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Towards Quantitative Imaging Biomarkers of Tumor Dissemination: a Multi-scale Parametric Modeling of Multiple Myeloma

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Abstract

The advent of medical imaging and automatic image analysis will bring the full quantitative assessment of lesions and tumor burden at every clinical examination within reach. This opens avenues for the development and testing of functional disease models, as well as their use in the clinical practice for personalized medicine. In this paper, we introduce a Bayesian statistical framework, based on mixed-effects models, to quantitatively test and learn functional disease models at different scales, on population longitudinal data. We also derive an effective mathematical model for the crossover between initially detected lesions and tumor dissemination. We finally propose to leverage this descriptive disease progression model into model-aware biomarkers for personalized risk-assessment, taking all available examinations and relevant covariates into account. As a use case, we study Multiple Myeloma, a disseminated plasma cell cancer, in which proper diagnostics is essential, to differentiate frequent precursor state without end-organ damage from the rapidly developing disease requiring therapy. After learning the best biological models for local lesion growth and global tumor burden evolution on clinical data, and computing corresponding population priors, we use individual model parameters as biomarkers, and can study them systematically for correlation with external covariates, such as sex or location of the lesion. On our cohort of 63 patients with smoldering Multiple Myeloma, we show that they perform substantially better than other radiological criteria, to predict progression into symptomatic Multiple Myeloma. Our study paves the way for modeling disease progression patterns for Multiple Myeloma, but also for other metastatic and disseminated tumor growth processes, and for analyzing large longitudinal image data sets acquired in oncological imaging. Our study deserves being validated on larger cohorts to establish its role in clinical decision making.

1. Introduction

Medical imaging of tumorous lesions is a means of choice for staging and monitoring patients with cancer. It enables early detection through population screening, permits to evaluate the growth of precursor lesions and assess qualitative and quantitative changes after clinical intervention (Fass, 2008). Although most imaging modalities allow for a volumetric quantification of lesions, current guidelines, like the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009), are based on the manual assessment of the diametric size of a few le-

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sions, for the sake of time, even if a large field of view image scan would have the potential to offer more and better information. To alleviate this problem, many tools for the automatic detection and segmentation of lesions are now becoming available for example in Positron Emission Tomography (Xu et al., 2017; Bieth et al., 2018) but also in Magnetic Resonance Imaging (MRI) (Kamnitsas et al., 2016) and Computer Tomography (CT) (Christ et al., 2016), due in particular to the advent of deep learning techniques in the medical imaging realm. They will bring the full quantitive assessment of individual tumorous lesions and whole tumor burden, at each medical examination, within reach. This raises the question of how to properly analyze these data, both focusing on static and dynamical properties.

Numerous theoretical models of cancer evolution have been developed, grasping some of the complexity of the biological processes at stake, both for general aspects or more specific to a particular pathology. Descriptive models have in particular been derived for single lesions (Simeoni et al., 2004; Ayati et al., 2010; Herman et al., 2011; Gerlee, 2013; Benzekry et al., 2014; Murphy et al., 2016) as well as for the distribution of disseminated tumors (Iwata et al., 2000; Baratchart et al., 2015). But those are in general not well tested, due to the lack of observations at the right scale, or to the rarity of fully quantitative population datasets. Furthermore, the models describe different modes of disease propagation, and the crossover between different scales and regimes has been very little studied. In this paper, we establish a novel scale-transient approach, fusing local and global tumor growth models, at the onset of disease dissemination. We show how one can deal with different local growth patterns of lesions and analyze their dissemination in order to model the tumor load. We embed those descriptive models into a probabilistic framework, to deal with inference from observed data, and use that framework to compare different model options and therefore learn the local and global tumor growth models. We will finally show that this functional-statistical modeling approach can be used to extract model-based biomarkers, e.g. for patient stratification, that could ultimately serve as an objective tool for clinical evaluation.

We consider Multiple Myeloma (MM) as a case study, see box 'Driving clinical problem'. MM displays a rapid development once the disease is manifest, but in the precursor phases of the disease, without myeloma related organ or tissue impairment, tumorous lesions and the tumor load are monitored via whole-body imaging over long time spans (Dimopoulos et al., 2015), alongside with serological and histological factors. It is therefore a typical example where proper image-based diagnosis and risk-assessment in the precursor states are crucial for making treatment decision (Ghobrial and Landgren, 2014; Ahn et al., 2015; van de Donk et al., 2016). This is posing hard problems in terms of analysis, and makes it a reference problem for empirical tumor growth modeling in disseminated diseases (Ghobrial, 2012). Our study will permit to validate key assumptions for the biological models at the organ and tissue level (Ayati et al., 2010) and for the dissemination process (Iwata et al., 2000), for the first time in a human population study.

2. Methods

Data-based tumor growth and disease progression modeling can be difficult, because available data are typically very limited in time. In particular, understanding free lesion growth, a cornerstone, is impeded by the occurrence of therapy, which usually begins soon after diagnosis. Animal models can help in that respect (Mehrara and Forssell-aronsson, 2014; Baratchart et al., 2015). But even with rather long time series, distinguishing between different growth models by individual curve fitting is very delicate (Murphy et al., 2016). Here we rely on microscopic biological models and translate them into clinically relevant observables: local lesion volumes and the tumor load. We propose a method to analyze longitudinal image time series of a population, in a hierarchical Bayesian framework (Ribba et al., 2012), both for lesion growth and tumor dissemination process. We also introduce covariates in a mixed-effect model (Lavielle, 2015), enabling statistical relevance tests of possible influential factors on the growth process.

2.1. Modeling approach

We analyze longitudinal data of a cohort of patients, as illustrated in Fig 1. At each observation time point, relevant features of all detectable lesions have been extracted, and used to compute the patient's tumor load, as detailed in Sec. 2.2. Local lesions were also re-identified in follow-up scans, in order to gather a database of lesion growth time series.

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The functional-statistical modeling approach is schematically presented in Fig 2. In Sec. 2.3, we introduce our multi-scale mathematical modeling of disease progression. We first propose several biophysical models for the local lesion growth [$V(t|r, v_0)$, blue boxes in Fig 2], corresponding to different scenarii at the microscopic scale (Simeoni et al., 2004; Ayati et al., 2010; Gerlee, 2013; Benzekry et al., 2014; Murphy et al., 2016). We also propose an effective model for the crossover from the single-lesion regime to the dissemination regime [$V_{\text{tot}}(t|R, V_0)$, green box in Fig 2], which builds on the local lesion growth model, as well as on the IKS model, a model for the dissemination process (Iwata et al., 2000).

Another necessary component to compare models with measurements, is the probabilistic model, which encodes how observations are generated from the predictive model [yellow boxes in Fig 2]. As detailed in 'Supplementary Method 1', we rely on mixed-effects models (Lavielle, 2015), that are adapted to population-based tumor growth modeling (Bastogne et al., 2010; Ribba et al., 2012; Hartung et al., 2014; Baratchart et al., 2015). We use a proportional error model, to account for a measurement error that increases with the size of the lesion, see Eq. (1) of 'Supplementary Method 1'. We also use log-normal population priors for the model parameters, $\theta \in \{r, v_0\}$ for the lesion growth and $\theta \in \{R, V_0\}$ for the tumor load, which we parametrize as $\log(\theta_j) = \log(\theta_{\text{pop}}) + \eta_j$ with $\eta_j \sim \mathcal{N}(0, \omega_\theta)$, such that θ_{pop} is the median value. Population priors permit to increase the statistical confidence on shorter time series, and to incorporate covariates into the predictive model. In the case of categorical covariates, we define a $\theta_{\text{pop},k}$ for each group k, and $\xi_k = \log(\theta_{\text{pop},k}) - \log(\theta_{\text{pop},0})$, where $k = 0$ is the reference group, as in Eq. (3) of 'Supplementary Method 1'.

The confrontation of each mathematical model with the corresponding dataset, and the estimation of the unknown model parameters, is made via the Stochastic Approximation of Expectation Maximization (SAEM) algorithm (Delyon et al., 1999; Kuhn and Lavielle, 2004; Samson et al., 2007) [gray arrows in Fig 2] introduced in 'Supplementary Method 2'. It learns the population parameters from the data. To quantify the accuracy of the predictive model on the observed data, we compute the log-likelihood (LLH). Model comparison is then performed thanks to the Bayesian and Akaike Information Criteria (BIC and AIC) and assessed with bootstrapping. Covariates are further tested with the Wald and Likelihood ratio (LR) tests, see 'Supplementary Method 3'. From the selected model and corresponding population priors, the individual parameters of a time series can be computed with a Maximum a posteriori (MAP) estimator [black arrow in Fig 2], cf 'Supplementary Method 2'. We propose to use them as biomarkers, and for SMM patients, we explicitly use the tumor load growth rate. Its power for risk-stratification is assessed with Receiver Operating Characteristic curves (Zweig and Campbell, 1993), Kaplan-Meier survival plots (Kaplan and Meier, 1958) and log-rank tests (Peto et al., 1977), as presented in 'Supplementary Method 4'.

2.2. *Tumor imaging data*

Our datasets result from the analysis of a large cohort of 63 SMM patients from the University Hospital of Heidelberg and the German Cancer Research Center, that both follow the same protocol for imaging and treatment decisions. We focus on the MRI modalities, which directly image focal lesions and the tumor load and is used to detect rapid progression to MM (Ghobrial and Landgren, 2014), whereas lytic bone lesions only appear at a later stage on CT scans. Our work follows a study for volumetry based biomarkers (Wennmann et al., 2018) in whole-body MRI scans. We use the same cohort and additionally analyzed all non whole-body scans that were available for those patients. In total, over 370 MR volumes were analyzed, with a median time interval of 1.1 years between scans, and a median patient follow-up time of 5.9 years. All detectable focal lesions were manually volumetrized, as illustrated on a T1-weighted sequence in Fig. 3, and tracked in time, as sketched in Fig 1, before the occurrence of the CRAB criteria or any systemic therapy. The manual volumetrization was performed by a research assistant with medical training, under the supervision of an experienced musculoskeletal radiology resident. When both T1- and T2-weighted sequences were available, the latter with fat suppression, the volume of the lesion was quantified in both modalities and averaged as in Ref. (Wennmann et al., 2018). This resulted in the detection of 180 lesions in 33 patients, each being observed at 2.19 different time points on average (8 time points for the longest observation).

Focal lesions series. Among those focal lesions, 49 were detected at 3 or more different points in time. 36 of this subset originate from 11 male patients (M), and the 13

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others from 8 female patients (F). The location of the tumor was also recorded and classified into 13 different anatomical regions (see 'Supplementary Table 1'). Those 49 series constitute the first dataset, with 3.96 time points per series on average, which is used for lesion growth modeling.

Tumor load series. We also derived the total tumor load for each patient, by summing up the volume of all detected lesions at each time point. In rare cases, focal lesions became too diffuse to be properly segmented or were targeted by a local therapy, like radiotherapy. As the tumor load is not expected to decrease in the absence of therapy, if a tumor had already been detected but could not be segmented, we filled-in the data with its last measured volume. Selecting the series with 3 or more time points, we constitute a dataset of 21 patient series (13M and 8F) bearing 1 to 16 tumors (median of 4) with an average of 4.48 time points per series and a median total observation time of 3.7 years. The analysis of those tumor load series is used for tumor load modeling.

Progression to MM. For the 26 patients with focal lesion measurements on at least two different time points, we create a tumor load dataset, as above, that we complement with the date of transition to the progressive state of MM, as defined by the CRAB-criteria from the IMWG (International Myeloma Working Group, 2003), the standard procedure until 2014. If the transition did not occur, the data is censored with the date of the last information about the patient. We use this dataset for a risk-analysis of SMM patients with focal lesions, comparing different radiological biomarkers.

2.3. Mathematical parametric models

The central elements of our modeling approach are descriptive functional models. We base our analysis on existing microscopic models of tumor and lesion growth in general (Simeoni et al., 2004; Gerlee, 2013; Benzekry et al., 2014; Murphy et al., 2016), as well as specific models for MM (Ayati et al., 2010; Herman et al., 2011), and for the dissemination process (Iwata et al., 2000). We aim at deriving tractable models of disseminative disease in a joint framework, and our approach is summarized in box 'Descriptive tumor load model'.

2.3.1. Lesion growth models

The lowest scale of our modeling approach is given by individual tumors, also called focal lesions in MM. In this paper we assume that all lesions follow the same parametric growth model, i.e. that the involved biological processes are the same. This is reasonable as the lesions are all developing in the bone marrow. But different lesions potentially have different parameters, e.g. initial volume and growth rate, that may depend, for example, on the local environment of the lesion (Kumar et al., 2017) as well as its subclonal mutation status (Rasche et al., 2017). We introduce below several general tumor growth models, which are biologically founded (Simeoni et al., 2004; Gerlee, 2013; Benzekry et al., 2014; Murphy et al., 2016), as well as a more specific one for the microscopic biology of MM focal lesions (Ayati et al., 2010), which we interpret at the macroscopic scale of interest. All models are later confronted with observations.

Linear growth. We first introduce the linear growth model, in which the volume of a lesion can be written as:

$$V(t) = v_0\,(r\,t + 1)\ , \tag{1}$$

where v_0 is the initial volume and r the growth rate, e.g. in month^{-1}. This simple model corresponds to a constant rate growth, and holds at the later stage of tumor growth in some cases (Simeoni et al., 2004; Benzekry et al., 2014; Murphy et al., 2016).

Cubic growth. A cubic growth corresponds to a rate of change of the volume proportional to the surface area of the tumor itself, in a spherical approximation, $\frac{\mathrm{d}V}{\mathrm{d}t} \propto V^{2/3}$, and reads

$$V(t) = v_0\,(r\,t + 1)^3\ . \tag{2}$$

This assumes that only the surface of the tumor is actively participating in the growth, which is justified in the case of a solid tumor eroding its environment at its border (Herman et al., 2011; Gerlee, 2013; Murphy et al., 2016), representing a plausible model for lytic bone lesions.

Exponential growth. Another important tumor growth model is the exponential growth,

$$V(t) = v_0 \exp(r\,t)\,. \tag{3}$$

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It corresponds to a volumic rate of change proportional to the volume, $\frac{\mathrm{d}V}{\mathrm{d}t} = rV(t)$. It therefore assumes that all cells of the tumor participate in its growth in the same manner, and typically holds in the early stages of tumor development (Gerlee, 2013; Benzekry et al., 2014; Murphy et al., 2016).

Diffusive growth. Ayati *et al.*, have derived in Ref. (Ayati et al., 2010) a mathematical model for bone remodeling and lesion growth in MM. Their modeling is based on a diffusion equation with a Gompertz-like saturation term for the local tumor density. In 'Supplementary Method 5', we show that it can be reduced to a two-parameters growth model for the tumor volume,

$$V(t) = v_0(r\,t + 1)^{3/2}\,, \tag{4}$$

which corresponds to a half-cubic growth law, lying between the linear and cubic growth. Such a growth law can also be justified by advanced considerations on the fractal nature of the tumor vasculature (Herman et al., 2011; Benzekry et al., 2014).

Those models, Eqs. (1)-(4), comprise two free parameters each, v_0 and r, which have a clear biophysical interpretation. There exists more involved models describing individual tumor growth with three parameters, for example the Gompertz and the van Bertalanffy models (Gerlee, 2013). Even more complex, are the models from Refs.(Herman et al., 2011) and (Ribba et al., 2012), which consider metabolic processes in details, but result in a high number of free parameters. For the sake of simplicity, and to avoid overfitting, given the limited length of the available time series, we restricted ourselves to the above models with two free parameters.

2.3.2. *Tumor load models*

The tumor load is obtained by summing up the volumes of all tumors detected in one patient, $V_{\mathrm{tot}} = \sum_{\mathrm{lesions}\,\ell} V_\ell$. We now consider how the local lesion growth models introduced above translate to this global scale. Let us distinguish between the volume of the putative initial lesion, V_{init}, which is the largest detected lesion at first observation time, and the volume of all subsequent disseminated lesions, V_{diss}:

$$V_{\mathrm{tot}}(t) = V_{\mathrm{init}}(t) + V_{\mathrm{diss}}(t)\,. \tag{5}$$

Note that we single out the first detectable lesion for modeling purposes, but this does not necessarily mean that it is the strict origin of the cancer. In the following, we simplify MM complex biology and assume that the cancer propagates from this leading cluster of cancerous cells, which grows and emits malignant cells, at a rate which depends on its size. Those in turn have a chance to settle in other locations, and give rise to further cell-emitting growing clusters, gradually making up the disseminated burden.

Early regime: initial lesion dominated. In the early stages of the disease, the initial cluster of malignant cells is the most prominent one and the disseminated burden V_{diss} can be neglected, such that

$$V_{\mathrm{tot}}(t) \sim V_{\mathrm{init}}(t)\,. \tag{6}$$

In that case, the tumor load growth model is the same as the lesion growth model in Eqs. (1)-(4).

Later regime: dissemination dominated. The Iwata-Kawasaki- Shigesada (IKS) mathematical model (Iwata et al., 2000) for metastasis formation seems particularly well suited to describe the evolution of MM. It assumes that growing tumors emit malignant cells at a rate proportional to the fraction of tumors cells in contact with blood vessels $w(v) = mv^\alpha$, where v is the volume of the tumor and α a fractal dimension related to the vascularization of the tumor. Similarly as above, α would be equal to 1 if the whole tumor volume can emit malignant cells, and $\alpha = 2/3$ if only the surface of a round-shaped tumor can emit malignant cells. Emitted malignant cells can develop into new lesions far away from the original site, which will grow following the same tumor model, and emit further malignant cells. Note that the model assumes that each lesion grows with the same parameters, which is not strictly the case, as they depend on the lesion's microenvironment and its subclonal mutation status status (Kumar et al., 2017; Rasche et al., 2017). However, as extra-medullar dissemination is rare in SMM, their growth conditions should be more homogeneous than in multi-organ metastasis.

In 'Supplementary Method 6' we present the IKS model and its solutions, as derived in Refs. (Iwata et al., 2000; Struckmeier, 2003; Evys et al., 2009). For the different tumor growth models described above, the number of disseminated lesions $N_{\mathrm{diss}}(t)$ and the disseminated burden $V_{\mathrm{diss}}(t)$ display an exponential asymptotic behaviour. Such

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that, as soon as the volume of the initial lesion becomes negligeable, we expect

$$V_{\text{tot}}(t) \sim V_{\text{diss}}(t) \sim_{t\to\infty} V_0 e^{Rt} \,. \tag{7}$$

Crossover regime: effective modeling. In the crossover regime, neither of the terms of Eq. (5) is negligeable. In the cases where $V_{\text{init}}(t)$ follows a power-law, [Eqs. (1), (2) and (4)], $V_{\text{tot}}(t)$ will effectively appear as a power-law with a higher power than $V_{\text{init}}(t)$, due to the exponential behaviour of $V_{\text{diss}}(t)$. We therefore propose the effective model

$$V_{\text{tot}}(t) = V_0\,(Rt+1)^B \,. \tag{8}$$

3. Results

In this section, we present the multi-scale modeling of disease progression in the SMM state. We compare several biologically-founded models for the growth of individual lesions, as well as for the tumor load, by confronting them with the datasets. We also carry out an analysis of the influence of the patient's sex and lesion location on the growth rate. We finally propose to consider the extracted parameters as model-based biomarkers, and we assess their predictive power for the transition to MM.

3.1. Modeling local lesion growth

Model:	no covariate	M/F cov. for r
Linear	2951.89 (0.12)	2952.99 (0.13)
Cubic	2954.65 (0.17)	2956.99 (0.19)
Exponential	2974.77 (0.22)	2976.85 (0.21)
Diffusive	2950.33 (0.17)	2952.96 (0.17)

Table 1: BIC values for different lesion growth models, in two mixed-effects models: without covariate (first column) and with the patient's sex as a covariate for r (second column).

Lesion growth model. Using the focal lesions dataset, we estimate the population parameters of a mixed-effect model without covariate, as presented in Sec. 2.1 with the different growth models introduced above, using SAEM. We compare a linear, a cubic, an exponential and a diffusive growth model [Eqs. (1)-(4)]. From the first column of Table 1, which presents the resulting BIC values for each model, we conclude that the diffusive growth model is selected, as it has the lowest BIC. It gives slightly better results than the linear and the cubic models (mean BIC separated by 5 resp. 13 confidence intervals), and much better than the exponential growth model. The learned population parameters for the diffusive model are $r_{\text{pop}} = 3.2(0.9) \times 10^{-2}$ month^{-1} and $v_{0,\text{pop}} = 393(72)$ mm^3, associated with the error parameter $b = 0.24(0.02)$, where the number between brackets is the standard deviation estimated from the Fisher information matrix. The predictions from the diffusive model are shown in Fig 4 for two patients, and further lesion time series are presented in 'Supplementary Figure 1'.

To assess the robustness and the generalizability of our model selection, we use a bootstrapping approach to resample our dataset, and compare the two best models selected above. Due to the difficulty of resampling observations when doing regression (Davison and Hinkley, 2013), we use case bootstrapping to preserve inter-series variability (Thai et al., 2014). We therefore create bootstrapped sample datasets by resampling individual tumor time series. Following Ref. (de Graft Acquah, 2012), we then repeat the model selection procedure on the two best performing models for each sample, and report the selection rate of each model (i.e. how often a model is ranked first according to the BIC):

Samples:	Diffusive (no cov.)	Linear (no cov.)
full dataset	1	0
10 samples	0.75	0.25
20 samples	0.775	0.225

The diffusive model is therefore selected for more than 3/4 of the bootstrapped samples, which confirms its selection.

Subgroup analysis. The statistical model introduced above allows for the introduction of covariates, as in Eq. (3) of 'Supplementary Method 1'. We introduce the sex of the patient (M/F) as a categorical covariate for the parameter r. For each of the four growth models, SAEM converges to prior distributions that correspond to a lower median growth rates r for women than men (i.e. $r_{\text{pop,F}} < r_{\text{pop,M}}$). With the diffusive model, we find $\xi_{\text{M}} = 0.664(0.59)$ with $\xi_{\text{F}} = 0$, which corresponds to a factor 1.9 for the ratio of the median rates. We also find that the LLH is improved compared to the no covariate case. However, the improvement is not large enough to compensate for the introduction of

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the extra model-parameter ξ_M, and the BIC does not improve, as can be seen from the second column of Table 1. In 'Supplementary Table 2', we report the AIC values for the same experiments. Using this less stringent criterion for model selection would select the M/F covariate split for some of the growth models. To lift this ambiguity, we proceed to the Wald and LR tests

Model:	Wald (p-value)	LR (p-value)
Linear	✗ (0.089)	✗ (0.0949)
Diffusive	✗ (0.26)	✗ (0.2617)

Using the threshold $p = 0.05$ on the p-values, both the Wald and the LR tests reject the covariate model. Thus using the sex as a covariate does not bring a statistically significant improvement for inferring the lesion growth rates.

Our model also permits to introduce multiclass categorical covariates, such as the lesion location categories presented in 'Supplementary Table 1'. In 'Supplementary Table 3', we illustrate this and test for the significance of this covariate. We find an indication that focal lesions might grow slower in long bones (humerus, femur and tibia), but the limited amount of data does not permit to draw clear conclusions.

3.2. *Modeling global tumor load*

Model:	no covariate	M/F cov. for R
Diffusive $B = 3/2$	1757.92 (0.13)	1755.52 (0.12)
IKS (exponential)	1745.42 (0.16)	1742.09 (0.12)
Power-law $B = 3$	1744.15 (0.14)	1741.40 (0.23)
Power-law $B = 6.5$	1741.30 (0.18)	1738.19 (0.11)

Table 2: BIC values for different tumor load growth models, in two mixed-effect models: without covariate (first column) and with the patient's sex as a covariate for R (second column).

Tumor load effective model. Using SAEM, we estimate the population parameters of a mixed-effect model without covariate, as presented in Sec. 2.1, with the different growth models introduced above [Eqs. (6)-(8)]. We test the diffusive model, which was selected for the lesion growth in the previous section, and should therefore hold at short times, together with the IKS model, which should hold when the dissemination process dominates and different power-laws for the crossover regime, with $B > 3/2$.

The resulting BIC values are presented in the first column of Table 2. We find that the IKS model performs much better than the diffusive model (mean BIC separated by 40 confidence intervals), confirming that the dissemination process plays a great role in the tumor load evolution. However, power-law models with $B \geq 3$, lead to further improved values of the BIC (mean BIC improved by 8 confidence intervals for $B = 6.5$), indicating that we are in the crossover regime. In 'Supplementary Table 4', we systematically look for the most appropriate effective model, and compare BIC values for different values of B. This selects $B = 6.5$ as the best effective model for this dataset.

Subgroup analysis. We now use the sex of the patient as a categorical covariate for the growth rate R, as in Eq. (3) of 'Supplementary Method 1'. The introduction of this additional population parameter permits to improve the BIC for each parametric model (see second column of Table 2), indicating that the patient's sex is relevant for modeling the evolution of the tumor load. We further proceed to the Wald and LR tests for the three best performing models

Model:	Wald (p-value)	LR (p-value)
IKS (exponential)	✓ (0.008)	✓ (0.0116)
Power-law $B = 3$	✓ (0.012)	✓ (0.0160)
Power-law $B = 6.5$	✓ (0.0074)	✓ (0.0131)

The Wald and the LR test p-values are all smaller than 5%, such that the covariate model is selected in all cases. The sex is thus a relevant covariate for the tumor load growth rate R, and in each model, we find $R_{\text{pop,F}} < R_{\text{pop,M}}$. For the power-law with $B = 6.5$, we report $R_{\text{pop,F}} = 2.9(1.3) \times 10^{-3}$ month^{-1} and $\xi_M = 1.47(0.55)$, such that the median of the male population, $R_{\text{pop,M}} = R_{\text{pop,F}} \times e^{\xi_M} = 12.6(5.7) \times 10^{-3}$ month^{-1}, is four times as high. Those prior distributions are presented with the individual infered values in box 'Tumor load modeling in SMM'. We also find $V_{0,\text{pop}} = 1350(500)$ mm^3, associated with the error parameter $b = 0.281(0.027)$. The predictions from this model are shown in Fig. 5 for two patients, together with the initial lesion. Predictions for the whole cohort are displayed in 'Supplementary Figure 2'. Further introducing the sex as a covariate for the initial volume V_0 or for ω_R, does not improve the BIC further, and gives negative Wald and LR tests, consistently over all growth models.

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To assess the robustness of our model selection, we repeat the bootstrapping strategy from above and create bootstrapped samples, by resampling the tumor load time series. We repeat the model selection procedure, for each sample, and report the selection rate of each model, for the three best-candidates and using M/F as a covariate:

Samples:	Power-law $B = 3$	Power-law $B = 6.5$	IKS (exponential)
full dataset	0	1	0
10 samples	0.25	0.65	0.1
20 samples	0.225	0.575	0.2

We see that the power-law model with $B = 6.5$ is selected in more than 50% of the cases, confirming our effective modeling approach for the crossover regime.

Dissemination. As a further check, we carried out in 'Supplementary Table 5' a similar model selection analysis, applied to $N_{\text{diss}}(t)$, the number of disseminated lesions. The IKS model directly models the distribution of disseminated lesions and we indeed find a clear selection of the exponential model for $N_{\text{diss}}(t)$, thus nicely complementing our analysis of the crossover regime. The introduction of the sex of the patient is, however, not conclusive: the model predicts a high ratio of the median of the rates in the two populations, but the Wald and LR tests do not permit to assert that those distributions are undistinguishable on this cohort.

3.3. Novel model-based biomarkers

Based on this careful mathematical modeling of the disease evolution, that is agnostic of the survival chances of the patient, we propose to use patients parameters as model-aware biomarkers for clinical use. We show below that the tumor load growth rate R provides a relevant risk-stratification for MM. We then compare it with other non-model-based radiological biomarkers, and find indications that R is more relevant than the other criteria.

Transition to MM. As described in Sec. 2.2, we select the patients with at least two focal lesion measurements (26 patients), and include the information on progression to MM. For those patients, we compute the tumor load growth rate R, using the best performing model and priors from above i.e. power-law with $B = 6.5$ and M/F as a covariate, and the resulting prediction curves are shown together with the measured data in Fig 6. Using a threshold R_{th}, we then use R to stratify patients into a low-risk ($R < R_{\text{th}}$) and a high-risk ($R \geq R_{\text{th}}$) group to progress to MM. For each possible value of R_{th}, we then compute the True Positive Rate (TPR) for the detection of patient who progress to MM during the observation time, and the False Positive Rate (FPR), measuring the false alarms, and report them in the Receiver Operating Characteristic (ROC) curve (Zweig and Campbell, 1993), red line in Fig 7(a). Using the median of all observed growth rates R as the stratification threshold, we obtain a TPR of 0.75 and a FPR of 0.1, as indicated by the red star. Considering the time of progression to MM, we show in Fig 7(b) the associated Kaplan-Meier (KM) curve (Kaplan and Meier, 1958). We compute the significance of the split with the log-rank test (Peto et al., 1977) and find a p-value of 0.00071, showing that the group compositions are statistically different. In 'Supplementary Figure 3', further searching for the best threshold in this population, we find that $R_{\text{th}} = 7.7 \times 10^{-3}$ month^{-1} gives a better p-value of 0.00003. We observe, however, that this precise threshold value might be overfitted to this dataset, and that all splits $R_{\text{th}} \in [1.7 \times 10^{-3}, 4 \times 10^{-2}]$ month^{-1} consistently give p-values lower than 0.05. R is therefore a very relevant biomarker to predict the transition to MM.

Comparison with other radiological criteria. We now compare this stratification with other MRI-based biomarkers. Previous studies (Hillengass et al., 2010; Merz et al., 2014; Brandelik et al., 2018; Wennmann et al., 2018) proposed radiological biomarkers for the risk stratification of SMM patients. Ref. (Brandelik et al., 2018) showed that volumetric measurements of tumors leads to a better assessment of the tumor load than diametric size, and Refs. (Merz et al., 2014; Wennmann et al., 2018) proposed to take into account the evolution between two measurements, by e.g. considering the rate of change of the tumor load (Wennmann et al., 2018). Here we therefore consider the following non-model-based biomarkers, which, for a fair comparison with the proposed biomarker R, are also volumetric and retrospectively based on all available measurements:

- the largest observed focal lesions number, $N_{\max} = \max_{t_i} N_{\text{tot}}(t_i)$,

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	Criteria	Median value	AUC	p-value	RR
I	$N_{\max}$	4 lesions	0.75	0.2038	2.39
II	$V_{\max}$	8816 mm^3	0.81	0.0116	5.28
III	$\Delta V/\Delta t\|_{\max}$	5.2×10^{-1} mm^3 month^{-1}	0.80	0.0130	5.13
IV	R	1.0×10^{-2} month^{-1}	0.94	0.0007	9.58

Table 3: Area Under the Curve (AUC) values of the ROC curves from Fig. 7(a), KM log-rank test p-values and Relative Risk (RR) for progression to MM, associated to the stratification into low- and high-risk groups when using the median observed value of different radiological criteria. Details on those tests for evaluating the discriminative power of biomarkers are given in 'Supplementary Method 4'.

II - the largest observed tumor load, $V_{\max} = \max_{t_i} V_{\text{tot}}(t_i)$,

III - the largest rate of change of the tumor load between two consecutive measurements, $\frac{\Delta V}{\Delta t}\Big|_{\max} = \max_{t_i} \frac{\Delta V_{\text{tot}}(t_i)}{\Delta t} = \max_{t_i} \frac{V_{\text{tot}}(t_{i+1}) - V_{\text{tot}}(t_i)}{t_{i+1} - t_i}$.

Figure 7(a) displays the ROC curves for those criteria, and we see that they provide a fair stratification as well, although not as good as the one provided by R. In Table 3, we report the corresponding Area Under the Curve (AUC) values, which reaches 0.94 for R. We also report the log-rank test p-values associated to the KM survival curves obtained using each of those criteria and taking the median observed value as stratification threshold, together with the associated Relative Risk (RR) (Stare and Maucort-Boulch, 2016). Criteria II and III are both providing a statistically relevant classification, with comparable p-values ~ 0.01 and comparable RRs $\sim 5.1 - 5.3$. In row IV, we see that the growth rates R – i.e. the model-based approach – provide the most relevant split, with a significantly lower p-value = 0.0007 and the best risk-stratification RR = 9.6, compared to other radiological criteria.

4. Discussion

Diffusive growth of local lesions. In Sec. 3.1, we analyzed disease progression at the local scale. We found that the growth of focal lesions in MM is best modeled by a diffusive growth, thereby confirming a basic hypothesis of Ayati *et al.* (Ayati et al., 2010) and is in line with phenomenological observations, in particular that lesions sometimes become too diffuse to be properly volumetrized. This could be further analyzed by the study of the evolution of lesion borders, possibly in multiple imaging modalities (Konukoglu et al., 2010; Lipkova et al., 2018) With respect to other tested models, we found that cubic growth, which would correspond to a solid tumor with a rate of growth proportional to the tumor surface, performed better than exponential growth. This does not come as a surprise, as it would correspond to a volumetric growth, implying that the newly generated mass is 'pushing' its surrounding, which may be rather unlikely to happen in a bone environment.

Effective model for the crossover to global dissemination. In Sec. 3.2, we considered the global propagation of the disease on the patient's scale, through the analysis of the tumor load. We showed that the diffusive growth parametric model does not translate to the tumor load as such. Here, a model taking the dissemination process into account, like the IKS model using an exponential term (Iwata et al., 2000), is likely more relevant in our SMM cohort, where most of the monitored patients show a progress in the number of lesions observed. Still, the tumor load model that aligns best with our observations is a power-law with $B = 6.5$. As summarized in box 'Descriptive tumor load model', we interpret this as a crossover from an initial diffusive regime (power-law with power 3/2) to an exponential dissemination regime. This is best effectively modeled by a power-law model with a higher power $B > 3/2$. Further tests on the number of disseminated lesions confirm that the basic assumptions of the IKS model (Iwata et al., 2000), i.e. exponential dissemination, apply in this cohort, see 'Supplementary Table 5'.

In the original paper, the IKS model was validated on one single patient with a metastatic hepatocellular carcinoma (Iwata et al., 2000) and has been further tested on one other patient with liver cancer and one with lung cancer in Ref. (Mehrara et al., 2013). A few population studies have been carried out on mice populations with orthotoptic cell implantation (Hartung et al., 2014; Baratchart et al., 2015), the observed dissemination dynamics also

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showing an overall good agreement with the IKS model, although Ref. (Baratchart et al., 2015) incorporated interaction between lesions growing in close vicinity to match the experimental conditions. The model has also been used to fit cross-sectional data on the risk of metastatic evolution in breast cancer (Barbolosi et al., 2011), using ad hoc parameters. We are, however, not aware of any previous longitudinal human population study of the IKS model, as well as an application in the context of MM. Such that our study, with 21 patients in the crossover regime and 13 series for the number of disseminated lesions (in 'Supplementary Table 5'), is unprecedented.

Role of the sex and other covariates. Our hierarchical statistical model is evaluated on the whole population jointly, and permits to systematically test for the impact of covariates on model parameters. We found that the patient's sex is a relevant covariate to predict the tumor load growth rate, with a median rate four times as high in the male population as in the female one. The role of the patient's sex in the incidence of MM is known (Raab et al., 2009; Roellig et al., 2015; Kumar et al., 2017), but no indication of its role in the disease evolution in the presence of focal lesions has been previously reported. However, it has been shown that activated estrogene receptors inhibit cell survival pathways and support cell apoptosis in MM (Sola and Renoir, 2007), which provides one possible explanation. This effect deserves to be further investigated on a larger cohort. The sex covariate alone is, however, a less relevant covariate for the local lesion growth modeling, indicating that other hidden covariates might play a role and could be added in the model as well. The location of focal lesions could be a candidate, and in 'Supplementary Table 3' we have found indication that long bones tend to have lower growth rates than other bones. Our sample size is, however, too small to carry out multi-covariate tests with enough statistical strength. The role of the sex covariate in tumor load modeling in our cohort could also be explained by a difference in the dissemination rate, but more statistical strength would be needed to conclude here as well.

Growth rates as model-based biomarkers. In Sec. 3.3, we identified the tumor load growth rate as viable image biomarker that is integrating information along the full observational sequence. We have shown that it provides a pertinent risk-stratification of SMM patients to develop end-organ damage and therefore transition to MM. This biomarker provides a better risk-stratification than other MRI-based biomarkers that have been suggested in the literature, even when few observations are present, gaining strength from the population priors. The biomarker gets refined over time when the number of observations increases, as it takes all available measurements into account, thereby confirming the unprecedented potential of model-based biomarkers for better and more personalized treatment decisions. This contrasts with current biomarkers, which consider the most recent examination only (International Myeloma Working Group, 2003; Rajkumar et al., 2014; Rajkumar, 2016). The model used for the biomarkers was derived on part of the population on which the biomarker is tested. This however does not lead to overfitting, as the model and the model selection process do not know about survival and progression to MM. We do acknowledge the limited size of the patient's cohort and the retrospective nature of the study, and for full clinical relevance, the proposed model-based radiological biomarkers should be combined with the remainder of MM biomarkers in future studies.

5. Conclusion

In this paper, we propose a descriptive functional-statistical framework to carry out multi-scale modeling of cancer evolution, from single lesion growth to global dissemination. Applying it to MM, we tested different mathematical models, which permits to confirm basic assumptions on disease progression (Ayati et al., 2010; Iwata et al., 2000), learned population priors, as well as tested the influence of various covariates, on clinical data. Our study establishes a new benchmark for the study of metastatic and disseminated diseases in general, and for understanding the progression of MM in particular. We also propose to use the inferred model parameters as biomarkers, and showed the relevance of the growth rate to predict the transition to overt MM in our dataset. We were able to show that biomarkers based on biologically-grounded, but tractable, models could be more significant than phenomenological ones, which offers new and unprecedented directions.

Model-based biomarkers could be used in the clinical routine, as inference of the individual parameters is very fast. Indeed, for our study, it takes 0.15s per patient on

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average with the Monolix software (Monolix). This computation could therefore be implemented after computer-aided segmentation of focal lesions in MRI for example. The use of whole-body imaging and whole-body lesion analysis is hindered by a lack of means to postprocess and analyze these added information. Our model now offers such means and, fosters the impact of high capacity data analytics in clinical decision making.

Future work should integrate other image-based and non-image-based, static and dynamical, features in a radiomics approach. One could in particular investigate related models for other observed parameters for MM, such as laboratory parameters that are known to correlate with the progression of the disease (Mai et al., 2015; Wennmann et al., 2018), genetic markers or cell-surface proteins measured with flow-cytometry (Flores-Montero et al., 2017). Next-generation sequencing, which is becoming available and permits to distinguish different clonal phenotypes of plasma cells (Takamatsu, 2017) would enable to analyse separately the role of different mutations in disease progression.

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Driving clinical problem

Multiple Myeloma is a cancer of plasma cells that is still incurable, with a median survival of 6 years at the time of diagnosis (Raab et al., 2009; Roellig et al., 2015; Kumar et al., 2017). It is a systemic cancer, which can be considered as a model for the cancer dissemination process (Ghobrial, 2012; Ghobrial and Landgren, 2014). Its development starts with the development and infiltration of clonal plasma cells within and into the bone marrow, homing into a niche and creating a micrometastasis. This initial cluster of malignant cells, can grow into a focal lesion and emit malignant cells that can in turn colonize other niches in the bone marrow. In overt MM, the malignancy causes end-organ damage, such as lytic bone lesions due to the perturbation of the bone remodeling cycle (Ayati et al., 2010).

The International Myeloma Working Group (IMWG) distinguishes two precursor stages, Monoclonal Gammopathy of Undertermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM), preceding symptomatic Multiple Myeloma. This advanced stage is defined by the occurrence of end organ damage, following the CRAB criteria: 'C' for calcium elevation, 'R' for renal insufficiency, 'A' for anemia and 'B' for bone damage, corresponding to the appearance of bone lytic lesions on skeletal radiography or CT (International Myeloma Working Group, 2003). In 2014, further malignancy criteria were added to the definition of symptomatic MM, such as the presence of more than one focal lesions in MRI (Rajkumar et al., 2014; Rajkumar, 2016).

The incidence of MGUS is high in the population (1% of persons over 50 (International Myeloma Working Group, 2003)) but only 15% of patients with MGUS will progress to MM (Kumar et al., 2017). Risk-stratification of patients in the early stages is therefore of primordial importance, to make treatment decisions (Ghobrial and Landgren, 2014; Ahn et al., 2015; van de Donk et al., 2016).

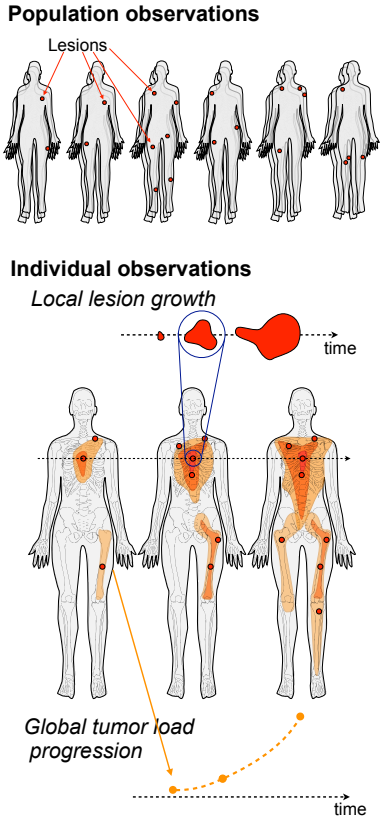

Figure 1: Overview of the approach: Observations and dataset.

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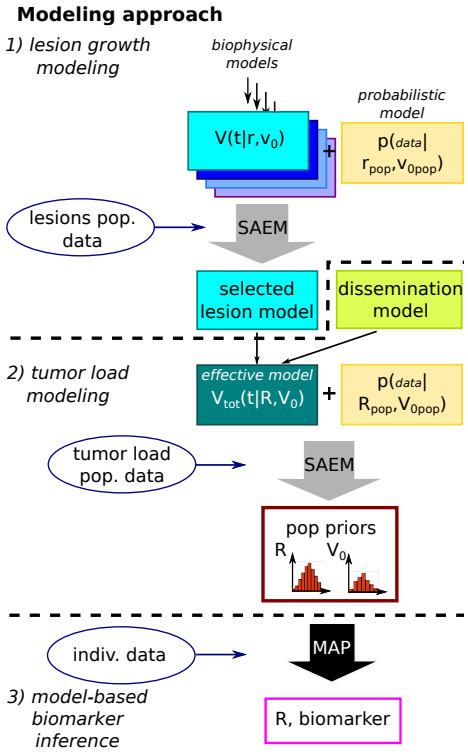


Figure 2: Overview of the modeling approach.

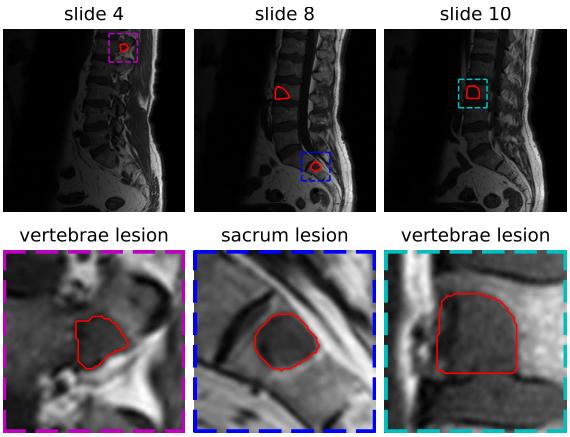


Figure 3: Three-dimensional segmentation and volumetrization of all visible hypo-intense focal lesions in a T1-weighted MRI sagittal MRI sequence.

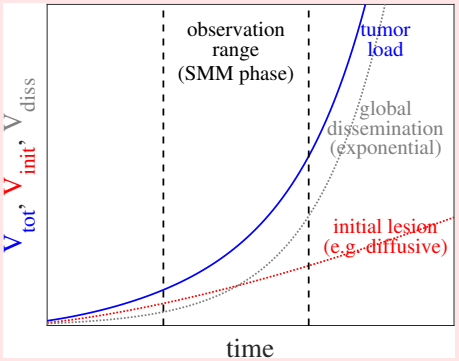
Descriptive tumor load model

The tumor load is made of the putative initial lesion and the disseminated burden:

$$V_{\text{tot}}(t) = V_{\text{init}}(t) + V_{\text{diss}}(t)$$

$V_{\text{init}}(t) \in$ {linear, cubic, diff., exp.} and $V_{\text{diss}}(t) \sim$ exp.
We propose an effective model in the observation range:

$$V_{\text{tot}}(t) \sim V_0\,(Rt+1)^B$$



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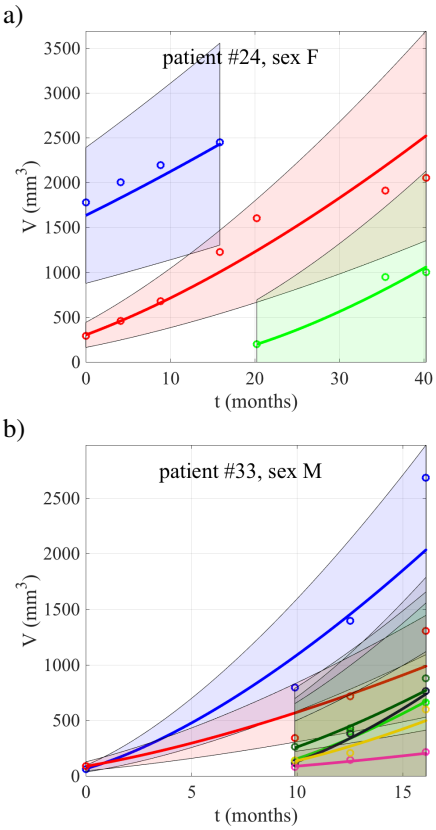

Figure 4: Local lesion growth time series (dots) with the predictions (solid lines) and the corresponding 95% error margin (shaded area), for (a) a female and (b) a male patient. The predictions are based on the SAEM results using the diffusive parametric growth model, Eq. (4), and no covariate.

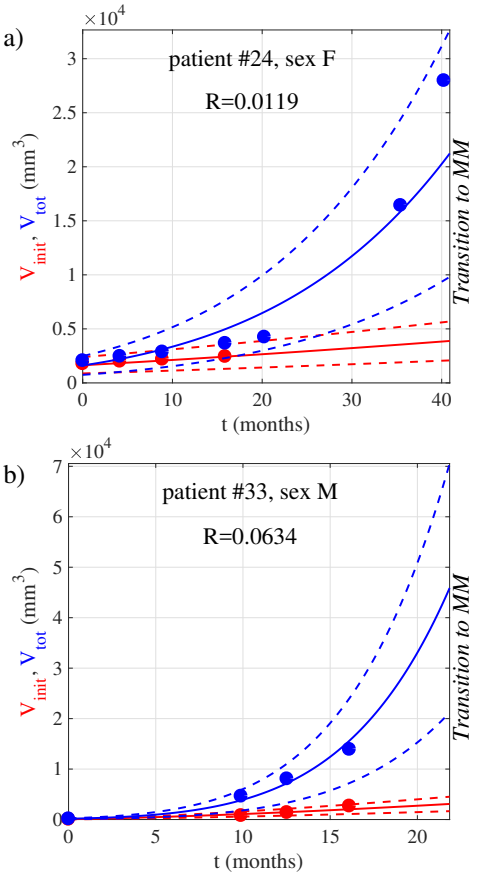

Figure 5: Tumor load $V_{tot}(t)$ (blue dots) and initial lesion $V_{init}(t)$ (red dots) time series with the predictions (solid lines) and the corresponding 95% error margin (dashed lines), for (a) a female and (b) a male patient, who both transition to MM. The predictions for the tumor load are based on the SAEM results using the power-law parametric model, Eq. (8) with $B = 6.5$, and a covariate model for the sex M/F.

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Tumor load modeling in SMM

We find the effective model

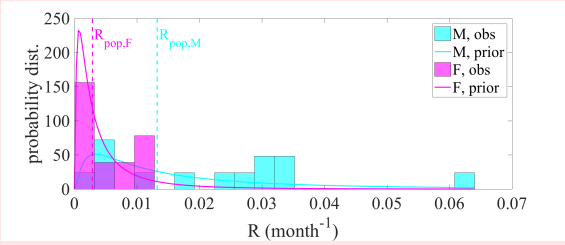
$$V_{\text{tot}}(t) = V_0\,(Rt+1)^{6.5}\ ,$$

with the following median population values:

- *Growth rates for males and females*

$R_{\text{pop,M}} = 12.6(5.7)\times 10^{-3}$ month^{-1}
$R_{\text{pop,F}} = 2.9(1.3)\times 10^{-3}$ month^{-1}

- *Initial volumes*: $V_{0,\text{pop}} = 1350(500)$ mm^3



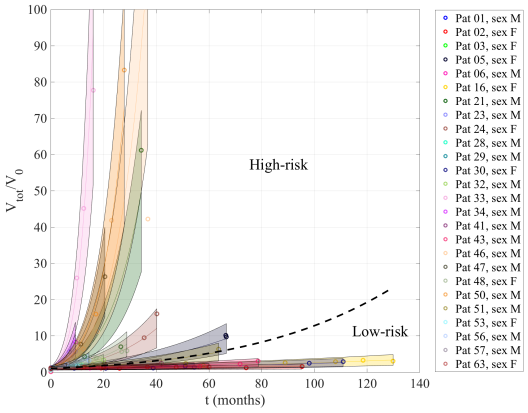


Figure 6: Rescaled tumor load series for patients with at least two time points, together with their fit using the best tumor load model and priors. The proposed risk groups are defined by the dashed separatrix.

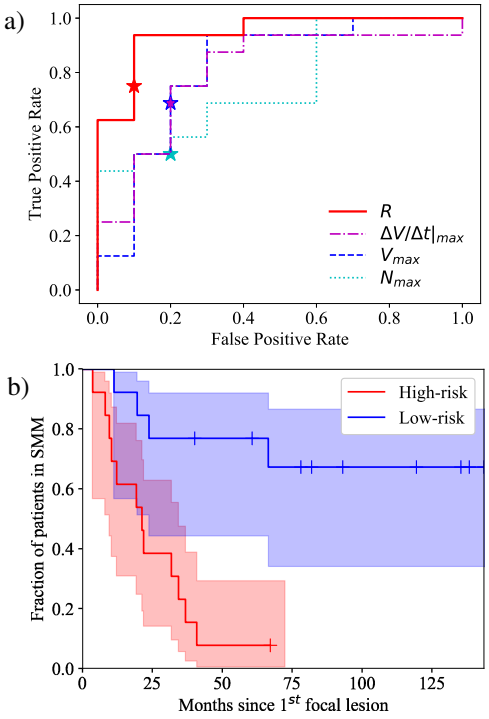


Figure 7: (a) ROC curve for different biomarkers, the red line corresponds to R. Stars indicate median splits, that are used in (a), (c) and Table 3. (b) Kaplan-Meier curve obtained for splitting this population into 2 groups using the median rate $R_{\text{th}} = 1\times 10^{-2}$ month^{-1}.