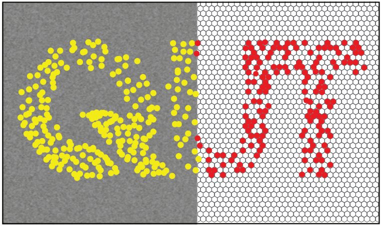
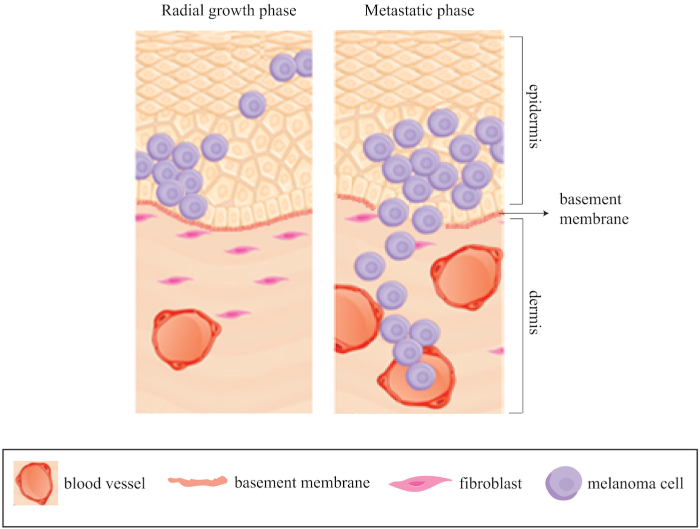


A Bayesian sequential learning framework to parameterise continuum models of melanoma invasion into human skin

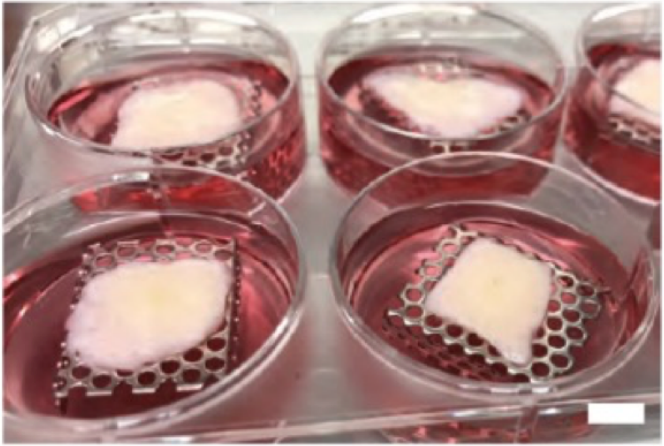
Alexander P Browning
Parvathi Haridas
Matthew J Simpson

Melanoma Invasion[1]



[1] Zaidi, Day & Merlino (2008)

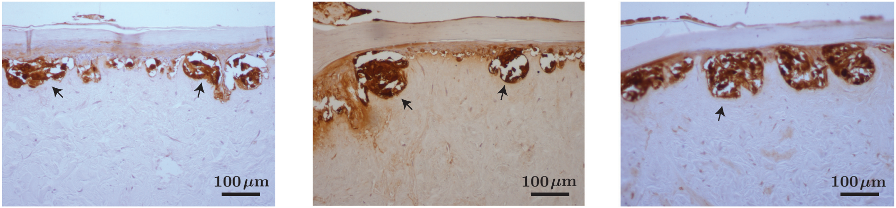
Melanoma Invasion[2]



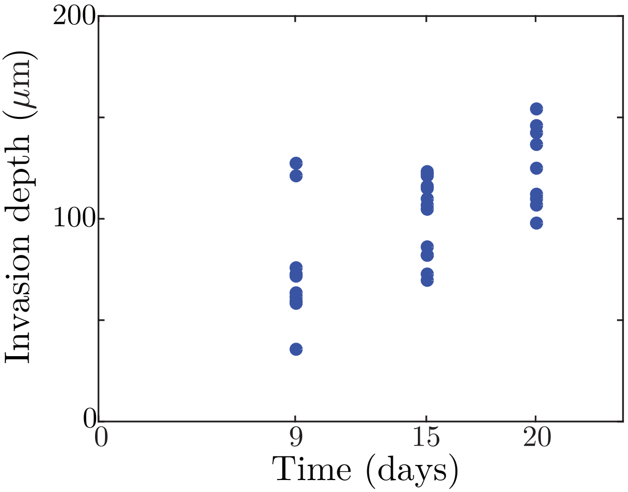
[2] Haridas et al. (2017)

Melanoma Invasion

(a) 9 days (b) 15 days (c) 20 days



Melanoma Invasion



Melanoma Invasion

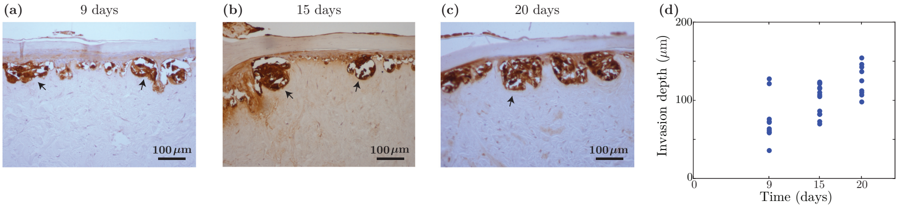
Model Melanoma, $c(x,t)$; Skin, $s(x,t)$, and; Protease, $p(x,t)$[3]:

$$
\begin{aligned}
\frac{\partial c}{\partial t} &= D\frac{\partial}{\partial x}\left[\left(1-\frac{s}{K}\right)\frac{\partial c}{\partial x}\right] + \lambda c\left(1-\frac{c+s}{K}\right),\\
\frac{\partial s}{\partial t} &= -lsp,\\
\frac{\partial p}{\partial t} &= mc - np.
\end{aligned}
$$

Never connected to data!

[3] Landman and Pettett (1998) and others

Melanoma Invasion



Typically, degradation of protease is relatively fast, therefore we model only Melanoma, $C(x,t)$ and Skin, $S(x,t)$:

$$
\begin{aligned}
\frac{\partial C}{\partial t} &= D\frac{\partial}{\partial x}\left[\left(1-\frac{S}{K}\right)\frac{\partial C}{\partial x}\right] + \lambda C\left(1-\frac{C+S}{K}\right),\\
\frac{\partial S}{\partial t} &= -\delta S C,
\end{aligned}
$$

Melanoma Invasion

- Model has three free parameters: $\mathbf{\Theta} = \langle \lambda, D, \delta \rangle$

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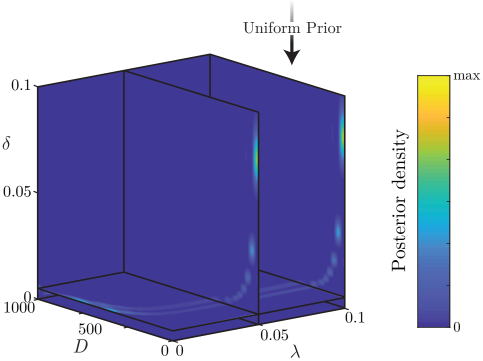
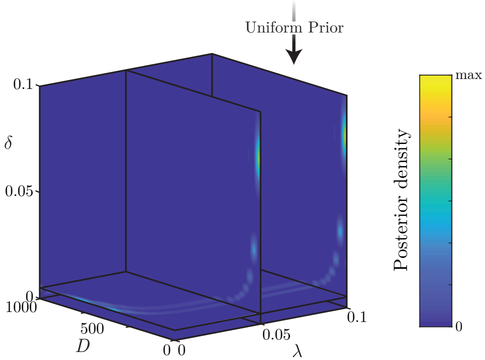
- Model has three free parameters: $\mathbf{\Theta} = \langle \lambda, D, \delta \rangle$
- Set model output, $M_3(t; \mathbf{\Theta})$, as the invasion depth, and assume normally distributed noise
- Using a Bayesian approach to parameter estimation, with a uniform prior, we obtain a probability density function:

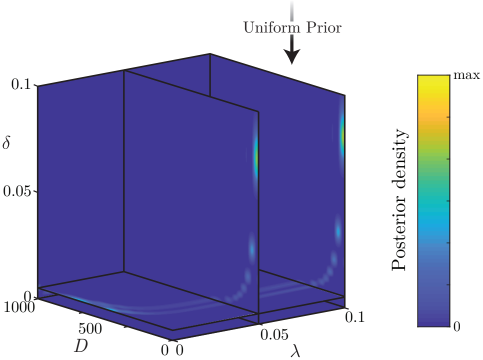


Melanoma Invasion



- Multimodal, difficult to pull point estimates

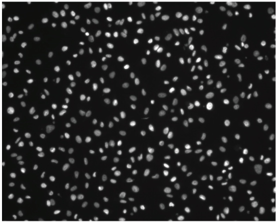
Melanoma Invasion



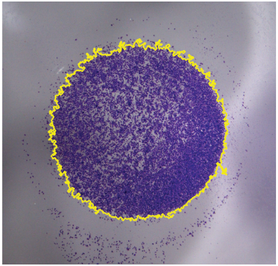
- Multimodal, difficult to pull point estimates
- From previous experimental studies, we know that $\lambda \approx 0.04$ /h and $D \approx 200 - 1000\ \mu\text{m}^2/\text{h}$.

Experimental Data[4]

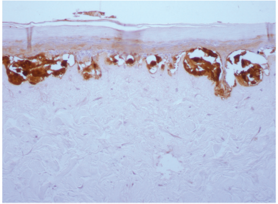
Type 1: Proliferation assay



Type 2: Barrier assay



Type 3: Invasion assay



[4] Treloar & Simpson (2013)

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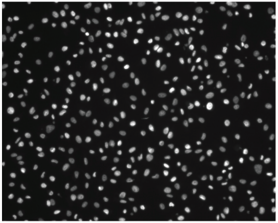
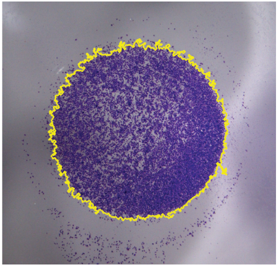


- Proliferation
- *(Motility)*

Type 2: Barrier assay



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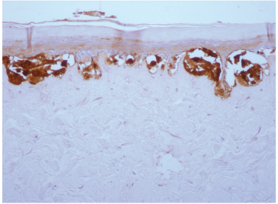

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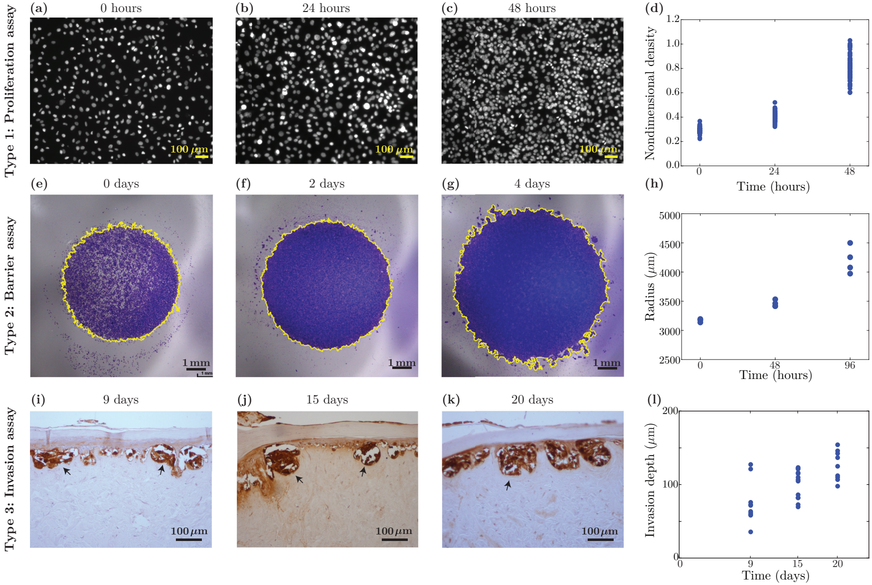
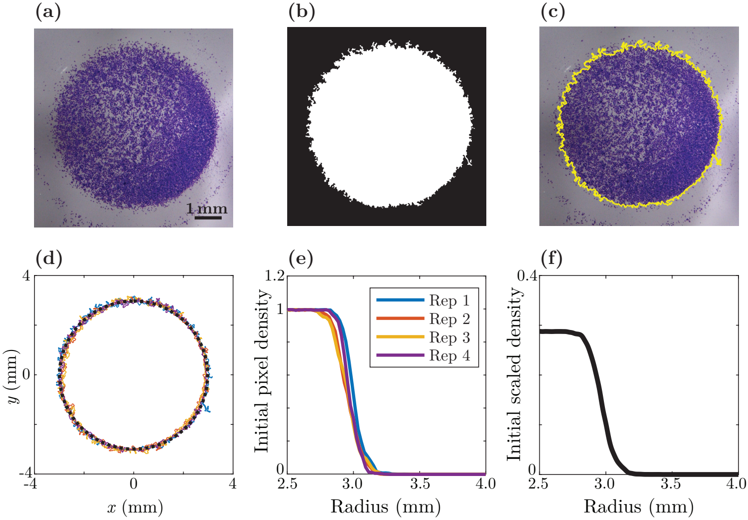


4 Treloar & Simpson (2013)

Edge Detection



Models

Proliferation rate, λ; Diffusivity, D, and; Skin degredation, δ.

Model 3. Invasion assay

$$\frac{\partial C}{\partial t} = D\frac{\partial}{\partial x}\left[(1-S)\frac{\partial C}{\partial x}\right] + \lambda C\left[1-C-S\right],$$
$$\frac{\partial S}{\partial t} = -\delta CS,$$

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Model 3. Invasion assay

- $C(0, r) = 0.78$ for $-20 < x < 0$ and 0 otherwise (cells on the surface of the dermis).
- $S(0, r) = 1$ for $x < 0$ and 0 otherwise (skin cells beneath the surface).

Model Observations

We denote $M_k(t; \mathbf{\Theta})$ as a summarised model observation from model $k = 1, 2, 3$, at time t, using parameter combination $\mathbf{\Theta} = \langle \lambda, D, \delta \rangle$.

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Model 3. The depth of the front of melanoma cells:

$$M_3(t; \boldsymbol{\Theta}) = \min\{x : C(x, t) = 0\}.$$

Likelihood

- We denote prior knowledge about parameters $p(\boldsymbol{\Theta})$. Here, we take $p(\boldsymbol{\Theta})$ to be a uniform distribution.

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- Likelihood: "Probability density of experimental data, given parameters"

$$\mathcal{L}_k(\mathbf{X}_k|\boldsymbol{\Theta}) = \prod_{i=1}^{n} \phi(y_i; M_k(t_i; \boldsymbol{\Theta}), \Sigma_k^2),$$

- ϕ is the normal density function and $\Sigma_k^2 \approx s_k^2$, where s_k^2 is the pooled sample variance.

Inference

- We apply Bayes' theorem to update our knowledge of the parameters with the likelihood:

$$\underbrace{p(\boldsymbol{\Theta}|\mathbf{X}_k)}_{\text{posterior}} \propto \underbrace{p(\boldsymbol{\Theta})}_{\text{prior}} \underbrace{\prod_{i=1}^{n} \phi(y_i; M_k(t_i; \boldsymbol{\Theta}), \Sigma_k^2)}_{\text{likelihood}}.$$

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- Note this formula only considers data from experiment k. We call this an *uninformed posterior*.

Inference

- By setting the prior for experiment $k = 2, 3$ to be the posterior from the previous experiment, we have an *informed posterior*:

$$\underbrace{p_k(\boldsymbol{\Theta}|\mathbf{X}_k)}_{\text{posterior for model } k} \quad \propto \quad \underbrace{p_{k-1}(\boldsymbol{\Theta}|\mathbf{X}_{k-1})}_{\text{posterior for model } k-1} \quad \prod_{j=1}^{n} \phi(y_j; M_k(t_j; \boldsymbol{\Theta}), \Sigma_k^2).$$

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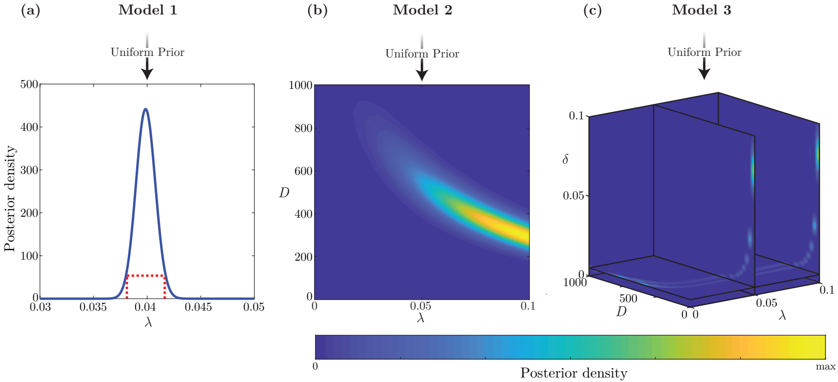
- We note this is equivalent to:

$$p_k(\boldsymbol{\Theta}|\mathbf{X}_k) = p(\boldsymbol{\Theta}|\{\mathbf{X}_i\}_{i=1}^{k}) \propto p(\boldsymbol{\Theta}) \prod_{i=1}^{k} \prod_{j=1}^{n_k} \phi(y_j; M_i(t_j; \boldsymbol{\Theta}), \Sigma_i^2).$$

Results

"Uninformed"



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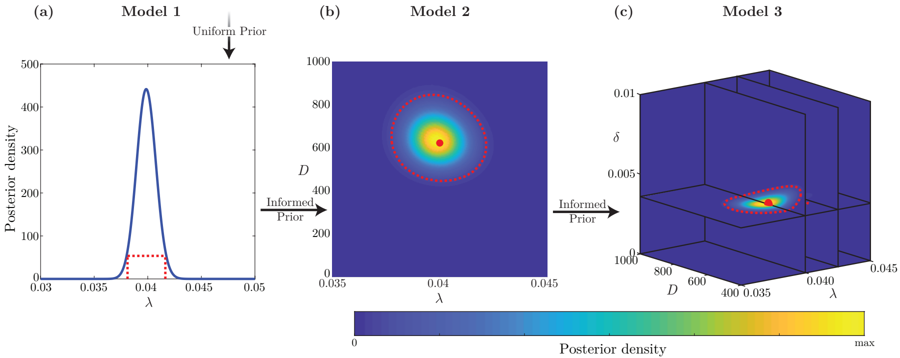


Model 3 Results

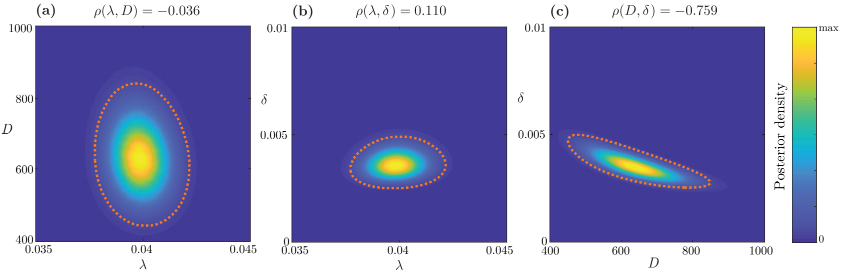


Figure: Bivariate marginal distributions

Model 3 Results

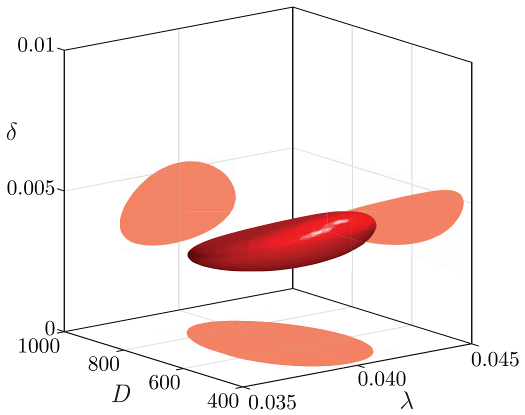
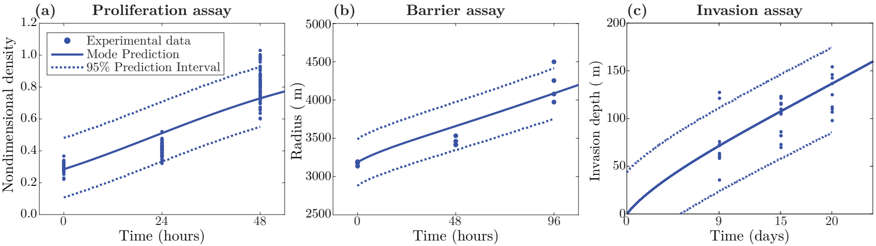


Figure: 95% Credible Region

Model Performance and Predictions



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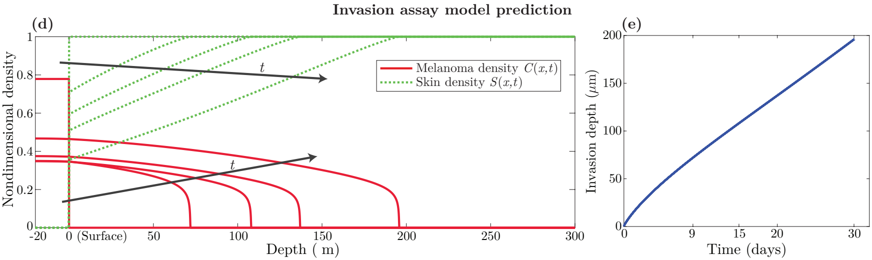

Other Inference Work

Melanoma Study

- Haridas P, **Browning AP**, McGovern J, McElwain DLS, Simpson MJ (2018)
  Three-dimensional experiments and individual based simulations show that cell proliferation drives melanoma nest formation in human skin tissue.
  BMC Systems Biology
- **Browning AP**, Haridas P, Simpson MJ (to appear)
  A Bayesian sequential learning framework to parameterise continuum models of melanoma invasion into human skin.
  Bulletin of Mathematical Biology

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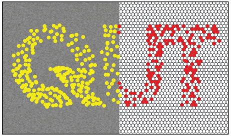

Individual Based Models

- **Browning AP**, McCue SW, Simpson MJ (2017)
  A Bayesian computational approach to explore the optimal duration of a cell proliferation assay.
  Bulletin of Mathematical Biology
- **Browning AP**, McCue SW, Binny RN, Plank MJ, Shah ET, Simpson MJ (2018)
  Inferring parameters for a lattice-free model of cell migration and proliferation using experimental data.
  Journal of Theoretical Biology

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- Professor Matthew Simpson and Dr Parvathi Haridas
- QUT High Performance Computing
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- BIRS
- Friends and family

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