A Challenge to New Cancer Therapy (BNCT) !

- Image reconstruction for BNCT-SPECT with conditional probability -

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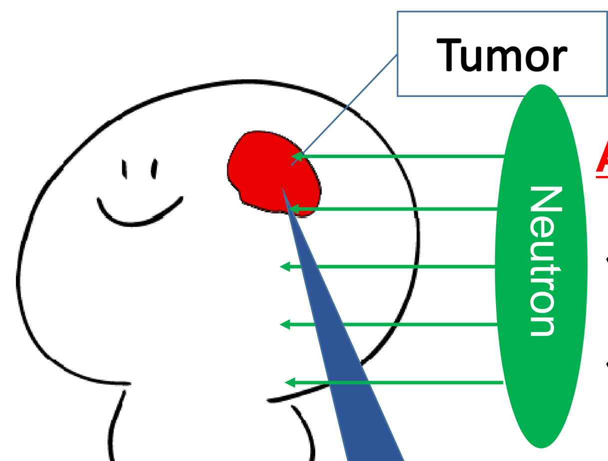
1. Introduction

Ministry of Health, Labour and Welfare reported: ～30 % Japanese people die of cancer.

✓Needless to say, the cancer is a national disease in Japan. Many medical doctors and engineers have researched on new cancer therapies having high treatment effects.

✓Recently, **Boron Neutron Capture Therapy (BNCT)** is known as one of the most promising radiotherapies for cancers. In this study, an image reconstruction technique has been examined for a SPECT system to monitor the treatment effect during the BNCT in real time. **This is an important technique which has not yet been established so far.**

1.1 What is BNCT?



BNCT is a radiotherapy using neutrons. Tumors previously and selectively loaded with ^{10}B can be killed by α-ray and ^{7}Li particles produced by neutron-^{10}B nuclear reaction.

Advantage : Cancer cells are selectively destroyed

Ranges of the two particles in tissue: ～ tumor cell size.

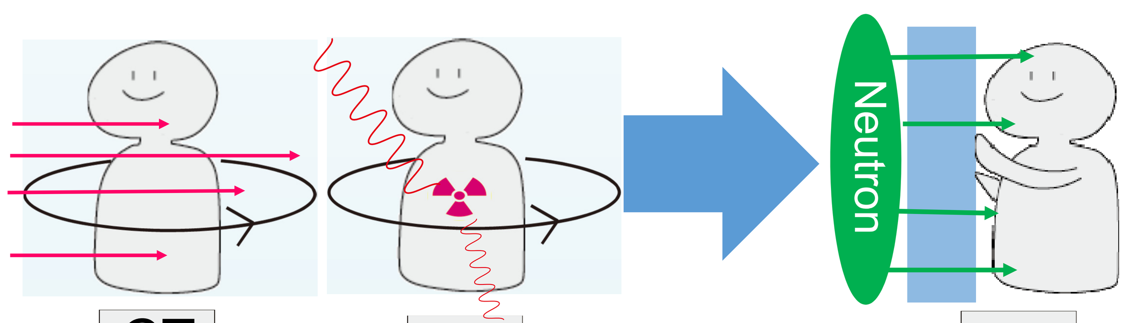
✓If ^{10}B is accumulated only in tumor cells, the tumor cells can selectively be killed, while neighboring cells are not damaged.

✓As a result, the same tumor can be treated repeatedly (impossible for other radiotherapies).

Neutron nuclear reaction with ^{10}B accumulated in cancer cell

$$^{10}B + n \rightarrow \alpha(1.47MeV) + {}^{7}Li(0.84MeV) + \gamma(0.478MeV)$$

1.2 A challenge to BNCT-SPECT



360° photographing can be performed in CT and SPECT.

360° photographing can NOT be performed in BNCT-SPECT.

✓A patient should be fixed firmly on a neutron exit window.

✓Thus impossible to rotate the patient and other measuring devices around the patient.

✓The number of SPECT views is limited to be approximately three.

✔A novel real-time SPECT is required to finally establish BNCT.

⇒Murata labo., Osaka Univ. has proposed a sophisticated BNCT-SPECT system.

In this study, **an image reconstruction technique for the system was examined.**

In cancer cells ^{10}B is loaded with a suitable chemical agent. 0.478MeV γ-rays emitted from neutron-^{10}B reaction are measured with detectors outside.

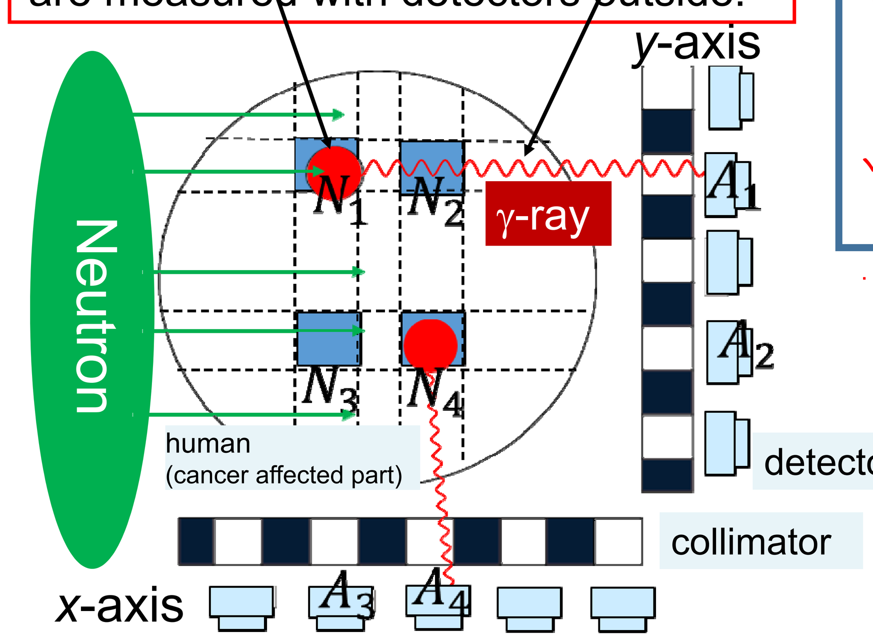
Idea / **Method**

Image reconstruction for BNCT-SPECT

✓ 478keV γ-rays measured during BNCT.

✓ Linear equations formed from the count, A (counts/s: CPS), and attenuation terms and detection efficiencies, R

✓ Neutron-^{10}B reaction rate is determined by solving the equations.

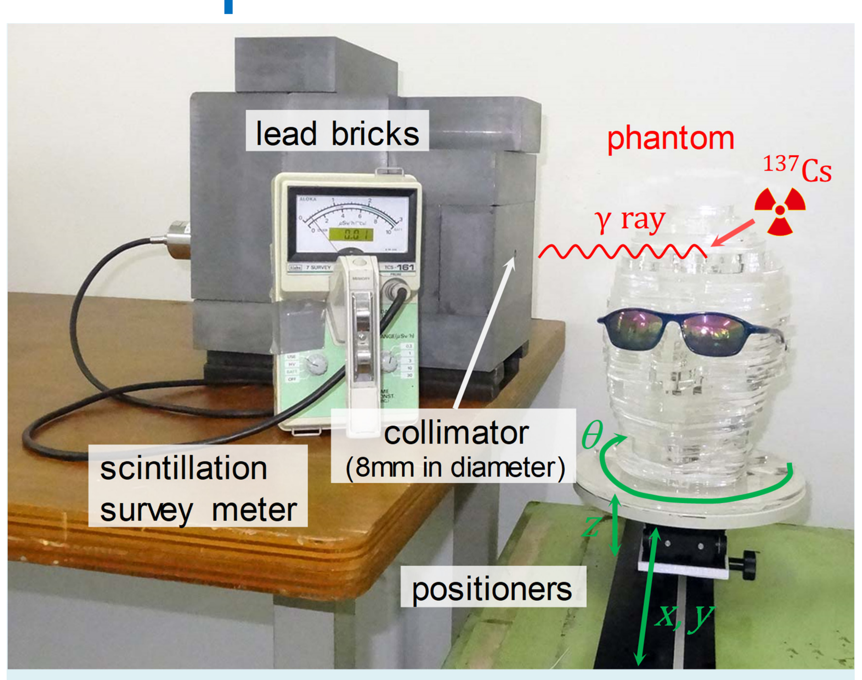


Schematic measuring concept of BNCT-SPECT.

From the left figure, nuclear reactions (in cancer cells) possibly happen in four places (■) . Simultaneous-linear-equation for the reaction rates, N_1~N_4, is expressed as

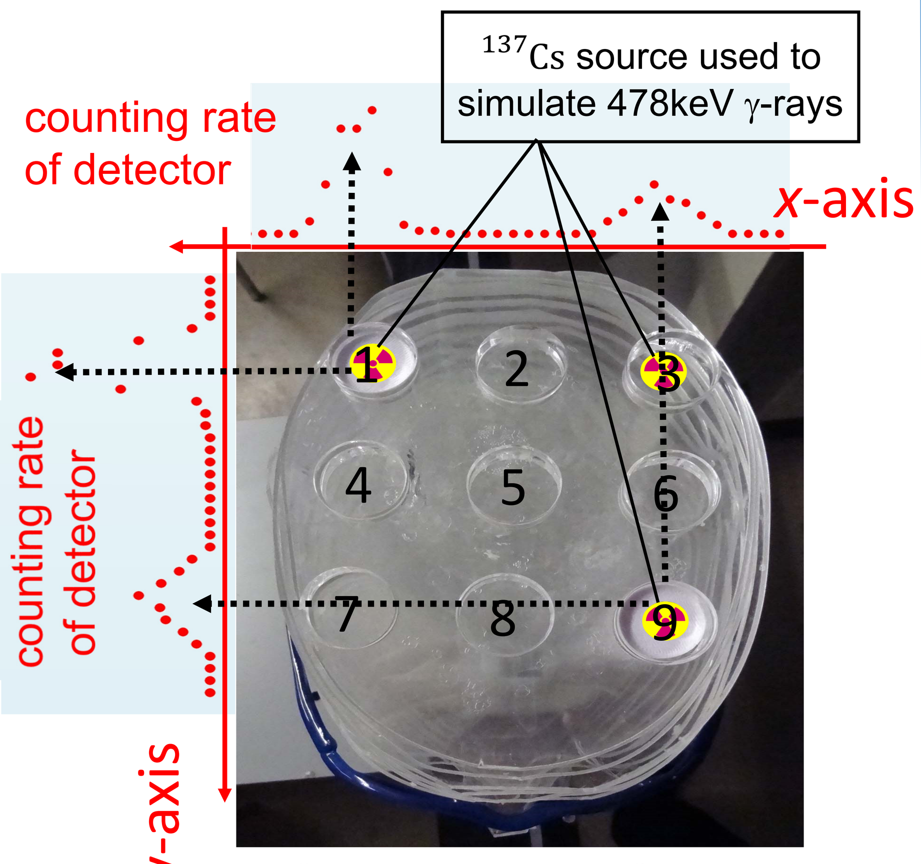
$$A_1 = R_{x1} \times N_1 + R_{x2} \times N_2$$
$$A_2 = R_{x3} \times N_3 + R_{x4} \times N_4$$
$$A_3 = R_{y2} \times N_2 + R_{y4} \times N_4$$
$$A_4 = R_{y1} \times N_1 + R_{y3} \times N_3$$

2. Experimental



Photograph of experimental system

An experimental system with standard γ-ray sources was developed to simulate the BNCT-SPECT.



Cross section of human head phantom.

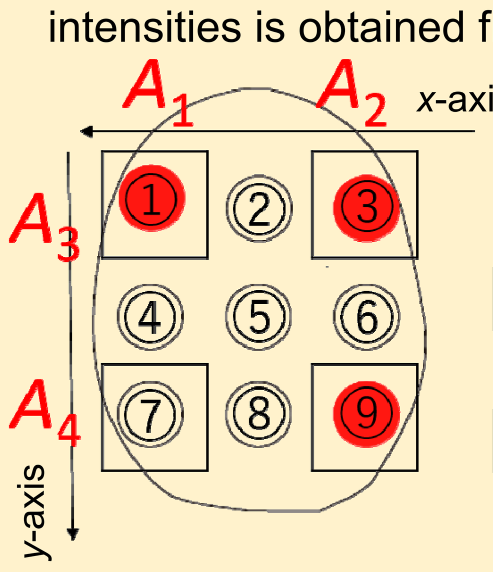
・In the case of 2×2 arrangement of radiation sources

A system of 4 linear equations to determine 4 intensities is obtained from 4 measured values.

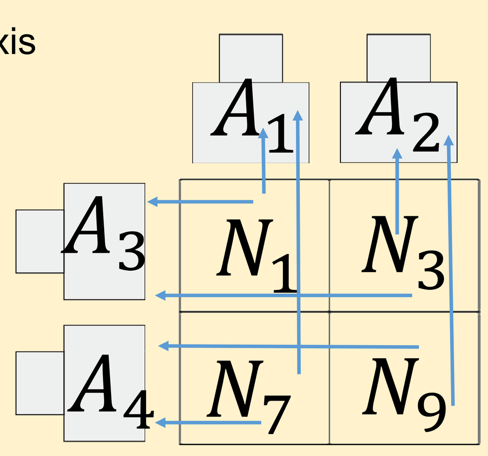
(**4 equations, 4 variables**)

$$A_1 = 3.70 \fallingdotseq 4.0\ N_1 + 0.96\ N_7$$
$$A_2 = 16.8 \fallingdotseq 4.1\ N_3 + 0.97\ N_9$$
$$A_3 = 7.69 \fallingdotseq 3.7\ N_1 + 0.95\ N_3$$
$$A_4 = 2.85 \fallingdotseq 3.7\ N_7 + 0.96\ N_9$$

Average error: 2800 %



Three radiation sources are set at positions, ①, ③ and ⑨.

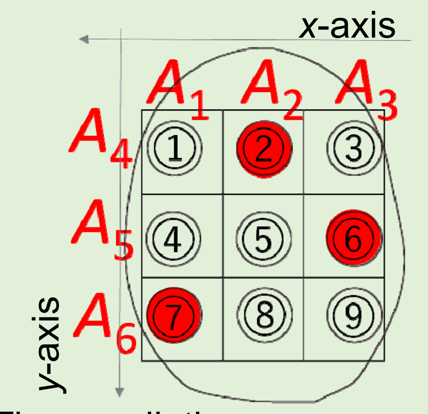


The problem becomes 2×2 arrangement for ①, ③, ⑦ and ⑨ positions.

Mathematical solutions	≠	True values
$N_1 = 12.0$ MBq		$N_1 = 0.91$ MBq
$N_3 = -39.3$ MBq		$N_3 = 2.90$ MBq
$N_7 = -46.1$ MBq		$N_7 = 0.00$ MBq
$N_9 = 180$ MBq		$N_9 = 2.90$ MBq

⇒ Acceptable solutions not obtained, because A and R have their uncertainties.

・In the case of 3×3 arrangement of radiation sources



Three radiation sources set at positions, ②, ⑥ and ⑦.

A system of 6 linear equations to determine 9 intensities is obtained from 6 measured values.

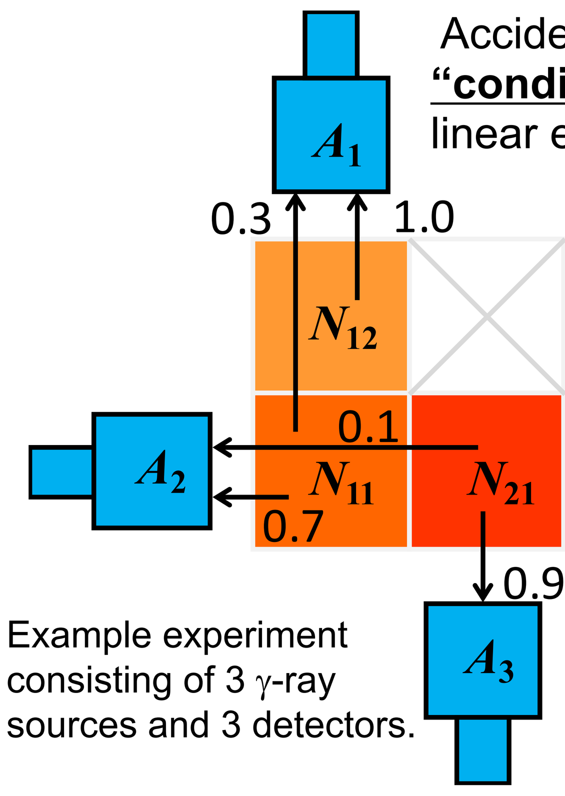
(**6 equations, 9 variables**)

$$A_1 = 2.78 \fallingdotseq 4.1\ N_1 + 2.0\ N_4 + 0.91\ N_7$$
$$A_2 = 38.7 \fallingdotseq 3.6\ N_2 + 1.7\ N_5 + 0.84\ N_8$$
$$A_3 = 5.77 \fallingdotseq 4.3\ N_3 + 2.0\ N_6 + 1.0\ N_9$$
$$A_4 = 10.5 \fallingdotseq 3.9\ N_1 + 1.9\ N_2 + 0.96\ N_3$$
$$A_5 = 2.78 \fallingdotseq 3.7\ N_4 + 1.8\ N_5 + 0.91\ N_6$$
$$A_6 = 19.4 \fallingdotseq 3.9\ N_7 + 1.9\ N_8 + 0.96\ N_9$$

This simultaneous-linear-equation cannot be solved mathematically. ≠ True value: $N_2 = 10$ MBq, $N_6 = 2.9$ MBq, $N_7 = 2.9$ MBq

⇒The 3×3 arrangement problem cannot be solved mathematically, because the number of variables are more than that of the equations.

3. Image reconstruction (radioactivity distribution estimation) with conditional probability



Example experiment consisting of 3 γ-ray sources and 3 detectors.

Accidentally, observing the equation, I found a **very simple way with "conditional probability"** For an experiment in the left, a system of 3 linear equations with 3 variables is obtained from 3 measured values.

True intensities $(N_{11}, N_{12}, N_{21}) = (100, 200, 300)$

Counting rates $(A_1, A_2, A_3) = (230, 100, 270)$

The simultaneous-linear-equation is expressed as

$$A_1 = 0.3 \times N_{11} + 1.0 \times N_{12} + 0.0 \times N_{21} = 230$$
$$A_2 = 0.7 \times N_{11} + 0.0 \times N_{12} + 0.1 \times N_{21} = 100$$
$$A_3 = 0.0 \times N_{11} + 0.0 \times N_{12} + 0.9 \times N_{21} = 270$$

Trying to calculate A_1 from true intensities and attenuation terms.

$$A_1 = 0.3 \times \overset{N_{11}}{100} + 1.0 \times \overset{N_{12}}{200} + 0 \times \overset{N_{21}}{300} = 230$$
$$= 30 + 200 + 0$$

Counting rate, A_1 (=230 CPS) is the sum of { 30 CPS from N_{11}, 200 CPS from N_{12}, 0 CPS from N_{21}.

It tells me, if one count in A_1 is detected,

conditional probability of A_1 coming from N_{11} $\left(\frac{30}{230}\right)$,

conditional probability of A_1 coming from N_{12} $\left(\frac{200}{230}\right)$,

conditional probability of A_1 coming from N_{21} $\left(\frac{0}{230}\right)$.

Can this simple way be effective to estimate true values ?

→ I tried to solve previous problems of 2×2 and 3×3 arrangements using conditional probabilities.

The above way is available, if the true values are known. In real experiments, one does not know the real values and in addition the measured values have their uncertainties.

Now let's assume a white spectrum as below.

$$(N^0{}_{11}, N^0{}_{12}, N^0{}_{21}) = (\mathbf{200}, \mathbf{200}, \mathbf{200}).$$

$$A'_1 = 0.3 \times 200 + 1.0 \times 200 + 0.0 \times 200 = 260$$
$$A'_2 = 0.7 \times 200 + 0.0 \times 200 + 0.1 \times 200 = 160$$
$$A'_3 = 0.0 \times 200 + 0.0 \times 200 + 0.9 \times 200 = 180$$

$$A'_1 = 0.3 \times \overset{N_{11}}{200} + 1.0 \times \overset{N_{12}}{200} + 0.0 \times \overset{N_{21}}{200} = 260$$
$$= 60 + 200 + 0$$

It means if one count is given to A'_1, the conditional probability of coming to A_1 from N_{11} is $\frac{60}{260}$.

⇒ Among A_1 the contribution from N_{11} is,

from N_{11} to A_1 (=230) : $\frac{60}{260} \times 230 = \mathbf{53.08}$ **CPS**

Similarly,

from N_{11} to A_2 (=100) : $\frac{0.7 \times 200}{160} \times 100 = \mathbf{87.92}$ **CPS**,

from N_{11} to A_3 (=270) : $\frac{0.0 \times 200}{180} \times 270 = \mathbf{0.0}$ **CPS**.

The sum: $N'_{11} = 53.08 + 87.92 + 0.0 = \mathbf{141}$ **CPS.**

I tried to estimate the radioactivities by this simple way.

✓Initial values:

$$(N^0{}_{11}, N^0{}_{12}, N^0{}_{21}) = (\mathbf{200}, \mathbf{200}, \mathbf{200})$$

✓The 1st estimation

$$(N'_{11}, N'_{12}, N'_{21}) = (\mathbf{141}, \mathbf{177}, \mathbf{283}).$$

✓The 2nd estimation

$$(N''_{11}, N''_{12}, N''_{21}) = (\mathbf{122}, \mathbf{186}, \mathbf{292})$$

Really close !

TRUE values of radiation intensities:

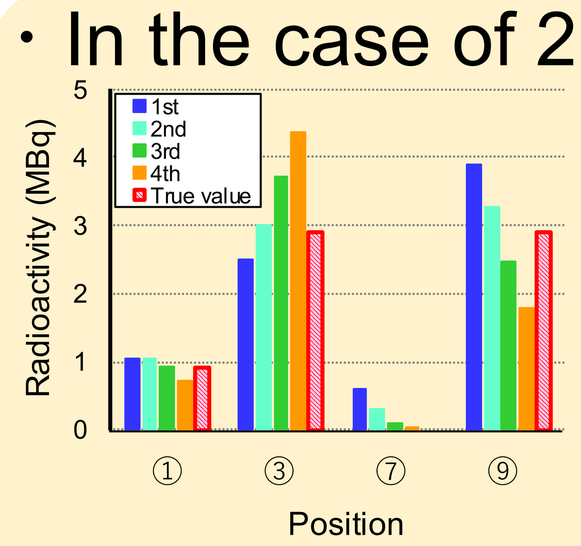
$$(N_{11}, N_{12}, N_{21}) = (\mathbf{100}, \mathbf{200}, \mathbf{300})$$

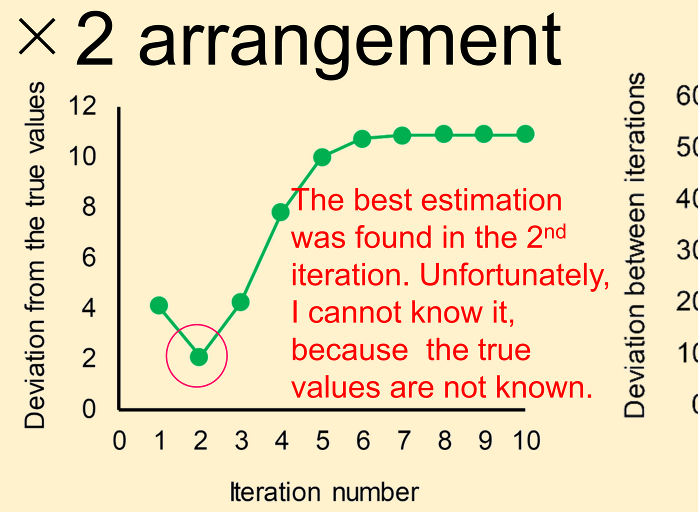
Cleary the values are approaching the true values.

I expect this proposed estimation procedure can be applied to the image reconstruction of BNCT-SPECT.

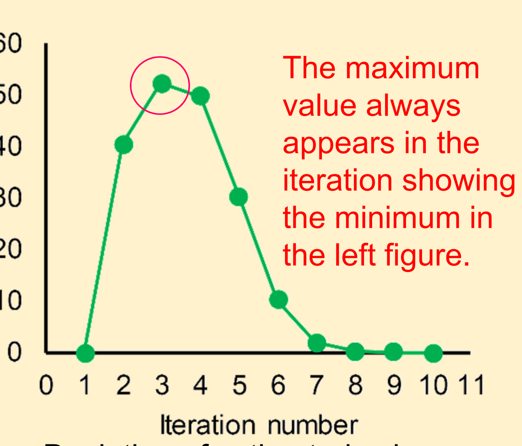
4. Try again ! : Estimate radioactivity by the procedure with conditional probability

・In the case of 2×2 arrangement





Deviation between the True and estimated values as a function of the number of iterations.



Deviation of estimated values between iterations as a function of the number of iterations.

・Estimation is possible in 2×2 (2nd iteration is the best).

・Deviation between iterations would become an index to estimate the necessary number of iterations.

→ An acceptably accurate results can be estimated by the proposed procedure with conditional probability.

2nd estimated values (deviation)

$N_1 = 1.0$ MBq (+0.1)
$N_3 = 3.1$ MBq (+0.2)
$N_7 = 0.3$ MBq (+0.3)
$N_9 = 3.3$ MBq (+0.4)

Average error: 8.1 %

・In the case of 3×3 arrangement

→ 3×3 arrangement cannot be solved mathematically. But I could successfully obtain estimated values by the proposed estimation procedure with conditional probability.

True values	6th estimated values
$N_2 = 10.0$ MBq	$N_2 = 10.3$ MBq
$N_6 = 2.90$ MBq	$N_6 = 0.02$ MBq
$N_7 = 2.90$ MBq	$N_7 = 0.05$ MBq

Average error: 26 %

5. Conclusion and future works

A basic estimation procedure for image reconstruction of BNCT-SPECT was proposed only with conditional probability. As a result of investigation especially for a 2×2 arrangement problem, the procedure was confirmed to be applicable. This work is summarized as, Yuri Morizane et al., "Simple Image Reconstruction Technique for BNCT-SPECT with Conditional Probability", PLOS ONE, which is under review now.

	mathematically	conditional probability
2×2	X	◎
3×3	Cannot solve	○

Future works

・Image of a large object ?

・Number of iterations ?

・Error propagation in the estimation process ?

新しいがん治療(BNCT)への挑戦！

～条件付確率を用いたBNCT用SPECT装置の画像再構成～

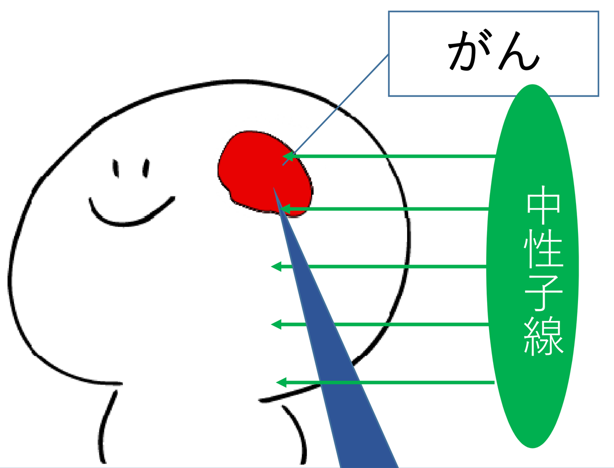
大阪府立大手前高等学校　３年 守實友梨

1. はじめに

厚生労働省によると、がんは死因の約3割をしめる日本の国民病である。現在様々な治療法が研究されているなか、外来治療が可能で、効果的な放射線治療として、ホウ素中性子捕捉療法(Boron Neutron Capture Therapy, BNCT)が注目されている。

本研究では大阪大学大学院工学研究科の村田研究室の協力のもと、**BNCTによる治療効果(治療されたがん細胞の位置)をリアルタイム計測するBNCT用のSPECT(単一光子放射断層撮影)装置の実現を目指し、その画像再構成法の検討**を行った。

1.1 BNCTとは



あらかじめホウ素(^{10}B)化合物をがん細胞にのみ蓄積させ、そこに中性子線をあてて核反応を起こし、その生成物(α線、^7Li)によりがん細胞を死滅させる放射線治療法。

メリット（がん細胞選択性）

・α線と ^7Liの飛距離は、たかだか細胞1個分(隣の細胞に届かない)

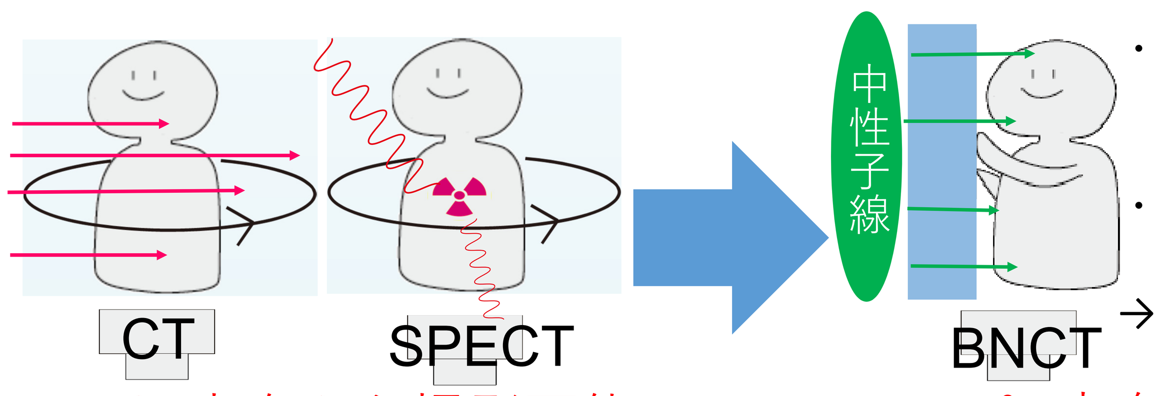
→　正常細胞を傷つけない

→　**同一箇所の複数回照射が可能**

がん細胞内で起こる^{10}Bと中性子の核反応

$$^{10}B + n \rightarrow \alpha(1.47MeV) + {}^7Li(0.84MeV) + \gamma(0.478MeV)$$

1.2 BNCT-SPECTへの挑戦



・中性子が出てくる壁にくっついて治療を受けるため、左右どちらかは塞がる

・上下前後にも障壁(ベッドやSPECT装置そのもの)が生じる

→　患者やSPECT装置を回すことができない。

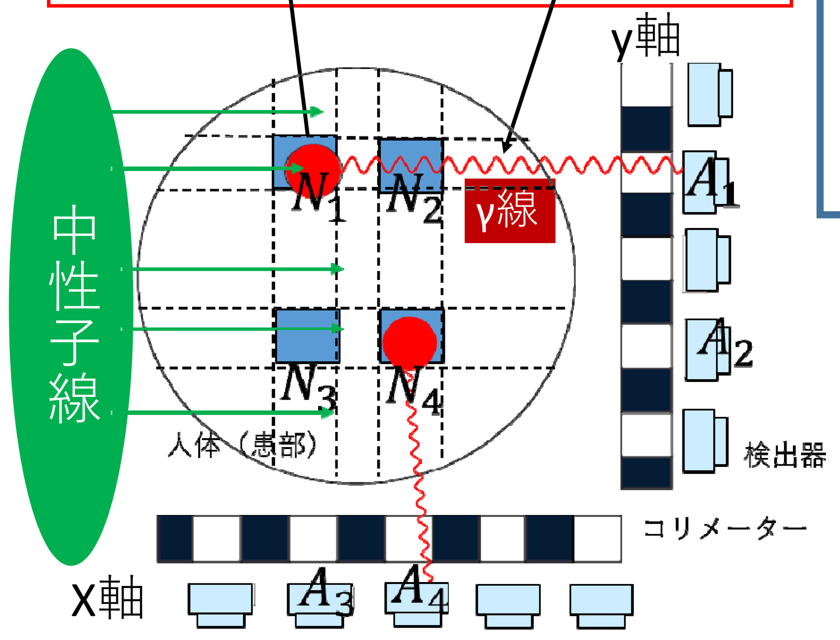
360°　方向から撮影可能　　360°　方向からの撮影は不可能

✔治療効果リアルタイム計測には新たなSPECT装置の開発が必要

⇒BNCT-SPECT装置を提案。**本研究ではその画像再構成法を検討する。**

原理図　　方法

がん細胞内で中性子と^{10}Bが核反応を起こし、0.478MeVのγ線を放出する。



BNCT-SPECT装置の原理図

BNCT-SPECTの画像再構成方法

⇒治療の際に起こる核反応から生じるγ線を測定し、得られた測定値A(counts/s:CPS)と減衰率R_x, R_yを使って以下のような連立方程式を立て、中性子反応率を推定。

この時、がんが存在する可能性のある位置は■の4か所。

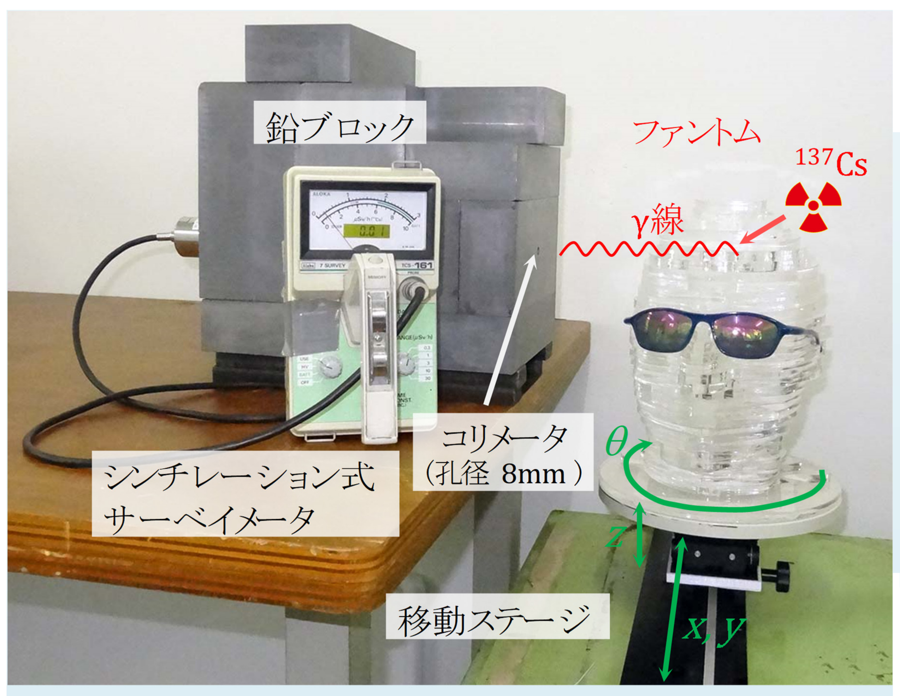
その強度をN_1～N_4とすると下の連立方程式が成り立つ。

$$A_1 = R_{x1} \times N_1 + R_{x2} \times N_2$$
$$A_2 = R_{x3} \times N_3 + R_{x4} \times N_4$$
$$A_3 = R_{y2} \times N_2 + R_{y4} \times N_4$$
$$A_4 = R_{y1} \times N_1 + R_{y3} \times N_3$$

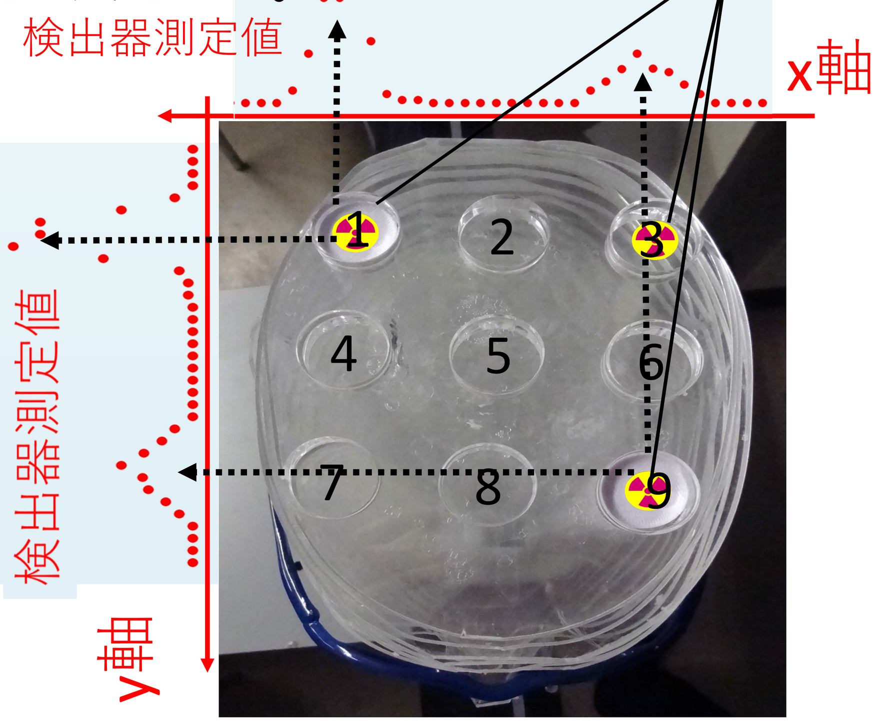
2. 実験

標準γ線源を用い、BNCT-SPECTを模擬した実験装置を自作し測定を実施した。

^{137}Cs線源(478keVγ線を模擬)



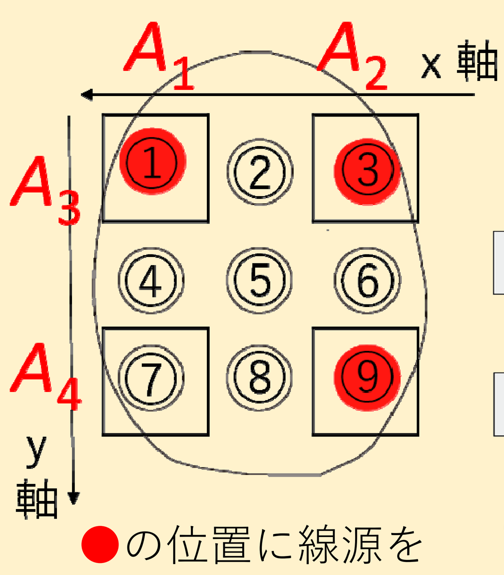
実験の様子



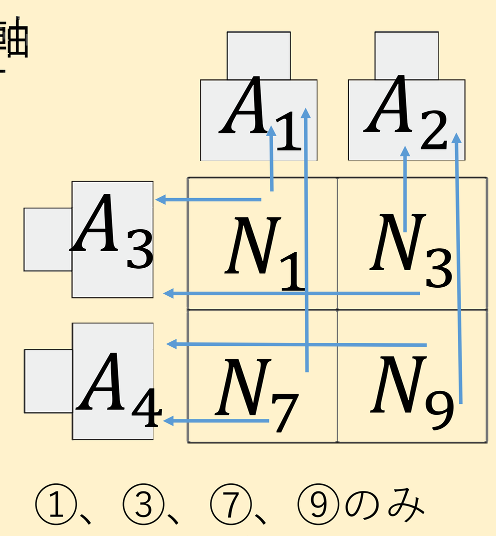
ファントムの断面と線源

・線源が2×2に並んでいる場合

測定値からたてた連立方程式（**式4個、変数4個**）



●の位置に線源を埋め込んだ。



①、③、⑦、⑨のみを考えればいいので2×2の問題となる。

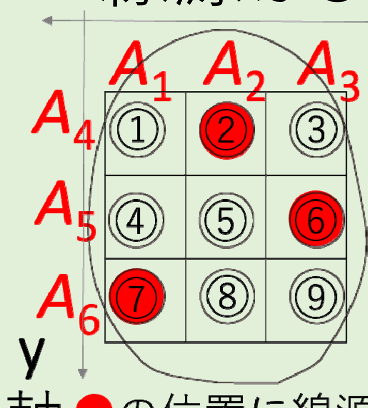
$$A_1 = 3.70 \fallingdotseq 4.0\ N_1 + 0.96\ N_7$$
$$A_2 = 16.8 \fallingdotseq 4.1\ N_3 + 0.97\ N_9$$
$$A_3 = 7.69 \fallingdotseq 3.7\ N_1 + 0.95\ N_3$$
$$A_4 = 2.85 \fallingdotseq 3.7\ N_7 + 0.96\ N_9$$

平均誤差: 2800%

上式の数学解		正解値
$N_1 =$ 12.0 MBq	≠	N_1 = 0.91 MBq
$N_3 = -39.3$ MBq		N_3 = 2.90 MBq
$N_7 = -46.1$ MBq		N_7 = 0.00 MBq
$N_9 =$ 180 MBq		N_9 = 2.90 MBq

⇒誤差のため値が一致しない。

・線源が3×3に並んでいる場合



●の位置に線源を埋め込んだ。

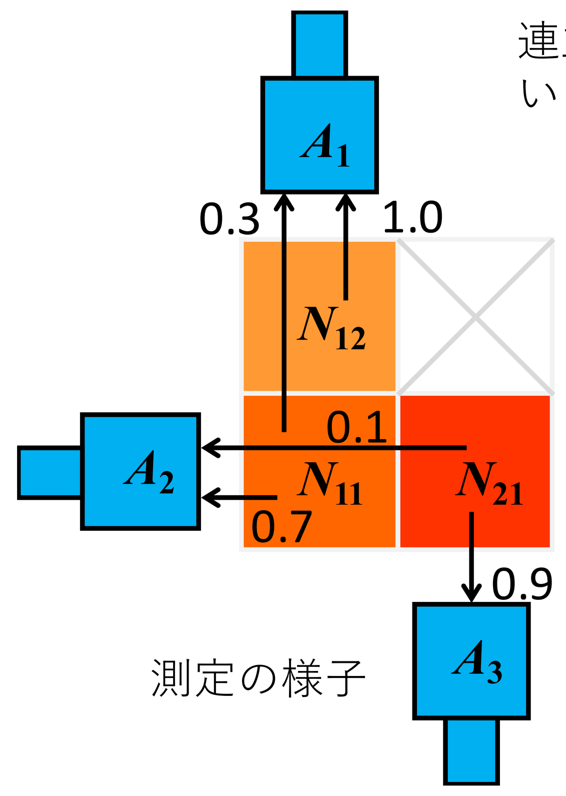
測定値から立てた連立方程式（**式6個、変数9個**）

$$A_1 = 2.78 \fallingdotseq 4.1\ N_1 + 2.0\ N_4 + 0.91\ N_7$$
$$A_2 = 38.7 \fallingdotseq 3.6\ N_2 + 1.7\ N_5 + 0.84\ N_8$$
$$A_3 = 5.77 \fallingdotseq 4.3\ N_3 + 2.0\ N_6 + 1.0\ N_9$$
$$A_4 = 10.5 \fallingdotseq 3.9\ N_1 + 1.9\ N_2 + 0.96\ N_3$$
$$A_5 = 2.78 \fallingdotseq 3.7\ N_4 + 1.8\ N_5 + 0.91\ N_6$$
$$A_6 = 19.4 \fallingdotseq 3.9\ N_7 + 1.9\ N_8 + 0.96\ N_9$$

左の式は数学的に解けない。 ≠ 正解値 N_2 = 10 MBq, N_6 = 2.9 MBq, N_7 = 2.9 MBq

⇒式よりも変数の数が多いため数学的には解けない

3. 条件付確率による画像化(線源強度推定)



測定の様子

連立方程式をよく見ると以下のような簡単なやり方に気づく。いま、左図(**式3個、変数3個の場合**)のような計測を行ったとする。

強度真値$(N_{11}, N_{12}, N_{21}) = (100, 200, 300)$

測定値　$(A_1, A_2, A_3) = (230, 100, 270)$

図の減衰率を用いて連立方程式を立てると

$$A_1 = 0.3 \times N_{11} + 1.0 \times N_{12} + 0.0 \times N_{21} = 230$$
$$A_2 = 0.7 \times N_{11} + 0.0 \times N_{12} + 0.1 \times N_{21} = 100$$
$$A_3 = 0.0 \times N_{11} + 0.0 \times N_{12} + 0.9 \times N_{21} = 270$$

ここで真値を用いて測定値を計算してみると

$$A_1 = 0.3 \times \overset{N_{11}}{100} + 1.0 \times \overset{N_{12}}{200} + 0 \times \overset{N_{21}}{300} = 230$$
$$= 30 + 200 + 0$$

$A_1 = 230$(CPS)のうち $\begin{cases} N_{11}\text{から } 30\ \text{CPS} \\ N_{12}\text{から} 200\ \text{CPS} \\ N_{21}\text{から } 0\ \text{CPS} \end{cases}$ 来たのではないか？

そう考えると、A_1で1カウント検出されたとき

$\begin{cases} N_{11}\text{からくる}\textbf{条件付確率は} \ \frac{30}{230} \\ N_{12}\text{からくる}\textbf{条件付確率は} \ \frac{200}{230} \\ N_{21}\text{からくる}\textbf{条件付確率は} \ \frac{0}{230} \end{cases}$

これを使えば真値がわからない場合でも推定できるのではないか？

→条件付確率で解いてみる

今、真値がわからないので$(N^0_{11}, N^0_{12}, N^0_{21}) = (\mathbf{200, 200, 200})$と仮定して考える。

上の連立方程式に仮定値を入れ計算すると

$$A'_1 = 0.3 \times 200 + 1.0 \times 200 + 0.0 \times 200 = 260$$
$$A'_2 = 0.7 \times 200 + 0.0 \times 200 + 0.1 \times 200 = 160$$
$$A'_3 = 0.0 \times 200 + 0.0 \times 200 + 0.9 \times 200 = 180$$

$$A'_1 = 0.3 \times \overset{N_{11}}{200} + 1.0 \times \overset{N_{12}}{200} + 0.0 \times \overset{N_{21}}{200} = 260$$
$$= 60 + 200 + 0$$

したがって、A'_1で1カウント検出されたとき

N_{11}からくる**条件付確率は** $\frac{60}{260}$

これより、$A_1 = 230$のうちN_{11}からくる放射線強度は

$\frac{60}{260} \times 230 = \mathbf{53.08\ CPS}$

であるとわかる。同様に、

$N_{11} \rightarrow A_2$ は $\frac{0.7 \times 200}{160} \times 100 = \mathbf{87.92\ CPS}$

$N_{11} \rightarrow A_3$ は $\frac{0.0 \times 200}{180} \times 270 = \mathbf{0.0\ CPS}$

なので、合計すると、

$$N'_{11} = \mathbf{53.08 + 87.92 + 0.0 = 141\ CPS}$$

このようにしてすべて解いてみる。

仮定値$(N^0_{11}, N^0_{12}, N^0_{21}) = (\mathbf{200, 200, 200})$の時、1回目の推定値を$N'_{11}, N'_{12}, N'_{21}$とすると

$(N'_{11}, N'_{12}, N'_{21}) = (\mathbf{141, 177, 283})$

もう1回繰り返すと2回目の推定値は

$(N''_{11}, N''_{12}, N''_{21}) = (\mathbf{122, 186, 292})$

近い！

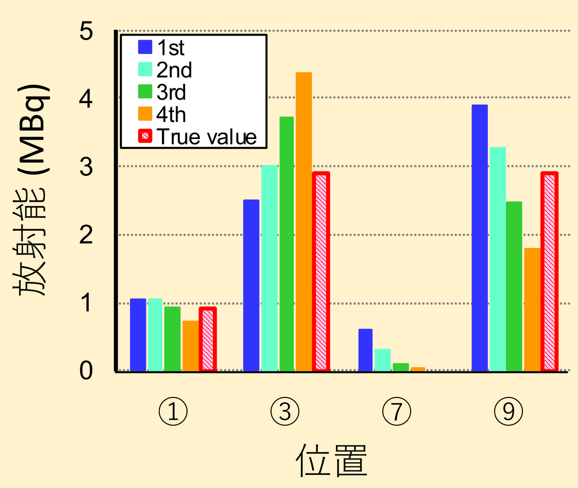
真値$(N_{11}, N_{12}, N_{21}) = (\mathbf{100, 200, 300})$

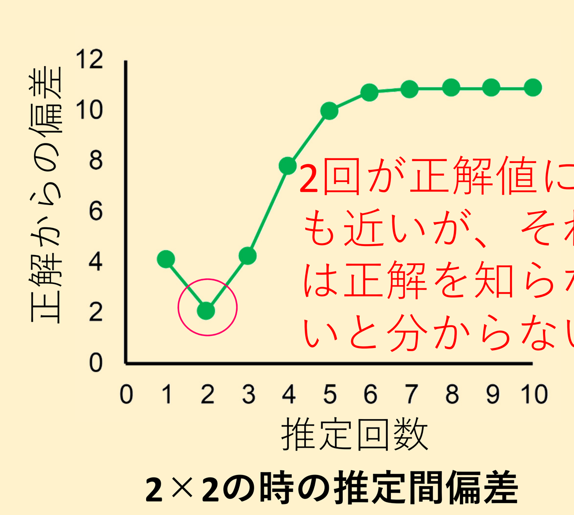
仮定値よりも段々と真値に近づく

条件付確率を使えば画像再構成が可能になるのではないか

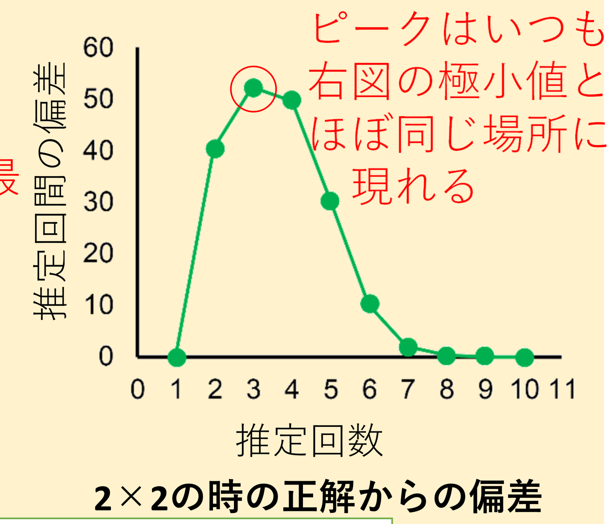
4. 条件付確率による実験解析の再挑戦

・2×2配列の場合





2×2の時の推定間偏差



2×2の時の正解からの偏差

・2×2では推定可能（2回目の推定がベスト）

・推定回数は、右図の通り、推定回間の偏差が最大になった推定回数前後が最適。

→条件付確率を使うと精度よく解けた

2回目(答えとの差)
N_1 = 1.0 MBq (+0.1)
N_3 = 3.1 MBq (+0.2)
N_7 = 0.3 MBq (+0.3)
N_9 = 3.3 MBq (+0.4)

平均誤差：8.1%

・3×3配列の場合

数学的には解けなかったが、条件付確率を使うと解くことができた

答え	6回目(答えとの差)
N_2 = 10.0 MBq	N_2 = 10.3 MBq (+0.3)
N_6 = 2.90 MBq	N_6 = 0.02 MBq(−2.8)
N_7 = 2.90 MBq	N_7 = 0.05 MBq(−2.9)

平均誤差：26%

5. 結論と今後の課題

下の表に示すように、BNCT-SPECTの画像の再構成は、条件付確率を用いた推定法により、実現できる可能性があることが判明した。なお本研究成果は2017年8月, Yuri Morizane et al., "Simple Image Reconstruction Technique for BNCT-SPECT with Conditional Probability", PLOS ONE, として論文投稿(査読)中である。

配置	連立方程式	条件付確率
2×2	×	◎
3×3	解けない	○

今後の課題

・被写体が大きいときは？

・推定回数の決め方は？

・推定の正確さは？