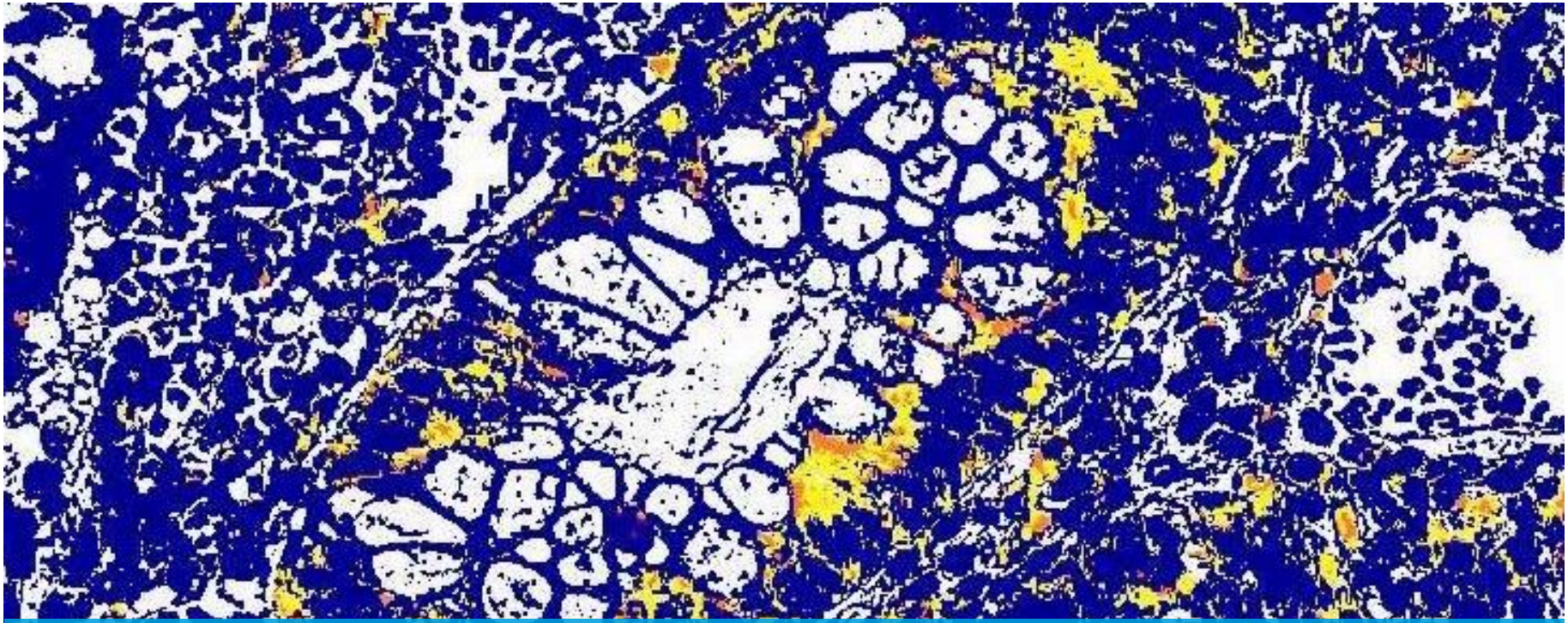

Advantages of using the Bayesian Framework for Modelling the relationship between Volume, Freezing Rate, Supercooling and Aggregation in Vaccines

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26/OCT/2023

Ulcerative colitis at 40x magnification

janssen | Pharmaceutical Companies of Johnson & Johnson

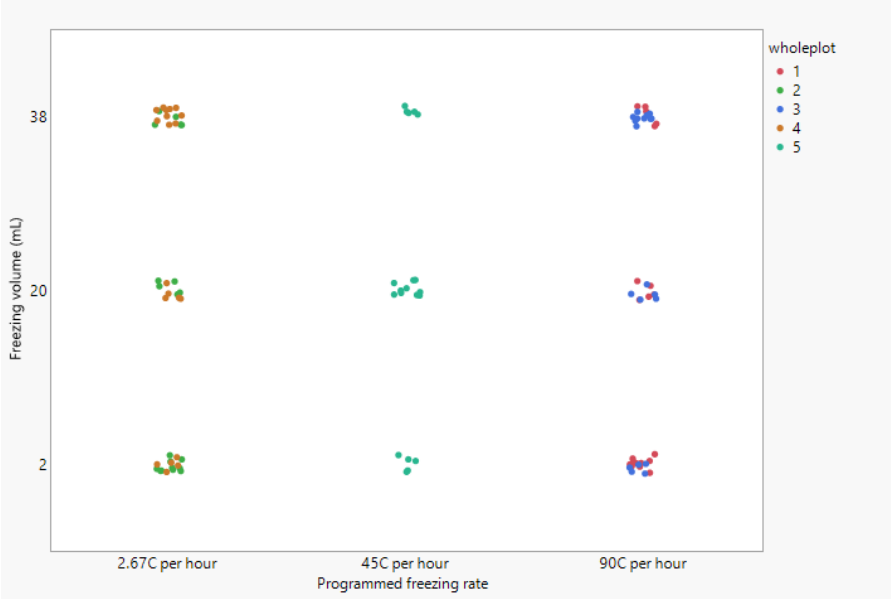
Introduction

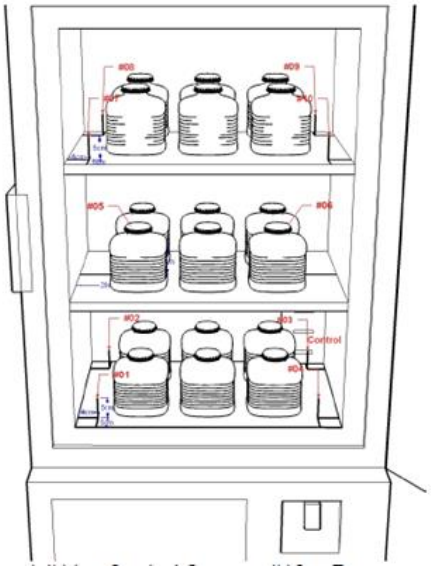
Can aggregation be prevented by freezing larger volumes and using fast freezing ranges?

Design of experiments

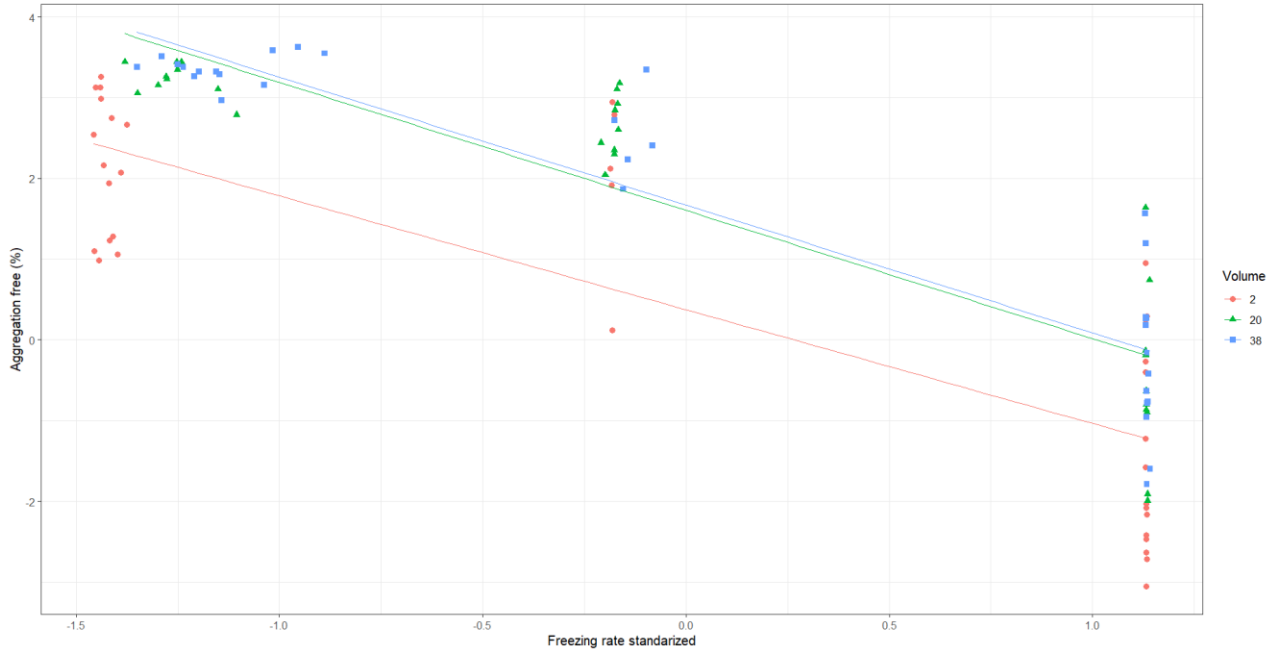
Split plot design with 5 whole plots with 20 experimental runs per whole plot

Factors included: Freezing Volume and freezing rate
Model: Response Surface Model (main and quadratic effects and second order interactions)
The experiment was performed with 3 different batches



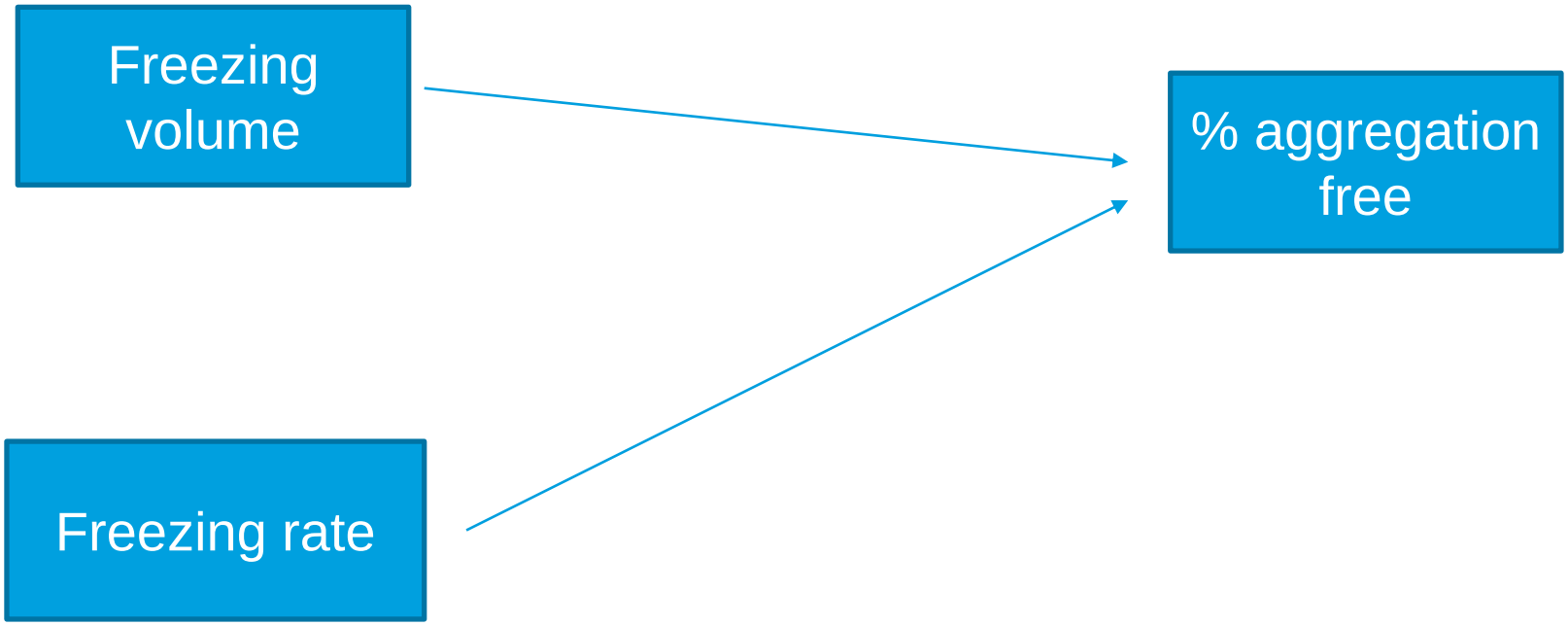


Results aggregation free (%)



- Higher volume ⟹ lower % aggregation
- Higher freezing rate ⟹ lower % aggregation
- Heterogeneous variance

Results aggregation



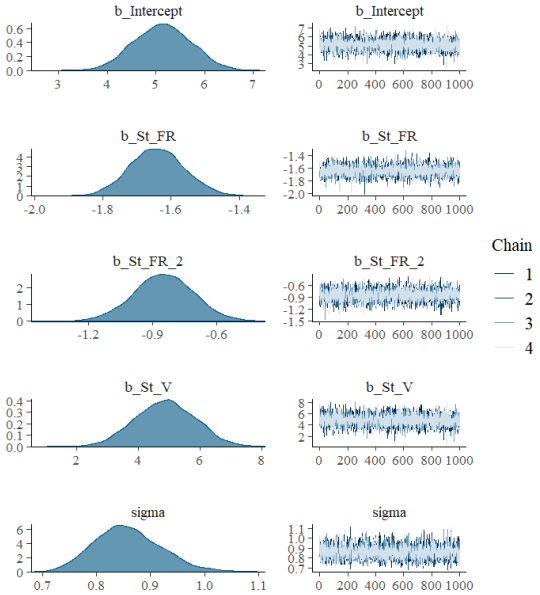
- The proposed design studies the direct influence of freezing volume and freezing rate on %aggregation free.

Results aggregation

A Student-t prior with 3 degrees of freedom was used for the intercept and a half-student-t prior with 3 degrees of freedom was used for the standard deviation.

Whole plot random effect was excluded because the between whole plots variation was very small compared to the within plot variation.

$$logit(y_i) \sim Normal(\mu_i, \sigma)$$
$$\mu_i = \alpha_1 + \beta FR + \varphi FR^2 + \gamma V$$




```
 Family: gaussian
  Links: mu = identity; sigma = identity
Formula: logit_ag ~ St_FR + St_FR_2 + St_V
   Data: data11 (Number of observations: 96)
  Draws: 4 chains, each with iter = 2000; warmup = 1000; thin = 1;
         total post-warmup draws = 4000

Population-Level Effects:
          Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
Intercept     5.13      0.60     3.99     6.30 1.00     5008     3392
St_FR        -1.64      0.08    -1.80    -1.48 1.00     4032     2648
St_FR_2      -0.85      0.14    -1.13    -0.57 1.00     4018     3163
St_V          4.87      0.98     3.00     6.80 1.00     4711     3327

Family Specific Parameters:
      Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
sigma     0.86      0.06     0.75     0.99 1.00     3618     2943
```

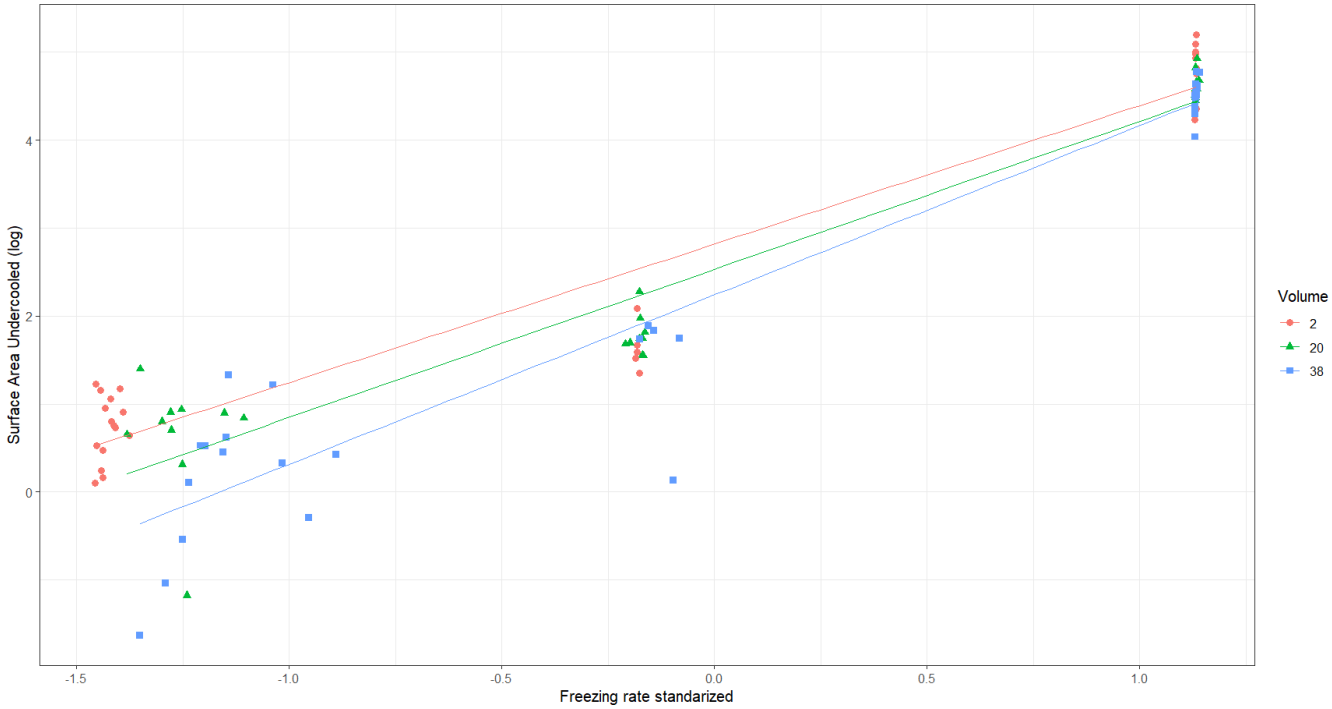
Supercooling

Measurements performed during the experiments identify a new covariate that could be measured, but not directly manipulated. This covariate is called supercooling

Definition: It is the phenomenon where a substance remains in a liquid state at a temperature below its normal freezing point.

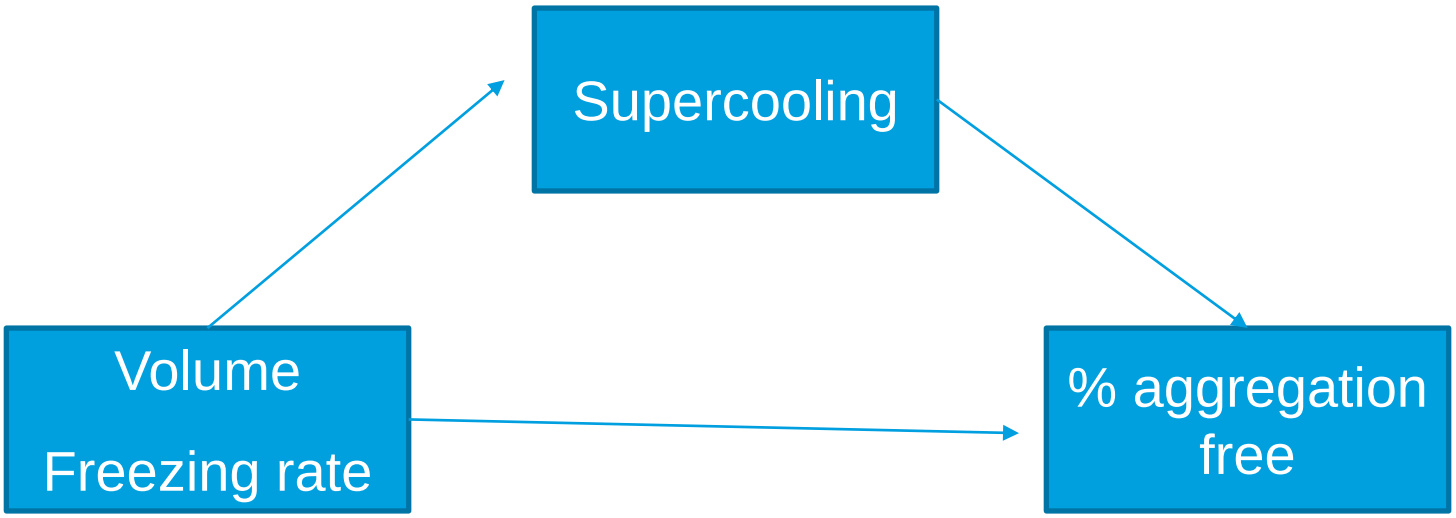
Measurements: surface area undercooled.

Supercooling



- Lower volume → Larger area undercooled
- Slower freezing rate → Larger area undercooled

Results aggregation free (%)



- Rather than a direct relationship between the experimental factors and %aggregation, volume and Freezing rage produce supercooling, which produces %aggregation.

Statistical Mediation

It is interesting to study the relationship between the covariate and the factors, and between the covariate and the outcome of the experiment because the covariate was a key to understand the kinetic aspects of the freezing of the product

- Mediation is a three variables system in which an independent variable causes a mediating variable, which, in turn, causes a dependent variable (Baron & Kenny, 1986; MacKinnon, 2008).
- The aim of mediation analysis is to determine whether the relation between the independent variable and the dependent variable is due, wholly or in part, to the mediating variable.

$$Y = \alpha_1 + \beta FR + \gamma V + e_1$$

$$M = \alpha_2 + \rho FR + \varphi V + e_2$$

$$\mathrm{Y} = \alpha_3 + \delta M + \beta' FR + \gamma' V + e_3$$

Mediation analysis using Bayesian Regression model

- WHY?
  - Probabilistic interpretation of the parameters and the conditional relationships between the variables.
  - Predictive distributions of aggregation outside the study range.
  - Possibility of updating the model with new information collected for larger volumes. …

Results

```
library(brms)

f1 <- bf(log_sup ~ St_FR + St_FR_2 + St_V)

f2 <- bf(logit_ag ~ St_FR + St_FR_2 + St_V + log_sup)

m12 <- brm(f1 + f2 + set_rescor(FALSE), data = data11,
cores = 4)

mediation(m2)
```

- Direct effect: median value of posterior samples from treatment of the outcome model
- Mediator effect: median value of posterior samples from mediator of the outcome model.
- Indirect effect: median value of the multiplication of the posterior samples from mediator of the outcome model and the posterior samples from treatment of the mediation model.
- Total effect: median value of sums of posterior samples used for the direct and indirect effect.
- The proportion mediated is the indirect effect divided by the total effect.

Results

Treatment: St_FR
Mediator : log_sup
Response : logitag

Effect	Estimate	95% ETI
Direct Effect (ADE)	-0.460	[-1.116, 0.205]
Indirect Effect (ACME)	-1.175	[-1.817, -0.528]
Mediator Effect	-0.658	[-1.015, -0.295]
Total Effect	-1.641	[-1.808, -1.471]

Proportion mediated: 71.62% [31.33%, 111.91%]

Treatment: St_V
Mediator : log_sup
Response : logitag

Effect	Estimate	95% ETI
Direct Effect (ADE)	3.541	[1.595, 5.362]
Indirect Effect (ACME)	1.274	[0.471, 2.410]
Mediator Effect	-0.653	[-1.008, -0.330]
Total Effect	4.850	[2.953, 6.781]

Proportion mediated: 26.27% [5.14%, 47.40%]

Results

$$logit(y_i) \sim Normal(\mu_i, \sigma)$$

$$Y_i = \alpha_1 + \beta FR + \varphi FR^2 + \gamma V + \delta M + \theta MV$$

```
library(brms)

M_1<-brm(logit_ag ~ St_FR + St_FR_2 + St_V + log_sup+
log_sup:St_V, prior=bprior, data= data11, cores=4 )
```

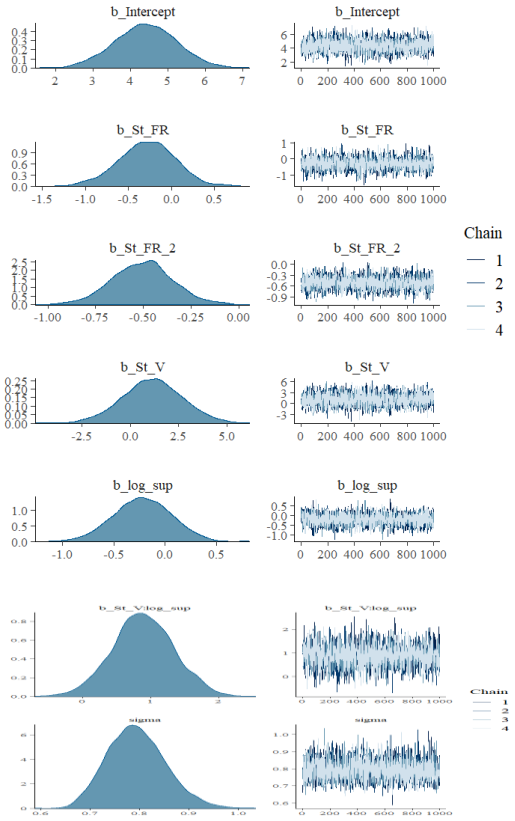
Results

The relationship between freezing rate and aggregation is mediated by supercooling, and the effect of supercooling on aggregation is higher for larger volumes.

```
 Family: gaussian
  Links: mu = identity; sigma = identity
Formula: logit_ag ~ St_FR + St_FR_2 + St_V + log_sup + log_sup:St_V
   Data: data11 (Number of observations: 96)
  Draws: 4 chains, each with iter = 2000; warmup = 1000; thin = 1;
         total post-warmup draws = 4000

Population-Level Effects:
             Estimate Est.Error l-95% CI u-95% CI  Rhat Bulk_ESS Tail_ESS
Intercept       4.412     0.829    2.776    6.014 1.001     2356     2644
St_FR          -0.284     0.336   -0.973    0.359 1.002     1886     1803
St_FR_2        -0.505     0.161   -0.826   -0.174 1.000     2335     2114
St_V            1.136     1.551   -1.946    4.184 1.002     2170     2435
log_sup        -0.221     0.280   -0.781    0.317 1.000     1990     2198
St_V:log_sup    0.890     0.450    0.016    1.771 1.001     1930     2093

Family Specific Parameters:
      Estimate Est.Error l-95% CI u-95% CI  Rhat Bulk_ESS Tail_ESS
sigma    0.794     0.059    0.688    0.918 1.000     2781     2622
```



Validation runs for larger volumes

Programmed FR	Measured FR	Volume.(mL)	logit Aggr	Predicted Old Model	Q2.5	Q97.5	Predicted new model	Q2.5	Q97.5
90C per hour	-84	100	3.44	5.25	3.28	7.20	3.84	1.63	6.05
90C per hour	-70	100	3.41	5.34	3.36	7.24	4.17	1.94	6.31
90C per hour	-70	100	3.44	5.37	3.46	7.32	4.27	2.15	6.47
90C per hour	-56	100	3.41	5.20	3.24	7.15	4.60	2.27	6.86
90C per hour	-68	100	3.48	5.35	3.42	7.26	4.48	2.12	6.81
90C per hour	-62	250	3.62	9.77	6.51	12.82	5.30	0.97	9.64
90C per hour	-62	250	3.62	9.79	6.66	12.92	5.12	0.41	9.80
90C per hour	-64	250	3.66	9.79	6.63	12.90	5.23	0.66	9.71
90C per hour	-64	250	3.71	9.80	6.60	12.97	4.70	-0.67	10.06
90C per hour	-68	250	3.71	9.84	6.73	13.10	4.75	-0.44	10.03
90C per hour	-53	500	3.66	17.02	11.17	22.82	4.38	-7.54	16.27
90C per hour	-55	500	3.75	17.10	11.39	22.79	3.79	-8.75	16.33
90C per hour	-53	500	3.66	17.02	11.25	22.81	4.02	-8.30	16.21
90C per hour	-57	500	3.66	17.15	11.38	23.00	4.11	-8.19	16.35
90C per hour	-75	500	3.58	17.29	11.41	23.05	5.74	-4.42	15.86
90C per hour	-71	500	3.58	17.27	11.43	23.26	5.20	-5.79	15.94
90C per hour	-63	500	3.62	17.24	11.31	23.09	3.76	-8.88	16.42
90C per hour	-69	500	3.66	17.30	11.48	23.00	5.72	-4.76	15.93
90C per hour	-77	500	3.62	17.28	11.52	23.04	6.13	-3.49	15.71

Summary

- The mediation analysis helped us to understand the relation between freezing rate, volume and aggregation and to build a model that could predict aggregation for larger volumes better than the original model.
- The relationship between freezing rate and percentage of aggregation free was mediated by supercooling and the relationship between supercooling and percentage of aggregation free changed across volumes.

Thank you very much!

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