

# Rapid Optimization Using a Design of Experiments Approach: Application to Aluminum- $^{18}\text{F}$ Fluoride Radiolabeling Method

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gbcm

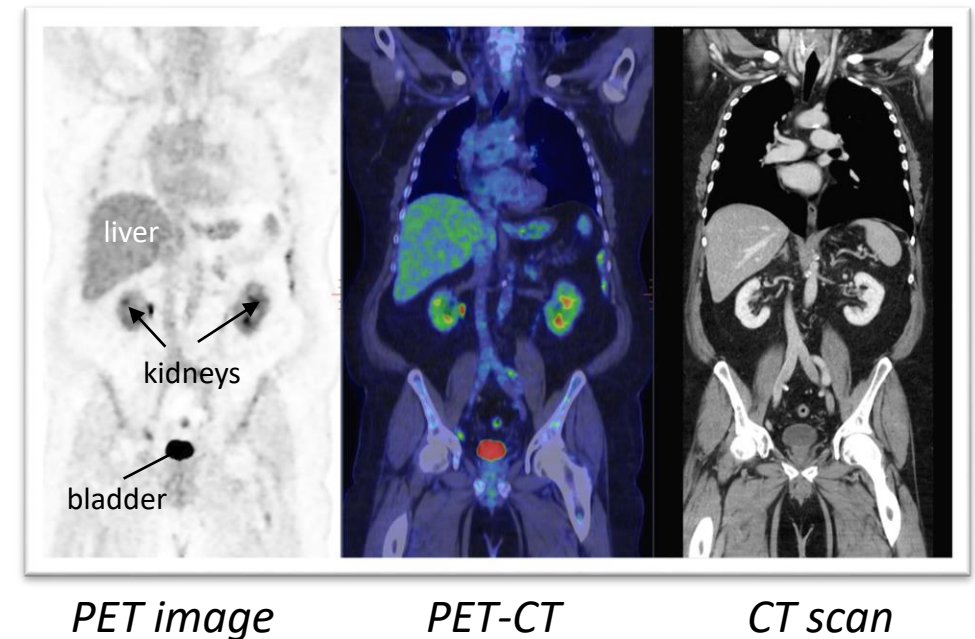
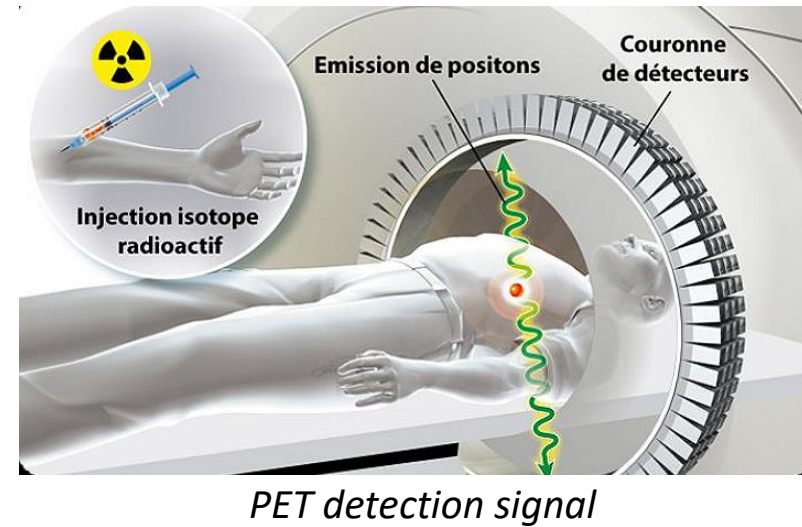
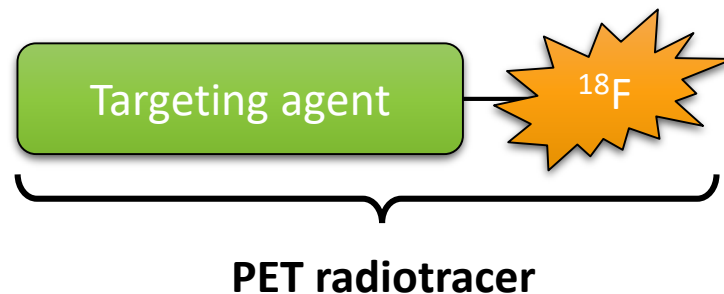
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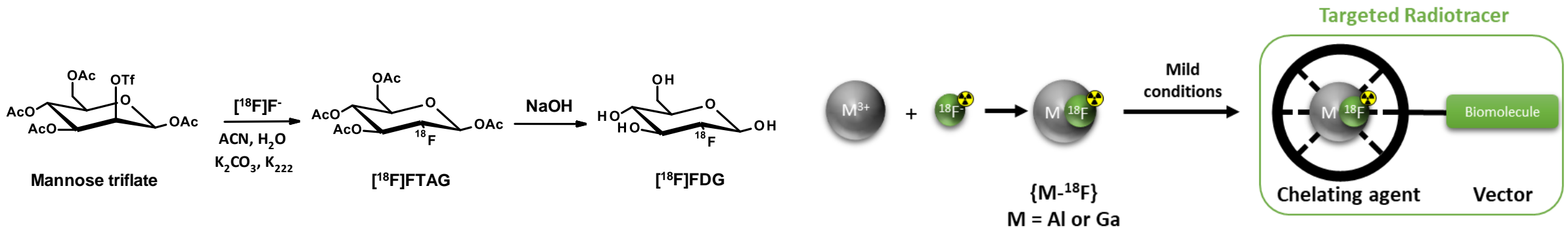
# PET imaging

- Positron Emission Tomography
- Nuclear Medicine
- Cancerology: diagnostic and therapy monitoring
- **PET-CT** Imaging technique
  - Non-invasive
  - High sensitivity and resolution
  - Simultaneous functional and anatomic information



# Fluorine-18 radiolabeling methods

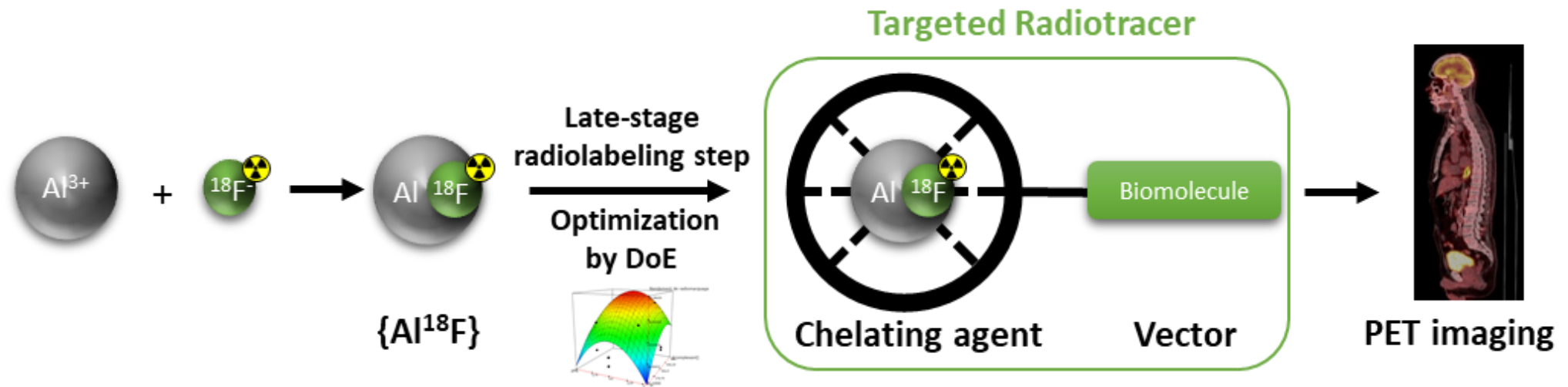
<p style="text-align: center;"><b>Conventional</b> Nucleophilic substitution</p>	<p style="text-align: center;"><b>Alternative</b> Complexation {metal - fluorine-18} Metal = Aluminium, Gallium</p>
Several steps, duration = 1 h	Last step, duration = 15 min
Fluorine-18 activation (anhydrous conditions, crown ether)	Aqueous medium
Organic solvents (ACN, DMSO, DMF)	Organic solvent optional (EtOH)
High temperature	No purification



McBride et al., *J. Nucl. Chem.* **2009**; Bhalla et al., *Chem. Eur. J.* **2015**

# Fluorine-18 labeling – Coordination chemistry

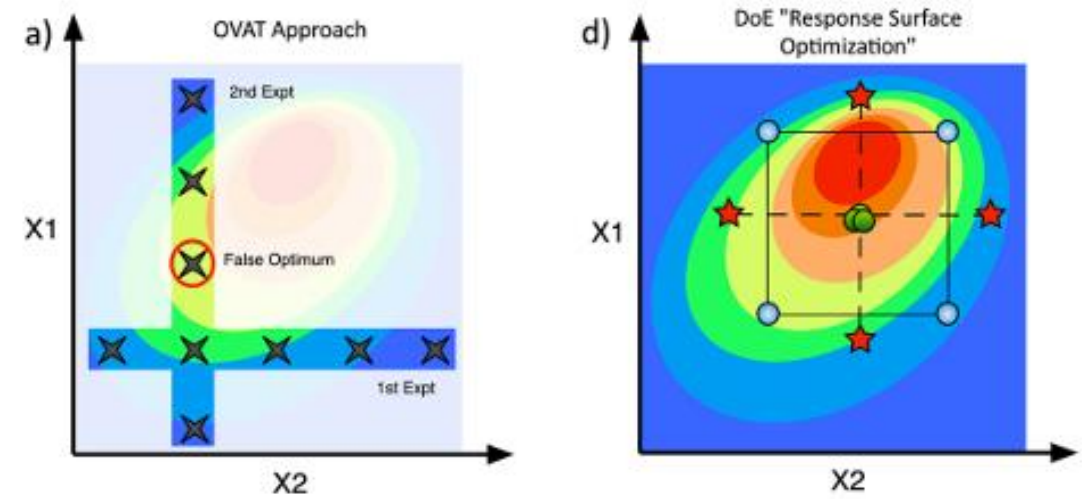
Optimize the {Al-<sup>18</sup>F} radiolabeling method by using a design of experiments approach



McBride et al., *J. Nucl. Chem.* **2009**; Fersing et al., *Molecules* **2019**

# Optimization: One Variable at a Time (OVAT) vs Design of Experiments (DoE)

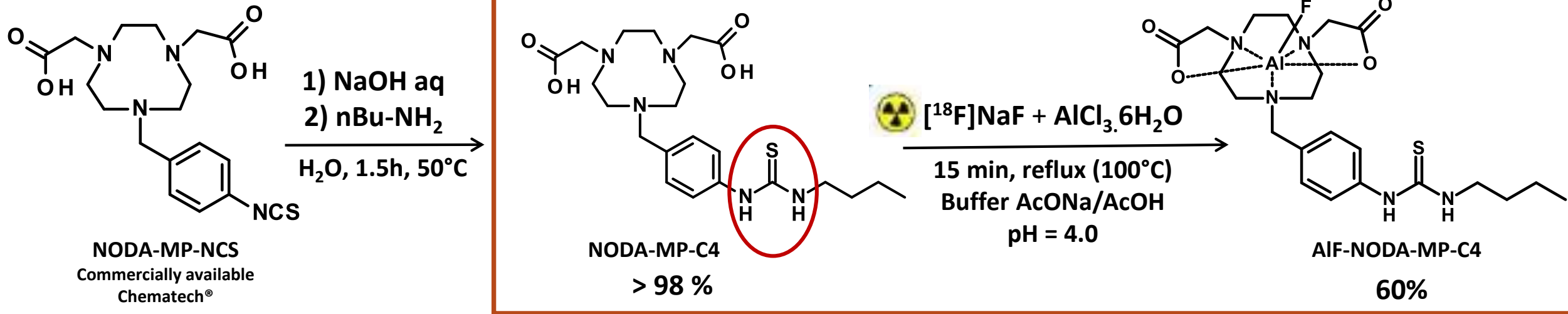
- OVAT: less precise, no interaction studied
- DoE
  - ✓ Reduced number of judicious tests
  - ✓ Robust modeling and predictive tool
    - effect of each variable parameter
    - interactions between the parameters
  - ✓ Knowledge of the process (experimental, bibliography)
  - ✓ Safety for operators (ionizing radiations)
  - ✓ Saving of time and experimental resources



Source: Bowden et al., *Sci. Rep.* 2019

# {Al-<sup>18</sup>F} radiolabeling – Our chemical model

## Radiosynthesis



Chelating agent = Al(III) : 60 nmol

[<sup>18</sup>F]NaF : 8 pmol (500 MBq)



[<sup>18</sup>F] F<sup>-</sup> : 1.3 · 10<sup>-4</sup> eq

# {Al-<sup>18</sup>F} radiolabeling step – Using a DoE

PARAMETERS

PROCESS

RESPONSE

Temperature

pH

Heating time

Chelating agent concentration

Volume

Aluminium/Chelator ratio

Nature and % of co-solvent

Aluminium/[<sup>18</sup>F]F ratio

[<sup>18</sup>F]NaF quality




Radiolabeling



Radiolabeling yield



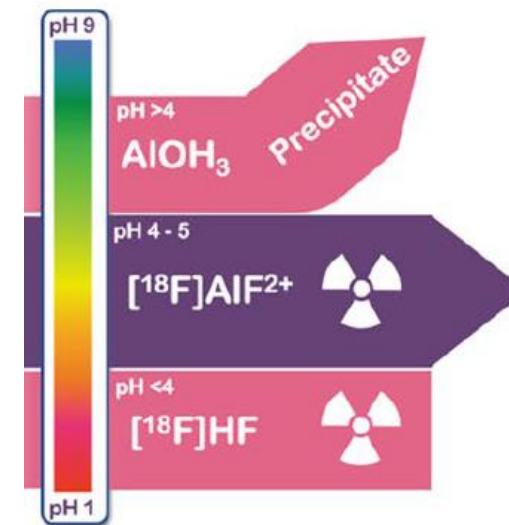
# {Al-<sup>18</sup>F}labeling step – Experimental design

Parameters	Min.	Max.	Ellistat® software 		
			0	-1	+1
pH	4	5	4.5	4.2	4.8
Chelating agent concentration (μM)	55	550	302.2	155.4	449.9
Ratio $\frac{\text{chelating agent}}{\text{aluminium}}$	1:1	3:1	2:1	1.4:1	2.6:1

Experimental procedure: others fixed parameters

- Temperature: reflux
- Time: 15 min
- Volume: 110 μL
- No organic co-solvent
- [<sup>18</sup>F]NaF activity ≈ cst (500 MBq)
- [<sup>18</sup>F]NaF quality ≈ cst (1 month)

Ellistat®: Response surface design > Centred composite



Source: Archibald and Allott, *EJNMMI Radiopharm. Chem.* 2021



# Centred composite design: construction with Ellistat®

Tests (Nb)	Chelat. agent/Aluminium	[Chelating agent]	pH
1	1.4	155.4	4.2
2	1.4	155.4	4.8
3	1.4	449.6	4.2
4	1.4	449.6	4.8
5	2.6	155.4	4.2
6	2.6	155.4	4.8
7	2.6	449.6	4.2
8	2.6	449.6	4.8
9	2	302.5	4.5
10	2	302.5	4.5
11	2	302.5	4.5
12	2	302.5	4.5
13	2	302.5	4.5
14	2	302.5	4.5
15	1	302.5	4.5
16	3	302.5	4.5
17	2	55	4.5
18	2	550	4.5
19	2	302.5	4
20	2	302.5	5

For 3 variable parameters  
 → 15 to 20 tests  
 → better if duplicated

« Basic » complete design (L8 table)  
 → 8 tests

**At the Center**  
 → 1 to 6 replicate tests  
 → better if done at different stages  
 of the experimental campaign

**On the Axes**  
 → min. & max. for each parameters  
 → 6 tests

# Centred composite design: experimental results

Test(Nb)	Chelat. agent/Aluminium	[Chelating agent]	pH	Radiolabeling yield	
1	1.4	155.4	4.2	26.6	53.8
2	1.4	155.4	4.8	45.2	51.8
3	1.4	449.6	4.2	75.6	74.8
4	1.4	449.6	4.8	75	72.3
5	2.6	155.4	4.2	21.8	26.4
6	2.6	155.4	4.8	12.5	19.7
7	2.6	449.6	4.2	30	67.9
8	2.6	449.6	4.8	41.7	68.9
9	2	302.5	4.5	70.8	66.7
10	2	302.5	4.5	56.1	62.8
11	2	302.5	4.5	55.8	62.6
12	2	302.5	4.5	70	64.4
13	2	302.5	4.5	72.4	59.4
14	2	302.5	4.5	70.5	71.1
15	1	302.5	4.5	70.1	74.7
16	3	302.5	4.5	49.6	60.6
17	2	55	4.5	1.7	13.6
18	2	550	4.5	63.6	73.9
19	2	302.5	4	15.9	19.7
20	2	302.5	5	18.2	26.7

Campaign on  
5 days  
(over 1 month)



Day 1

Day 2

Day 3

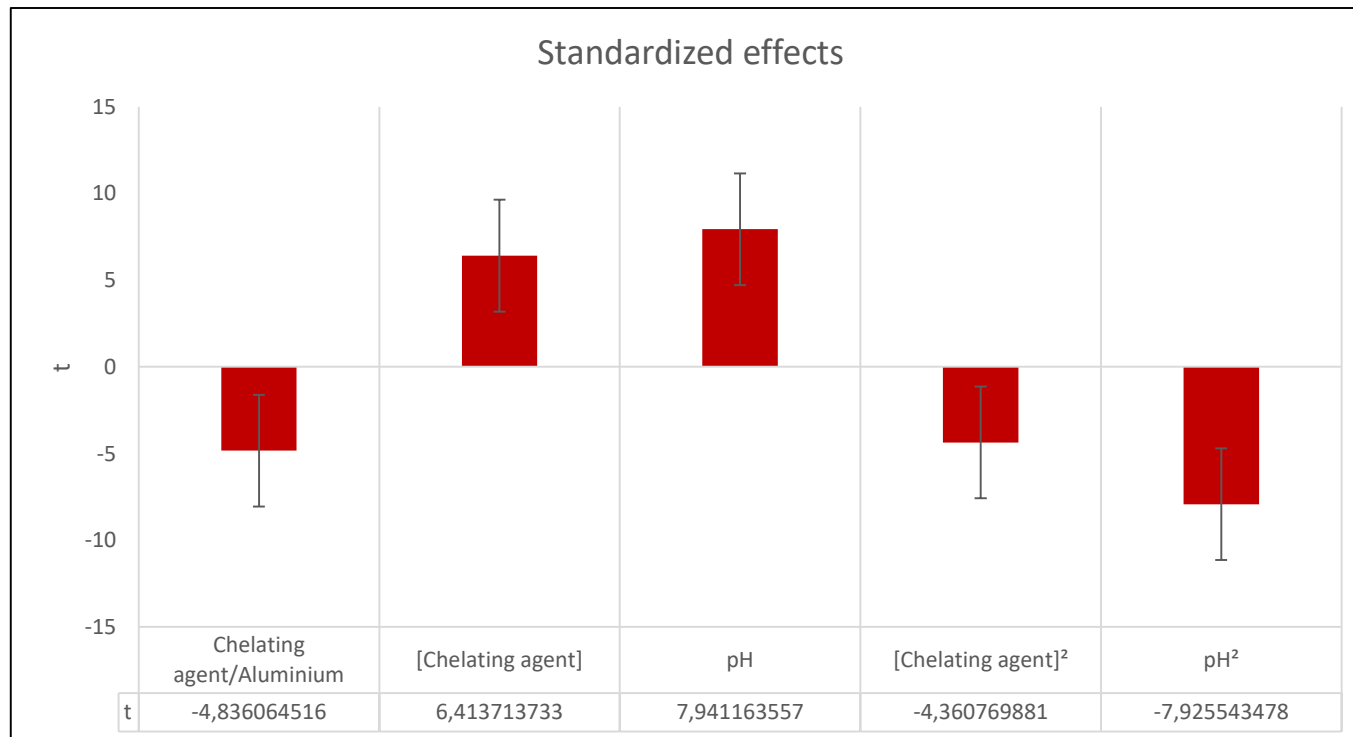
Day 4

Day 5

# Model (transfer function) with Ellistat®

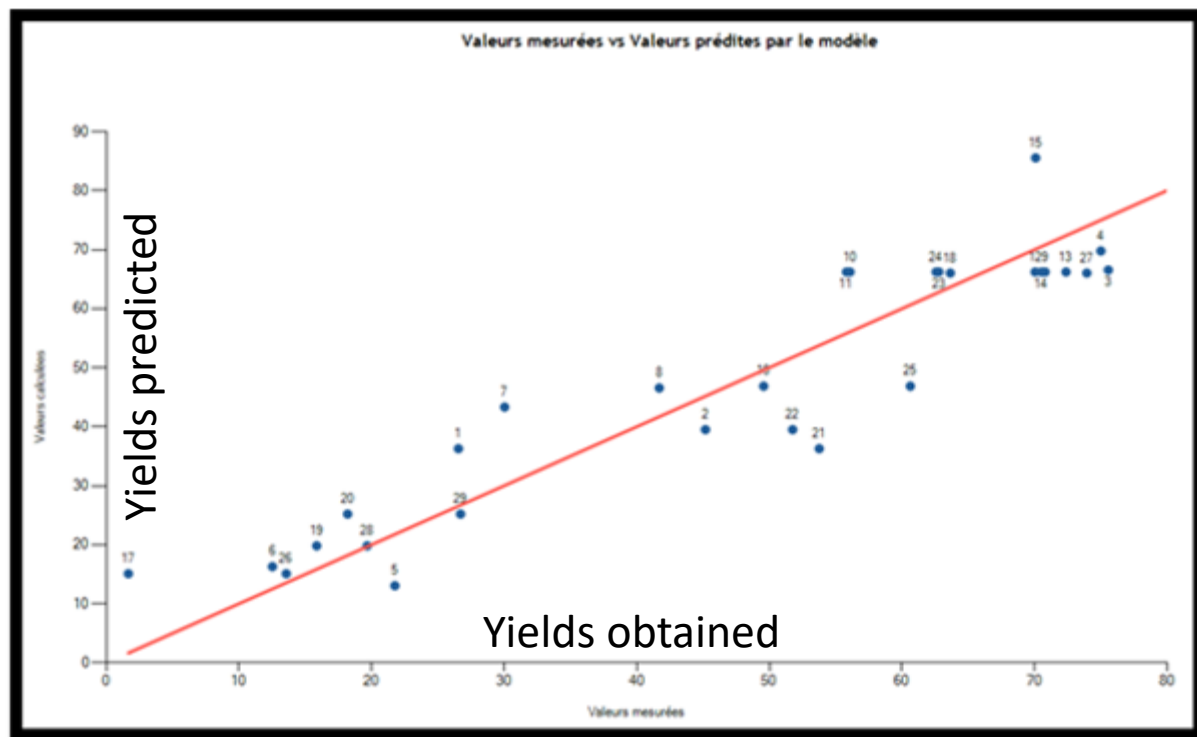
Radiolabeling yield

$$= -3234 - 14.99 \times \frac{\text{Chelating agent}}{\text{Aluminium}} + 0.3316 \times [\text{Chelating agent}] + 1477 \times \text{pH} - 0.0003614 \times [\text{Chelating agent}]^2 - 160.4 \times \text{pH}^2$$



- No second order interaction
- but ... **quadratic effects** (pH, [chelating agent])

# Model robustness – Quality of the prediction

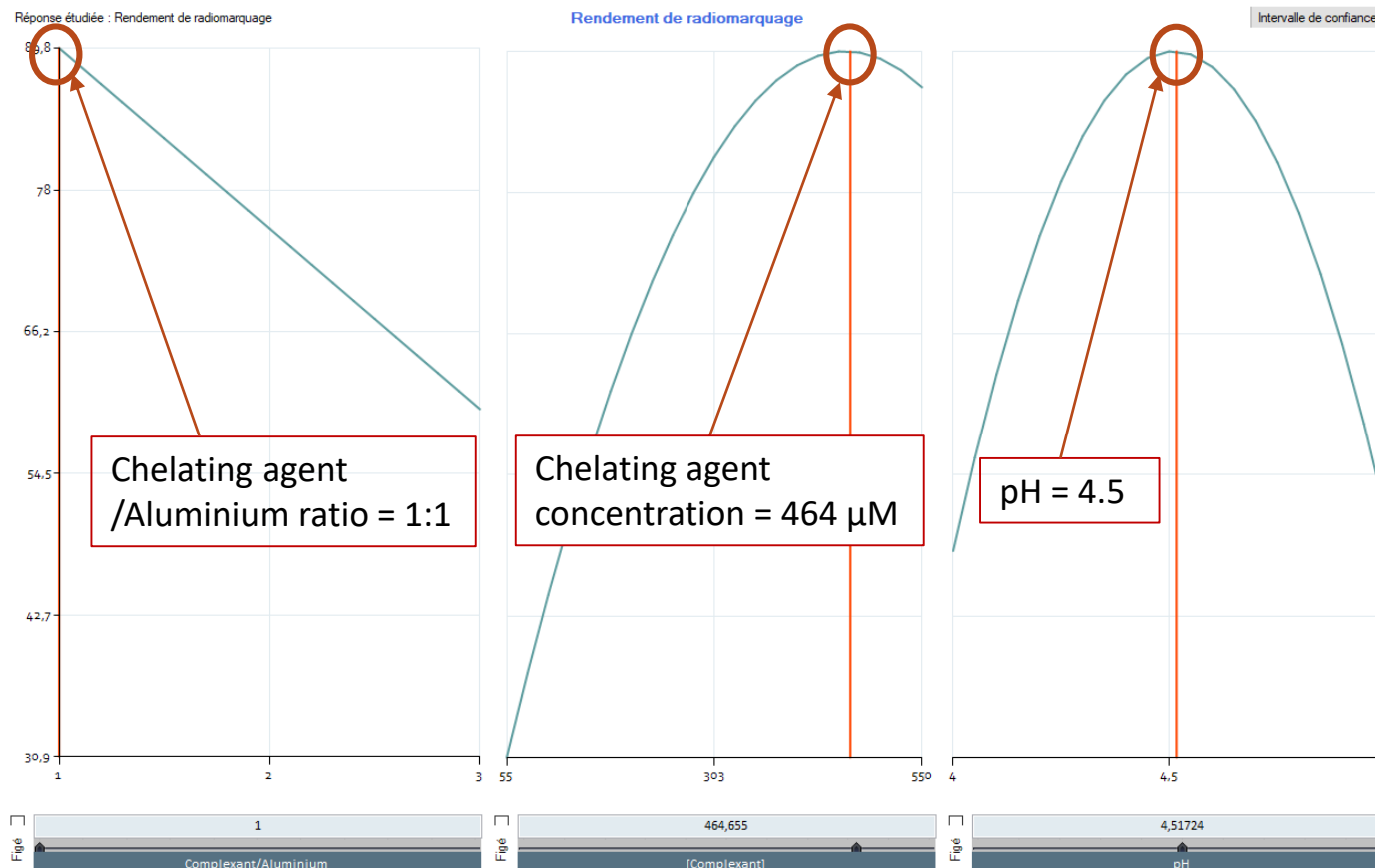


- $R^2 = 86.3\%$  😊
- Good correlation between radiolabeling yields predicted vs obtained

# Prediction for a maximized radiolabeling yield

Radiolabeling yield

$$= -3234 - 14.99 \times \frac{\text{Chelating agent}}{\text{Aluminium}} + 0.3316 \times [\text{Chelating agent}] + 1477 \times \text{pH} - 0.0003614 \times [\text{Chelating agent}]^2 - 160.4 \times \text{pH}^2$$



**Maximized yield predicted: 89.8 %**

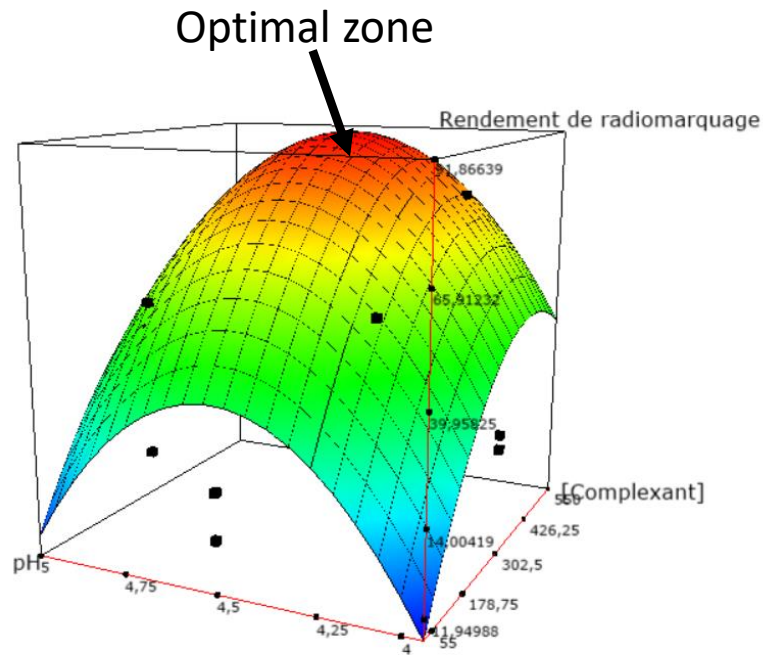
**Yields obtained (triplicate):**

- 80.4 %
- 75.9 %
- 79.1 %

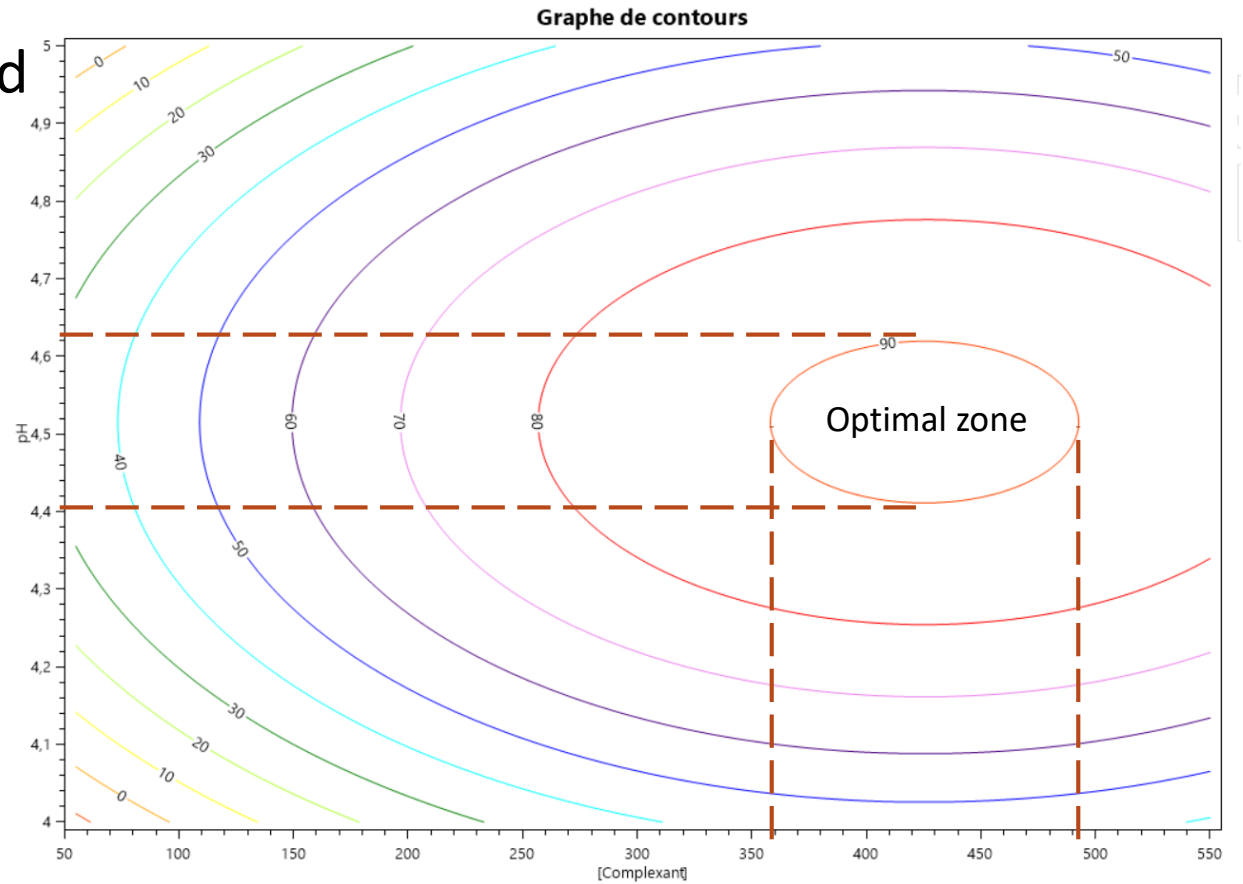
**78 ± 2 %** 😊

# Response surface representations

- Parameters: [chelating agent], pH
- Quadratic effect on the radiolabeling yield



3D



2D

# Conclusions

- $^{18}\text{F}$  labeling by  $\{\text{Al-}^{18}\text{F}\}$  coordination implemented in our radiopharmacy
- Optimization of the radiolabeling step by DoE
  - 40 tests, experimental campaign of 5 days over 1 month
  - Radiolabeling yield optimisation: from 60% to 78 %
  - Radioprotection for operators improved
  - Saving time and resources (high-value)
- Use DoE optimization to develop new targeted PET-tracers (thermosensitive biomolecule)



# Acknowledgements

le cnam

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# Thanks for your attention



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