The ABCs of XMLs

Journal Publishing for Digital Age and Beyond

Nahrizul Adib Kadri, Ph.D.

Head, Department of Biomedical Engineering, University of Malaya, Malaysia

Managing Editor, Biomedical Imaging and Intervention Journal
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Outline

- What is XML?
- Why do we need XML?
- How to go about it?
- Take home message

What is it?

- XML = Extensible Markup Language
- Designed for web use, to overcome limitations of HTML
  - Based on SGML (used in publishing)
  - Main HTML problems: rendering and processing

```
<p><b>Mrs. Mary McGoon</b>
<br>
1401 Main Street
<br>
Anytown, NC 34829</p>
```

What is it?

Tag

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<address>
  <name>
    <title>Mrs.</title>
    <first-name>
      Mary
    </first-name>
    <last-name>
      McGoon
    </last-name>
  </name>
  <street>
    1401 Main Street
  </street>
  <city>Anytown</city>
  <state>NC</state>
  <postal-code>
    34829
  </postal-code>
</address>
```

Element

Mrs. Mary McGoon
1401 Main Street, Anytown, NC 38429

M. McGoon
1401 Main Street,
Anytown, NC 38429

Why do we need XML?

- Rendering and processing contents

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Article

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REVIEW ARTICLE

Review of 18F-FDG synthesis and quality control

S Yu PhD

Departments of Nuclear Medicine & PET and Experimental Surgery, Singapore General Hospital, Singapore

ABSTRACT

This review article covers a concise account on fludeoxyglucose (^{18}F-FDG) synthesis and quality control procedures with emphasis on practical synthesis Currently, ^{18}F-FDG is the most successful PET radiopharmaceutical so far. The advancement in synthesis and quality control of ^{18}F-FDG, together with its approval by the US FDA and the availability of reimbursement, are probably the main reasons for the flourish of clinical PET over the last 20 years. ^{18}F-FDG can be synthesised by either electrophilic fluorination or nucleophilic fluorination reaction. Nucleophilic fluorination using mannose triflate as precursor and Kryptofix or tetrabutylammonium salts (TBA) is widely used because of higher yield and shorter reaction time. The quality control requirements of ^{18}F-FDG can be found in United States Pharmacopeia (USP), British Pharmacopeia (BP), European Pharmacopeia (EP) and the Chemistry.

Scopus

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Review of ^{18F}-FDG synthesis and quality control (Review)

Yu, S.
Department of Nuclear Medicine, Department of PET and Experimental Surgery, Singapore General Hospital, Outram Road, Singapore

Abstract

View references

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Review of ^{18}F-FDG Synthesis and Quality Control

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Keywords: Fludeoxyglucose (^{18}F-FDG), positron emission tomography (PET), quality control (QC)

INTRODUCTION

^{18}F-FDG is a glucose analogue in which the hydroxyl group on the 2-carbon of a glucose molecule is replaced by a fluoride atom. Like glucose, ^{18}F-FDG is taken up into living cells by facilitated transport and then phosphorylated by hexokinase. Unlike glucose, ^{18}F-FDG cannot undergo further metabolism because the hydroxyl group at the 2-carbon is a requirement for the process [1-2]. Nevertheless, ^{18}F-FDG is a good indicator of glucose uptake and cell viability.

The uptake of glucose analogues into living cells also depends on modifications of various carbons at different positions. It has been shown that the specificity of 3-deoxyglucose (3-DG) and 4 deoxyglucose (4-DG) towards hexokinase reduced by 100-fold [3], hence 3-DG and 4-DG were not retained inside the cells. Similarly, 3-fluoro-deoxyglucose and 4-fluoro-deoxyglucose do not accumulate in living cells as much as ^{18}F-FDG. Although the nucleophilic substitution reaction is more widely used nowadays, the electrophilic fluorination reaction has an important place in the synthesis of ^{18}F-FDG.

* Corresponding author. Present address: Departments of Nuclear Medicine & PET and Experimental Surgery, Singapore General Hospital, Outram Road, Singapore. Tel.: +(65) 6326-5666; E-mail: adzyyu@yahoo.com.sg (Sidney Yu).

SYNTHESIS OF ^{18}F-FDG BY ELECTROPHILIC FLUORINATION

The first synthesis of ^{18}F-FDG was carried out in Brookhaven National Laboratory by Wolf *et al.* in 1976 by electrophilic fluroination [4]. As shown in Figure 1, electrophilic fluorination refers to the addition of fluorine atoms across a double bond, producing a difluoro derivative of the parent compound. The electrophilic fluorination by Wolf *et al.* involved the use of 3, 4,6-tri-O-acetyl-D-glucal as precursor. The glucal was treated with ^{18}F-F_2 to produce a 3:1 mixture of ^{18}F labelled difluoro-glucose and difluoro-mannose derivatives. The difluoro-glucose derivative was separated and hydrolysed with hydrochloric acid to form 2-fluoro-2-deoxyglucose (Figure 2). The yield was 8% and the synthesis time was 2 hours [4].

Despite the low yield and long synthesis time, the Brookhaven team was able to collaborate with The Hospital of the University of Pennsylvania to map glucose metabolism in human brain [4]. This was the first ^{18}F-FDG trial in human.

Several improvements to the electrophilic fluorination described above were made thereafter. One of the most useful modifications was the use of acetylhypofluorite ^{18}F-CH_3CO_2F. The acetylhypofluorite can be produced *in situ* from ^{18}F-F_2. The yield was higher and the synthesis reaction was easier to control [4-6].

The major limitation of electrophilic fluorination was that only 50% of the radioactive fluorine atoms were incorporated into the precursors. In addition, the ^{18}F-F_2 was produced from a Neon gas target with 0.1% to 1% of fluorine gas via a ^{20}Ne(d,α)^{18}F reaction. The specific activity is lower due to the presence of the non-radioactive fluorine gas. The maintenance and operation of a Neon target is troublesome and the yield of ^{18}F was much lower than with the ^{20}Ne(d,α)^{18}F reaction than with the ^{18}O(p,n)^{18}F reaction. [4, 7-8]

SYNTHESIS OF ^{18}F-FDG BY NUCLEOPHILIC FLUORINATION

Many attempts have been made to develop a nucleophilic substitution for the synthesis of ^{18}F-FDG. This included the use of ^{18}F-CsF, ^{18}F-Et_4NF, and ^{18}F-KHF [4, 9-14]. But the major breakthrough was reported in 1986 by Hamacher *et al.* who had used Kryptofix 222™ as a catalyst [15]. The reaction had a consistent yield of over 50% and the reaction time was shortened to 50 min.

Nucleophilic substitution is a chemical reaction involving the addition of a nucleophilic molecule (highly negatively charged molecule) into a molecule with a leaving group (electron drawing group attached to the parent molecule through an unstable chemical bond). Figure 3 is a general scheme for an SN2 nucleophilic substitution reaction. The nucleophilic molecule has a high affinity towards the relatively electron deficient centre in the parent molecule created by the electron pulling leaving group. As a result, the nucleophilic molecule forms a covalent bond with the parent molecule and displaces the leaving group. The stereo-configuration of the parent molecule is also changed.

In the synthesis of ^{18}F-FDG, ^{18}F ion is the nucleophile. The precursor is mannose triflate in which the 1,3,4,6 position carbons of a mannose molecule are protected with an acetyl group and triflate is the leaving group at the 2-carbon. In the presence of Kryptofix 222™ as catalyst and acetonitrile as solvent, ^{18}F ion approaches the mannose triflate at the 2-carbon, while the triflate group leaves the protected mannose molecule to form ^{18}F-FDG (Figure 4).

Although synthesis of ^{18}F-FDG can be carried out in different computer controlled automatic synthesizers, the nucleophilic process proceeds in roughly same stages:

Removal of ^{18}F from the ^{18}O water coming out from the cyclotron target

Fluorine has a high hydration energy, so water is not a suitable solvent in this synthesis. Polar aprotic solvent such as acetonitile should be used in an SN2 nucleophilic substitution reaction. Since ^{18}F is produced by a ^{18}O(p,n)^{18}F reaction, it is necessary to isolate the ^{18}F ion from its aqueous environment. The most convenient way to isolate is to use a light QMA (Quaternary ammonium anion exchange) Sep-Pak column (Accell Plus QMA Sep-Pak™). The ^{18}F is retained by or via an ion-exchange reaction and allowed the ^{18}O-water to flow through. The retained ^{18}F is then eluted with an acetonitrile solution of Kryptofix and potassium carbonate (Figure 5).

In an aqueous environment, any negatively charged ions must be accompanied by positively charged counterparts. Usually, the ^{18}F washed out from the cyclotron target is accompanied by traces of metal ions from the surface of the target body. When passing through the light QMA anion exchange ion, the ^{18}F$^-$ is retained and the metal ions will be lost in the ^{18}O water. Hence, it is necessary to introduce a positively charged counter ion to restore the ^{18}F$^-$ reactivity before evaporation of residual ^{18}O enriched water [16].

Several types of positively charged counter ions have been used, including large metal ions such as rubidium or caesium; potassium ion complexed by a large ring structure such as Kryptofix 222™ and tetrabutylammonium salts [16-17]. Kryptofix 222™ is a cyclic crown ether (Figure 6), which binds the potassium ion, preventing the formation of ^{18}F-KF. Thus, potassium acts as the counter ion of ^{18}F to enhance its reactivity but does not interfere with the synthesis.

Since Kryptofix 222™ causes apnoea and convulsion, all automatic synthesis modules have multiple removal steps so that there is only negligible amount of Kryptofix in the final ^{18}F-FDG products.

Why do we need XML?

- Indexing and abstracting services (PubMed, DOAJ)
  - Exceptions e.g. Scopus, EBSCO

crossref.org

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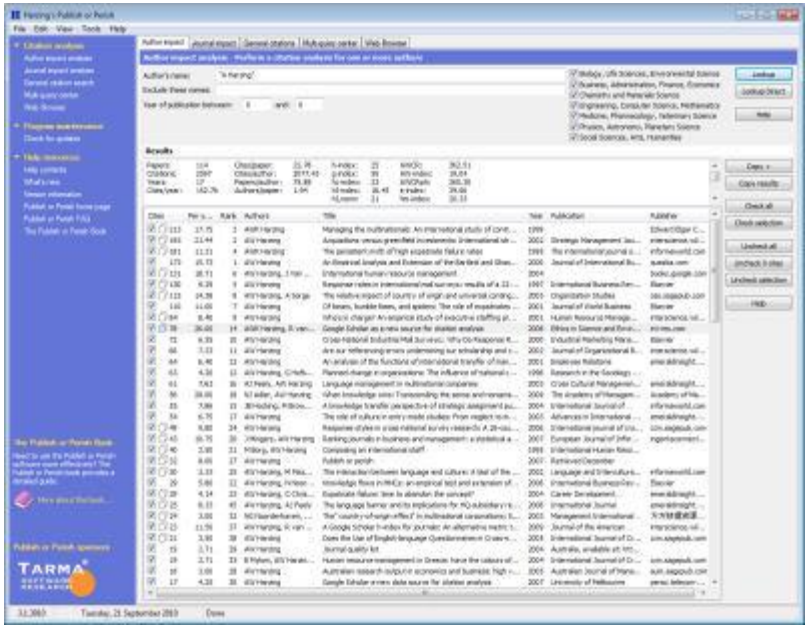
Why do we need XML?

- "Different users, different uses"
  - Journal Citation Report® (ISI Web of Knowledge)
  - Publish or Perish software (Google Scholar)
  - Scimago (Scopus)



SJR
SCImago Journal & Country Rank

Biomedical Imaging and Intervention Journal

Scope:

The Biomedical Imaging and Intervention Journal (biij) is an open access multidisciplinary peer-reviewed quarterly online journal, published by the Department [...]

Show full scope

Charts | Data

Indicators	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
SJR	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,031	0,036	0,040	0,044	0,043	0,028
Total Documents	0	0	0	0	0	0	11	55	57	33	34	38	10
Total Docs. (3years)	0	0	0	0	0	0	0	11	66	123	145	124	105
Total References	0	0	0	0	0	0	155	948	1.332	556	508	811	411
Total Cites (3years)	0	0	0	0	0	0	0	1	17	39	53	43	8
Self Cites (3years)	0	0	0	0	0	0	0	1	5	0	2	4	0
Citable Docs. (3years)	0	0	0	0	0	0	0	9	55	101	120	102	87
Cites / Doc. (4years)	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,11	0,31	0,39	0,41	0,43	0,12
Cites / Doc. (3years)	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,11	0,31	0,39	0,44	0,42	0,09
Cites / Doc. (2years)	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,11	0,31	0,36	0,39	0,18	0,10
References / Doc.	0,00	0,00	0,00	0,00	0,00	0,00	14,09	17,24	23,37	16,85	14,94	21,34	41,10
Cited Docs.	0	0	0	0	0	0	1	11	24	34	30	6	
Uncited Docs.	0	0	0	0	0	0	10	55	99	111	94	99	
% International Collaboration	0,00	0,00	0,00	0,00	0,00	0,00	9,09	14,04	15,15	8,82	23,68	0,00	

Display journal title

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<a href="http://www.scimagojr

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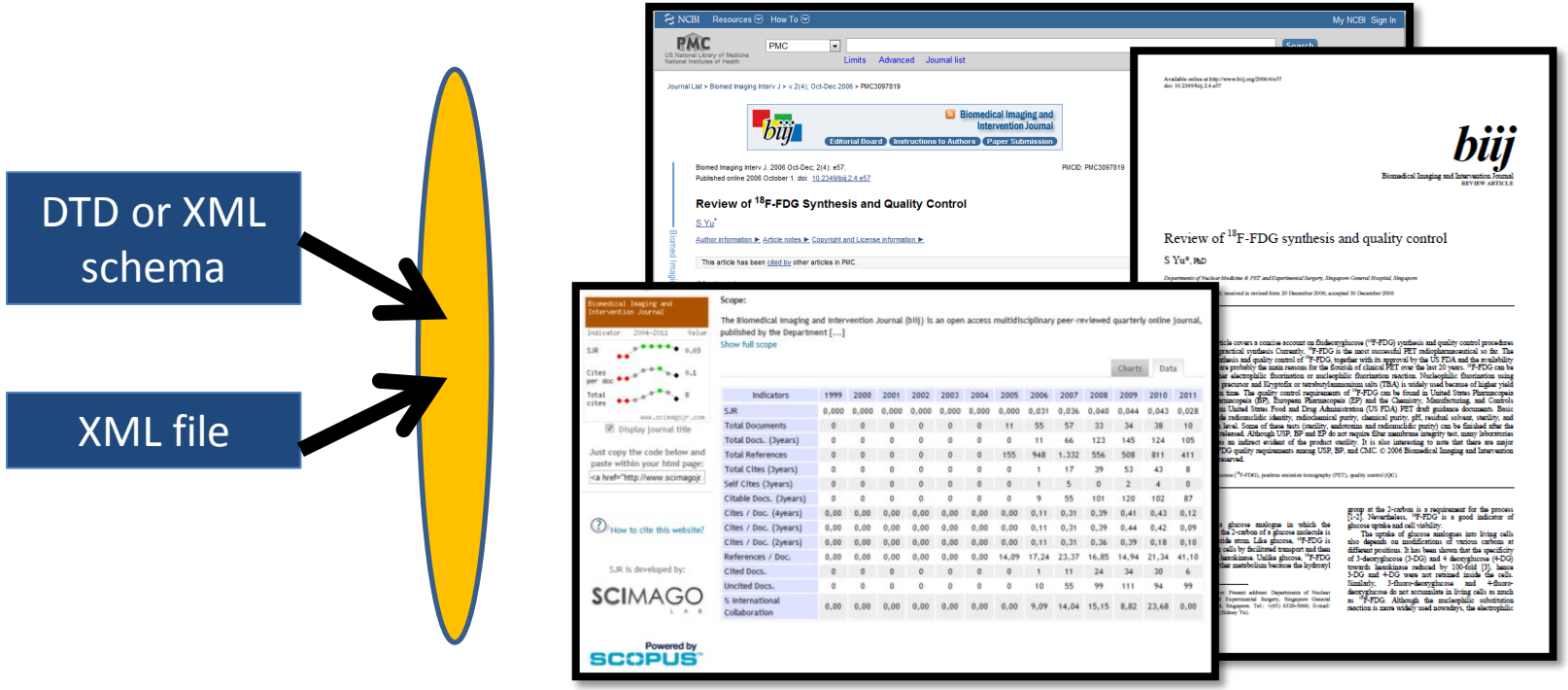
How to go about it?

- XML requires
  - Document Type Definition (DTD) or XML Schema
  - Well-defined XML files



How to go about it?

How to go about it?

- Get an example file, and modify to our contents

PMC Requires:

1. XML Coding: A separate XML data file for the full text of each article.
2. Images: The original high-resolution digital image files for all figures in each article.
3. PDF: A PDF file for each article.
4. Supplementary Data: Spreadsheets, video files, etc. available with the article.
5. Delivery: Files must be named and packaged for PMC.

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Example XML File

The example file below contains only one record.

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    <authors>
      <author>
        <name>Fritz Haber </name>
        <email>fritz.haber@some.university.org</email>
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      </author>
    </authors>
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        Universitaty of B
      </affiliationName>
      <affiliationName affiliationId="3">
        University of C
      </affiliationName>
    </affiliationsList>
```

Take home message

- XML is THE data format of choice
  - Editable by anyone, anywhere, using anything (really)
- No need to know the details: leave it to the professionals
  - Hand-coding is cumbersome
  - Standards keep improving
  - Always backward compatible

The end

- Thanks for your attention
- For more details, read up on XML at World Wide Web Consortium (W3C) website
- Contact me at nahrizuladib@um.edu.my