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Context

The liver is the most frequent site of colorectal cancer (CRC) metastases. The vascular endothelial growth factor (VEGF) pathway plays a critical role in mediating angiogenesis. Clinical efficiency of anti-VEGF bevacizumab (Avastin®), has been demonstrated in the treatment of solid tumours in association with classical chemotherapy.¹ Contrast-enhanced ultrasound (CEUS) can be used for imaging the vascular network² and thus evaluate the influence of anti-angiogenic treatments on the progression of vascularisation in hepatic metastases.³ However, this assessment is limited due to its high inter-occasion and inter-operator variability.

Objectives

- Building a mechanistic model of metastatic liver CEUS using population compartmental analysis
- Investigating the relationship between initial metastasis vascularisation quantification and survival of mCRC patients treated with bevacizumab.

Patients and Materials

STIC-Avastin was a French multicenter non-comparative, prospective, open-label, observational study (NCT00489697).⁴ Previously untreated metastatic CRC patients received four cycles of bevacizumab 5 mg/kg intravenously every 2 weeks in combination with chemotherapy. CEUS imaging were performed at inclusion for 103 patients. For each CEUS, 34 to 112 intensity measurement over time were available for metastasis and reference tissue regions of interest (ROI).

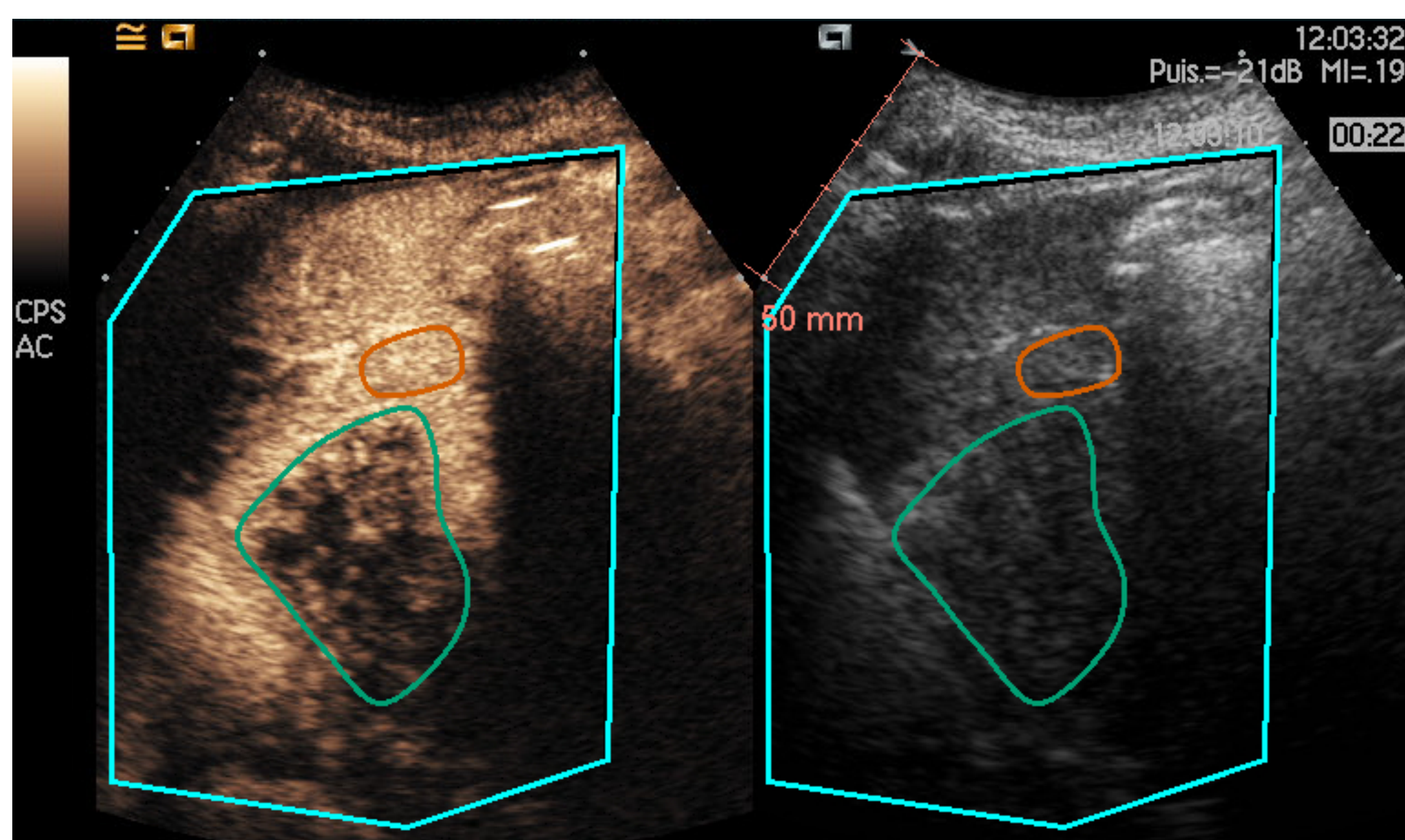
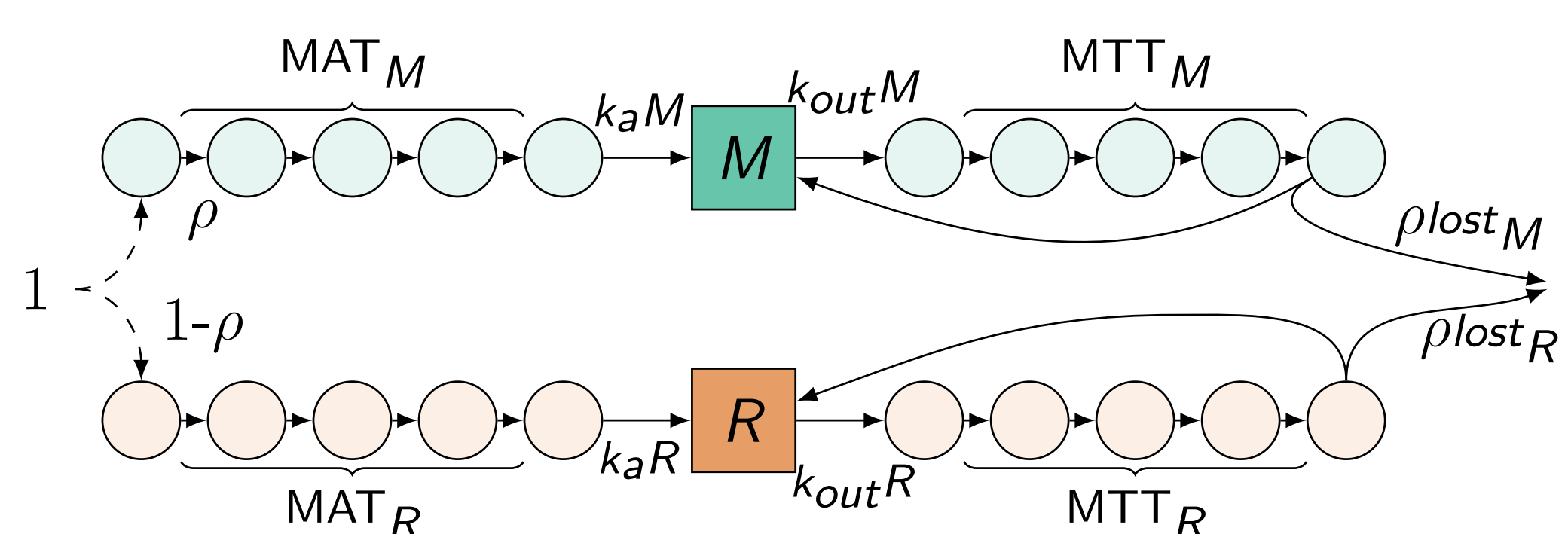


Figure 1. Contrast-enhanced (left) and mode B (right) liver echography. Intensity is measured in metastasis (green) and reference (orange) tissue.

Model



Fitting

The model describes two observation compartments M and R, representing metastasis and reference tissue ROIs, respectively. For each observation compartment, a proportion of the relative dose of contrast agent is absorbed by a chain of transit compartments (MAT: mean absorption time) and partly redistributed by a second chains of transit compartments (MTT mean transit time) with a lost proportion.

Table 1. Population parameters: All parameters were correctly estimated. *Normal and **Probit distributions.

The model describes correctly the high inter-individual variability of the data. The estimation of scale parameters allowed comparing the dynamics of different CEUS from different centers.

Results

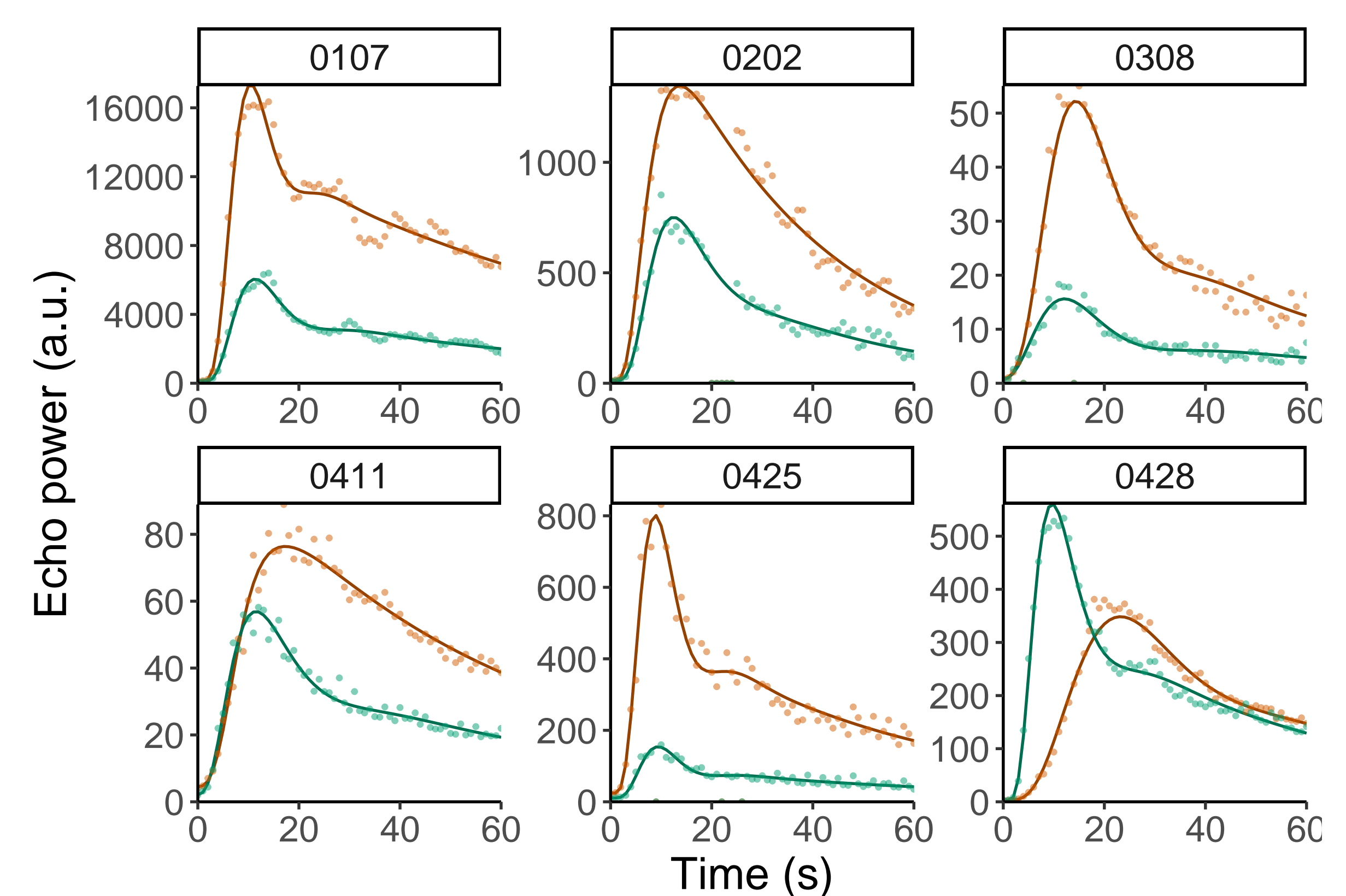


Figure 2. Observed (dots) and model predicted (lines) echographic power over time in metastasis (green) and reference (orange) tissue, for 6 patients.

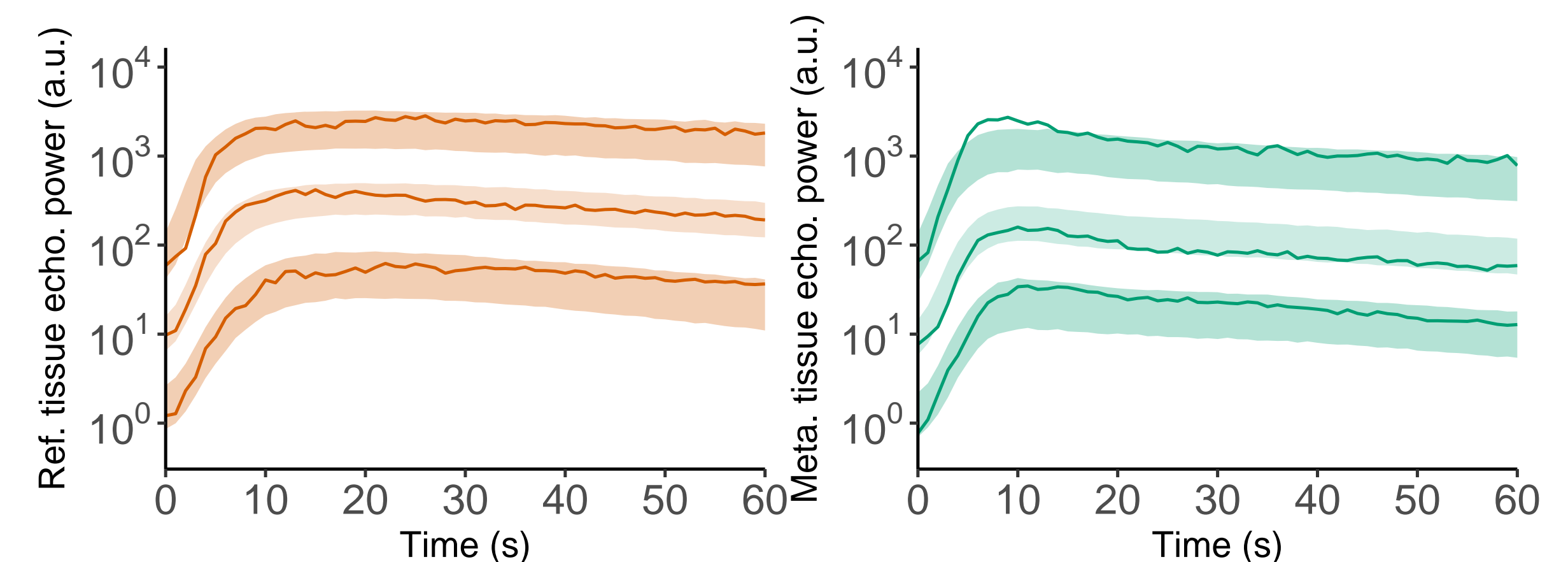
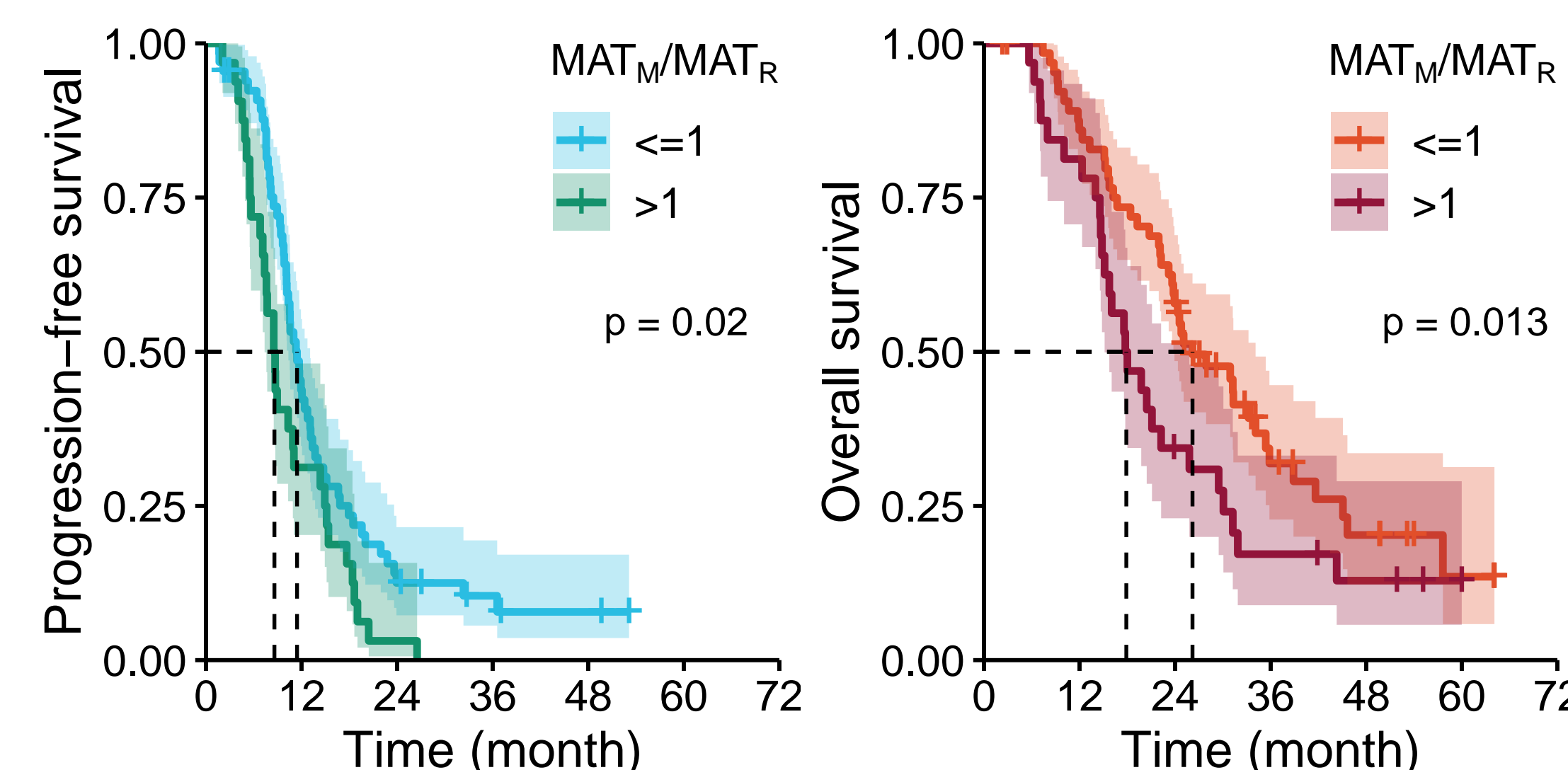


Figure 3. Visual predictive check: 10th, 50th and 90th empirical (lines) and theoretical (level of 90%) percentiles.

Survival analysis



Influences of M/R parameters ratios were tested against progression-free (PFS) and overall (OS) survivals. Patients with higher MAT_M than MAT_R before treatment had a significant poorer PFS and poorer OS.

Conclusions and perspectives

Population compartmental analysis of CEUS gives robust and cross-centre estimation of metastatic vascularisation dynamics. This allows to identify CRC patients with excessive metastatic vascularisation who would derive more benefit from an anti-VEGF treatment.

This quantification can be tested as early predictor of clinical efficacy of anti-angiogenic treatments in mCRC, which should be evaluated further in upcoming clinical trials.

References

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- [4] Caulet *et al.* 2016. Bevacizumab pharmacokinetics influence overall and progression-free survival in metastatic colorectal cancer patients. Clin. Pharmacokinet.