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A binary gas transport model Improves the prediction of mass transfer in freeze drying

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1 Title:

2 **A binary gas transport model improves the prediction of mass**
3 **transfer in freeze-drying**

4
5 Short title: Binary gas transport model in freeze-drying

6
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20
21 Abstract

22 Monitoring partial vapor pressure in the freeze-drying chamber is a cheap,
23 global and non-intrusive way to assess the end of the primary drying stage.
24 Most existing dynamic freeze-drying models which predict this partial
25 pressure describe mass transfer between the product and the condenser via
26 a mass transfer resistance or a mass transfer coefficient. Experimental
27 evidence suggests that such models can be significantly in error for some

28 values of the sublimation flux, leading to physically inconsistent
29 predictions and possibly incorrect assessment of primary drying
30 termination, with potential risk of product damage if moving to secondary
31 drying and increasing shelf temperature while some ice is still present.
32 Assuming a binary gas transport model for vapor and inert gas leads to
33 improved and consistent predictions and explains the apparent variation of
34 the mass transfer resistance with total pressure, shelf temperature and
35 product sublimation area.

36

37 *Keywords:* lyophilization, dynamic model, mass transfer, convection,
38 diffusion

39

40

41

INTRODUCTION

42 Freeze-drying (lyophilization) is widely used for long term preservation of thermosensitive
43 biological material and pharmaceuticals, such as proteins, vaccines, bacteria, mammalian cells
44 and high quality food.^[1, 2] It removes water or an organic solvent in a way that minimizes the
45 modification of the molecular structure of the active ingredient and creates a porous matrix
46 with high rehydration properties. Freeze-drying remains a costly process, however, and lot of
47 research was devoted to its optimization, often based on mathematical modeling.^{[2, 3, 4, 5, 6, 7, 8,}
48 ^{9, 10, 11, 12]}

49 The process consists of three main steps: freezing, ice removal by sublimation (primary
50 drying) and unfrozen water removal by desorption from the solid matrix (secondary drying).
51 The primary drying stage is usually the most time and energy consuming part of a freeze-
52 drying cycle. A lot of research has been devoted to the development of methods to precisely
53 and consistently identify the end of the primary drying. Most of these methods rely on the
54 monitoring of the vapor partial pressure in the freeze-drying chamber, either directly
55 (moisture sensors such as aluminum oxide probes) and/or indirectly (Pirani gauge, mass
56 spectrometer, Tunable Diode Laser Absorption Spectroscopy (TDLAS)).^[13, 14] Moreover,
57 abundant literature is available concerning modeling of primary freeze-drying for optimizing

58 this step of the process off line and also more recently in real time.^[11, 12, 15] Models often
59 predict the product temperature and the sublimation flux. The rate of solvent vapor removal
60 from the product is usually described as being governed by three barriers or resistances:
61 resistance of the dried-product layer, resistance of the containers (vials and stoppers), and
62 resistance of the chamber to condenser pathway. Since the gas phase is mainly vapor during
63 the primary drying and gradients of concentrations are small, true diffusion, or flow under the
64 influence of a concentration gradient, is often considered of minor importance and models
65 focus on bulk flow mechanisms.^[16] The resistance of the dried product layer and of the
66 containers has been studied both theoretically and experimentally by many groups. These
67 studies present two limitations, however. Firstly, the chamber resistance is usually neglected
68 because of measurement difficulties, or it is estimated by rather complex approaches
69 involving Computational Fluid Dynamics (CFD) simulations.^[17, 18, 19, 20] Secondly, the partial
70 vapor pressure is usually not predicted but taken as fixed and equal to the total chamber
71 pressure, despite its importance for real time optimization and freeze-drying control.^{[3, 10, 21, 22,}
72 23, 24]

73 Our group previously developed a one-dimensional heat and mass transfer model, which can
74 accurately represent both the primary and secondary drying stages and the gradual transition
75 between them.^[9] When adapting it to other freeze-dryers and to bacterial suspensions,
76 however, it turned out that the determined chamber resistance strongly varied with total
77 pressure and shelf temperature. Moreover, for a sufficiently high sublimation flux, e.g.
78 generated by a high shelf temperature at the beginning of the primary drying, the model can
79 predict a partial vapor pressure higher than the total one, which is obviously incorrect.

80 In the present study the chamber resistance was experimentally determined and a model of
81 mass transfer between the freeze-drying chamber and the condenser is proposed for the
82 solvent vapor and inert gas pair. The model is based on the mass transfer theory in binary gas
83 mixtures and includes bulk flow and mutual diffusion terms. This model improved the
84 prediction of the chamber vapor pressure and of the primary drying termination. It also
85 accounted for apparent variations of the effective mass transfer resistance with total pressure,
86 shelf temperature and product sublimation area.

87

MATERIALS AND METHODS

88 *Determination of the mass transfer resistance (vapor flow) of the chamber to condenser*
89 *pathway*

90 Experiments were carried out on a LyoBeta special freeze-dryer (Telstar, Terrassa, Spain)
91 equipped with 5 thermocouples, a capacitive manometer and a Pirani gauge. Purified water
92 and bacterial cell suspensions were successively considered.

93 A stainless steel tray was filled with purified water to a thickness of 3 cm. The evaporative
94 flow was determined using the gravimetric method. After freezing the water at -50°C (cooling
95 rate of 0.6 °C/min), and sublimation time between 4 and 8 hours depending on the
96 experimental conditions, the process was stopped and the tray was weighted to determine the
97 amount of water removed and thus the evaporative flux (F_V , in kg s⁻¹). The mass transfer
98 coefficient (k_m , kg s⁻¹ Pa⁻¹), or, equivalently, resistance of the chamber to condenser pathway
99 (r_m , Pa s kg⁻¹) was determined from Eq. 1:

100 Eq. 1
$$F_V = k_m(P_{V1} - P_{V2}) = \frac{P_{V1} - P_{V2}}{r_m}$$

101 with P_{V1} , the water vapor partial pressure just above the product (Pa), estimated from the ice
102 temperature and P_{V2} , the water vapor partial pressure at the condenser (Pa), estimated from
103 the condenser temperature.

104 The effect of three process variables on the effective mass resistance (r_m) value was
105 investigated: sublimation area (0.033, 0.074 and 0.15 m²), chamber pressure (10, 20, 40 and
106 60 Pa) and shelf temperature (-15, 0 and 15°C).

107 *Freeze-drying experiments with bacterial suspensions*

108 Lactic acid bacteria were produced by fermentation in controlled conditions of pH and
109 temperature.^[25] After concentration, the bacterial cells were re-suspended in a 1:2
110 cells/protective medium ratio. The protective medium was composed of 200 g/L of sucrose
111 and 0.15 M of NaCl. A stainless steel tray was filled with 450g of bacterial suspension and
112 the following freeze-drying protocol was applied: freezing at -50°C (cooling rate of
113 0.6°C/min); primary drying at -20, 0 or 25°C; secondary drying at 25°C for 8 hours. The total
114 chamber pressure was controlled at either 20 or 60Pa. Thermocouples were placed at the
115 bottom of the product in the centre of the tray.

116 *Estimation of partial vapor pressure from the Pirani gauge*

117 The reading of a Pirani gauge in a pure gas is proportional to the pressure of the gas and to the
118 molecular heat conductivity of the gas.^[26] The main gases present in the freeze-drying
119 chamber are solvent vapor (usually water) and an inert gas such as nitrogen or air. Let

120 Eq. 2
$$\alpha = \frac{\lambda_v}{\lambda_N}$$

121 be the ratio of the molecular heat conductivities. This ratio is equal to 1.6 for the water vapor
122 and nitrogen pair. If the Pirani gauge is calibrated with inert gas, nitrogen in the present case,
123 then the reading in pure solvent vapor will be:

124 Eq. 3
$$P_V^p = \alpha P_V$$

125 In a gas mixture, the Pirani gauge will measure the sum of heat fluxes due to conduction in
126 each gas. The reading will be:

127 Eq. 4
$$P^p = \alpha P_V + P_N$$

128 In contrast, the capacitive sensor will give the true total pressure:

129 Eq. 5
$$P_t = P_V + P_N$$

130 From these two readings, one can determine the partial pressures of vapor and inert gas:

131 Eq. 6
$$P_V = \frac{P^p - P_t}{\alpha - 1}$$

132 Eq. 7
$$P_N = \frac{\alpha P_t - P^p}{\alpha - 1}$$

133 *Numeric calculations*

134 Calculations were performed with Matlab™ 8 software (The MathWorks Inc., Natick, MA)
135 equipped with the Statistics Toolbox and the Global Optimization Toolbox.

136 MASS TRANSFER MODELS BETWEEN CHAMBER AND CONDENSER

137 *Mass transfer resistance model*

138 In most previously developed freeze-drying models, the mass flux between the freeze-drying
139 chamber containing the product (location 1) and the condenser (location 2) was either

140 ignored, considering the vapor pressure in the freeze-drying chamber as given,^[3, 10, 21, 22, 23] or
141 expressed via a mass transfer coefficient (k_m) or, equivalently, via a mass transfer resistance
142 (r_m),^[9, 12, 27, 28, 29] as given by Eq. 1.

143 Note that in Eq. 1 the mass flux is proportional to the partial vapor pressure difference
144 between the two locations. Vapor pressure P_{V2} is usually fixed by the condenser temperature,
145 while the mass flux F_V is mostly determined by the heat transfer flux from the temperature-
146 controlled shelf to the product, i.e. by the shelf temperature and the product sublimation area.
147 If the mass transfer resistance was constant, as it is usually assumed, then the partial vapor
148 pressure in the chamber P_{V1} would result from Eq. 1. If the mass flux was high enough, due
149 for example to high shelf temperature, a model based on Eq. 1 could even give a vapor
150 pressure higher than the total chamber pressure, which is obviously impossible. A more
151 consistent mass transfer model is developed in the next section.

152 *Binary gas transport model*

153 Consider a mixture of two gases at low pressure; in the case of freeze-drying these gases
154 would be solvent vapor, usually water, released from the product and captured by the
155 condenser and the inert gas, usually nitrogen, used to control the total chamber pressure. To
156 determine the relevant mass transport theory, the Knudsen number, defined as the ratio of the
157 free mean path of the molecules and the characteristic dimension of the system, was
158 estimated. In the considered conditions, the free mean path is of order of 0.5mm at 20Pa,
159 while the typical diameter of the chamber to condenser duct is 100mm. Knudsen diffusion can
160 thus be safely neglected for the chamber to condenser pathway considered here, since
161 $K_n \approx 5 \times 10^{-3}$. Note that this is usually not the case in the porous product layer where the pore
162 size can be much less than 0.5mm, but mass transport in the porous layer is out of the scope
163 of the present study.

164 The classical theory of binary diffusion in gases states that the molar flux density of solvent
165 vapor, in stationary coordinates, is given by:^[30]

166 Eq. 8
$$N_V = x_V(N_V + N_N) - (c_V + c_N)D_{VN}\nabla x_V$$

167 where N_V and N_N are molar flux densities, c_V and c_N molar concentrations of vapor and
168 nitrogen respectively, x_V is the molar fraction of vapor and D_{VN} is the mutual diffusion
169 coefficient. The first term on the right-hand side of Eq. 8 results from the bulk motion of the
170 fluid while the second one expresses the diffusion of vapor due to its molar fraction gradient.

171 Assuming pseudo-stationary conditions, compared to the duration of a freeze-drying cycle
 172 which is of one or several days, and assuming insignificant leaks in the freeze-drying
 173 chamber, the net inert gas flux is negligible compared to the vapor flux:

174 Eq. 9
$$N_N \approx 0$$

175 Usual variables in freeze-drying are mass fluxes instead of molar fluxes and partial pressures
 176 instead of molar fractions and concentrations. Using the ideal gas law one gets:

177 Eq. 10
$$x_V = \frac{P_V}{P_V + P_N} = \frac{P_V}{P_t}$$

178 Eq. 11
$$c_V + c_N = \frac{P_V + P_N}{RT} = \frac{P_t}{RT}$$

179 Eq. 12
$$f_V = M_V N_V$$

180 With these substitutions, and assuming that the variation of total pressure between freeze-
 181 drying chamber and condenser is small compared to the variation in vapour partial pressure,
 182 Eq. 8 becomes:

183 Eq. 13
$$f_V(P_t - P_V) = -\frac{M_V}{RT} P_t D_{VN} \nabla P_V$$

184 To solve Eq. 13, it is assumed that the vapour flux between the product and the condenser is
 185 essentially one-dimensional. This assumption is relatively sound for freeze-driers equipped
 186 with a condenser separated from the main freeze-drying chamber by a pipe, as is the case in
 187 the present study, but it is questionable when the product and the condenser are situated in the
 188 same cavity. With this assumption, Eq. 13 can be integrated between the freeze-drying
 189 chamber (location 1) and the condenser (location 2) giving:

190 Eq. 14
$$F_V = A f_V = \frac{A M_V}{l_{eff} RT} P_t D_{VN} \ln \frac{P_t - P_{V2}}{P_t - P_{V1}}$$

191 where F_V is the vapor mass flux, while A and l_{eff} are the diffusion cross-section area and
 192 effective duct length respectively. The effective length accounts for the presence of inlet and
 193 outlet sections, bends, valve and other elements that can introduce additional resistances.

194 The mutual gas diffusion coefficient D_{VN} is inversely proportional to the total pressure, thus
 195 the product $P_t D_{VN}$ is constant.^[30] For a given freeze-dryer geometry (l_{eff} , A) a constant β can
 196 be introduced:

197 Eq. 15
$$\beta = \frac{l_{eff} R}{AM_V P_t D_{VN}}$$

198 so that

199 Eq. 16
$$F_V = \frac{1}{\beta T} \ln \frac{P_t - P_{V2}}{P_t - P_{V1}}$$

200 The dependence of the mass flux on the partial vapor pressures given by Eq. 16 appears quite
 201 different from Eq. 1. It can be shown, however, using a first order Taylor series expansion of
 202 the logarithm function, that Eq. 1 is an approximation of Eq. 16 in the case when the vapor
 203 pressures are much less than the total pressure:

204 Eq. 17
$$\ln \frac{P_t - P_{V2}}{P_t - P_{V1}} \approx \frac{P_{V1} - P_{V2}}{P_t} \quad \text{if } P_{V1} \ll P_t \text{ and } P_{V2} \ll P_t$$

205 It should be noted, however, than in freeze-drying the condition $P_{V1} \ll P_t$ is usually *not*
 206 satisfied as the gas in the freeze-drying chamber during primary drying is mostly solvent
 207 vapor. The approximation given by Eq. 17 is thus not expected to be valid. This can explain
 208 the mentioned inconsistency with Eq. 1 and the apparent variation of the effective mass
 209 transfer resistance with total pressure and mass flux, as further discussed below. For now,
 210 note that Eq. 16 can accommodate arbitrarily large vapor fluxes without P_{V1} exceeding P_t ,
 211 provided that the difference $P_t - P_{V1}$ becomes small enough, while remaining positive.

212

213 RESULTS AND DISCUSSION

214 *Experimental determination of chamber to condenser mass transfer resistance*

215 Table 1 summarizes the experimental values of the mass transfer resistance of chamber to
 216 condenser pathway measured for various process conditions.

217 The effective mass transfer resistance appeared to increase when increasing chamber pressure,
 218 decreasing shelf temperature and decreasing sublimation area. The mass transfer resistance
 219 was thus inversely correlated with the sublimation flux. Increasing the sublimation rate

220 resulted in an apparent decrease of the effective mass transfer resistance of the chamber to
221 condenser pathway. These observed variations support the idea that the mass transfer
222 resistance is only an effective model parameter and a different perspective is needed to get a
223 more physically meaningful description of the transfer phenomena. This is further discussed
224 in the next sections.

225 *Prediction of partial vapor pressure in the chamber by the two modeling approaches:*
226 *resistance vs. binary gas transport*

227 The predictions of the previously developed freeze-drying model,^[9] adapted for bacterial
228 suspension conditioned in trays, were compared to experimental measurements acquired in
229 freeze-drying experiments performed as described in the “Materials and methods” section.
230 Two versions of the model were tested, one based on a mass transfer resistance between the
231 chamber and the condenser (Eq. 1) and the other based on the binary gas transport assumption
232 (Eq. 16). Details of the existing model^[9] adaptation to the new freeze-dryer, container and
233 product, as well as implementation details of the new chamber-to-condenser mass transport
234 model based on Eq. 16 are given in the Appendix. The model parameters (notably k_m and β)
235 were determined by fitting the models to some of the experimental data obtained in bacterial
236 suspension experiments (Appendix and Table 2)

237 An example of the predictions of the two versions of the model are shown in Figure 1, for two
238 experiments performed at 0°C shelf temperature/60Pa chamber pressure and 25°C/20Pa,
239 respectively. These are validation experiments not used for model parameter identification.
240 Dotted lines represent calculations based on the mass transfer resistance model and solid lines
241 correspond to the binary gas transport model.

242 The experiment at 0°C/60Pa (Figure 1, left panels) illustrates a situation where the prediction
243 of the primary drying termination differs by about 2 hours between the considered models.
244 The end of the primary drying was arbitrarily defined here as the moment when the
245 sublimation flux (Figure 1C) decreased below 5% of its maximum value. The resistance
246 model predicts the end of the primary drying at about 11h, in agreement with measured
247 product temperature approaching the shelf temperature (Figure 1A), while the binary gas
248 model predicts the end at about 13h, in agreement with the decrease of vapor pressure in the
249 chamber (Figure 1B). Note that product temperature measurement is a local one, potentially
250 disturbed by the presence of the probe, while partial vapor pressure measurement is a global
251 one, representative of the whole product in the freeze-dryer. Vapor pressure should thus be

252 preferred to assess the end of the primary drying.^[14] It is also non intrusive and usually more
 253 conservative, minimizing the risk of premature temperature increase and product damage, if
 254 some ice was still present when starting the secondary drying step.

255 The experiment at 25°C/20Pa (Figure 1, right panels) illustrates a situation where both models
 256 predict the same end point of the primary drying (11h), but the vapor pressure predicted by
 257 the resistance model is completely in error. Compared to the previously described experiment
 258 (0°C/60Pa), in this case the heat transfer resistance from the shelf to the product is higher due
 259 to lower chamber pressure (lower contribution of the gas conduction), but this is nearly
 260 compensated by a higher shelf temperature, leading to a similar heat flux. The net result is a
 261 similar primary drying time and sublimation flux (Figure 1C) for both experimental
 262 conditions. As expected from Eq. 1, a similar sublimation flux implies a similar vapor
 263 pressure calculated with the resistance model, around 50Pa in this case (Figure 1B), but this
 264 value is 2.5 times higher than the total pressure, which is obviously incorrect. In contrast, the
 265 binary gas model based on Eq. 16 consistently predicts a vapor pressure close to, but slightly
 266 less than the total one, as physically expected.

267 Both these examples suggest that the binary gas transport model should be preferred to the
 268 resistance model. Similar trends were observed in all performed experiments with bacterial
 269 suspensions (data not shown). The properties of the proposed binary gas transport model are
 270 further examined in the following sections.

271

272 *Effective mass transfer resistance of the chamber to condenser pathway*

273 Since Eq. 1 and Eq. 14 are two different ways of expressing the same vapor flux based on
 274 different physical assumptions, these equations can be used to define an effective mass
 275 transfer resistance of chamber to condenser pathway as:

276 Eq. 18
$$r_m = \frac{1}{k_m} = \frac{l_{eff}RT(P_{V1} - P_{V2})}{AM_V P_t D_{VN} \ln \frac{P_t - P_{V2}}{P_t - P_{V1}}} = \beta T \frac{P_{V1} - P_{V2}}{\ln \frac{P_t - P_{V2}}{P_t - P_{V1}}}$$

277 It readily appears from Eq. 18 that this resistance is not constant but is an effective model
 278 coefficient that depends on the actual values of the total and vapor pressure.

279 The effective mass transfer resistance given by Eq. 18 is plotted in Figure 2 (solid line) as a
 280 function of the vapor pressure near the product (P_{V1}), for two different total pressures ($P_t = 20$

281 and 60Pa) used in our experiments. The vapor pressure near the condenser was fixed to a low
282 value $P_{12} = 0.055$ Pa, corresponding to a typical condenser temperature of -80°C . For
283 comparison, the value of r_m determined for the mass transfer resistance model in the same
284 conditions is also given in Figure 2 (dotted line).

285 Firstly, Figure 2 indicates that the effective mass transfer resistance strongly increases with
286 the total pressure. This was expected from the experimental data in Table 1 and confirms the
287 usual practice of performing freeze-drying at low pressure to improve mass transfer.

288 Secondly, the effective mass transfer resistance predicted by the binary gas model approaches
289 zero when the vapor pressure in the chamber approaches the total pressure. This was expected
290 from the mathematical analysis of Eq. 18 and is consistent with the fact that partial vapor
291 pressure in the chamber cannot exceed the total one, whatever the sublimation flux. Note that
292 this is not the case with a constant mass transfer resistance, when the vapor pressure in the
293 chamber can formally exceed the total pressure for a sufficiently high sublimation flux in Eq.
294 1.

295 Finally, Figure 2 shows that the value of the mass transfer resistance determined using the
296 resistance model based on Eq. 1 is situated between the bounds given by Eq. 18, as expected.
297 The effective resistance given by the binary gas transport model is close to this value for
298 vapor pressures very close to the total pressure. This means that the vapor pressure calculated
299 by the binary gas model for the primary drying is most of the time very close to the total
300 pressure, as observed in Figure 1 and well known from freeze-drying practice. This is further
301 illustrated in the following section.

302 *Sublimation flux and predicted vapor pressure in the chamber*

303 In usual freeze-drying conditions the sublimation mass flux is the result of several process
304 parameters (Table 1), such as total chamber pressure (that changes both heat and mass
305 transfer), shelf temperature and sublimation interface area, etc. For the mass transfer
306 resistance model given by Eq. 1, the predicted vapor pressure in the freeze-drying chamber
307 varies linearly with the mass flux (dotted line in Figure 3) and can, as already mentioned,
308 exceed the total pressure, for example in the case of a sufficiently high shelf temperature
309 (Figure 1, right panels). In contrast, the vapor pressure predicted by the gas diffusion model
310 given by Eq. 16 asymptotically tends towards the total pressure for high sublimation mass
311 fluxes, which is physically consistent (solid lines in Figure 3). This also corroborates the well

312 known fact that gas composition in the freeze-drying chamber is dominated by vapor during
313 most of the primary drying stage, when sublimation fluxes are high (approaching $2 \times 10^{-5} \text{ kg s}^{-1}$
314 in the considered experimental setting).

315 *Sublimation flux and effective mass transfer resistance of the chamber to condenser pathway*

316 Considering the effect of the sublimation mass flux in the binary gas transport model gives a
317 common framework to understand the apparent variations of the effective mass transfer
318 resistances observed in Table 1 for different shelf temperatures and sublimation interface
319 areas. Increasing both these variables increases the sublimation flux and this, in turn, causes
320 an apparent reduction of the effective mass transfer resistance (Figure 4). For sublimation
321 fluxes approaching $2 \times 10^{-5} \text{ kg s}^{-1}$, representative of the primary drying in the considered
322 experiments (Figure 1), the mass transfer resistance determined for the resistance model is
323 intermediate between those calculated with the binary gas model for 20 and 60Pa total
324 pressure. This reflects the compromise that the model fitting procedure finds to accommodate
325 experiments performed at both these pressures, but the achieved compromise underestimates
326 the vapor pressure at 60Pa and overestimates it at 20Pa, as already shown in Figure 1.

327 *The binary gas transport model needs a unique constant parameter*

328 As an additional difference between the two models, note that in the mass transfer resistance
329 model the value of the resistance between the chamber and the condenser pathway is only an
330 effective model parameter that appears to be a function of several process variables (Table 1):
331 total pressure, shelf temperature and product sublimation area. Accounting for this would
332 require varying the resistance in a tricky and ad-hoc manner. Considering a constant value of
333 the mass transfer resistance ($r_m = 2.78 \times 10^6 \text{ Pa s kg}^{-1}$ in our case) leads to poor predictions and
334 inconsistencies, such as calculated partial vapor pressure in the chamber exceeding the total
335 one (Figure 1 and Figure 3). On the contrary, binary gas diffusion theory states that the
336 product $P_t D_{VN}$ is constant and therefore in the binary gas transport model the analogous
337 parameter β , given by Eq. 15, is constant. All solid plots in Figures 1–4 were obtained with
338 the same value of $\beta = 2.66 \times 10^3 \text{ s kg}^{-1} \text{ K}^{-1}$.

339 *In-process mass flux estimation and detection of the primary drying termination*

340 Eq. 16 could be used in principle for obtaining vapor flow rate estimations based on total and
341 partial pressure measurements, and thus act as an in-process mass flow meter. In practice,

342 however, estimations of “high” vapor flow rates (i.e. when the partial vapor pressure
343 approaches the total one) are expected to be inaccurate due to the vapor saturation of the
344 chamber illustrated in Figure 3: a wide range of sublimation fluxes corresponds to almost
345 identical partial vapor pressures, very close to the total chamber pressure. For example, with
346 the considered values of the parameters (Appendix) at a total pressure of 60Pa, a vapor
347 pressure of 59.99Pa corresponds to a sublimation flux of $1.14 \times 10^{-5} \text{kg s}^{-1}$, while a vapor
348 pressure of 58.99Pa corresponds to a sublimation flux of $0.53 \times 10^{-5} \text{kg s}^{-1}$. In other words, an
349 uncertainty of only 1Pa in the measurement of the vapor pressure would induce a factor 2
350 error on the flux value, which is clearly inappropriate for practical use.

351 On the contrary, Figure 3 suggests that the estimation of “low” vapor fluxes (i.e. when the
352 partial vapor pressure is well below the total one) based on pressure measurements could be
353 quite accurate. For example, vapor pressures of 30 and 29Pa correspond to vapor fluxes of
354 $0.091 \times 10^{-5} \text{kg s}^{-1}$ and $0.086 \times 10^{-5} \text{kg s}^{-1}$ respectively; a measurement uncertainty of 1Pa would
355 induce only about 5% error on the vapor flux.

356 Above considerations suggest that the proposed model is appropriate for a safe detection of
357 the primary drying termination because a decrease of the vapor pressure well below the total
358 one indicates a strong decrease of the sublimation flux. Continuing the above numerical
359 examples, a vapor pressure in the chamber decreasing to the half of the total pressure
360 corresponds to a factor 10 reduction of the sublimation flux. Of course, exact significance of
361 “high” and “low” mass fluxes and the relevant decrease of vapor pressure depend on
362 numerical values grouped in the parameter β defined by Eq. 15, and also involved in Eq. 16.

363 Finally, note that the proposed in-process flow estimation method based on total and partial
364 pressure measurements in the chamber is complementary to the method described by Patel et
365 al.^[31], based on differential pressure measurement between the chamber and the condenser.
366 Indeed, the former works well for low sublimation fluxes while the latter is expected to be
367 more accurate when the sublimation flux, and hence the measured pressure difference, are
368 large.

369 CONCLUSIONS

370 Results presented in this paper suggest that using one-dimensional mass transfer theory in
371 binary gas mixtures to describe vapor transfer between the freeze-drying chamber and the
372 condenser should be preferred to the mass transfer resistance approach. Advantages of the

373 binary gas transport model include: (i) prediction of the vapor pressure in the freeze-drying
 374 chamber closer to the experimental one, leading to more reliable prediction of the end of the
 375 primary drying; (ii) calculated values of the vapor pressure physically consistent with the total
 376 pressure, whatever the sublimation vapor flux; (iii) need to determine a single model
 377 parameter for a given freeze-dryer geometry, independent on the operating conditions (total
 378 pressure, shelf temperature, ice sublimation area).

379 The main drawback of the mass diffusion model is the non-linear dependence between the
 380 vapor flux and vapor pressure, which can somewhat complicate model simulations. Solution
 381 of non-linear differential and algebraic equation sets is already part of most freeze-drying
 382 models, however, and the additional difficulty introduced by the diffusion model is expected
 383 to be minor, as confirmed by the authors' experience.

384 The assumption of one-dimensional mass transfer between the freeze-drying chamber and the
 385 condenser could be questioned in the future, especially for freeze-dryers with the condenser
 386 situated in the freeze-drying chamber. The challenge would be to end up with a reasonably
 387 simple closed-form relationship between mass flux and pressure, in order to maintain the
 388 overall model minimalism and short simulation time.

389 NOMENCLATURE

390	c	molar concentration	kmol m^{-3}
391	f	mass flux density	$\text{kg s}^{-1}\text{m}^{-2}$
392	k	mass transfer coefficient	$\text{kg s}^{-1}\text{Pa}^{-1}$
393	l	diffusion length	m
394	r	mass transfer resistance	Pa s kg^{-1}
395	x	molar fraction	kmol kmol^{-1}
396	A	diffusion cross-section area	m^2
397	D	mutual diffusion coefficient	$\text{m}^2 \text{s}^{-1}$
398	F	mass flux	kg s^{-1}
399	K_n	Knudsen number	–
400	M	molar mass	kg kmol^{-1}

401	N	molar flux density	$\text{kmol s}^{-1}\text{m}^{-2}$
402	P	pressure	Pa
403	R	ideal gas constant	$\text{J kmol}^{-1} \text{K}^{-1}$
404	T	absolute temperature	K
405	Greek letters		
406	α	heat conductivity ratio	–
407	β	mass transfer parameter	$\text{s kg}^{-1} \text{K}^{-1}$
408	λ	heat conductivity	$\text{Wm}^{-1} \text{K}^{-1}$
409	Subscripts		
410	1	freeze-drying chamber, near product	
411	2	condenser	
412	3	ice sublimation front	
413	4	product top	
414	<i>eff</i>	effective	
415	m	mass	
416	t	total	
417	N	inert gas, nitrogen	
418	V	solvent vapor, water	

419 Superscript

420 P measured by Pirani gauge

421

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 425 212754.

426

427 APPENDIX: EMBEDDING THE BINARY GAS TRANSPORT EQUATION IN A
428 COMPLETE FREEZE-DRYING MODEL

429 The binary gas transport equation proposed in this paper (Eq. 16) describes the mass flux
430 between the freeze-drying chamber and the condenser, in replacement of the more classical
431 equation involving a mass transfer resistance or a mass transfer coefficient (Eq. 1). Both
432 equations were tested in conjunction with an existing freeze-drying model, described in full
433 detail previously.^[9]

434 In a first step, the parameters of the existing model^[9] based on Eq. 1 were re-estimated to
435 account for a different freeze-dryer (LyoBeta special freeze-dryer from Telstar, Terrassa,
436 Spain, instead of SMH15 freeze dryer from Usifroid, Maurepas, France), a different container
437 (metallic tray instead of glass vial) and a different product (lactic acid bacterial suspensions in
438 sucrose medium instead of polyvinylpyrrolidone). Parameters related to the sorption isotherm
439 and to the glass transition of the product were determined with the methodology described
440 previously.^[25] Parameters related to the heat and mass transfer in the freeze-dryer and in the
441 product were estimated by fitting the product temperature and vapor pressure predicted by the
442 model to experimental measurements. Four experiments were used simultaneously for model
443 parameter estimation, performed in the following combinations of shelf temperature and total
444 chamber pressure: -20°C/20Pa, -20°C/60Pa, 25°C/20Pa and 25°C/60Pa. A genetic
445 optimization algorithm (Global Optimization Toolbox for Matlab, Natick, MA) was used for
446 parameter identification. Since the considered optimization algorithm is stochastic, the
447 parameter set with the best fit from 8 independent optimization runs was selected. Most
448 optimization runs consistently converged to similar sets of parameters, usually within ±10%.
449 Model parameters used in the present study are listed in Table 2.

450 In a second step, the original mass transfer equation between the chamber and the condenser
451 (Eq. 1) was replaced by the newly proposed one (Eq. 16) and the parameter estimation
452 procedure was repeated using the same data and the same algorithm. The estimated parameter
453 values are also given in Table 2. As expected, the estimated values of the parameters are
454 similar between the two models, with the exception of the parameter describing mass transfer
455 between the freeze-drying chamber and the condenser (k_m for the resistance model and β for
456 the binary gas transport model), which have different physical meanings.

457 Since the newly introduced equation is nonlinear and the vapor pressure in the chamber is
458 unknown *a priori*, the sublimation flux cannot be determined explicitly as in the resistance

459 version of the model.^[9] The vapor pressure in the chamber (P_{V1}) was considered as an
460 additional state variable and the corresponding mass balance equation in the freeze-drying
461 chamber was added to the existing set of differential equations:

462 Eq. 19
$$\frac{M_V V_1}{RT} \cdot \frac{dP_{V1}}{dt} = F_{V31} - F_V$$

463 Here V_1 is the freeze-drying chamber volume, F_V is the chamber to condenser vapor flux
464 given by Eq. 16 and F_{V31} is the sublimation vapor flux between the ice sublimation front
465 (location 3) and the freeze-drying chamber (location 1), given by:

466 Eq. 20
$$F_{V31} = \frac{1}{\frac{1}{k_{m34}} + \frac{1}{k_{m41}}} (P_{V3} - P_{V1})$$

467 where k_{m34} and k_{m41} are the mass transfer coefficients between the sublimation front and the
468 product top (location 4), and between the product top and the chamber, respectively. Thus,
469 both mass fluxes involved in Eq. 19 can be written explicitly in terms of known (fixed or
470 state) variables (P_{V1} , P_{V2} , and P_{V3}).

471 Note that in the original freeze-drying model vapor accumulation in the freeze-drying
472 chamber was neglected, based on a time scale analysis.^[9] This is formally equivalent to
473 setting the chamber volume $V_1 \approx 0$ in Eq. 19, which would thus become an algebraic instead
474 of a differential equation. This version of the model was also tested but not retained, due to
475 occasional failures in solving the equation set during parameter identification. Observed
476 difficulties are likely to be related to the specific differential-algebraic equations (DAE)
477 solver available in Matlab (ode15s) which had numerical problems with some sets of
478 parameters tested by the optimisation algorithm.

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572 Figure captions

573

574 Figure 1. Comparison between experimental measurements and simulations with the binary
575 gas transport and resistance models, for two experiments with lactic acid bacteria
576 suspensions (left panel 0°C/60Pa, right panel 25°C/20Pa). (A): Shelf and product
577 temperatures, (B): Total and vapour pressures, (C): Sublimation fluxes. Bold: shelf
578 temperature and total pressure, symbols: measurements, solid: binary gas model, dotted:
579 resistance model, vertical line: end of primary drying.

580

581 Figure 2. Variation of the effective mass transfer resistance with the vapor and total pressure.
582 Numeric values are for lactic acid bacteria suspension. Solid: binary gas model, bold: total
583 pressure 60Pa, thin: total pressure 20Pa, dotted: resistance model.

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585 Figure 3. Predicted vapor pressure as a function of the sublimation mass flux. Numeric values
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589 Figure 4. Apparent variation of the effective mass transfer resistance of the chamber to
590 condenser pathway as a function of the sublimation mass flux. Numeric values are for
591 lactic acid bacteria suspension. Solid: binary gas transport model, bold: total pressure
592 60Pa, thin: total pressure 20Pa, dotted: resistance model.

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596 Table 1. Chamber to condenser mass transfer resistance measured with pure ice.

597

Total chamber pressure (Pa)	Shelf temperature (°C)	Sublimation interface area (m ²)	Chamber to condenser resistance (10 ⁶ Pa s/kg)
10	0	0.074	0.65
20			1.29
40			2.64
60			3.72
40	-15	0.074	4.31
	0		2.64
	15		1.61
20	0	0.033	2.34
		0.074	1.29
		0.15	0.67

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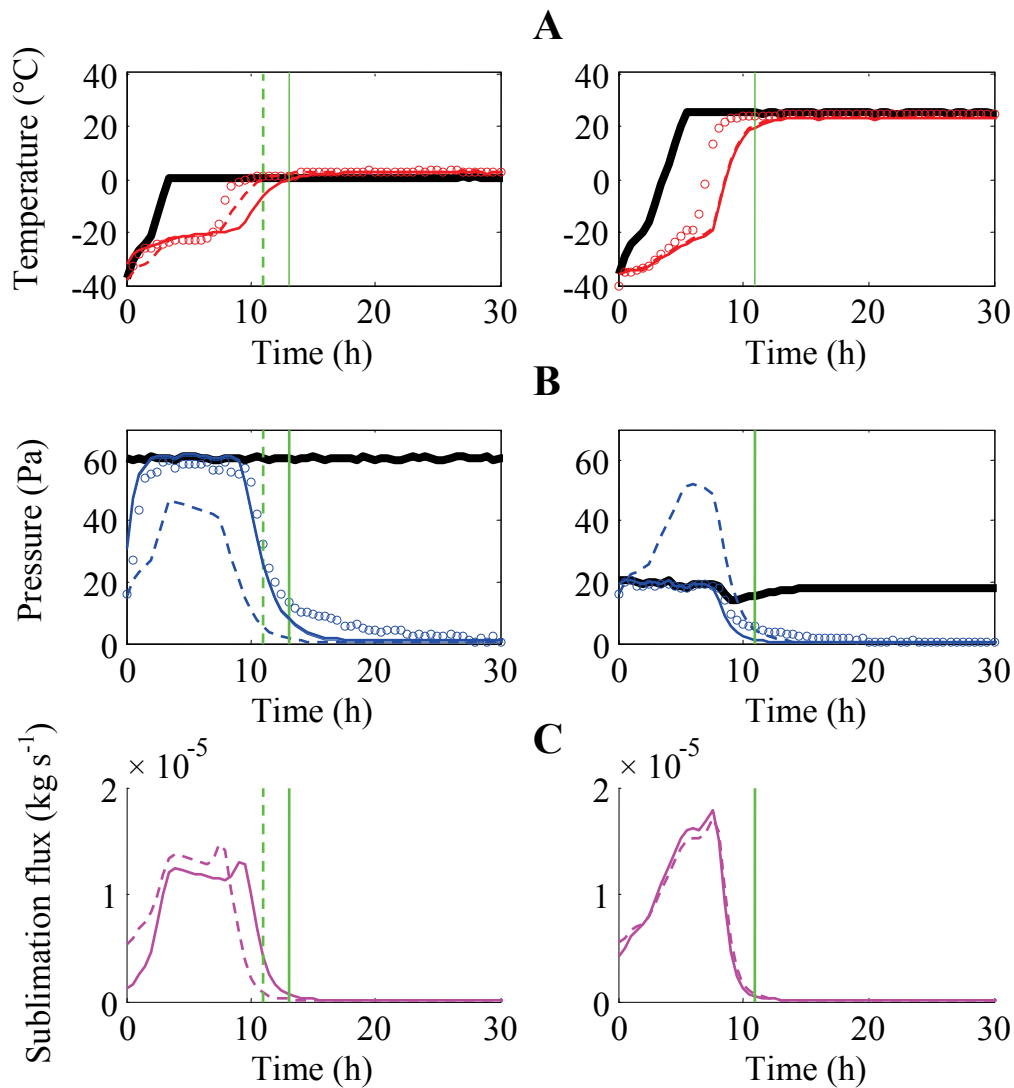
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600 Table 2. Values of the freeze-drying model parameters

<i>Parameters defined by the experimental setup</i>		
Number of trays (-)	1	
Sublimation area (m ²)	0.0745	
Mass of dry product (kg)	0.0736	
Mass of ice (kg)	0.3763	
Product height in the tray (m)	0.0067	
Volume of the freeze-drying chamber (m ³)	0.202	
<i>Parameters specific for the product formulation, determined in separate experiments^[25]</i>		
Sorption isotherm, wet basis (kg kg ⁻¹)	$\frac{0.3190a_w}{(1 - 0.9827a_w)(1 + 6.3668a_w)}$	
Characteristic desorption time (s)	10100	
Glass transition temperature of the frozen product (°C)	-36	
Glass transition temperature of the perfectly dry product (°C)	75.6	
Gordon-Taylor coefficient for glass transition temperature (-)	8.2	
<i>Heat and mass transfer parameters determined by model fitting</i>		
	<i>Mass transfer resistance model</i>	<i>Binary gas transport model</i>
Heat transfer coefficient by contact and radiation, between shelf and product bottom (W m ⁻² K ⁻¹)	6.74	7.29
Heat transfer coefficient by gas conduction, between shelf and product bottom (W m ⁻² K ⁻¹ Pa ⁻¹)	0.400	0.366
Heat conductivity between sublimation front and product top (W m ⁻¹ K ⁻¹)	0.0957	0.0996
Heat transfer coefficient between product top and chamber walls (W m ⁻² K ⁻¹)	3.79	3.03
Vapor conductivity between sublimation front and product top (kg s ⁻¹ m ⁻¹ Pa ⁻¹)	2.07×10 ⁻⁸	1.98×10 ⁻⁸
Vapor transfer coefficient between product top and chamber (kg s ⁻¹ m ⁻² Pa ⁻¹)	8.12×10 ⁻⁵	3.68×10 ⁻⁴
Vapor transfer coefficient between chamber and condenser k_m (kg s ⁻¹ Pa ⁻¹)	3.60×10 ⁻⁷	Not applicable
Vapor transfer parameter between chamber and condenser β (s kg ⁻¹ K ⁻¹)	Not applicable	2.66×10 ³
Residual frozen layer thickness for gradual transition between primary and secondary drying (m)	0.00173	0.00170
Effective chamber wall temperature (°C)	15.3	13.9

601 Complete model equations and exact definitions of the model parameters are given in ref.^[9]

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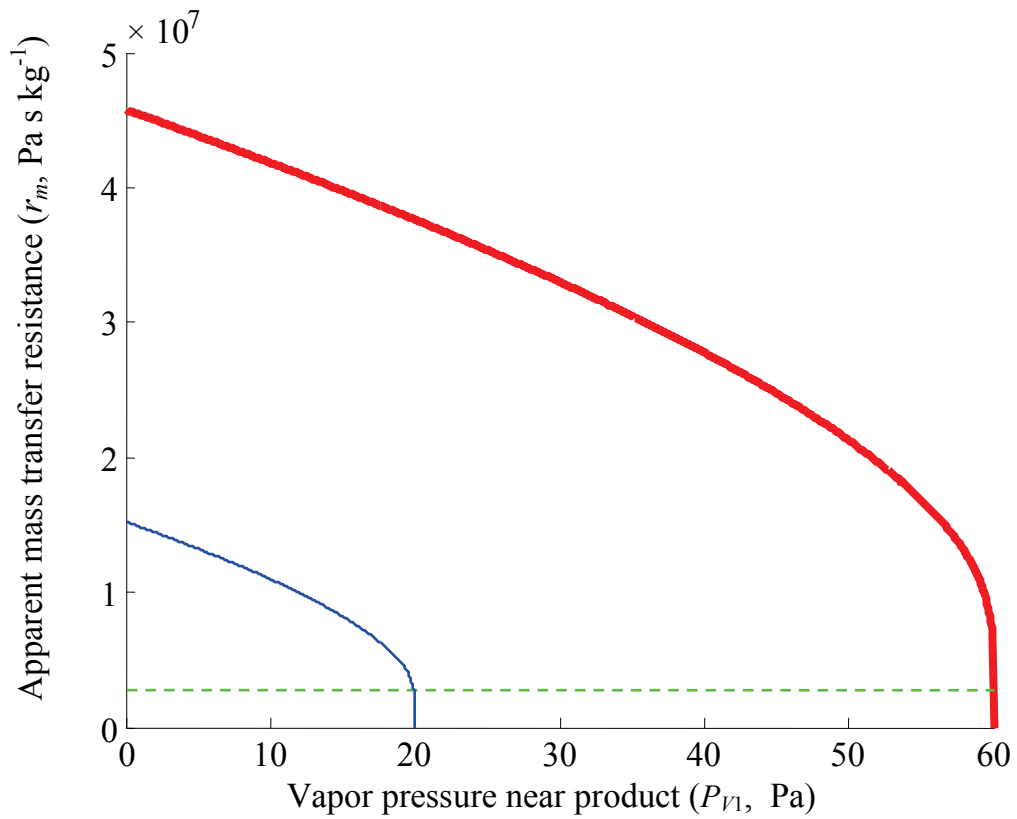
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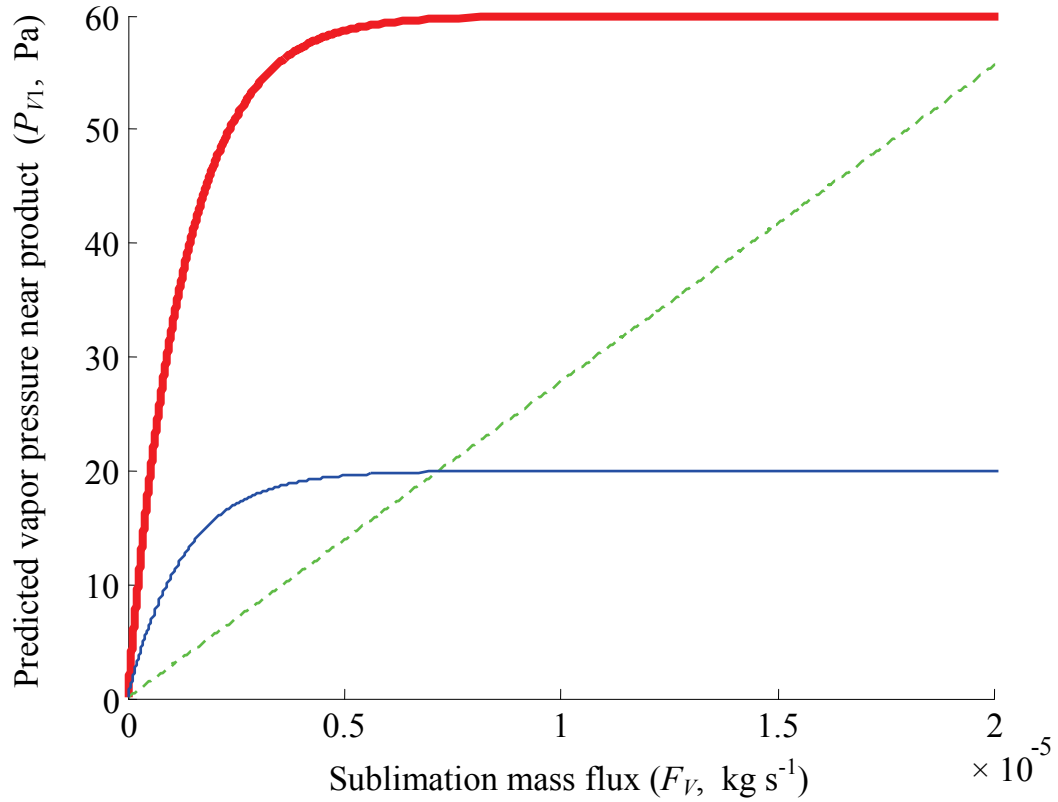
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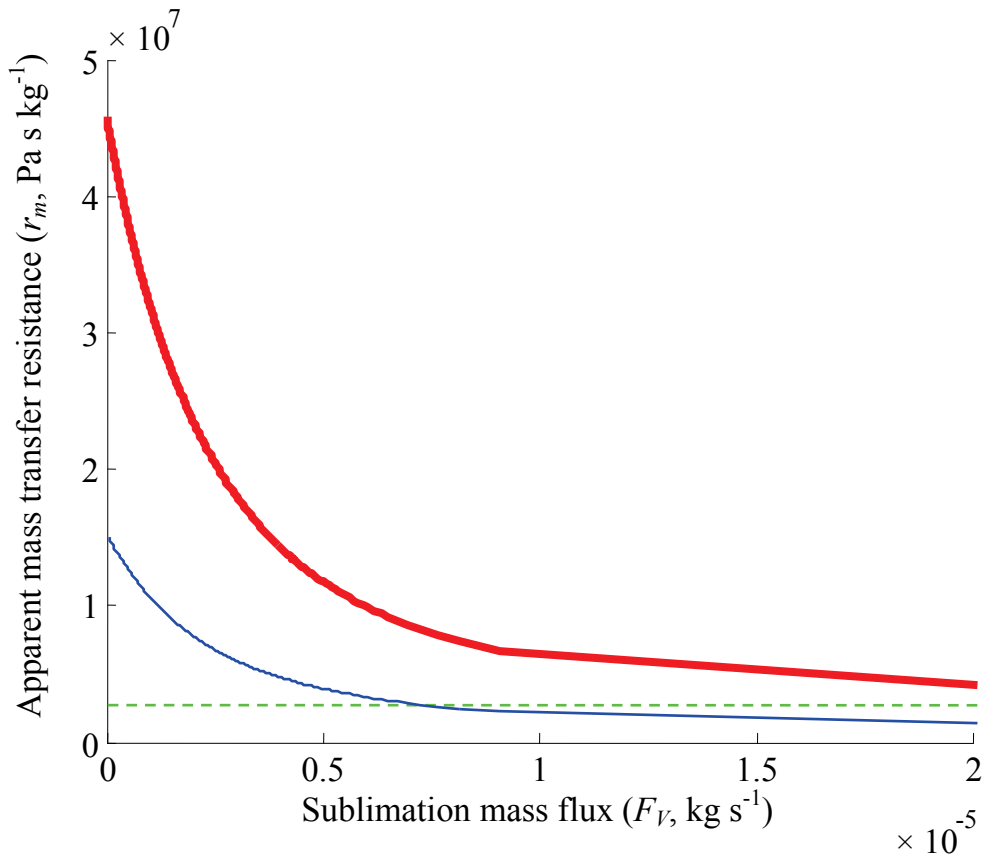
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