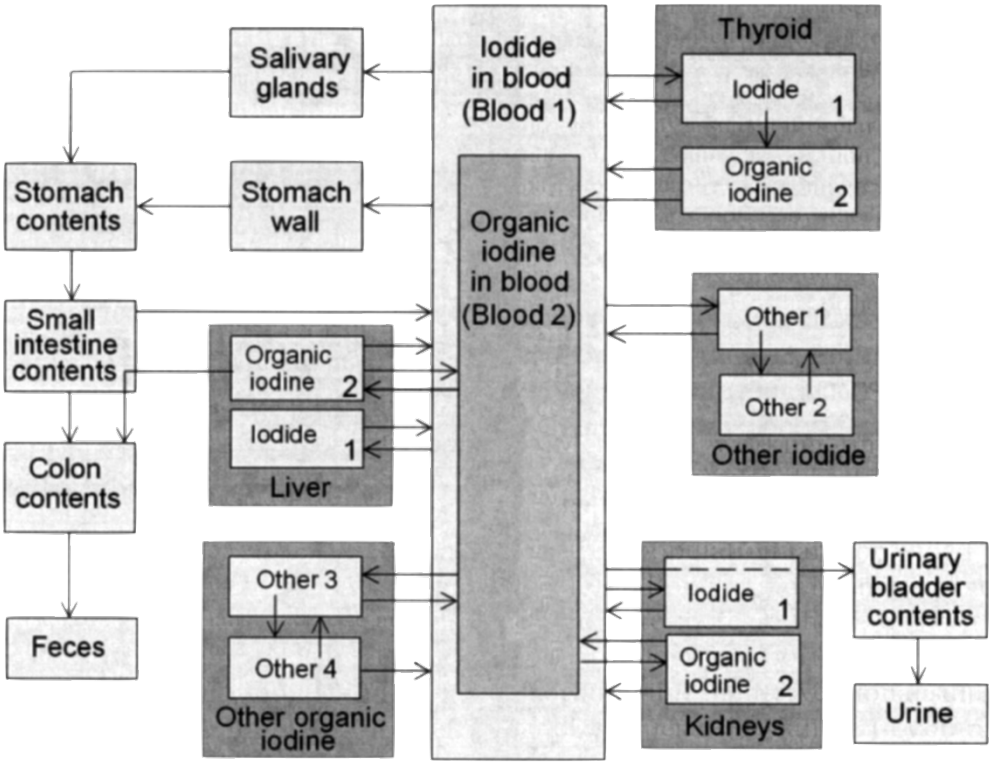


Figure 2.3. ICRP 137 Iodine Biokinetic Model

Table 2.2. ICRP 137 iodine biokinetic model baseline parameter values (ICRP 2017)

Pathway	Transfer rate (per day)
Blood 1 to Thyroid 1	7.26
Blood 1 to urinary bladder contents	11.84
Blood 1 to salivary gland	5.16
Blood 1 to stomach wall	8.6
Blood 1 to Other 1	600
Blood 1 to Kidneys 1	25
Blood 1 to Liver 1	15
Salivary gland to oral cavity	50
Stomach wall to stomach contents	50
Thyroid 1 to Thyroid 2	95
Thyroid 1 to Blood 1	36
Thyroid 2 to Blood 2	0.0077
Thyroid 2 to Blood 1	0
Other 1 to Blood 1	330
Other 1 to Other 2	35
Other 2 to Other 1	56
Kidneys 1 to Blood 1	100
Liver 1 to Blood 1	100
Blood 2 to Other 3	15
Other 3 to Blood 2	21
Other 3 to Other 4	1.2
Other 4 to Other 3	0.62
Other 4 to Blood 1	0.14
Blood 2 to Kidneys 2	3.6
Kidneys 2 to Blood 2	21
Kidneys 2 to Blood 1	0.14
Blood 2 to Liver 2	21
Liver 2 to Blood 2	21
Liver 2 to Blood 1	0.14
Liver 2 to right colon contents	0.08

ICRP 137 added compartments for the kidneys and liver that are both further divided into organic iodine and inorganic iodide compartments. The liver compartment is specified in the model because it is considered the main repository for hormonal iodine from metabolism of thyroid hormones (ICRP 2017). The model added kidney compartments due to the organ's known

accumulation of inorganic iodide and hormonal iodine (ICRP 2017). The blood and thyroid compartments were also given subcompartments separating organic iodine and inorganic iodide.

Compartment Blood 1 is treated as a well-mixed pool of blood plasma and red blood cells (ICRP 2017). Iodide in Blood 1 that travels to the thyroid is received by Thyroid 1 and is then transferred to Thyroid 2 with some minor clearance of iodide back to Blood 1 (ICRP 2017). The conversion of iodide to organic iodine happens in Thyroid 2. Thyroid 2 transfers the organic iodine to Blood 2 with possible minor clearance to Blood 1 depending on individual dietary iodine content (Leggett 2010). The ICRP assigned a baseline value of zero for the activity leakage from Thyroid 2 to Blood 1 (ICRP 2017). The model baseline parameter values also assume a balance between dietary stable iodine intake and hormonal iodine secretion of the thyroid but did introduce an equation, $\lambda = 16.34/[0.98(Y/S) - 0.2]$ day^{-1}, correcting for dietary intake (Y) to rate of secretion (S) ratio that adjusts the Blood 1 to Thyroid 1 transfer coefficient (λ) as necessary.

Inorganic iodide and organic iodine in extrathyroidal tissues not including kidneys and liver are represented as multiple Other compartments. Other 1 (fast) and Other 2 (slow) represent the turnover rates of the exchangeable inorganic iodide pool, while Other 3 (fast) and Other 4 (slow) describe the exchangeable organic iodine pool (ICRP 2017). The ICRP 137 iodine biokinetic model assumes that the removal of iodine from the body is only due to urinary and fecal excretion. Inorganic iodide translocated from the blood to the kidneys is filtered and can either be reabsorbed into the blood or transferred to the urinary bladder contents to be excreted as urine. Organic iodine in Liver 2 is secreted to the small intestine where unabsorbed iodine is transferred to the colon for fecal excretion (ICRP 2017).

Chapter 3:

DATA AND METHODOLOGY

3.1. 1960s Radioiodine Data

The 1965 radioiodine data of Hays and Solomon was used to assess the ICRP 78 iodine biokinetic model. The data involves the intravenous injection of 30-microcuries carrier-free iodine-131 (^{131}I) in saline solution of nine healthy young adult male subjects. Hays and Solomon (1965) measured and calculated the ^{131}I radioactivity in the plasma, thyroid and urinary excretion of the subjects for the first three-hour period post intake. The mean data values provided by Hays and Solomon (1965) for the nine subjects are shown in Table 3.1.

Table 3.1. Hays and Solomon 1965 Radioiodine Data

Time (min)	Plasma (µCi/L)	Thyroid (µCi)	Urine (µCi)	Time (min)	Plasma (µCi/L)	Thyroid (µCi)	Urine (µCi)
5	2.03	0.45		95	0.96	2.78	
10	1.75	0.86		100	0.92	2.93	
15	1.62	1.16	1.24	105	0.90	3.00	
20	1.50	1.29		110	0.88	3.12	
25	1.40	1.45		115	0.88	3.12	
30	1.33	1.62	2.13	120	0.87	3.27	5.53
35	1.27	1.73		125	0.87	3.27	
40	1.22	1.88		130	0.86	3.30	
45	1.20	1.96		135	0.84	3.39	
50	1.16	2.08		140	0.82	3.45	
55	1.13	2.17		145	0.83	3.54	
60	1.10	2.31	3.43	150	0.81	3.69	6.46
65	1.04	2.42		155	0.80	3.66	
70	1.01	2.48		160	0.80	3.75	
75	1.01	2.56		165	0.80	3.75	
80	0.99	2.60		170	0.79	3.87	
85	0.98	2.67		175	0.78	3.99	
90	0.96	2.77	4.53	180	0.78	3.99	7.35

Blood samples (3 ml) and thyroidal activity measurements were made every 5 minutes after the ^{131}I intravenous injection. Urine samples were collected at 15 minutes and 30 minutes post-injection and thereafter every 30 minutes (Hays and Solomon 1965). The measurements were conducted until 180-minutes post-injection. The mean cumulative ^{131}I activity in urine was calculated from the incremental measurement of activity in the urinary excretion. The mean standard deviations for each data group (blood, thyroid, and urine) were calculated from the averaged coefficient of variations determined from each subject. A mean standard deviation of 23% was found for plasma, 58% for the thyroid, and 54% for urine. These relatively large standard deviations were attributed to the inherent variability between the nine subjects (Hays and Solomon 1965).

3.2. Biokinetic Model Fitting and Optimization Using SAAM II

3.2.1. SAAM II Compartmental

SAAM (Simulation Analysis and Modeling) II is a computer software package designed for modeling, simulation, and analysis of compartmental models used in metabolic, biological, and pharmaceutical systems (TEG 2017). SAAM II has two modeling applications: numerical and compartmental. Users can use SAAM II Numerical application to create models by defining sets of mathematical terms and equations directly in the software. The SAAM II Compartmental application automatically generates a system of differential equations based on the created model structure and allows users to define additional equations for their model (TEG 2017). The Compartmental application also provides users a selection of tools to build visual representations of models by selecting compartments and flow lines on a toolbox in a point-and-click manner (see Figure 3.1). The Compartmental application also allows users to input sample data and define

experiments to fit model parameters to experimental datasets. SAAM II solves the compartmental model by integrating its differential equations over the time period specified in the experiment using the designated parameter values. Additional equations defined by the user are also evaluated in each calculation.

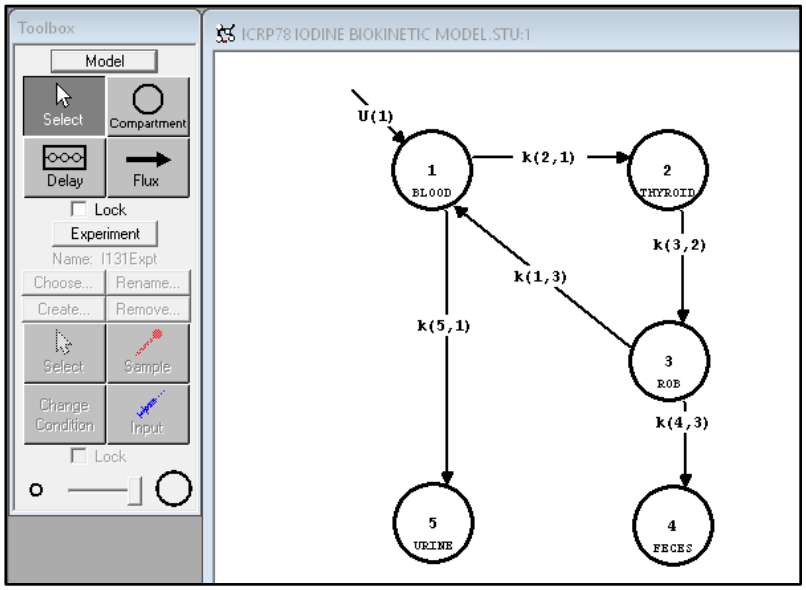
3.2.2. ICRP 78 Iodine Biokinetic Model in SAAM II

The ICRP 78 iodine biokinetic model was reconstructed in SAAM II Compartmental application (see Figure 3.1a). The blood, thyroid, rest of the body (ROB), feces, and urine compartments were used in this reconstruction for a total of five compartments labeled 1, 2, 3, 4, and 5, respectively. The transfer coefficients between two compartments are labelled in SAAM as "k(source compartment, target compartment)". The variable U(1) symbolizes the initial intake/uptake in compartment 1. The values of the transfer coefficients were assigned to the appropriate compartments (see Table 3.2). The experiment performed by Hays and Solomon was reconstructed in SAAM II using the Experiment tools on the SAAM II Compartmental toolbox (see Figure 3.1b). The compartments in experiment mode have the labels q1, q2, q3, q4, and q5 for the blood, thyroid, ROB, feces, and urine, respectively. The single bolus intake of 30 μCi from Hays and Solomon (1965) data is entered as the input variable ex1. The sample data for the plasma, thyroid, and urine are assigned to their corresponding compartments. The plasma data (s1) was assigned to q1, thyroidal uptake data (s2) was assigned to q2, and the urinary excretion (s3) data was assigned to q5.

Table 3.2. ICRP 78 iodine biokinetic model transfer coefficient parameter values

Transfer Coefficient	TARGET	SOURCE	Transfer Coefficient Base Value
k(1,3)	BLOOD	ROB	0.04621
k(2,1)	THYROID	BLOOD	0.83168
k(3,2)	ROB	THYROID	0.008664
k(4,3)	FECES	ROB	0.01155
k(5,1)	URINE	BLOOD	1.9408

(a)



(b)

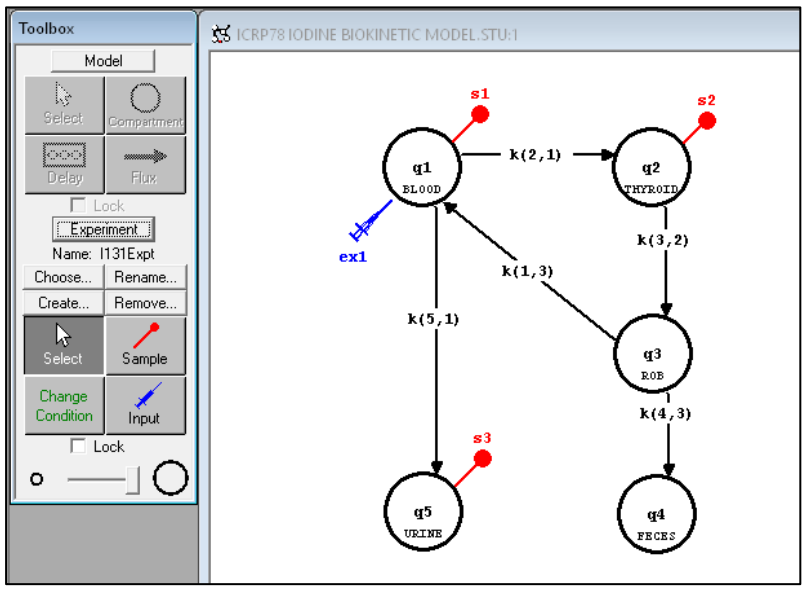


Figure 3.1. ICRP 78 Iodine Biokinetic Model built in SAAM II Compartmental using Model tools (a) and Experiment tools (b)

3.2.3. Acquisition of AIC Scores

SAAM II was used to solve the ICRP 78 iodine biokinetic model using the base model parameters and the Hays and Solomon (1965) data. The software provides various measures of the fit, including AIC, Bayesian Information Criterion (BIC), and the objective function, R(p), of the fitted model. SAAM II produces the best fit model by minimizing the objective function (for non-Bayesian parameters) (TEG 2017):

$$R(p) = \frac{1}{M}\sum_{j=1}^{j}\sum_{i=1}^{N_j}\left(ln\left[V_{i,j}\left(s\left(\hat{p},t_{i,j}\right),y_{i,j},\hat{v}_j\right)\right] + \frac{\left(y_{i,j}-s\left(\hat{p},t_{i,j}\right)\right)^2}{V_{i,j}\left(s\left(\hat{p},t_{i,j}\right),y_{i,j},\hat{v}_j\right)}\right) \quad (3.1)$$

where:

p	vector of adjustable parameters
j	number of data set
N_j	number of data points in the j-th data set
M	total number of data points; $M = N_1 + N_2 + \ldots + N_j$
$y_{i,j}$	i-th datum in the j-th data set
$s\left(\hat{p},t_{i,j}\right)$	the model value or sample value corresponding to $y_{i,j}$ at time $t_{i,j}$
$\hat{v}_j$	variance parameter in the j-th data set
$V_{i,j}\left(s\left(\hat{p},t_{i,j}\right),y_{i,j},\hat{v}_j\right)$	variance model for $y_{i,j}$

The study used non-Bayesian parameters because the mean and/or range values of the transfer coefficients are not known. SAAM II estimates a normalized value of AIC which is calculated by minimizing the objective function R(p),

$$AIC_{SAAM} = \frac{L + N_p}{M} \quad (3.2)$$

where N_p is the number of adjustable parameters in the model (plus the number of variance parameters if relative weights are considered), M is the total number of data points, and L = $\left(\frac{M}{2}\right)\left(R(p) + ln(2\pi)\right)$. The AIC as described in the literature and presented in equation 2.1 was calculated from the normalized AIC value provided by SAAM II. The general calculation is shown in Appendix A.

3.2.4. Single Parameter Optimization

The transfer coefficients of the base model were optimized one at a time while keeping the other four coefficients fixed to their respective base values (Table 3.2). Each single parameter optimization routine was assigned a model number, M1A, M1B, M1C, M1D, and M1E (see Table 3.3). This is done to distinguish among the model fits created with optimized transfer coefficients. These model fits are referred to as pseudo-models in the present study. The AIC scores of each pseudo-model compared to the base model's AIC were determined to assess the ICRP 78 iodine biokinetic model transfer coefficients.

Table 3.3. Single parameter optimization routine

Model	Optimized Transfer Coefficient	Compartments	
		Target	Source
M1A	k(1,3)	Blood	ROB
M1B	k(2,1)	Thyroid	Blood
M1C	k(3,2)	ROB	Thyroid
M1D	k(4,3)	Feces	ROB
M1E	k(5,1)	Urine	Blood

3.3. Data Analysis

3.3.1. Assigning AIC scores

The AIC score used for analysis is the AIC_c value defined in equation 2.3 because of the small ratio of sample size to maximum number of adjustable parameters. The total number of data points from the Hays and Solomon (1965) data set is M = 79, while the model has a maximum number of 5 adjustable parameters. The AIC differences between the base model and each of the pseudo-models, each with optimized transfer coefficients were determined. These ΔAIC scores were used to calculate the relative likelihood, and subsequently the Akaike weights, of the base model and the pseudo-models. The relative changes between the base and optimized values of the transfer coefficients for each optimization routine were also determined. This is done to assess the magnitude, direction, and range of the change caused by optimization.

3.3.2. Multi-Parameter Optimization of Influential Transfer Coefficients

The optimized transfer coefficients producing the largest effect on the model (i.e. the pseudo-models with highest Akaike weights) were identified. These influential transfer coefficients were optimized in pairs (two-at-a-time). The AIC scores of the pseudo-models created from the paired optimization were obtained and were compared to the base model's AIC value. The relative changes in the transfer coefficient values were determined. All the identified influential transfer coefficients were also optimized simultaneously (all at once). The AIC score of this pseudo-model with multiple optimized parameters was compared to that of the base model. The relative changes in transfer coefficient values were also found. This multi-parameter optimization routine was performed to account for the correlation of model parameters.

Chapter 4:

RESULTS AND DISCUSSION

4.1. ICRP 78 Iodine Biokinetic Model Single Parameter Optimization Routine

4.1.1. Single (One-at-a-time) Transfer Coefficient Optimization

The study assumes that the ICRP 78 iodine biokinetic model is an adequate representation of iodine movement in the human body. This assumption suggests that optimizing the ICRP 78 base model based on a given dataset should not lead to substantial change in transfer coefficient values. The relative change in transfer coefficient values of the ICRP 78 iodine biokinetic model after single (one-at-a-time) parameter optimization are shown in Table 4.1.

Table 4.1. Optimized values and relative changes of the ICRP 78 iodine biokinetic model transfer coefficients after single (one-at-a-time) parameter optimization

Model	Optimized Transfer Coefficient	Compartment		Base value (day^{-1})	Optimized value (day^{-1})	Relative Change (%)
		Target	Source			
M1A	k(1,3)	Blood	ROB	0.04621	-104.6 +/- 8.1	$-2.26x10^5$
M1B	k(2,1)	Thyroid	Blood	0.83168	1.5 +/- 0.1	81
M1C	k(3,2)	ROB	Thyroid	0.008664	-8.4 +/- 1.7	$-9.72x10^4$
M1D	k(4,3)	Feces	ROB	0.01155	NA	NA
M1E	k(5,1)	Urine	Blood	1.9408	2.6 +/- 0.2	34

The optimization routine results show that the k(1,3) transfer coefficient, describing the translocation of iodine from the rest of the body to the blood, exhibited the largest deviation from its base value among all investigated transfer coefficients. Keeping all other four transfer coefficients fixed, the k(1,3) base value of 0.04621 day^{-1} decreased about 226,000% to achieve a good model fit (M1A) to the dataset. The negative optimized rate of -104.6 +/- 8.1 day^{-1} for k(1,3) implies that the iodine content in the "rest of the body" is not translocating to the blood during the

first three-hour period post-intake. The recycling process described by the k(1,3) transfer coefficient may not be observable in the short-term iodine uptake period of the given dataset. The apparent absence of early-term recycling can be an important consideration when conducting dose assessment and dose estimation.

The transfer coefficient k(2,1) had a relative change of 81% after optimization. The k(2,1) base value of 0.83168 day^{-1} increased to 1.5 +/- 0.1 day^{-1} to achieve a good fitting model (M1B). The relative percent change from the base value to the optimized rate suggests that the iodine movement from the blood to the thyroid as observed from the given dataset is much faster than that of the k(2,1) base quantity.

The optimization of k(3,2) resulted in a substantial change in the transfer coefficient value. The k(3,2) base value of 0.008664 day^{-1} decreased about 97,200% to attain a good model fit (M1C) with an optimized rate of -8.4 +/- 1.7 day^{-1}. The negative value may indicate that the translocation described by transfer coefficient k(3,2) may not be observable in an early-term uptake period such as that of the given dataset.

The optimized k(5,1) transfer coefficient experienced the smallest deviation from the base value among all investigated transfer coefficients. The k(5,1) value increased by approximately 34% to obtain a good fitting model (M1E) with an optimized rate of 2.6 +/- 0.2 day^{-1}. The relative change in the transfer coefficient value may imply that the iodine movement from the blood to the urine as described by the base k(5,1) value is relatively slower compared to that observed from the measured data.

The transfer coefficient k(4,3), describing the movement of iodine from the rest of the body to feces, was not able to be optimized. The optimization of the k(4,3) based on the given dataset

resulted in a nonconvergence error. This is attributed to the lack of data measurements for fecal excretion in the three-hour period dataset.

4.1.2. Single Parameter Optimization AIC Scores

The ability of AIC to provide a measure of parsimony and an estimate of the predictive accuracy of a model is used to evaluate the reliability of the ICRP 78 iodine biokinetic model. The pseudo-models produced from single parameter optimization of the base model transfer coefficients were fitted to the given dataset. Each pseudo-model fit has an AIC score, which estimates the balance of goodness-of-fit and complexity of the pseudo-model. A lower AIC score is generally considered more favorable as it suggests a more parsimonious model. The AIC scores of the base model and the pseudo-model fits obtained from single parameter optimization are shown on Table 4.2. Each optimized transfer coefficient produced a model fit with an AIC score lower than the base model. Therefore, based on AIC principles, each of the pseudo-models produced from one-at-a time parameter optimization of the transfer coefficients have a better balance of goodness-of-fit and complexity than the ICRP 78 iodine biokinetic model.

Table 4.2. AIC scores of the ICRP 78 iodine biokinetic model and the model fits after a single (one-at-a-time) parameter optimization routine.

Model	Optimized Transfer Coefficient	Compartment		AIC_c
		Target	Source	
Base Model				157.4
M1A	k(1,3)	Blood	ROB	153.8
M1B	k(2,1)	Thyroid	Blood	73.0
M1C	k(3,2)	ROB	Thyroid	125.5
M1D	k(4,3)	Feces	ROB	NA
M1E	k(5,1)	Urine	Blood	134.9

The difference between two AIC scores provides an estimate of how much more likely one model is compared to another model. The base model ΔAIC was calculated from equation 2.4 as $\Delta AIC_{base} = AIC_{base} - AIC_{pseudo\text{-}model}$. The higher the ΔAIC_{base} means the weaker the evidence is to support the base model compared to a particular pseudo-model. The ΔAIC scores of the base model relative to the pseudo-model fits are shown in Table 4.3. The ΔAIC for each pseudo-model is zero because the AIC_i ($AIC_{pseudo\text{-}model}$) in equation 2.4 will equal to AIC_{min}. The calculations for the ΔAIC are shown in Appendix B. The AIC differences show that there is strong evidence to support that each of the pseudo-model fits obtained from single (one-at-a-time) optimization of transfer coefficients is a better representation of the given dataset than the base model.

Table 4.3. ΔAIC scores of the ICRP 78 iodine biokinetic model compared to the single (one-at-a-time) parameter optimization model fits.

Model	**Optimized Transfer Coefficient**	**ΔAIC**				
Base Model		3.6	84.4	31.9	NA	22.6
M1A	k(1,3)	0				
M1B	k(2,1)		0			
M1C	k(3,2)			0		
M1D	k(4,3)				NA	
M1E	k(5,1)					0

Determining the relative likelihood further demonstrates how much more plausible one model is than another candidate model. The weighted relative likelihood or Akaike weights were determined to show how much more likely the base model is compared to the different pseudo-models and vice versa. The Akaike weight of the base model is expected to be about 0.5 to 1 because of the initial assumption that the ICRP 78 iodine biokinetic model adequately represents the movement of iodine in the body. This assumption also suggests that optimizing each of the

transfer coefficients should not have a great effect on the goodness-of-fit of the base model. Table 4.4 shows the Akaike weights of each pseudo-model compared to the base model. The relative likelihood and Akaike weight computations are shown in Appendix C.

Table 4.4. Akaike weights of the ICRP 78 iodine biokinetic model compared to the single (one-at-a-time) parameter optimization model fits.

Model	**Optimized Transfer Coefficient**	**Akaike Weights w_i**				
Base Model		0.14	0.00	0.00	NA	0.00
M1A	k(1,3)	0.86				
M1B	k(2,1)		1.00			
M1C	k(3,2)			1.00		
M1D	k(4,3)				NA	
M1E	k(5,1)					1.00

The results show that each optimized transfer coefficient produced a model fit with an Akaike weight greater than that of the base model. The base model scored an Akaike weight of 0 when compared to M1B, M1C, and M1E, with each pseudo-model having an Akaike weight of 1. The base model scored an Akaike weight of 0.14 when compared to pseudo-model M1A, which had an Akaike weight of 0.86. These results suggest that the base model is less likely to be the most adequate representation of the given dataset than each of the pseudo-models. Optimizing the transfer coefficients one at a time should not have produced model fits with such higher Akaike weights than the base model if the base parameter values were indeed adequate descriptions of iodine translocation in the body.

4.2. ICRP 78 Iodine Biokinetic Model Multi-Parameter Optimization Routine

4.2.1. Paired Parameter Optimization

The pseudo-models created from the single parameter optimization of transfer coefficients k(2,1) (blood to thyroid), k(3,2) (thyroid to rest of the body), and k(5,1) (blood to urine) scored the highest Akaike weights as previously shown in Table 4.3. These transfer coefficients are classified in the study as influential parameters that led to substantial improvements in the model fit. These identified influential transfer coefficients were optimized in pairs (two-at-a-time) to account for correlated model parameters (see Table 4.5).

Table 4.5. Optimized values and relative changes of the ICRP 78 iodine biokinetic model transfer coefficients after paired (two-at-a-time) parameter optimization

Model	Optimized Transfer Coefficients	Compartment		Base value (day^{-1})	Optimized value (day^{-1})	Relative Change (%)
		Target	Source			
M2A	k(2,1)	Thyroid	Blood	0.83168	2.59 +/- 0.19	212
	k(3,2)	ROB	Thyroid	0.008664	11.5 +/- 1.7	1.33×10^5
M2B	k(2,1)	Thyroid	Blood	0.83168	1.68 +/- 0.08	97
	k(5,1)	Urine	Blood	1.9408	2.78 +/- 0.19	43
M2C	k(3,2)	ROB	Thyroid	0.008664	-8.86 +/- 1.7	-1.02×10^5
	k(5,1)	Urine	Blood	1.9408	2.62 +/- 0.19	35

Pseudo-models M2A, M2B, and M2C are the resulting model fits from the paired optimization of transfer coefficients k(2,1) and k(3,2), k(2,1) and k(5,1), and k(3,2) and k(5,1), respectively. Each optimized transfer coefficients exhibited a relatively large change in value when compared to their respective base model quantities. This is consistent with the observations from the single parameter optimization routine.

The k(2,1) and k(3,2) transfer coefficients that were simultaneously optimized to produce M2A each experienced an increase in magnitude of 212% and 1.33×10^5%, respectively. The paired optimization (M2B) of k(2,1) and k(5,1) transfer coefficients also resulted in a relatively large increase in the transfer coefficient values compared to the base quantities. The k(2,1) transfer coefficient had a relative change of 97%, while k(5,1) increased 43% from the base value. The paired optimization of k(3,2) and k(5,1) transfer coefficients (M2C) resulted in a 35% increase in magnitude for k(5,1), while k(3,2) decreased by -1.02×10^5%.

The pseudo-models M2A and M2C show conflicting optimized values for the k(3,2) transfer coefficient. Optimizing k(3,2) with k(2,1) while keeping the other transfer coefficients fixed to their respective base values, resulted in an increase in the iodine translocation from the thyroid to the rest of the body from 0.008664 day^{-1} to 11.5 +/- 1.7 day^{-1}. However, optimizing k(3,2) with k(5,1) while keeping the other transfer coefficients at their appropriate base values, resulted in a significant decrease in the k(3,2) transfer coefficient value from 0.008664 day^{-1} to -8.86 +/- 1.7 day^{-1}. This negative optimized rate implies that iodine may not be translocation from the thyroid to the rest of the body during this early term uptake, which opposes the positive rate observed from M2A. The contradicting optimized values of k(3,2) in M2A and M2C are notable because both paired optimization routines were performed based on the same dataset. These results suggest that the k(3,2) transfer coefficient may be unreliable in describing early-term kinetics of iodine in the human body.

4.2.2. Paired Parameter Optimization AIC Scores

The pseudo-models produced from the paired parameter optimization of the base model transfer coefficients were fitted to the given dataset. Each pseudo-model fit has an AIC score

quantifying the balance between the goodness-of-fit and complexity of the pseudo-model. The AIC scores of the base model and the pseudo-model fits obtained from paired parameter optimization are shown on Table 4.6. Each pair of optimized transfer coefficients produced a model fit with an AIC score lower than the base model. These results suggest that based on AIC principles, each of the pseudo-model produced from the paired optimization of transfer coefficients had a better balance of goodness-of-fit and complexity than the ICRP 78 iodine biokinetic model.

Table 4.6. AIC scores of the ICRP 78 iodine biokinetic model and the model fits after a paired parameter optimization routine.

Model	**Optimized Transfer Coefficients**	**Compartment**		**AIC_c**
		Target	**Source**	
Base Model				157.4
M2A	k(2,1) k(3,2)	Thyroid ROB	Blood Thyroid	-7.28
M2B	k(2,1) k(5,1)	Thyroid Urine	Blood Blood	30.65
M2C	k(3,2) k(5,1)	ROB Urine	Thyroid Blood	101.02

Determining the AIC differences provides valuable information on the relative evidence supporting a particular model when compared to other models. The ΔAIC scores of the base model relative to the pseudo-model fits are shown in Table 4.7. Similar to the single parameter optimization, the base model's ΔAIC scores were calculated from equation 2.4 as $\Delta AIC_{base} = AIC_{base} - AIC_{pseudo\text{-}model}$ (see Appendix B). The ΔAIC for each pseudo-model is zero because the AIC_i ($AIC_{pseudo\text{-}model}$) in equation 2.4 will equal to AIC_{min}. The AIC differences show that there is strong evidence to support that each of the pseudo-model fits obtained from paired (two-at-a-time)

optimization of transfer coefficients is a better approximation of the given dataset than the base model.

Table 4.7. ΔAIC scores of the ICRP 78 iodine biokinetic model compared to the paired parameter optimization model fits.

Model	**Optimized Transfer Coefficients**	**ΔAIC**		
	Base Model	164.7	126.8	56.4
M2A	k(2,1) & k(3,2)	0		
M2B	k(2,1) & k(5,1)		0	
M2C	k(3,2) & k(5,1)			0

The weighted relative likelihood (Akaike weights) were determined to show how much more likely the base model is compared to the different pseudo-models and vice versa. The initial assumption that the ICRP 78 iodine biokinetic model adequately represents the movement of iodine in the body means that the Akaike weight of the base model is expected to be about 0.5 to 1. Table 4.8 shows the Akaike weights of each pseudo-model compared to the base model. Each pair of optimized transfer coefficients produced a model fit with an Akaike weight greater than the base model. Pseudo-models M2A, M2B, and M2C each had an Akaike weight of 1, while the base model scored an Akaike weight of 0 when compared to each of these models. These results suggest that the base model is less likely to be the most adequate representation of the given dataset than each of the pseudo-model, which is consistent with the observations from the single parameter optimization routine. The two-at-a-time optimization of the transfer coefficients should not have produced model fits with such higher Akaike weights than the ICRP 78 model if the base parameter values were indeed adequate descriptions of iodine translocation in the body.

Table 4.8. Akaike weights of the ICRP 78 iodine biokinetic model compared to the paired parameter optimization model fits.

Model	Optimized Transfer Coefficients	Akaike Weights w_i		
	Base Model	0.00	0.00	0.00
M2A	k(2,1) & k(3,2)	1.00		
M2B	k(2,1) & k(5,1)		1.00	
M2C	k(3,2) & k(5,1)			1.00

4.2.3. Three-Parameter Optimization

Influential parameters k(2,1), k(3,2), and k(5,1) were optimized simultaneously producing pseudo-model M3 as shown in Table 4.9. All three transfer coefficients experienced a large increase in their respective values after the three-parameter optimization routine. The k(3,2) transfer coefficient, describing iodine translocation from the thyroid to the rest of the body had the most substantial change in magnitude from 0.008664 day^{-1} to 10.3 +/- 1.6 day^{-1}. The transfer coefficient k(2,1) representing movement of iodine from the blood to the thyroid increased from 0.83168 day^{-1} to 2.57 +/- 0.19 day^{-1}. Iodine translocation from the blood to the urine characterized by the k(5,1) transfer coefficient experienced a 44% increase in value from 1.9408 day^{-1} to 2.80 +/- 0.15 day^{-1}.

Table 4.9. Optimized values and relative changes of the ICRP 78 iodine biokinetic model transfer coefficients after a three-parameter optimization routine

Model	Optimized Transfer Coefficients	Compartment		Base value (day^{-1})	Optimized value (day^{-1})	Relative Change (%)
		Target	Source			
M3	k(2,1)	Thyroid	Blood	0.83168	2.57 +/- 0.19	209
	k(3,2)	ROB	Thyroid	0.008664	10.3 +/- 1.6	1.19×10^5
	k(5,1)	Urine	Blood	1.9408	2.80 +/- 0.15	44

4.2.4. Three-Parameter Optimization AIC Scores

M3 was fitted to the given dataset to produce an AIC score estimating the balance between the goodness-of-fit and complexity of the pseudo-model. The AIC, ΔAIC, and weighted relative likelihood w_i of the ICRP 78 iodine biokinetic model and the pseudo-model fit obtained from three-parameter optimization are shown on Table 4.10. The calculations are provided in Appendix B and C.

Table 4.10. AIC scores of the ICRP 78 iodine biokinetic model transfer coefficients after a three-parameter optimization routine

Model	Optimized Transfer Coefficients	Compartment		AIC_c	ΔAIC	Akaike Weights w_i
		Target	Source			
	Base Model			157.43	198.3	0.00
M3	k(2,1)	Thyroid	Blood			
	k(3,2)	ROB	Thyroid	-40.88	0	1.00
	k(5,1)	Urine	Blood			

Simultaneously optimizing the influential transfer coefficients produced a model fit with an AIC score substantially lower than the base model. Pseudo-model M3, which was produced from the three-parameter optimization of transfer coefficients, had a better balance of goodness-of-fit and complexity than the ICRP 78 iodine biokinetic model. There is strong evidence to support that the pseudo-model fit obtained from the simultaneous optimization of the influential transfer coefficients is a better approximation of the Hays and Solomon (1965) dataset compared to the base model.

Chapter 5:

CONCLUSION AND RECOMMENDATION

5.1. Conclusions

The principles of AIC were used to evaluate the reliability of the ICRP 78 iodine biokinetic model (base model) transfer coefficients. The study was conducted under the assumption that the base model was an adequate representation of iodine metabolism in the body. This initial assumption implies that optimizing the transfer coefficients should not cause the optimized values to greatly deviate from their respective base quantities. The relative likelihood of the base model must also be generally greater than or equal to the relative likelihoods of each pseudo-model produced from the optimization of transfer coefficient(s).

Four out of the five transfer coefficients of the ICRP 78 iodine biokinetic model are greatly affected by model optimization. The study was not able to investigate the transfer coefficient (k(4,3)) describing iodine translocation from the rest of the body to the feces due to the lack of available data on iodine uptake. However, each of the investigated transfer coefficients experienced relatively large change in their respective values when optimized to the given dataset. Furthermore, the k(3,2) transfer coefficient had optimized values that changed in opposite directions when subjected to the different optimization routines. The optimization routines performed on transfer coefficients k(1,3) (rest of the body to blood), k(2,1) (blood to thyroid), k(3,2) (thyroid to the rest of the body), and k(5,1) (blood to urine) consistently produced pseudo-models with weighted relative likelihoods (Akaike weights) much greater than the ICRP 78 base model. The relative likelihood of the base model compared to each of the pseudo-models in the study suggests that there is weak evidence to support that the ICRP 78 iodine biokinetic model is

the best approximation of the given dataset. These results are inconsistent with the initial assumption that the ICRP 78 iodine biokinetic model was an adequate representation of iodine translocation in the human body.

5.2. Recommendations

The assessment of the ICRP 78 iodine biokinetic model showed results suggesting that the use of compartments and fitted mathematical quantities to describe metabolic and physiological processes involving iodine in the human body may not consistently be reliable. The transfer coefficients substantially change when optimized to the given dataset. Optimizing the transfer coefficients produced pseudo-models that are statistically better representations of iodine movement in the body compared to the ICRP 78 base model. Considering different approaches to internal dosimetry modeling can be valuable in order to provide more accurate and precise description of iodine translocation in the human body. Future efforts in internal dosimetry modeling might benefit from developing more physiologically based parameters from known behavior of radioactive material in the body. It may also be possible to use exponential equations to describe the translocations of iodine instead of the linear differential equations used in the typical compartmental models.

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APPENDICES

Appendix A: Calculation of AIC from the Normalized AIC of SAAM II

Appendix B: Calculation of ΔAIC Scores

Appendix C: Calculation of Weighted Relative Likelihood/Akaike Weights (wi)

APPENDIX A: CALCULATION OF AIC FROM THE NORMALIZED AIC OF SAAM II

SAAM II AIC: $AIC_{SAAM} = \frac{L+ N_p}{M}$

where:

- N_p is the number of adjustable parameters in the model (plus the number of variance parameters if relative weights are considered)
- L is calculated from the objective function R(p), which is minimized to produce the best fitting model; L = $\left(\frac{M}{2}\right)\left(R(p) + ln(2\pi)\right)$
- M is the total number of data points

Literature AIC: $AIC = -2\ln(\hat{L}) + 2K$

where:

- K is the number of adjustable parameters in the model
- $\hat{L}$ is the maximum likelihood function of the best fitting model

$$AIC = AIC_{SAAM} * 2M = \frac{L + N_p}{M} * 2M$$

$$AIC = 2L + 2N_p$$

APPENDIX B: CALCULATION OF ΔAIC SCORES

$$\Delta AIC = AIC_i - AIC_{min}$$

Single Parameter Optimization

- M1A:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M1A} = 157.43 - 153.83 = 3.6$

  $\Delta AIC_{M1A} = AIC_{M1A} - AIC_{min} = AIC_{M1A} - AIC_{M1A} = 0$

- M1B:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M1B} = 157.43 - 73.0 = 84.4$

  $\Delta AIC_{M1B} = AIC_{M1B} - AIC_{min} = AIC_{M1B} - AIC_{M1B} = 0$

- M1C:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M1C} = 157.43 - 125.5 = 31.9$

  $\Delta AIC_{M1C} = AIC_{M1C} - AIC_{min} = AIC_{M1C} - AIC_{M1C} = 0$

- M1E:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M1E} = 157.43 - 134.9 = 22.5$

  $\Delta AIC_{M1E} = AIC_{M1E} - AIC_{min} = AIC_{M1E} - AIC_{M1E} = 0$

Paired Parameter Optimization

- M2A:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M2A} = 157.43 - (-7.28) = 164.7$

  $\Delta AIC_{M2A} = AIC_{M2A} - AIC_{min} = AIC_{M2A} - AIC_{M2A} = 0$

- M2B:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M2B} = 157.43 - 30.65 = 128.8$

  $\Delta AIC_{M2B} = AIC_{M2B} - AIC_{min} = AIC_{M2B} - AIC_{M2B} = 0$

- M2C:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M2C} = 157.43 - 101.0 = 56.4$

  $\Delta AIC_{M2C} = AIC_{M2C} - AIC_{min} = AIC_{M2C} - AIC_{M2C} = 0$

Three-Parameter Optimization

- M3:

  $\Delta AIC_{base} = AIC_{base} - AIC_{min} = AIC_{base} - AIC_{M3} = 157.43 - (-40.88) = 198.31$

  $\Delta AIC_{M3} = AIC_{M3} - AIC_{min} = AIC_{M3} - AIC_{M3} = 0$

APPENDIX C: CALCULATION OF WEIGHTED RELATIVE LIKELIHOOD / AKAIKE WEIGHTS (w_i)

$$w_i = \frac{e^{-\frac{1}{2}(\Delta AIC_i)}}{\sum_{r=1}^{R} e^{-\frac{1}{2}(\Delta AIC_r)}}$$

Single Parameter Optimization

- M1A:

$$w_{base} = \frac{e^{-\frac{1}{2}(3.6)}}{e^{-\frac{1}{2}(3.6)} + e^{-\frac{1}{2}(0)}} = 0.14$$

$$w_{M1A} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(3.6)} + e^{-\frac{1}{2}(0)}} = 0.86$$

- M1B:

$$w_{base} = \frac{e^{-\frac{1}{2}(84.4)}}{e^{-\frac{1}{2}(84.4)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M1B} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(84.4)} + e^{-\frac{1}{2}(0)}} = 1$$

- M1C:

$$w_{base} = \frac{e^{-\frac{1}{2}(31.9)}}{e^{-\frac{1}{2}(31.9)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M1C} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(31.9)} + e^{-\frac{1}{2}(0)}} = 1$$

- M1E:

$$w_{base} = \frac{e^{-\frac{1}{2}(22.5)}}{e^{-\frac{1}{2}(22.5)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M1E} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(22.5)} + e^{-\frac{1}{2}(0)}} = 1$$

Paired Parameter Optimization

- M2A:

$$w_{base} = \frac{e^{-\frac{1}{2}(164.7)}}{e^{-\frac{1}{2}(164.7)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M2A} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(164.7)} + e^{-\frac{1}{2}(0)}} = 1$$

- M2B:

$$w_{base} = \frac{e^{-\frac{1}{2}(128.8)}}{e^{-\frac{1}{2}(128.8)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M2B} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(128.8)} + e^{-\frac{1}{2}(0)}} = 1$$

- M2C:

$$w_{base} = \frac{e^{-\frac{1}{2}(56.4)}}{e^{-\frac{1}{2}(56.4)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M2C} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(56.4)} + e^{-\frac{1}{2}(0)}} = 1$$

Three-Parameter Optimization

- M3:

$$w_{base} = \frac{e^{-\frac{1}{2}(198.31)}}{e^{-\frac{1}{2}(198.31)} + e^{-\frac{1}{2}(0)}} = 0$$

$$w_{M3} = \frac{e^{-\frac{1}{2}(0)}}{e^{-\frac{1}{2}(198.31)} + e^{-\frac{1}{2}(0)}} = 1$$