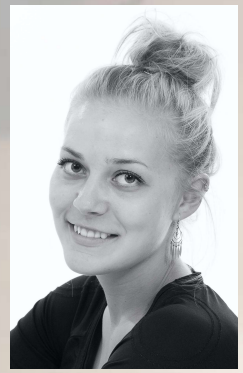
# Making life simpler ... and better

## Model maintainence



Helene Fog Froriep Halberg
& Rasmus Bro
University of Copenhagen

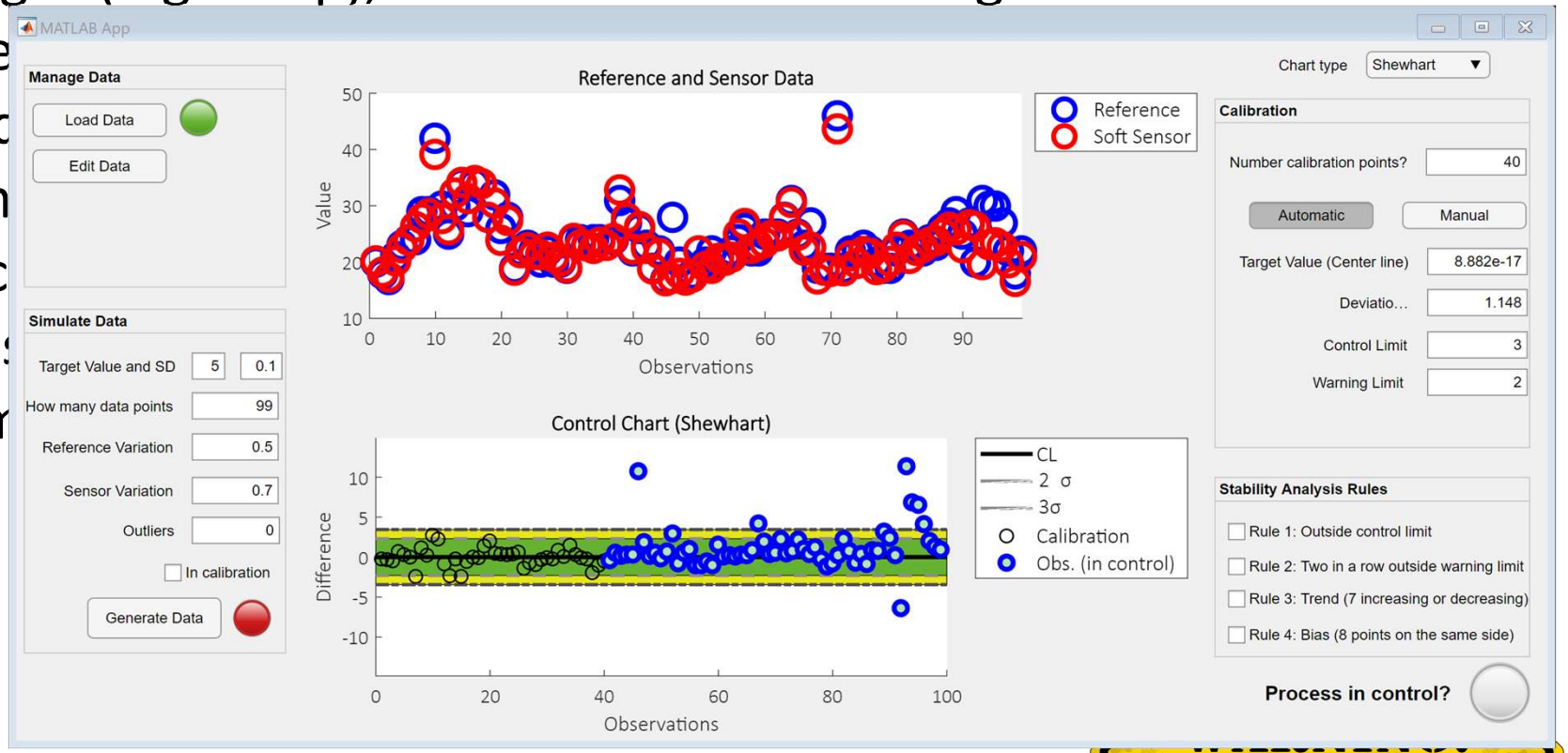
Anette Yde Holst
Arla Foods amba

# How to make sure that calibration models are still working?

- After big changes (e.g. lamp), instrument is run through normal performance test including check on some 20 samples that are not outliers and span the model space (ASTM D6122,ISO 12099)
- Every spectrum is assessed statistically (e.g. Q & $T^2$) to be within the model space. If ok, predict (ASTM D6122)
- Collect control samples e.g. daily that are also measured with the reference method. Monitor the bias in control charts or similar


# How to predict correctly?

- When big changes (e.g. lamp), instrument is run through normal performance te
not outliers and
- Every spectrum
the model spac
- Collect control
the reference m
similar





# How to predict correctly?

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- Every spectrum is assessed statistically (e.g. Q & $T^2$) to be within the model space. If ok, predict (ASTM D6122)
- Collect control samples e.g. daily that are also measured with the reference method. Monitor the bias in control charts or similar
- After 30 samples have been acquired, a proper statistical test is used to prove that the calibration model performs according to specifications (ASTM D6708)


# How to predict correctly?

- When big changes (e.g. lamp), instrument is run through normal performance test including check on some 20 samples that are not outliers *and span the model space* (ASTM D6122,ISO 12099)
- Every spectrum is assessed statistically (e.g. Q & $T^2$) to be within the model space. If ok, predict (ASTM D6122)
- Collect control samples e.g. daily that are also measured with the reference method. Monitor the bias in control charts or similar
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# How to predict correctly?

Calls for a correction. Identify whether the problems is caused by

- Instrument
- Samples
- Calibration model

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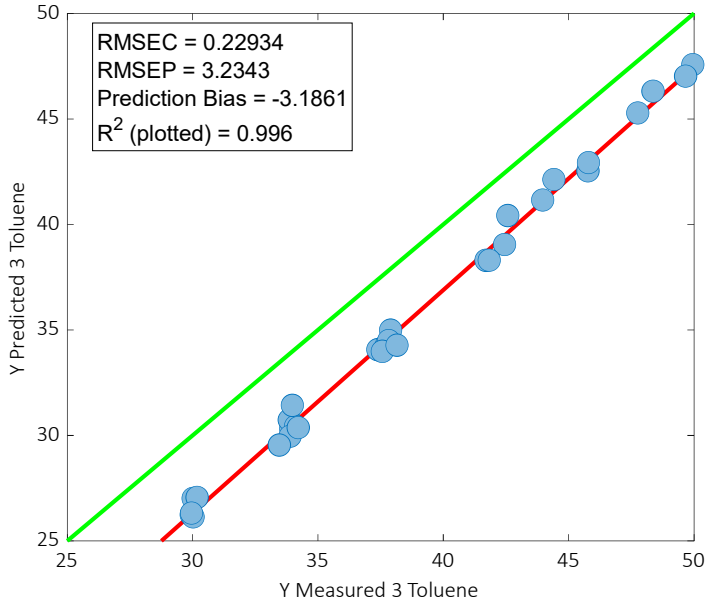
- After 30 samples have been acquired, a proper statistical test is used to prove that the calibration model performs according to specifications (ASTM D6708)


# How to predict correctly?

Calls for a correction. Identify whether the problems is caused by

- Instrument
- Samples
- **Calibration model**

1. Bias correction




# Correcting a calibration model

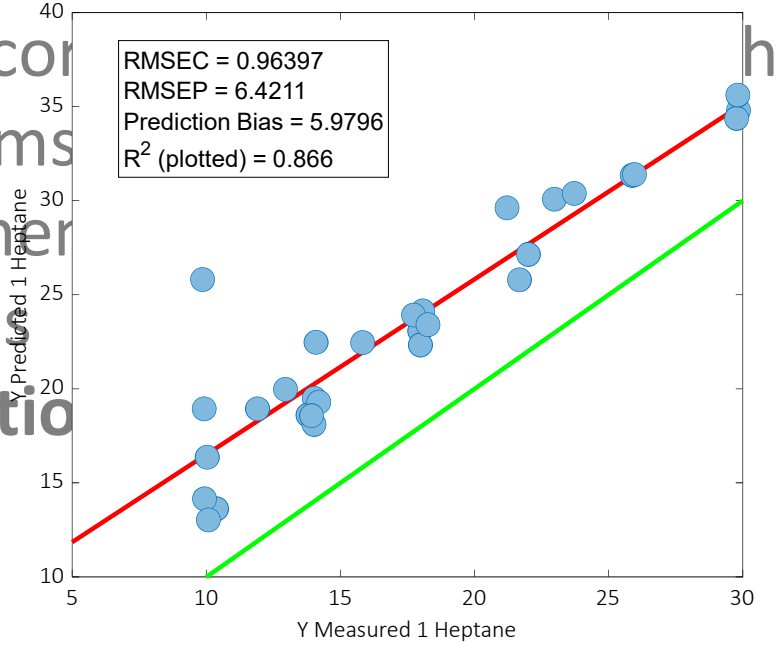
Calls for a correction. Identify whether the problems is caused by

- Instrument
- Samples
- **Calibration model**

1. Bias correction
2. Maybe slope as well but generally not
3. Severe slope calls for re-calibration

# Correcting a calibration model

Calls for a cor her
the problems
- Instrumer
- Samplee
- **Calibratio**

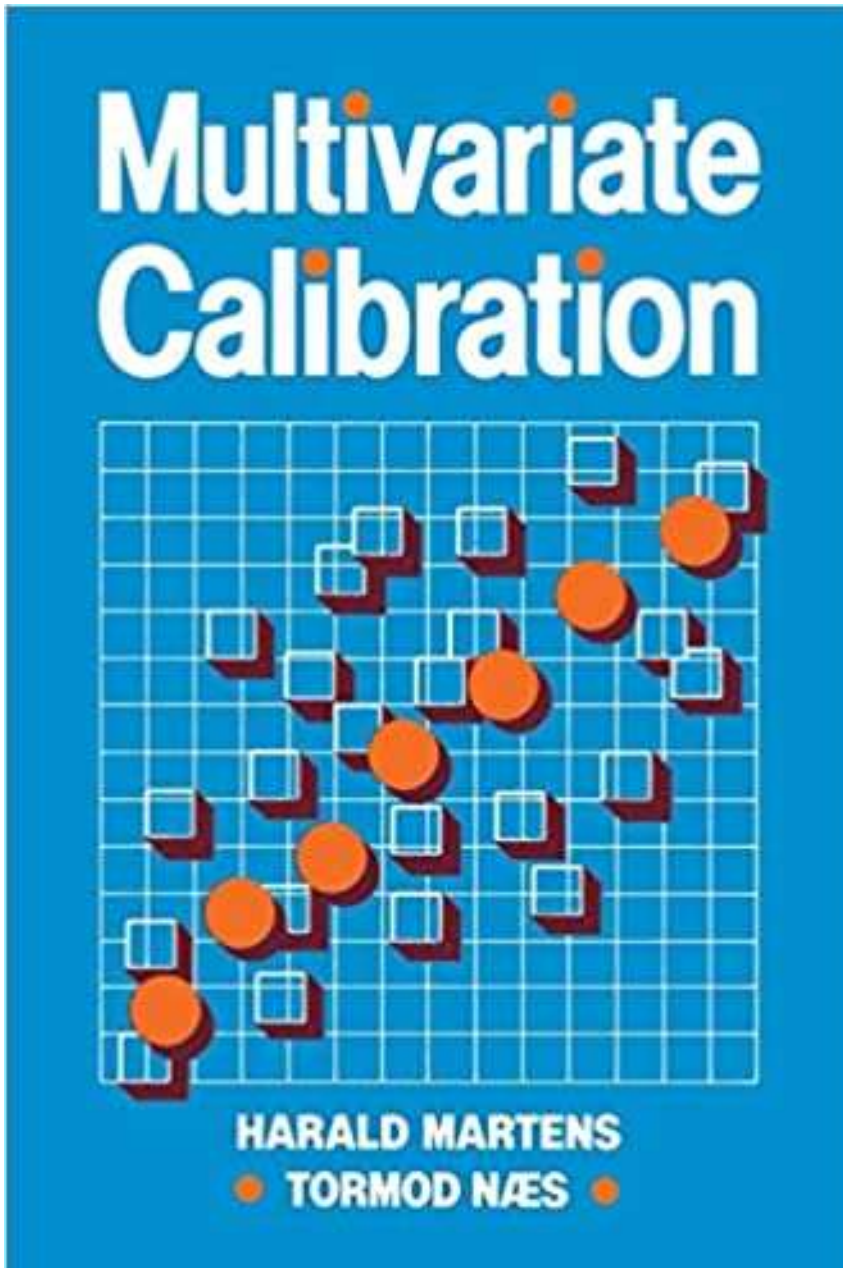



1. Bias correction
2. Maybe slope as well but generally not
3. Severe slope calls for re-calibration
4. Increased variance calls for re-calibration

# Correcting a calibration model

# Maintaining calibration models is a significant task*

** And often conveniently left out of the business case. Even more so in 'modern' machine learning contexts*



*"At Novo Nordisk we are currently developing several chemometrics models for near infrared applications.*

*After validation and implementation of the models it is extremely important to minimize the need for model maintenance. Because, in a highly regulated pharmaceutical production that is working after Good Manufacturing Practice (GMP) it is very costly to update a chemometric model.*

*Any new technologies, algorithms and methodologies that can reduce the need for model maintenance, will benefit the pharmaceutical industry greatly."*

*Erik Skibsted, Principal Scientist PhD*

*Novo Nordisk, Oral Protein Formulation, Team Real Time Release Testing*

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*Erik Skibsted, Principal Scientist*

*Novo Nordisk, Oral Protein Release Testing*

PAT/QbD

https://bit.ly/3jNW5De

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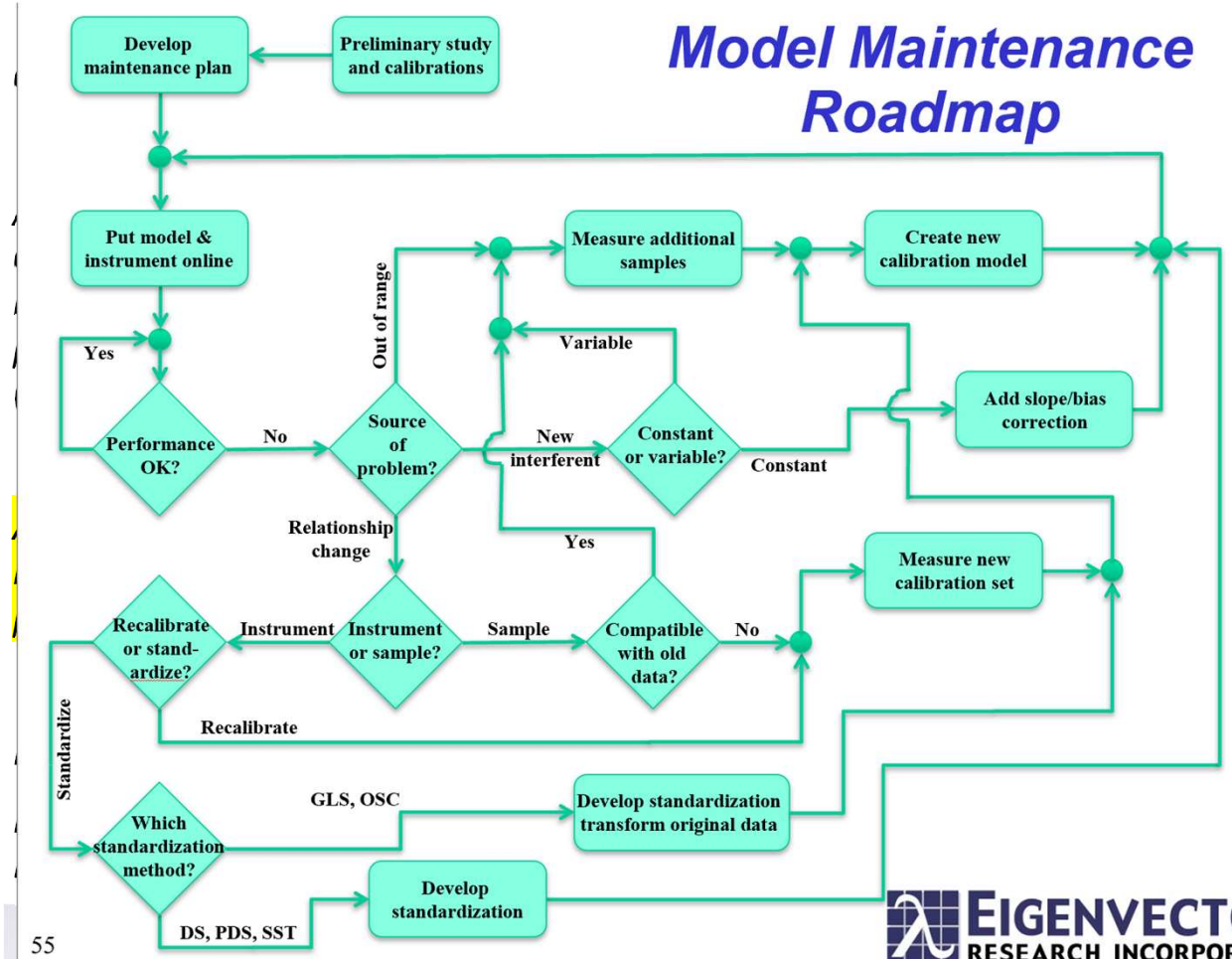
*Corresponding author
Eigenvector Research, Inc.,
Wenatchee, WA 98801, USA



Barry M. Wise

PEER REVIEWED

Model maintenance:
the unrecognized cost in PAT and QbD





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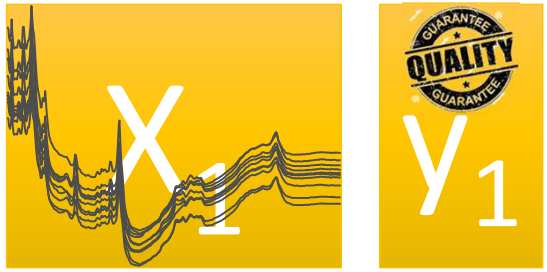
Model maintenance:
the unrecognized cost in PAT and QbD

- Dairy receives biproducts from dairies worldwide
- Biproduct paid on composition – hence calibration models used
- Each dairy/product have their own calibration model
- Expensive maintenance

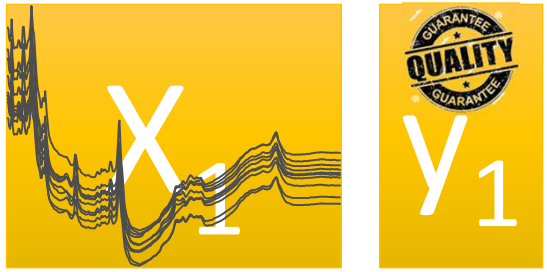






PLS model
of dataset 1

# The problem – use case





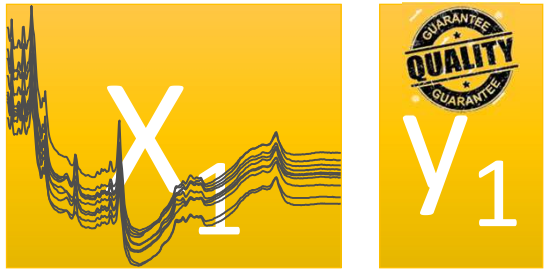


PLS model
of dataset 1



PLS model
of dataset 2

# The problem – use case







PLS model
of dataset 1





PLS model
of dataset 2

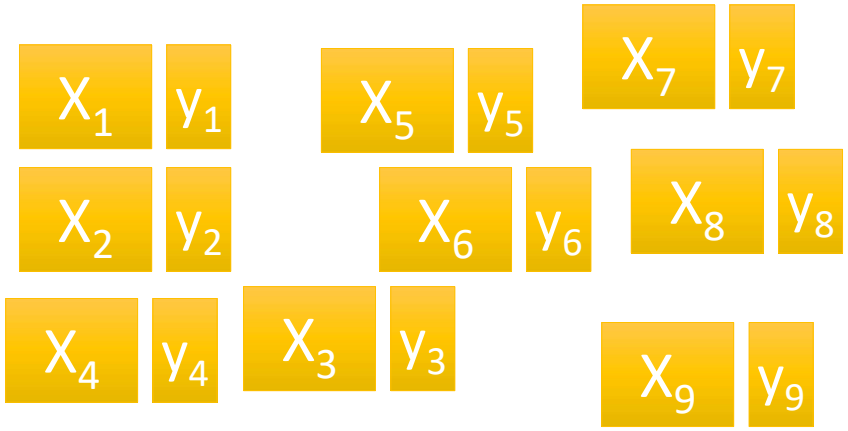
Many companies are maintaining tens, hundreds and even thousands of calibration models

# The problem – use case


# The problem – use case

# The solution

Merge all models into one. Is that optimal?




# Traditional solution

$x_1$ $y_1$

$x_2$ $y_2$

$x_4$ $y_4$

$x_3$ $y_3$

$x_5$ $y_5$

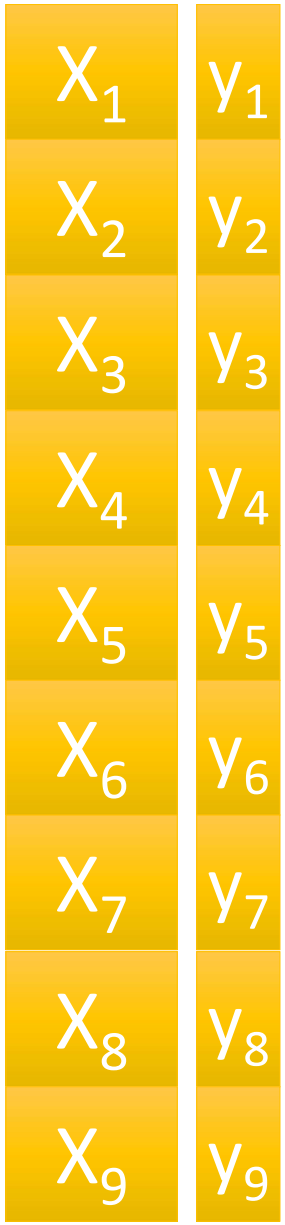
$x_6$ $y_6$

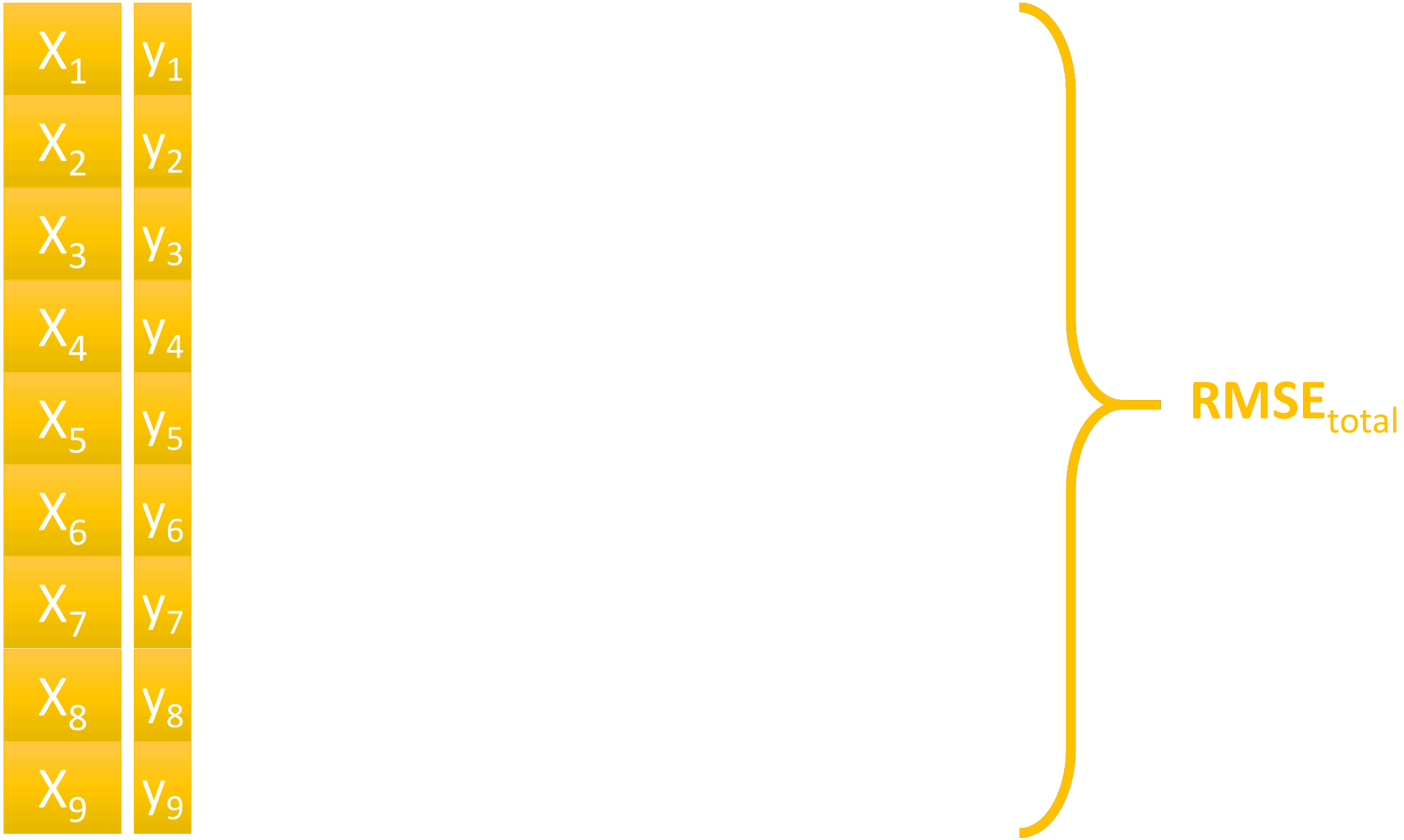
$x_7$ $y_7$

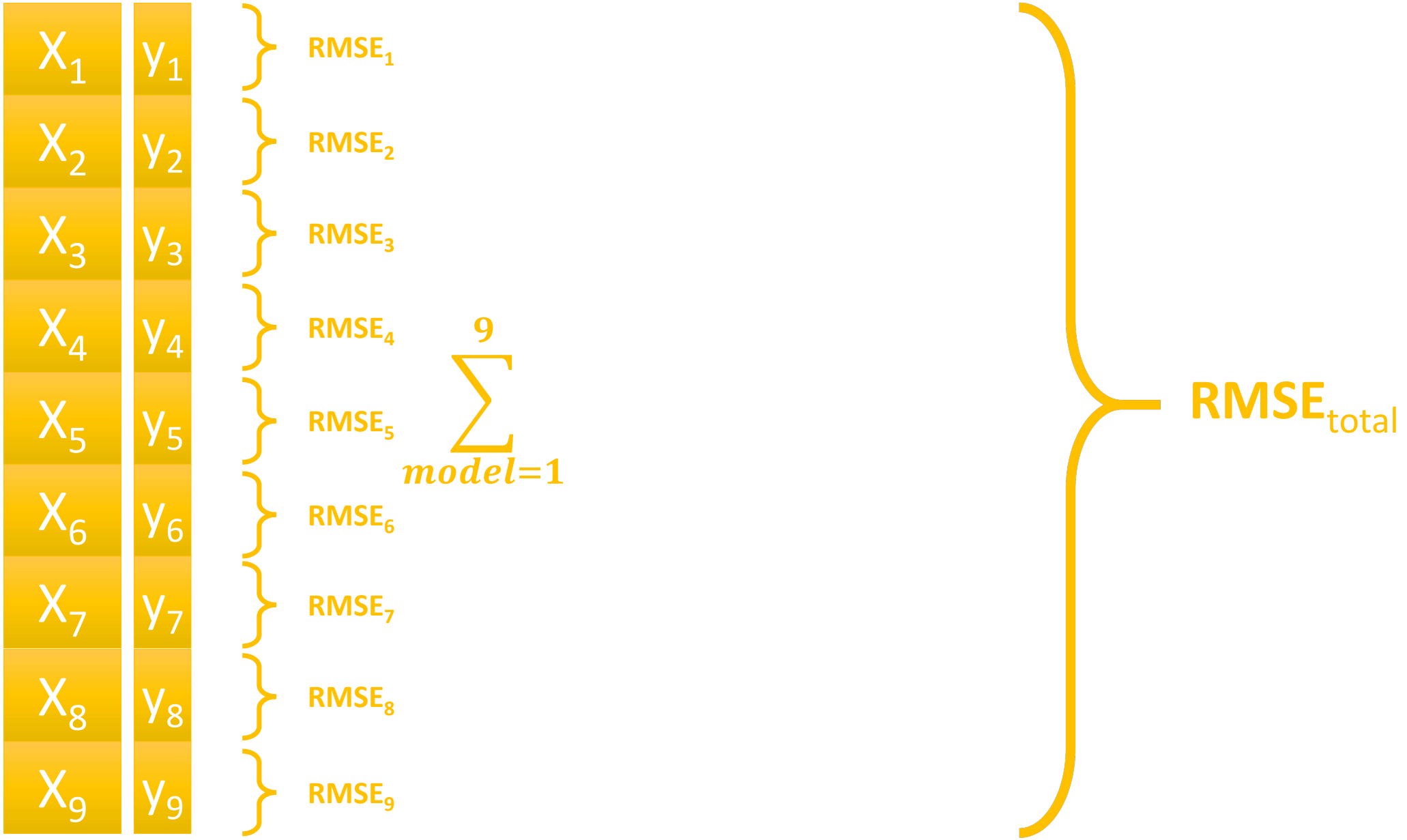
$x_8$ $y_8$

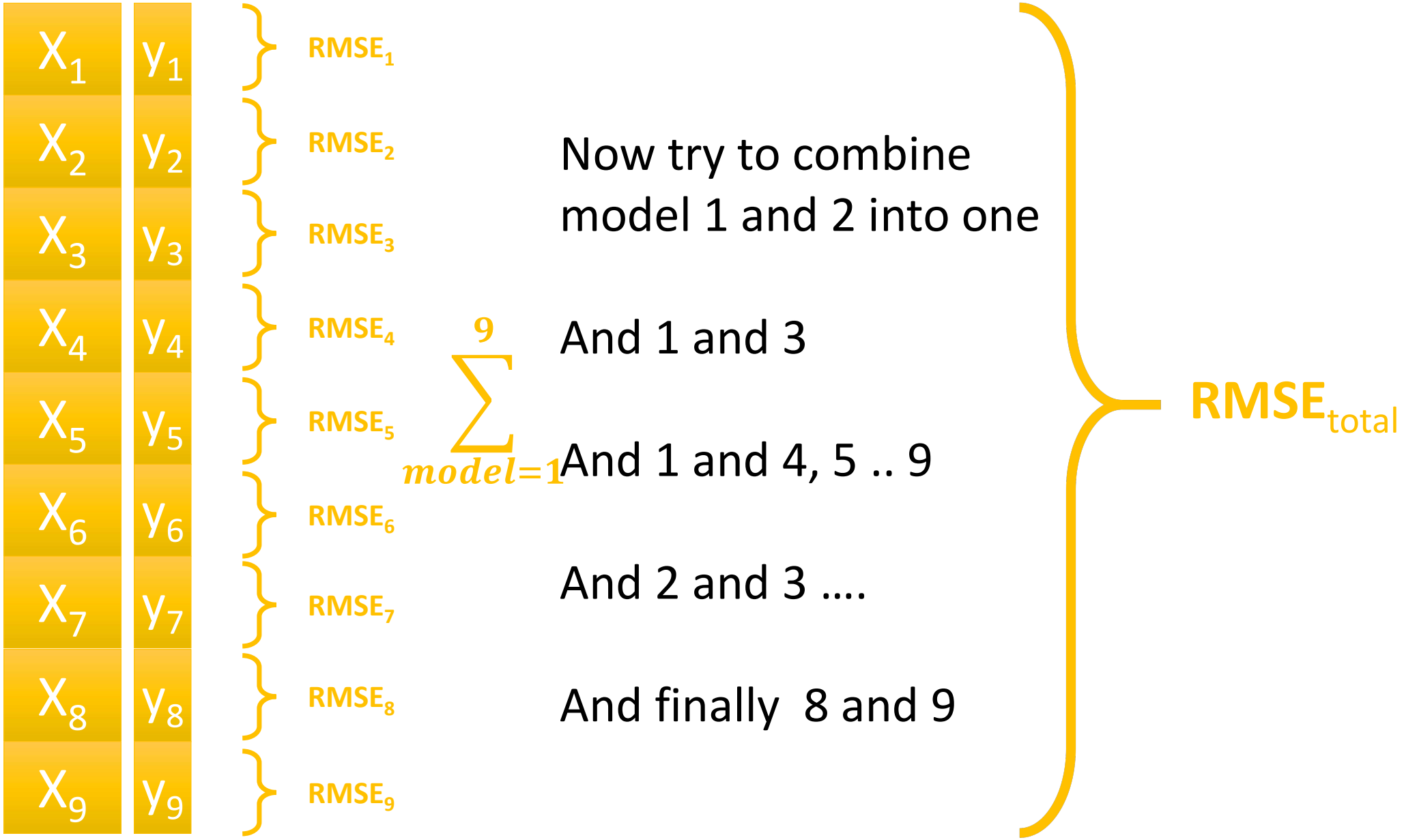
$x_9$ $y_9$

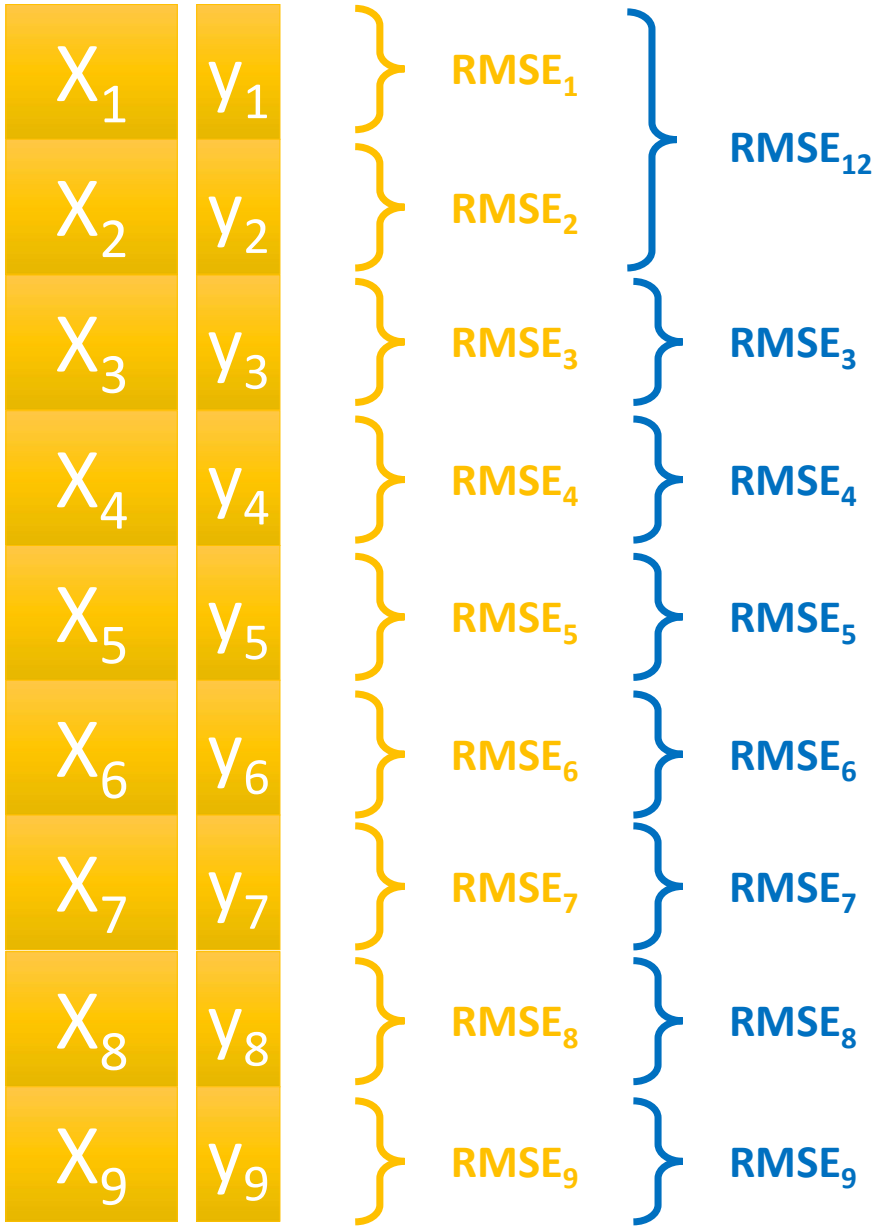
| | |
|---|---|
| $X_1$ | $y_1$ |
| $X_2$ | $y_2$ |
| $X_3$ | $y_3$ |
| $X_4$ | $y_4$ |
| $X$ | $y$ |


$x_1$ $y_1$
$x_2$ $y_2$
$x_3$ $y_3$
$x_4$ $y_4$
$x_5$ $y_5$
$x_6$ $y_6$
$x_7$ $y_7$
$x_8$ $y_8$
$x_9$ $y_9$

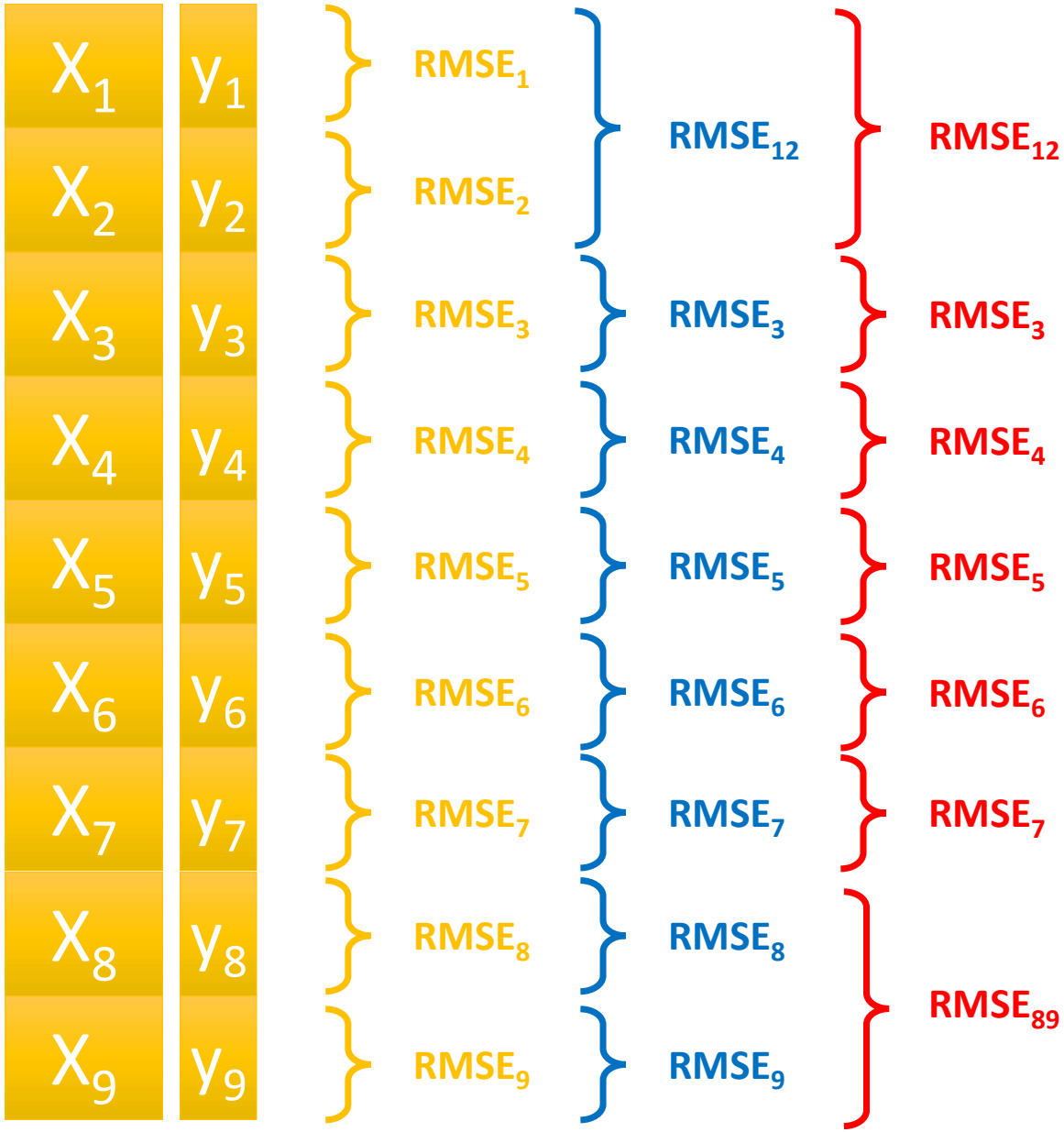

$X_1$ $y_1$
$X_2$ $y_2$
$X_3$ $y_3$
$X_4$ $y_4$
$X_5$ $y_5$
$X_6$ $y_6$
$X_7$ $y_7$
$X_8$ $y_8$
$X_9$ $y_9$
$RMSE_{total}$


X1
y1
X2
y2
X3
y3
X4
y4
X5
y5
X6
y6
X7
y7
X8
y8
X9
y9
RMSE1
RMSE2
RMSE3
RMSE4
RMSE5
RMSE6
RMSE7
RMSE8
RMSE9
9
∑
model=1
RMSEtotal

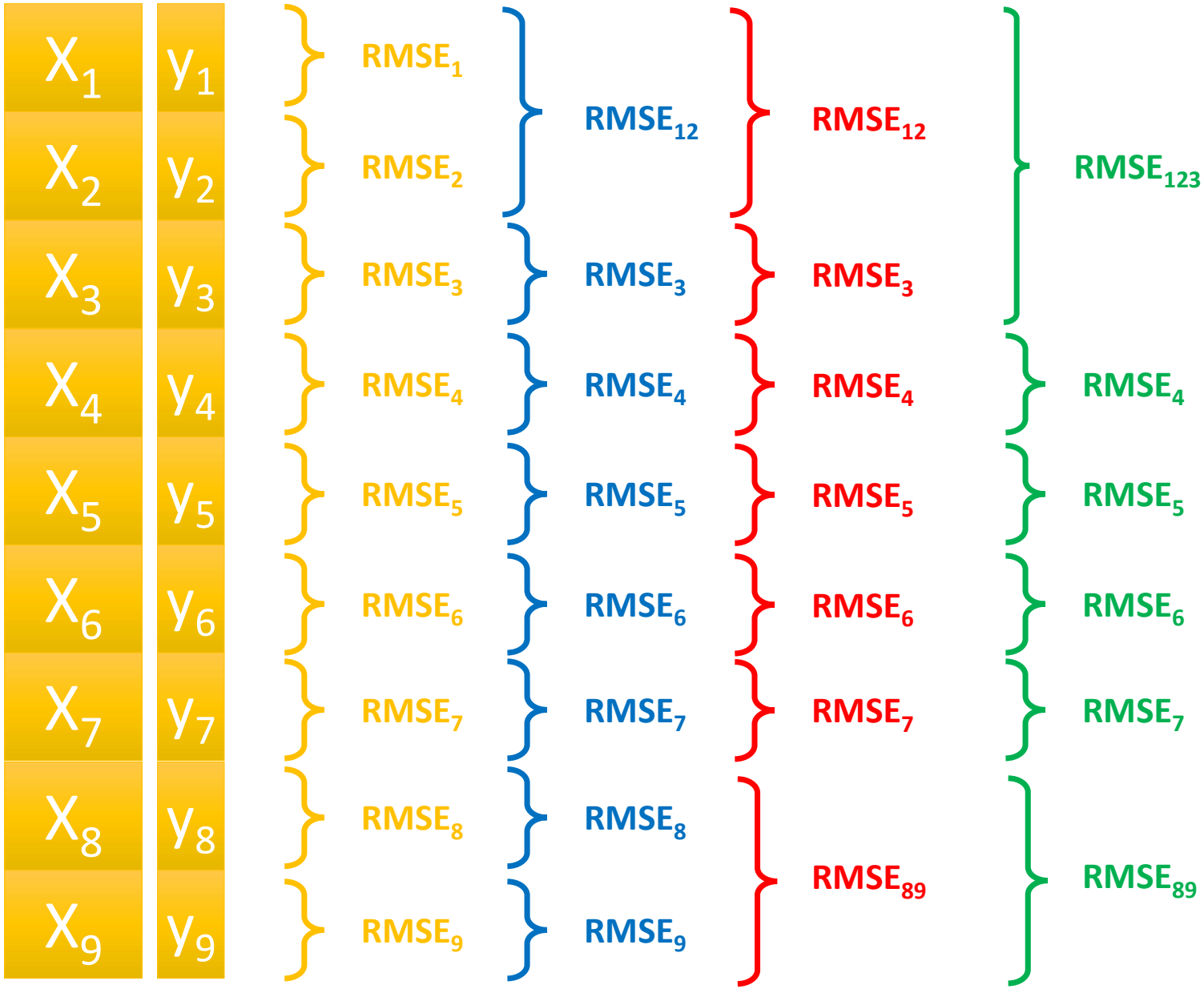

X1 y1
X2 y2
X3 y3
X4 y4
X5 y5
X6 y6
X7 y7
X8 y8
X9 y9
RMSE1
RMSE2
RMSE3
RMSE4
RMSE5
RMSE6
RMSE7
RMSE8
RMSE9
$\sum_{model=1}^{9}$
Now try to combine model 1 and 2 into one
And 1 and 3
And 1 and 4, 5 .. 9
And 2 and 3 ….
And finally 8 and 9
RMSEtotal

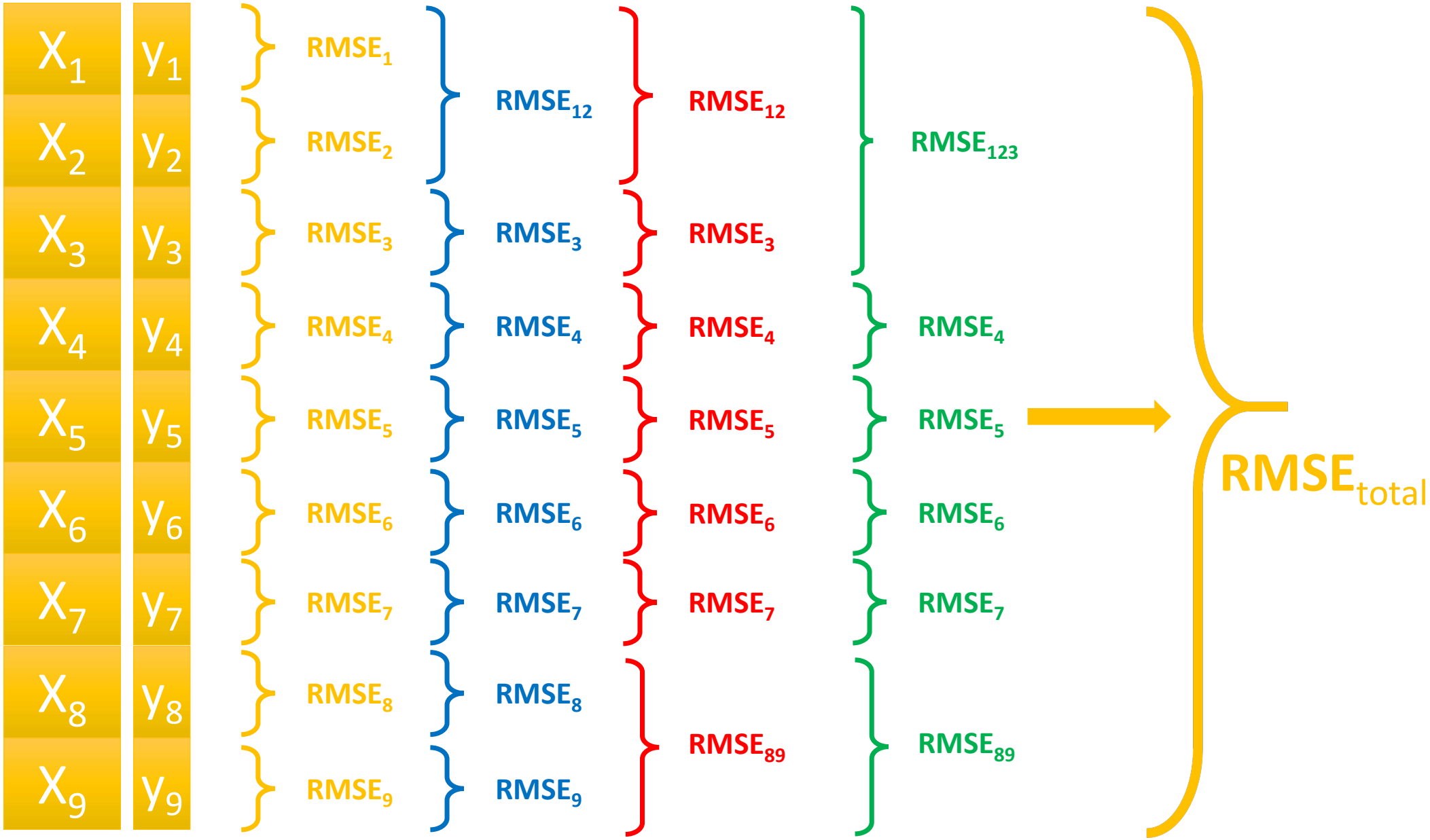


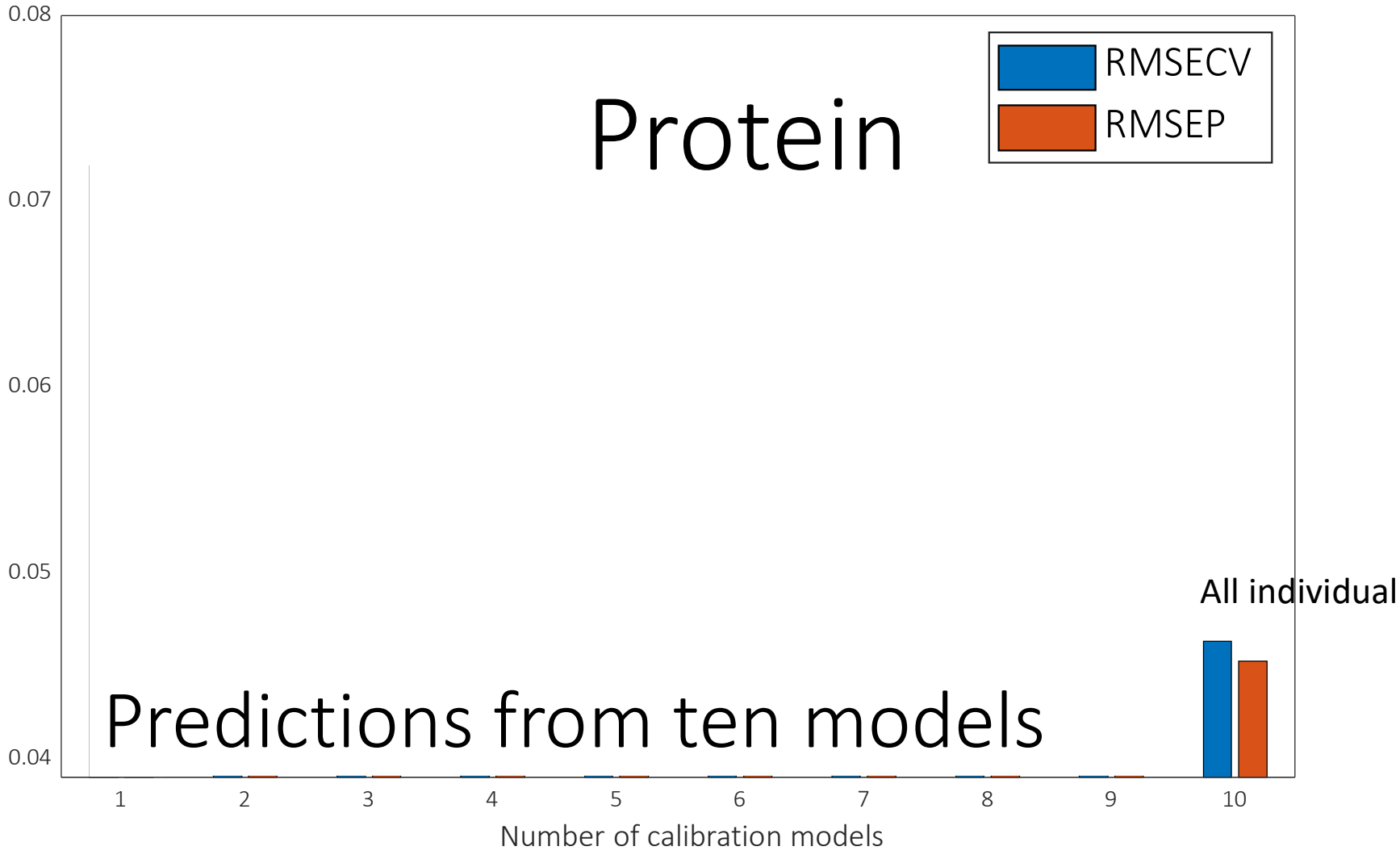

Merge the two that gives the lowest overall RMSE

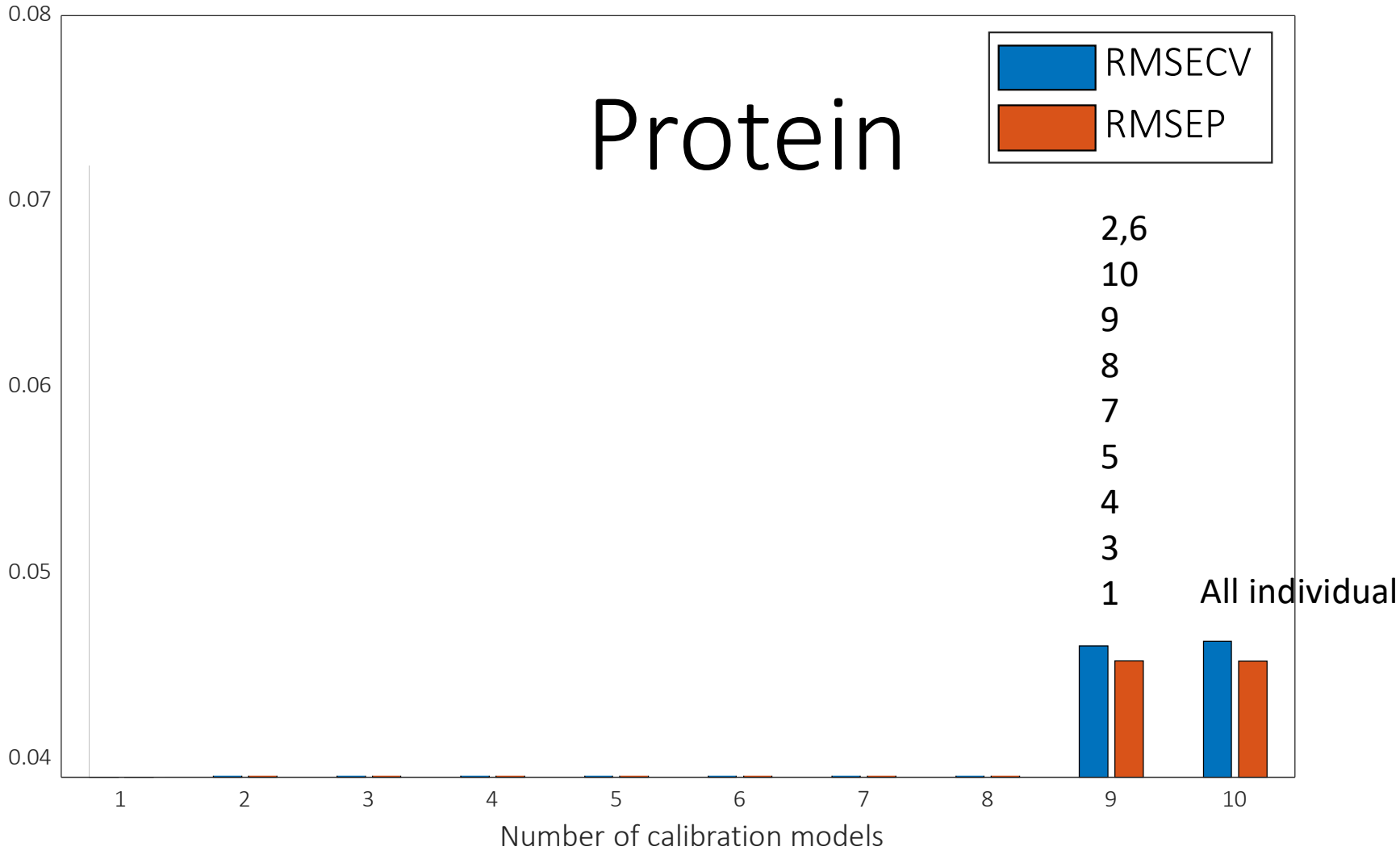


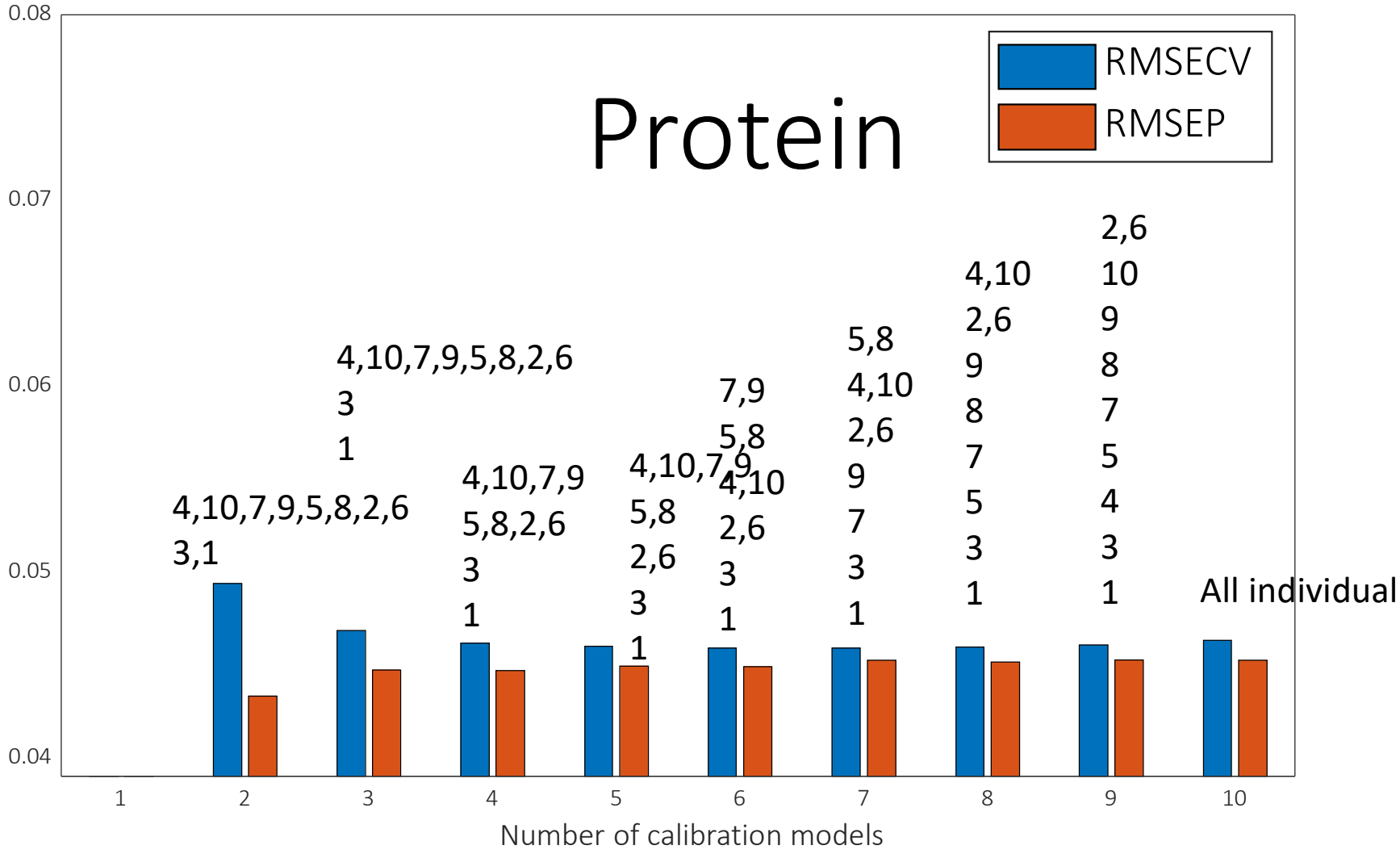

Do the same thing with the eight models now available

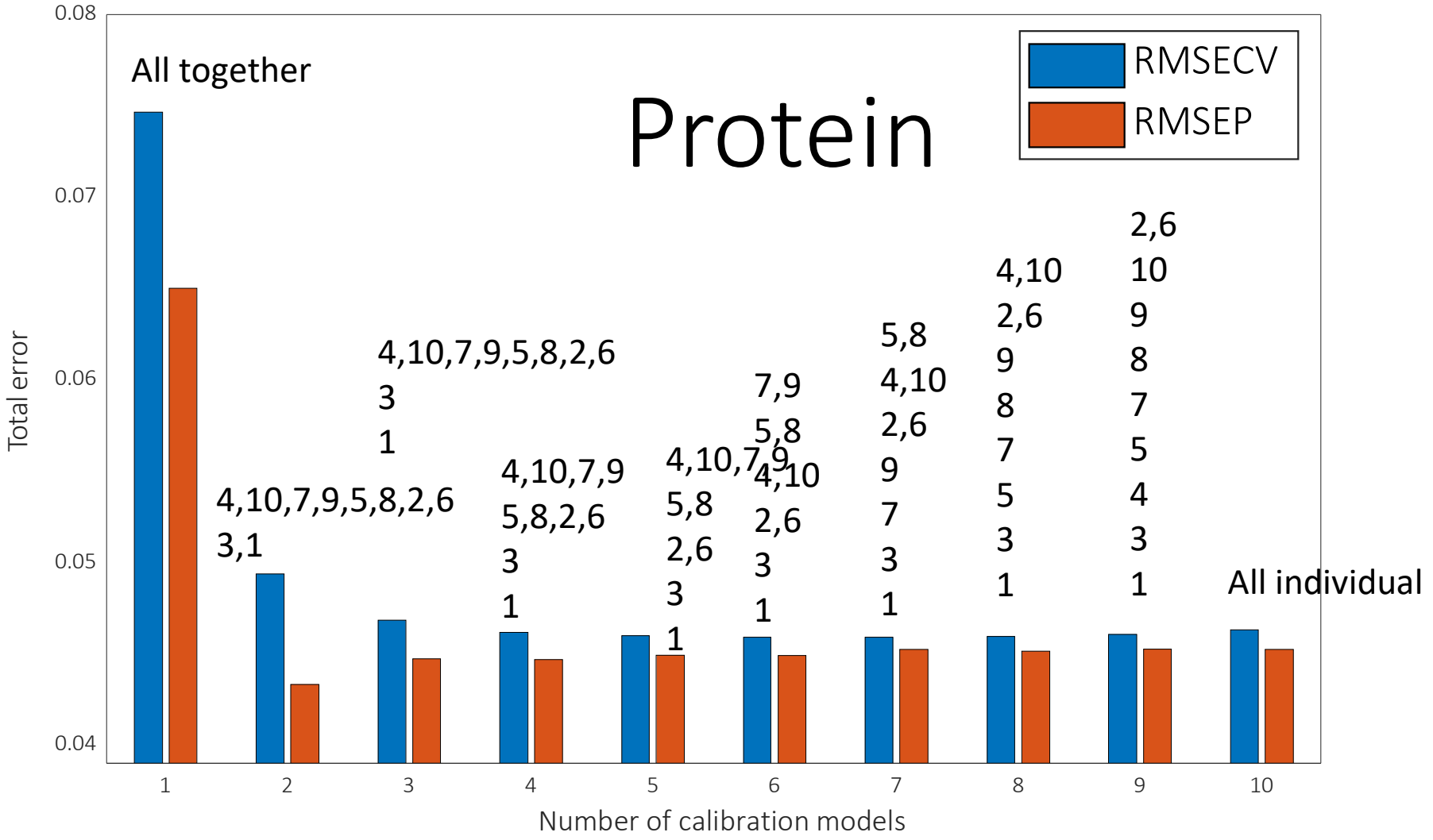

$X_1$ $y_1$
$X_2$ $y_2$
$X_3$ $y_3$
$X_4$ $y_4$
$X_5$ $y_5$
$X_6$ $y_6$
$X_7$ $y_7$
$X_8$ $y_8$
$X_9$ $y_9$
$RMSE_1$
$RMSE_2$
$RMSE_3$
$RMSE_4$
$RMSE_5$
$RMSE_6$
$RMSE_7$
$RMSE_8$
$RMSE_9$
$RMSE_{12}$
$RMSE_3$
$RMSE_4$
$RMSE_5$
$RMSE_6$
$RMSE_7$
$RMSE_{89}$
$RMSE_{12}$
$RMSE_3$
$RMSE_4$
$RMSE_5$
$RMSE_6$
$RMSE_7$
$RMSE_{89}$
$RMSE_{123}$
$RMSE_4$
$RMSE_5$
$RMSE_6$
$RMSE_7$
$RMSE_{89}$


X1
y1
X2
y2
X3
y3
X4
y4
X5
y5
X6
y6
X7
y7
X8
y8
X9
y9
RMSE1
RMSE2
RMSE3
RMSE4
RMSE5
RMSE6
RMSE7
RMSE8
RMSE9
RMSE12
RMSE3
RMSE4
RMSE5
RMSE6
RMSE7
RMSE89
RMSE12
RMSE3
RMSE4
RMSE5
RMSE6
RMSE7
RMSE89
RMSE123
RMSE4
RMSE5
RMSE6
RMSE7
RMSE89
RMSEtotal

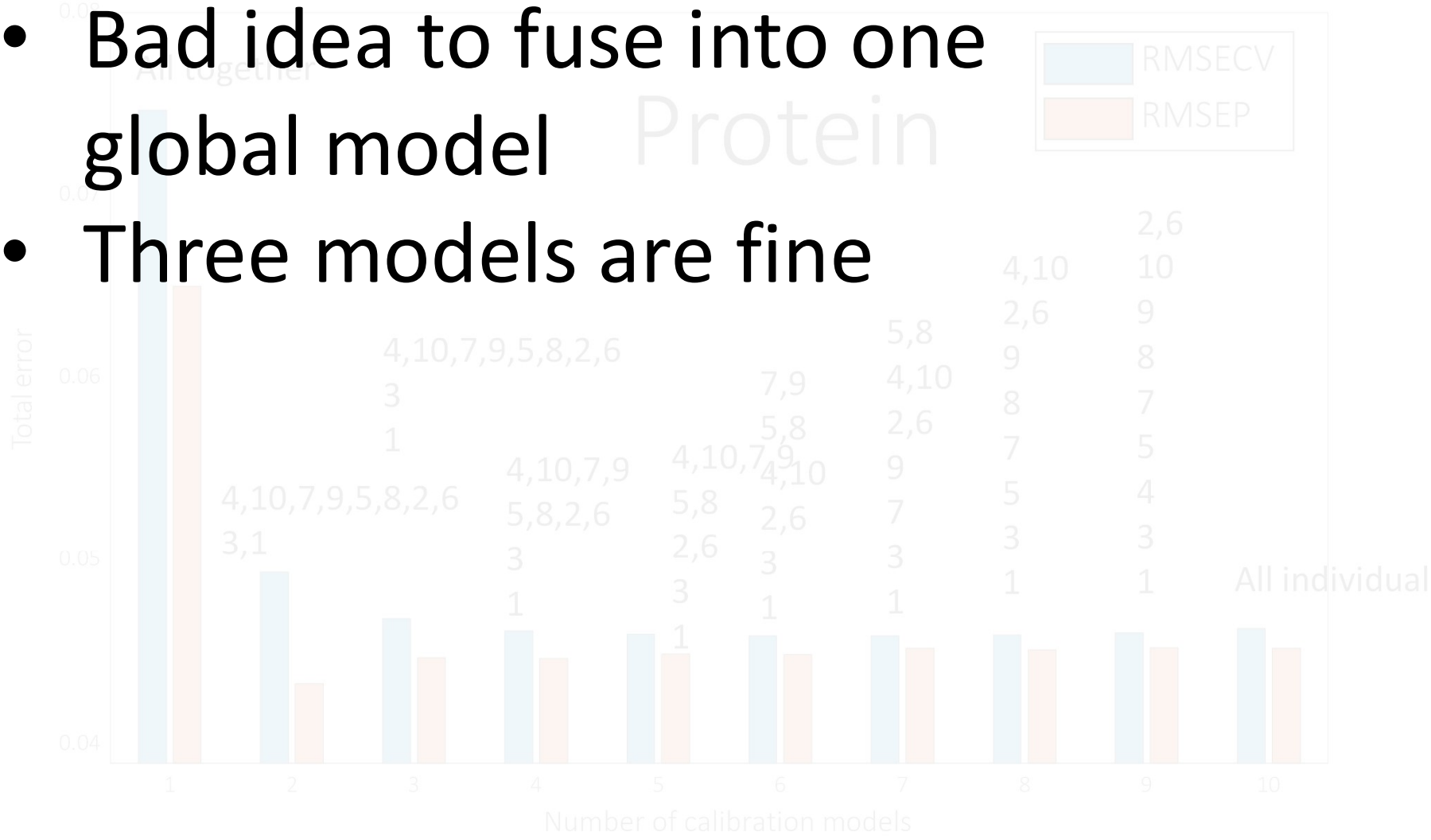

Protein
RMSECV
RMSEP
0.08
0.07
0.06
0.05
0.04
All individual
Predictions from ten models
1
2
3
4
5
6
7
8
9
10
Number of calibration models


Protein
RMSECV
RMSEP
0.08
0.07
0.06
0.05
0.04
2,6
10
9
8
7
5
4
3
1
All individual
1
2
3
4
5
6
7
8
9
10
Number of calibration models

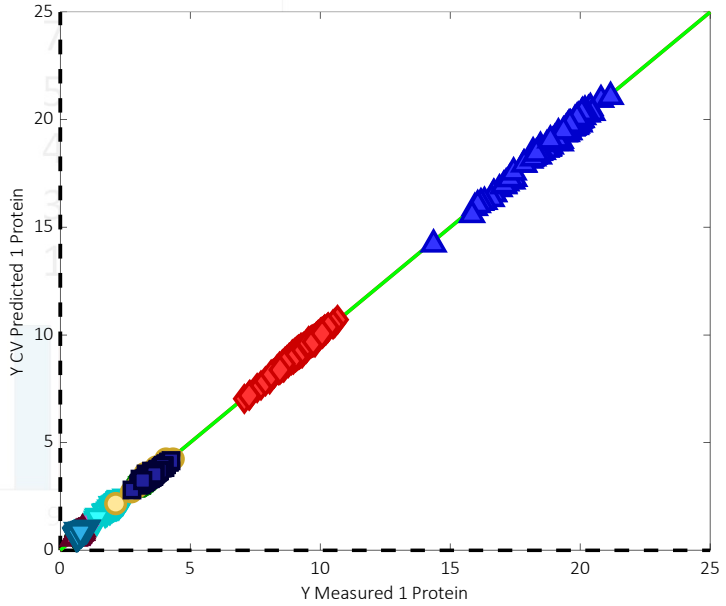

Protein
RMSECV
RMSEP
0.08
0.07
0.06
0.05
0.04
4,10,7,9,5,8,2,6
3,1
4,10,7,9,5,8,2,6
3
1
4,10,7,9
5,8,2,6
3
1
4,10,7,9
5,8
2,6
3
1
7,9
5,8
4,10
2,6
3
1
5,8
4,10
2,6
9
7
3
1
4,10
2,6
9
8
7
5
3
1
2,6
10
9
8
7
5
4
3
1
All individual
1
2
3
4
5
6
7
8
9
10
Number of calibration models


Protein
RMSECV
RMSEP
All together
4,10,7,9,5,8,2,6
3,1
4,10,7,9,5,8,2,6
3
1
4,10,7,9
5,8,2,6
3
1
4,10,7,9
5,8
2,6
3
1
7,9
5,8
4,10
2,6
3
1
5,8
4,10
2,6
9
7
3
1
4,10
2,6
9
8
7
5
3
1
2,6
10
9
8
7
5
4
3
1
All individual
Total error
0.08
0.07
0.06
0.05
0.04
1
2
3
4
5
6
7
8
9
10
Number of calibration models

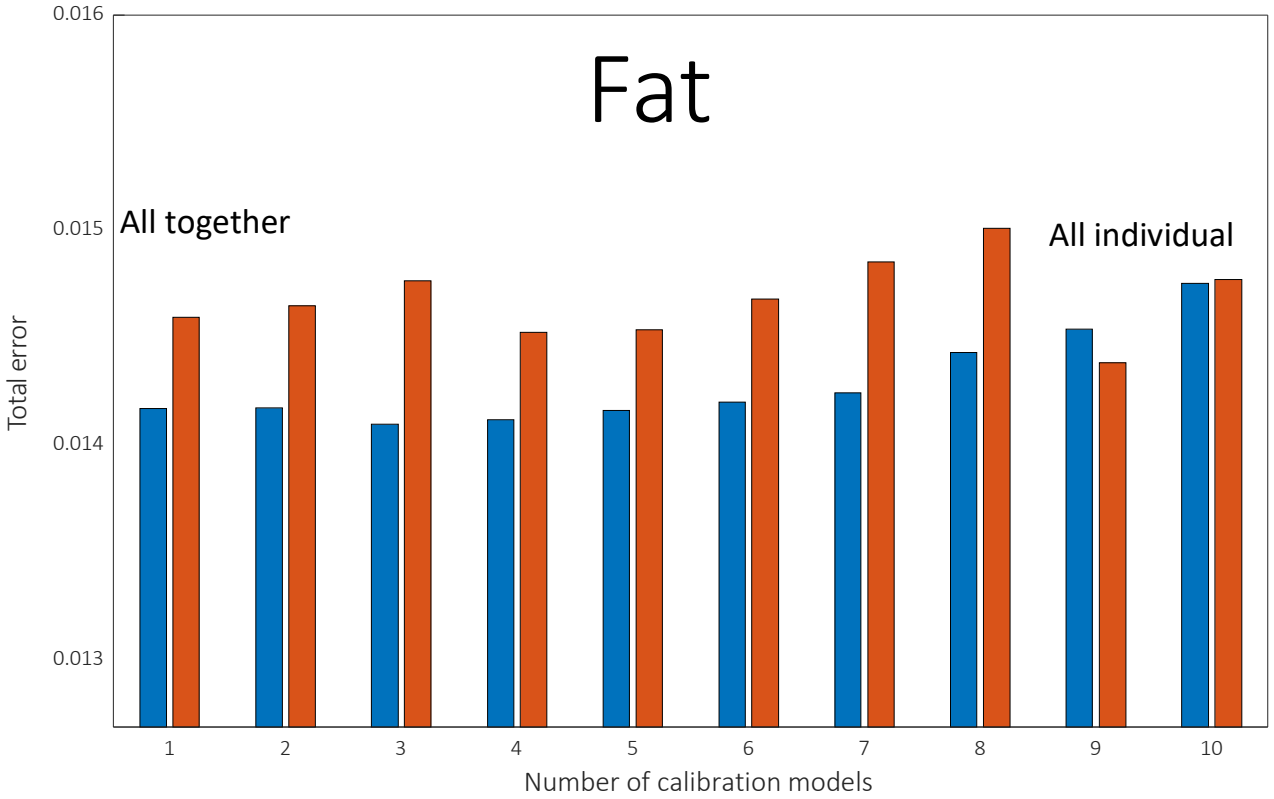
- Bad idea to fuse into one global model
- Three models are fine



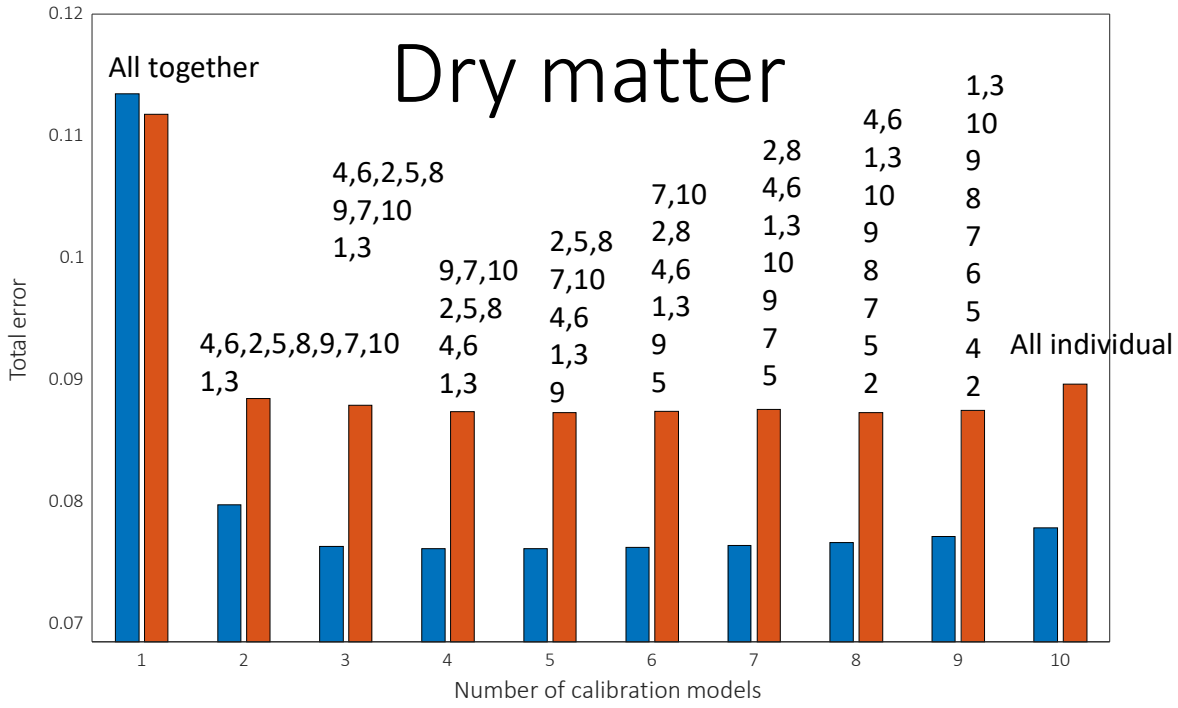
- Bad idea to fuse into one global model
- Three models are fine
- Similar results when grouping according to protein level



# No reason to have separate fat models



# Two models for dry matter



Matlab tool available

- We can automatically fuse models
- We can select the balance between #models and performance
- Lower maintenance
- Increased robustness´
- Basically model clustering/fusion

So … making life simpler and better