Emulation and History Matching

Part 2: Methodology and Implementation

5TH ANNUAL DISEASE MODELING SYMPOSIUM

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I. Andrianakis (LSHTM),
with funding from a Medical Research Council (UK) grant
on Model Calibration (MR/J005088/1)

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- We will describe the core scientific questions a modeller may wish to answer.

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- This can then be used to make future predictions, to analyse effects of interventions and to design future data collection.

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Andrianakis, I., Vernon, I., McCreesh, N., McKinley, T.J., Oakley, J.E., Nsubuga, R., Goldstein, M., White, R.G.: Bayesian history matching of complex infectious disease models using emulation: A tutorial and a case study on HIV in uganda. PLoS Comput Biol. 11(1), 1003968 (2015)

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- This involves the specification of many complex multivariate distributions related to all uncertain quantities of interest, which may or may not be warranted at this stage.

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- Calibration data provided by a general population cohort in Uganda.

Mukwano: 22 Model input parameters

Number	Input description	Abbr.	Min.	Max.
1	Proportion of men in the high sexual activity group	*mhag*	0.01	0.5
2	Proportion of women in the high sexual activity group	*whag*	0.01	0.5
3	Mixing by activity group [ϵ]	*mag*	0	1
4	High activity contact rate (risk behaviour 1) [partners/yr]*	*hacr1*	0	10
5	Low activity contact rate (risk behaviour 1) [partners/yr]*	*lacr1*	0	2
6	Start year for risk behaviour 2	*sy2*	1986	1992
7	High activity contact rate (risk behaviour 2) [partners/yr]*	*hacr2*	0	10
8	Low activity contact rate (risk behaviour 2) [partners/yr]*	*lacr2*	0	2
9	Start year for risk behaviour 3	*sy3*	1998	2002
10	High activity contact rate (risk behaviour 3) [partners/yr]*	*hacr3*	0	10
11	Low activity contact rate (risk behaviour 3) [partners/yr]*	*lacr3*	0	2
12	Mean HIV transmission probability per sex act during primary stage of infection (mean of male to female and female to male transmission probabilities)	*atp*	0	1
13	Ratio of male to female/female to male transmission probabilities	*rtp*	1	3
14	Proportion of low activity men in high concurrency group	*lmhc*	0	1
15	Proportion of low activity women in high concurrency group	*lwhc*	0	1
16	Male concurrency parameter in high concurrency group (risk behaviour 1)	*mchc1*	0	1
17	Female concurrency parameter in high concurrency group (risk behaviour 1)	*fchc1*	0	1
18	Male concurrency parameter in high concurrency group (risk behaviour 2)	*mchc2*	0	1
19	Female concurrency parameter in high concurrency group (risk behaviour 2)	*fchc2*	0	1
20	Male concurrency parameter in high concurrency group (risk behaviour 3)	*mchc3*	0	1
21	Female concurrency parameter in high concurrency group (risk behaviour 3)	*fchc3*	0	1
22	Duration of long-duration partnerships [years]	*dlp*	5	20

Mukwano: 22 Model input parameters

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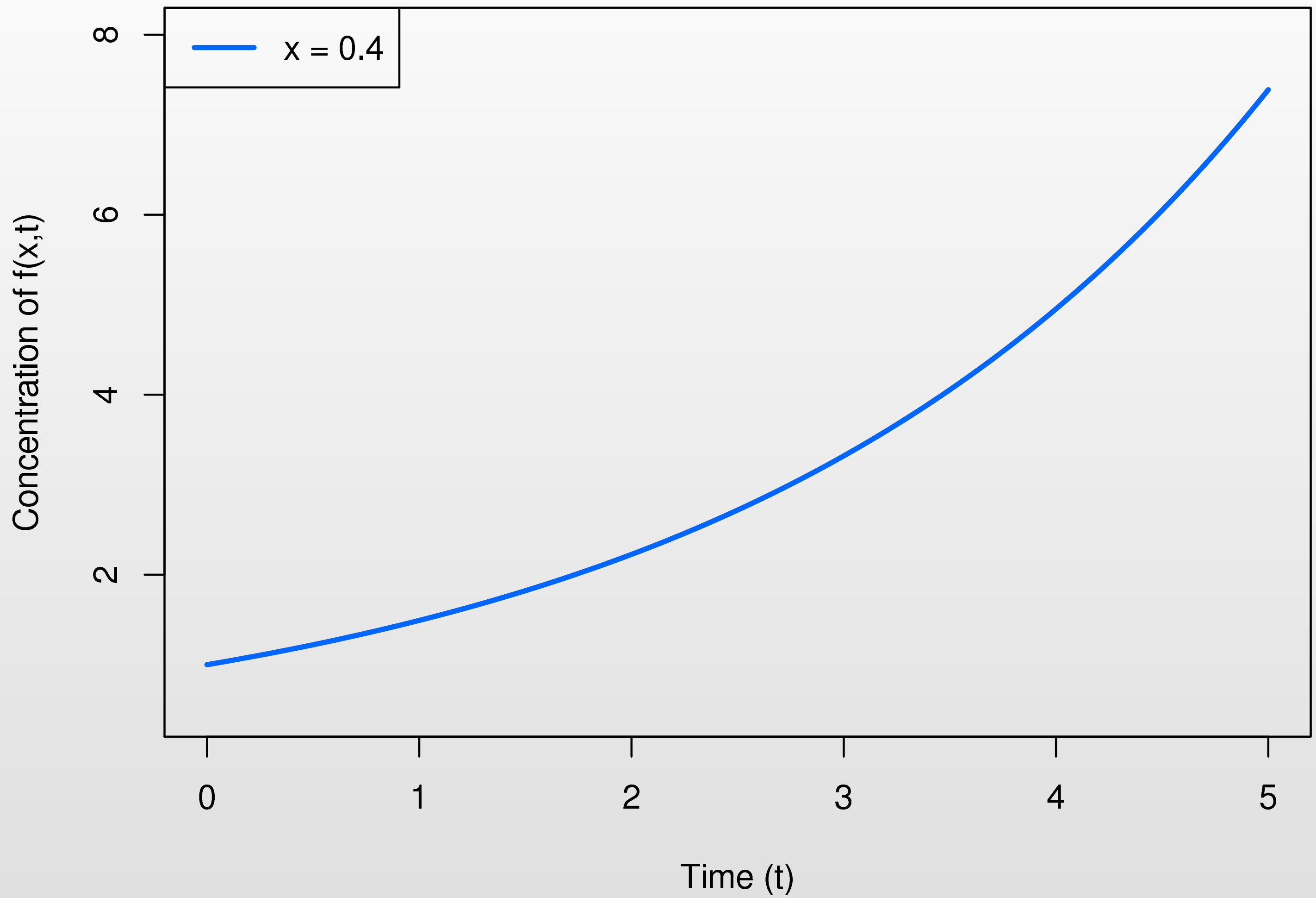
Number	Output description	Abbr.	Min.	Max.
1	Population size in 2008 (male)	*psm*	2986	3650
2	Population size in 2008 (female)	*psf*	3374	4124
3	Average male partnership incidence in 2008 (partners/year)	*ampi*	0.4	0.489
4	HIV prevalence in 1992 (male)	*p92m*	0.084	0.112
5	HIV prevalence in 1992 (female)	*p92f*	0.096	0.124
6	HIV prevalence in 2001 (male)	*p01m*	0.07	0.09
7	HIV prevalence in 2001 (female)	*p01f*	0.083	0.107
8	HIV prevalence in 2007 (male)	*p07m*	0.06	0.084
9	HIV prevalence in 2007 (female)	*p07f*	0.093	0.119
10	Point prevalence of men with 1 long duration partnership in 2008 (%)	*m1l*	34.62	42.31
11	Point prevalence of men with 1 short duration partnership in 2008 (%)	*m1s*	10.86	13.27
12	Point prevalence of men with 1 partnership (either type) in 2008 (%)	*m1*	37.83	46.24
13	Point prevalence of men with 2+ long duration partnerships in 2008 (%)	*m2l*	3.38	4.13
14	Point prevalence of men with 2+ short duration partnerships in 2008 (%)	*m2s*	1.69	2.07
15	Point prevalence of men with 2+ partnerships (any combination) in 2008 (%)	*m2*	8.66	10.59
16	Point prevalence of women with 2+ long duration partnerships in 2008 (%)	*w2l*	0.85	1.03
17	Point prevalence of women with 2+ short duration partnerships in 2008 (%)	*w2s*	0.42	0.52
18	Point prevalence of women with 2+ partnerships (any combination) in 2008 (%)	*w2*	2.17	2.65

Plots of output: 1D example



- One “model run” with the input parameter $x = 0.4$
- If we did not know the analytic solution for $f(x, t)$ this would be generated by numerically solving the differential equation.

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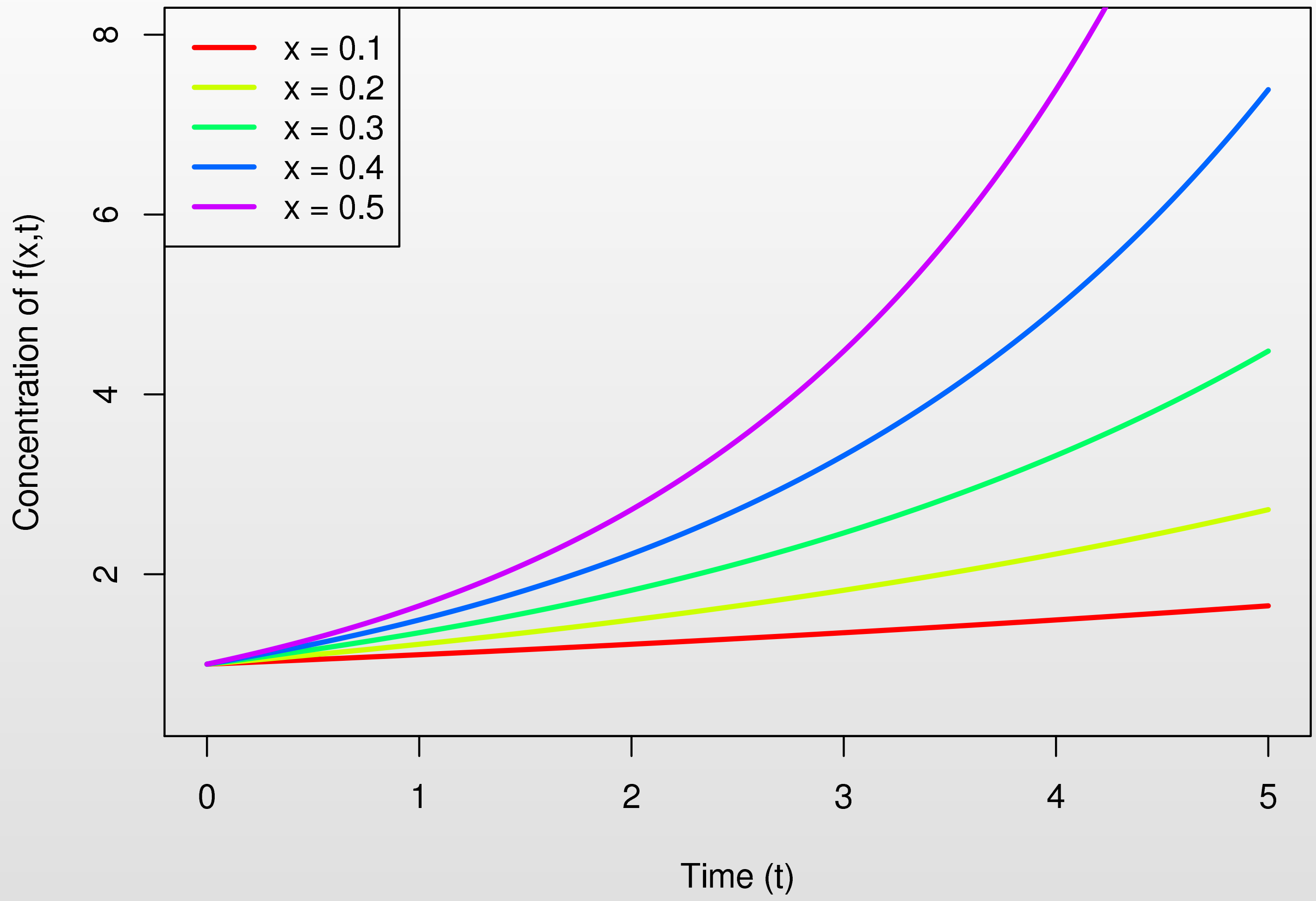

- Five model runs with the input parameter varying from $x = 0.1$ to $x = 0.5$

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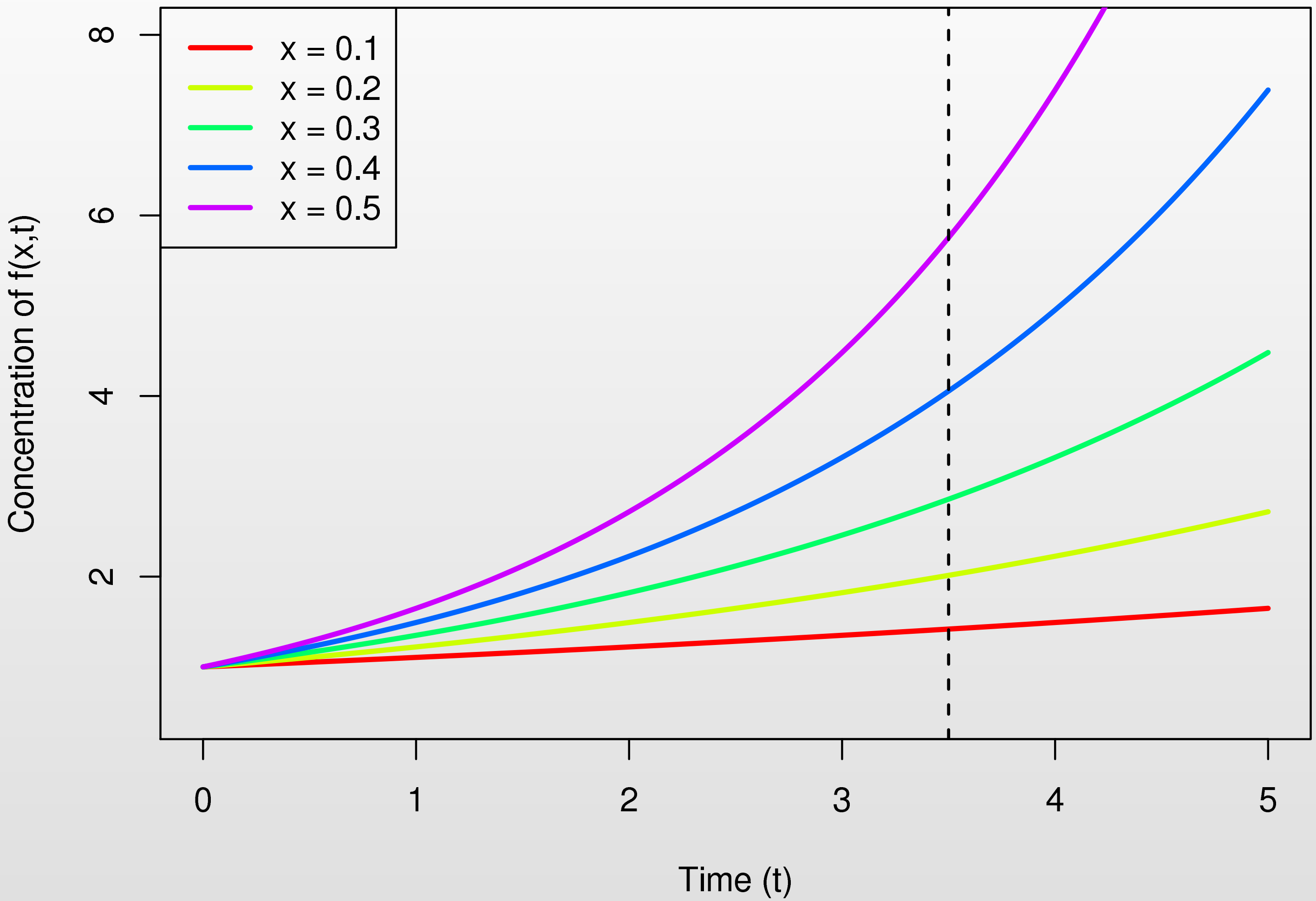

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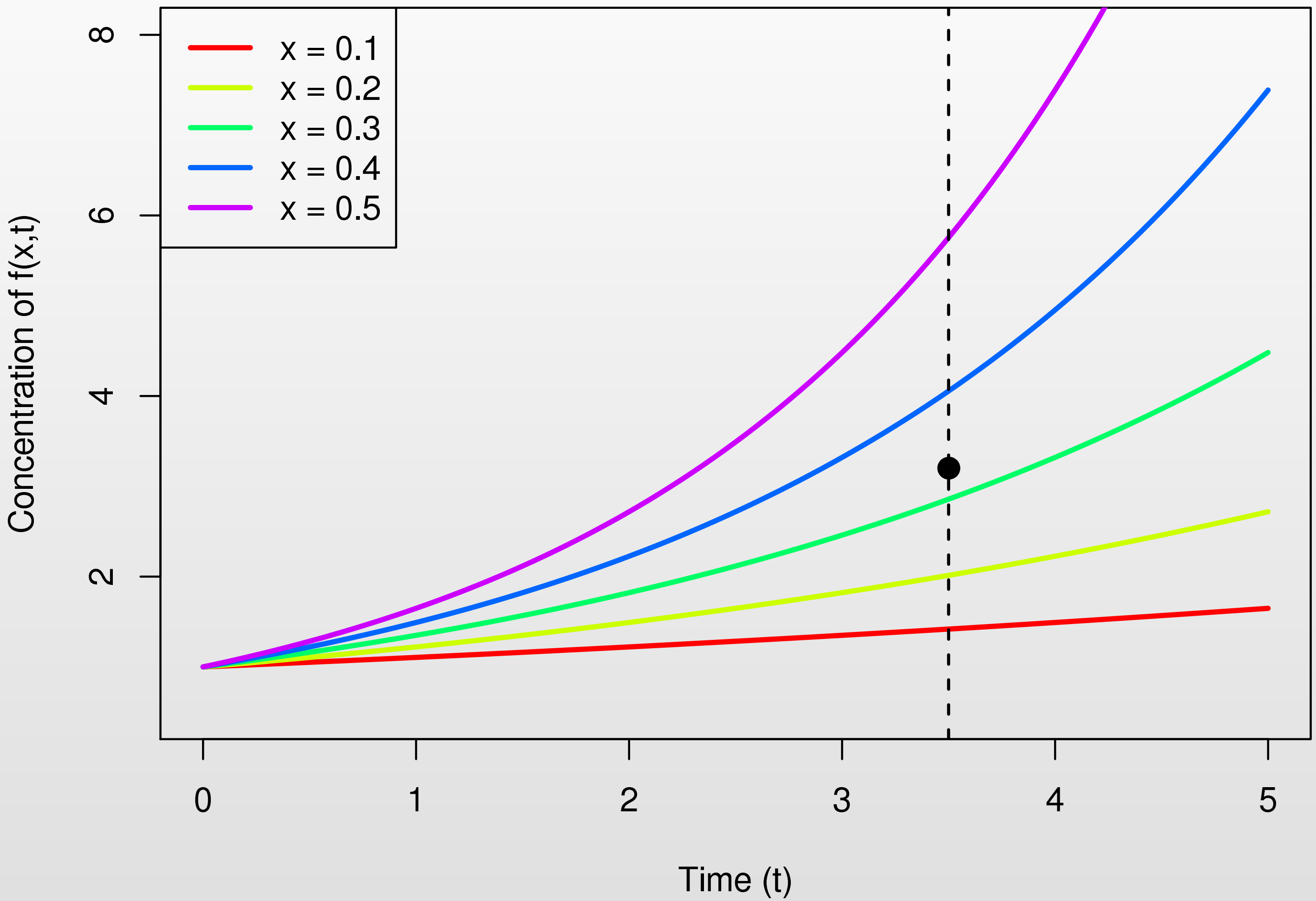

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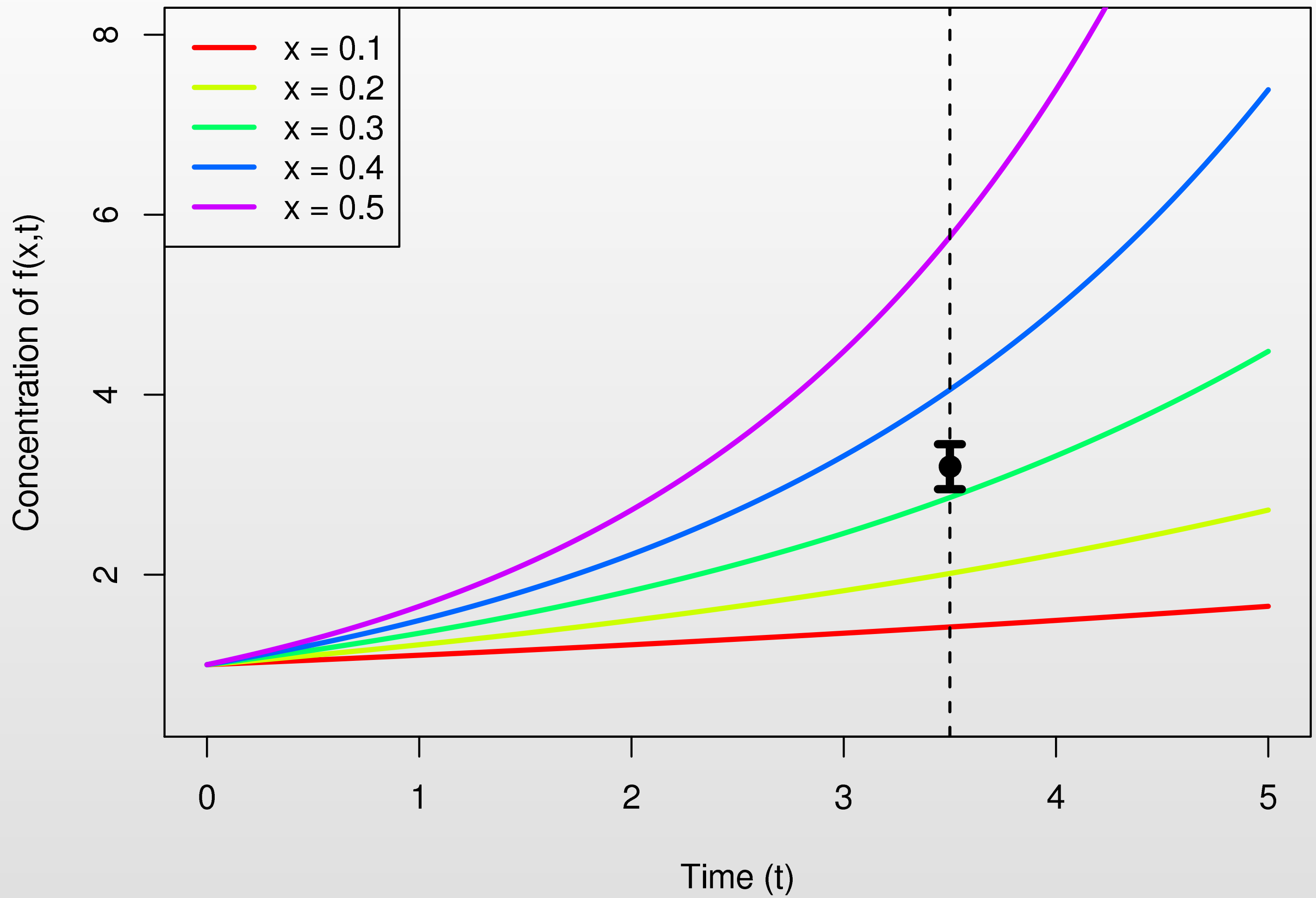

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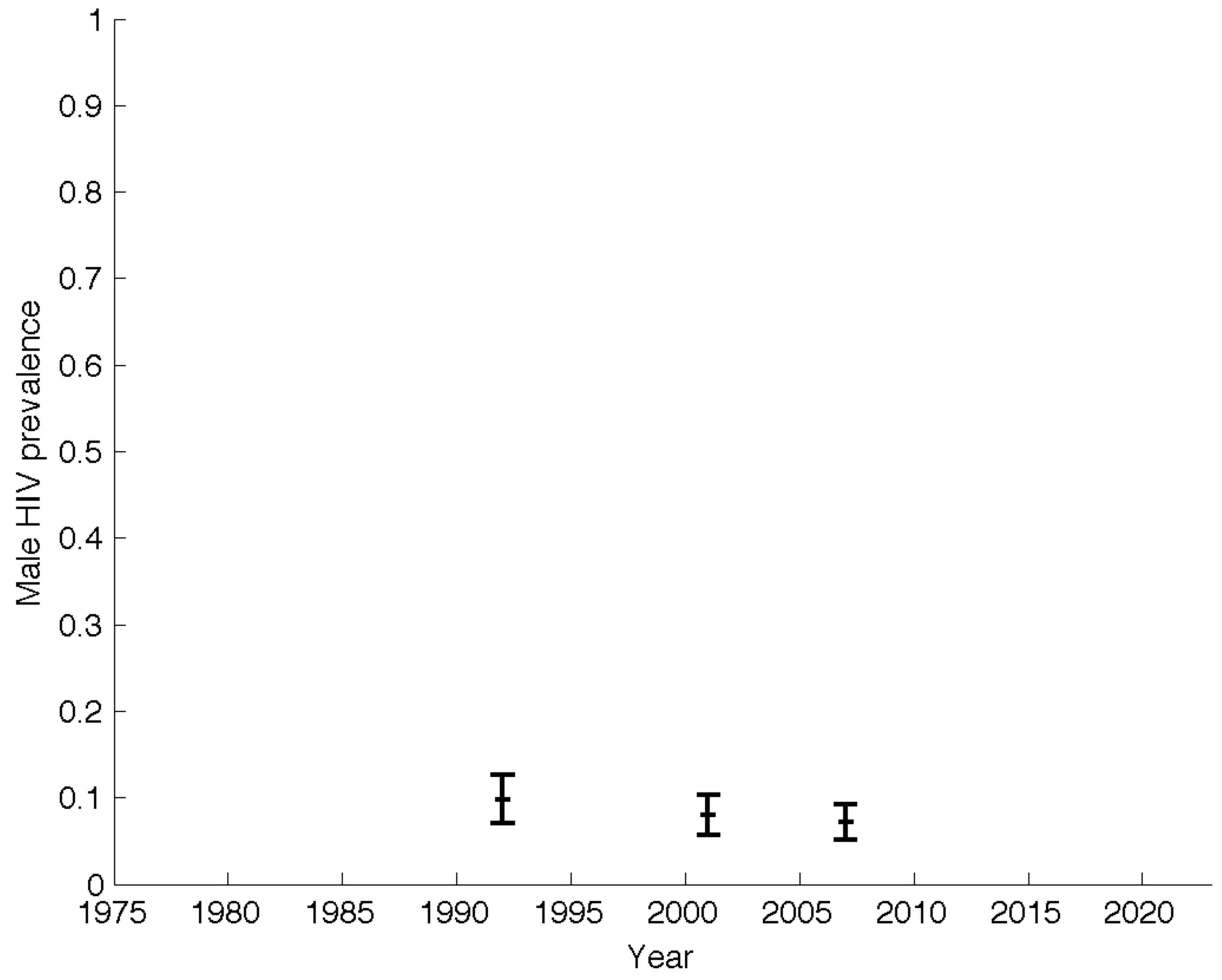
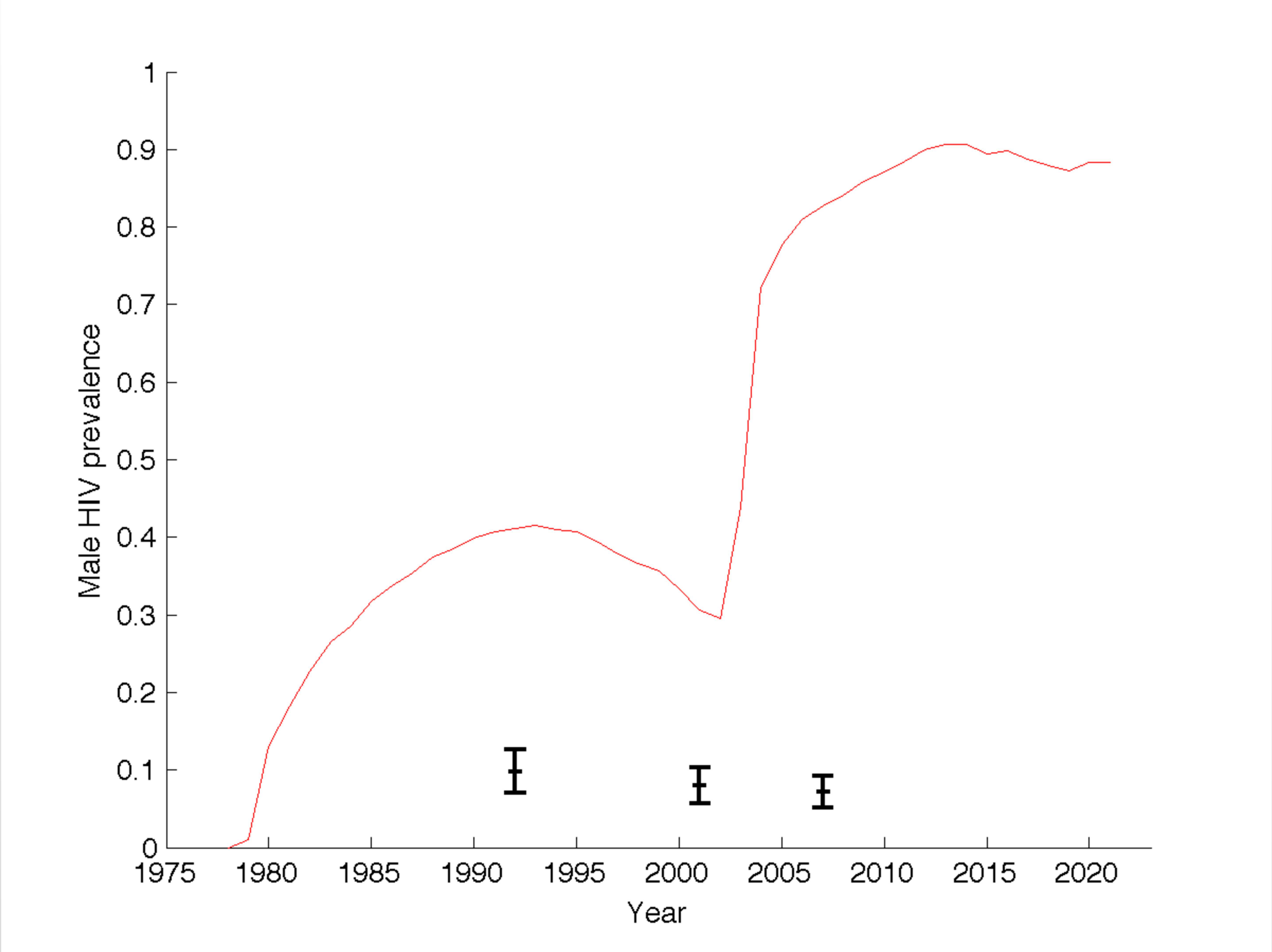


Mukwano Output: Male HIV Prevalence (1 Run)



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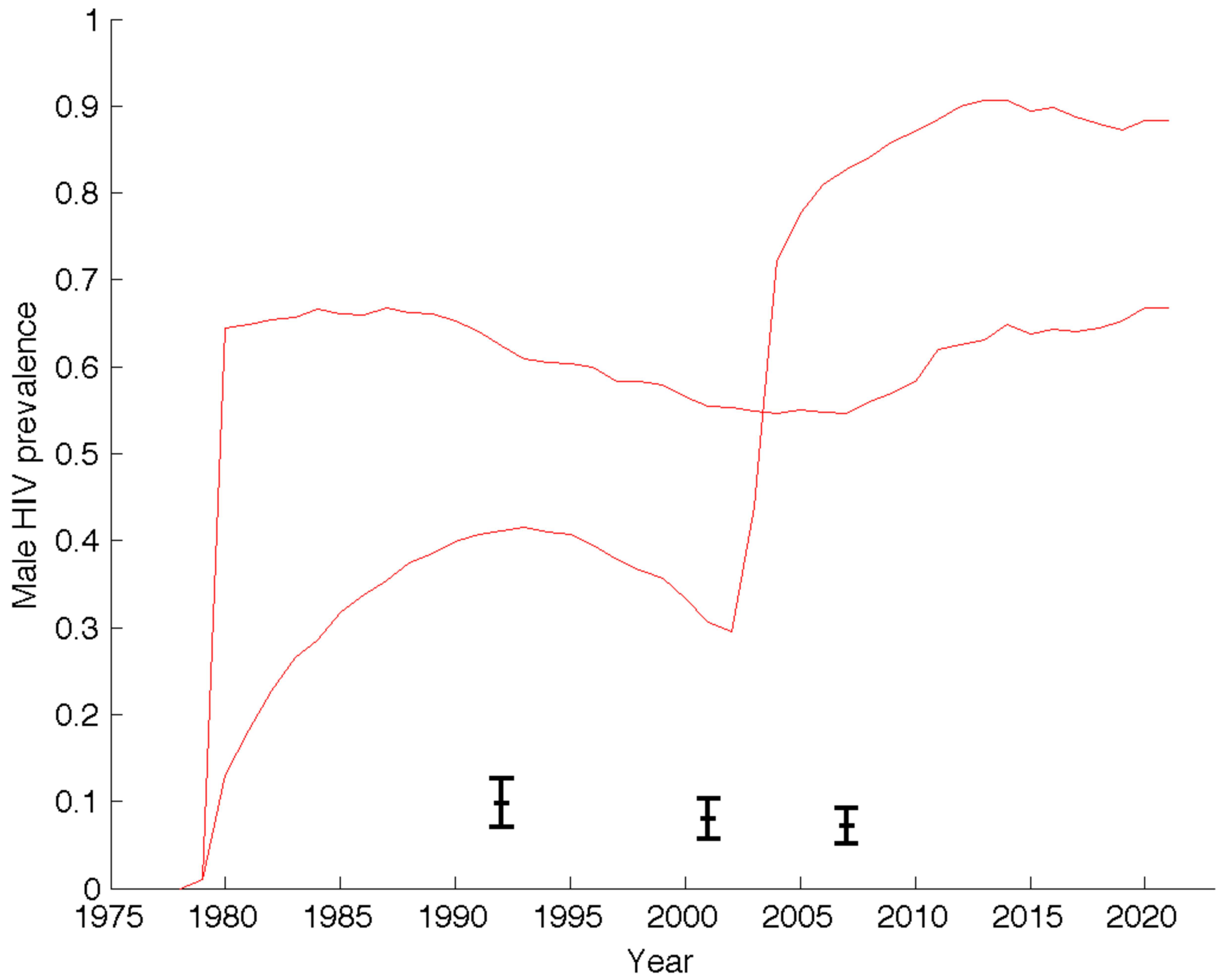
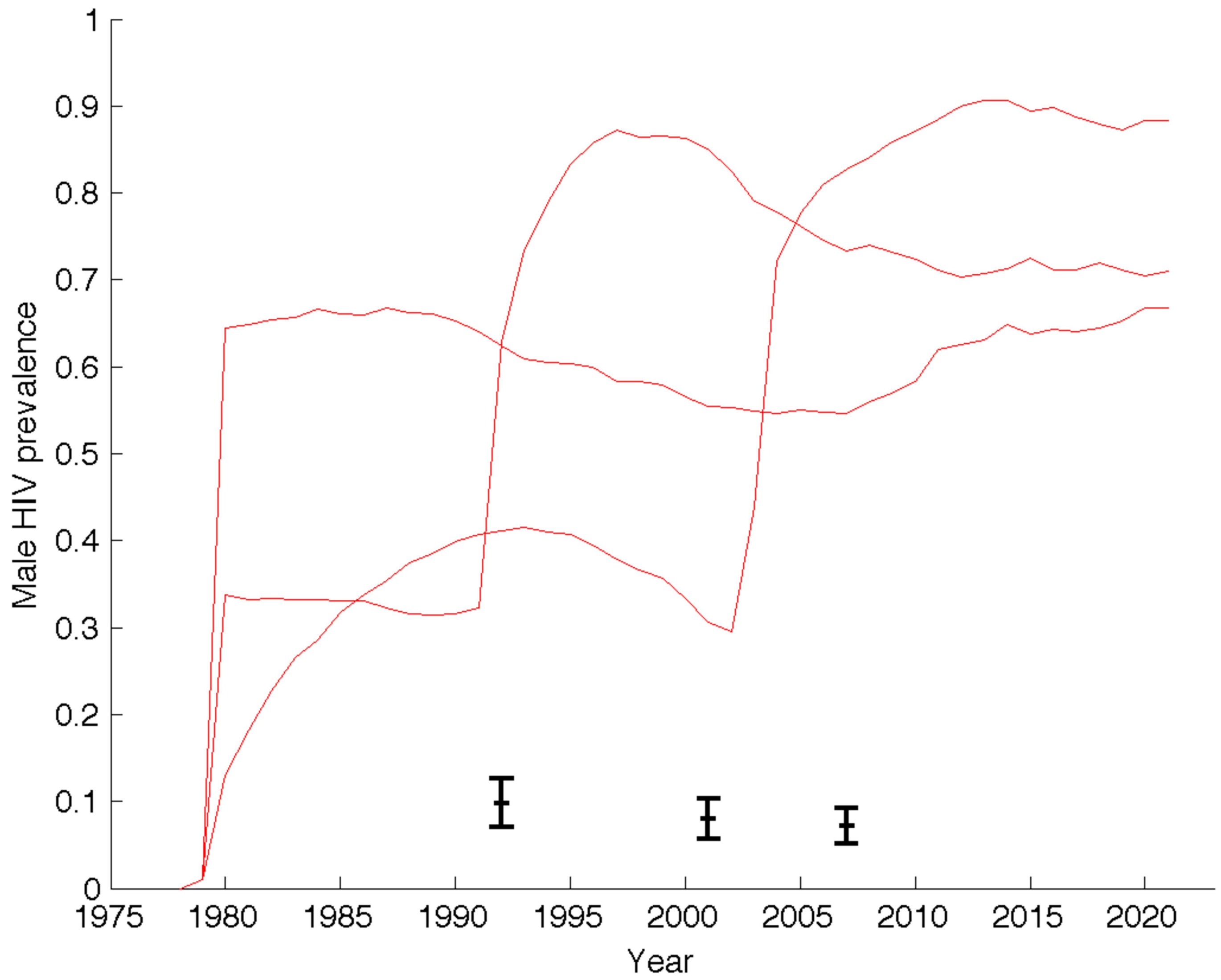
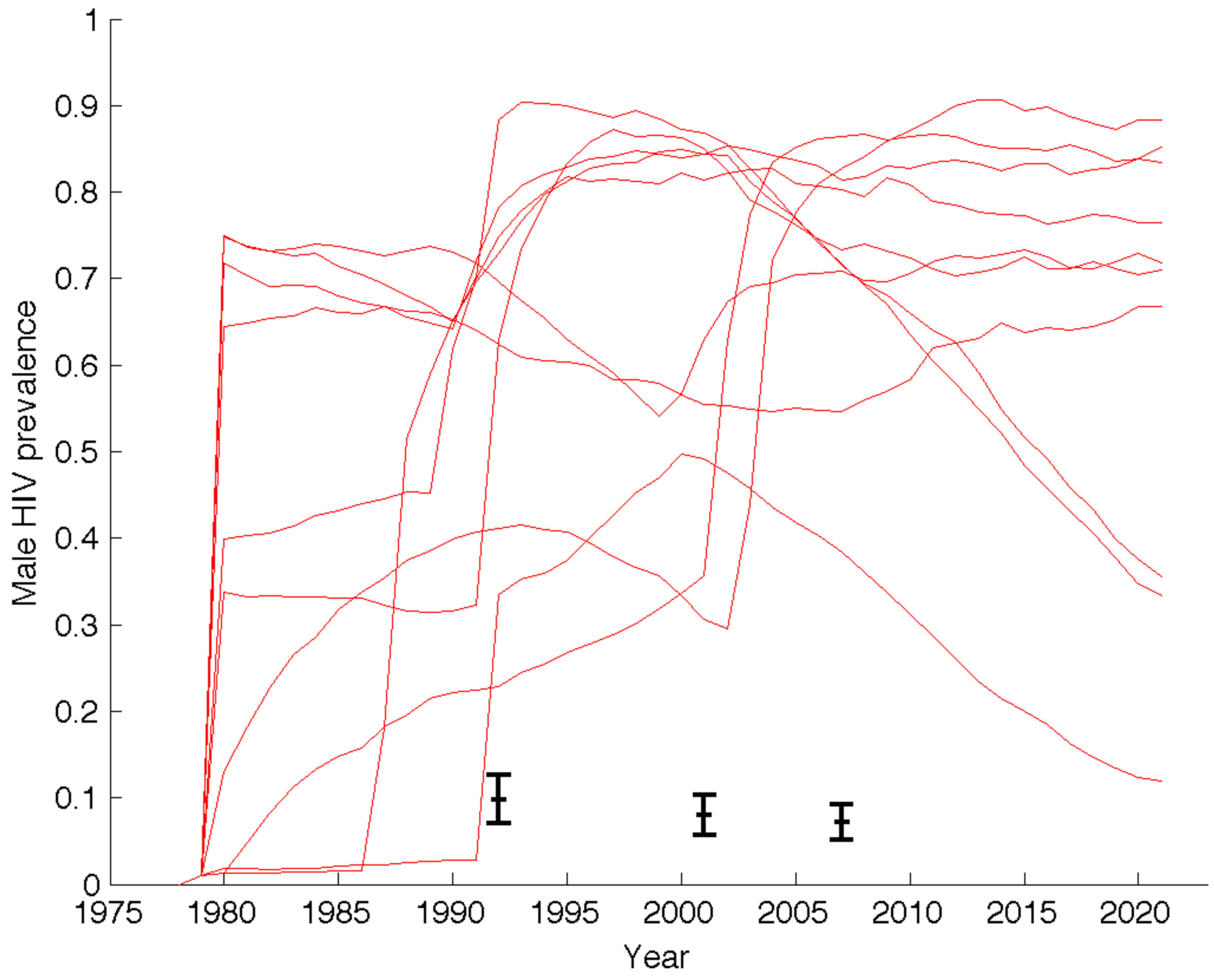


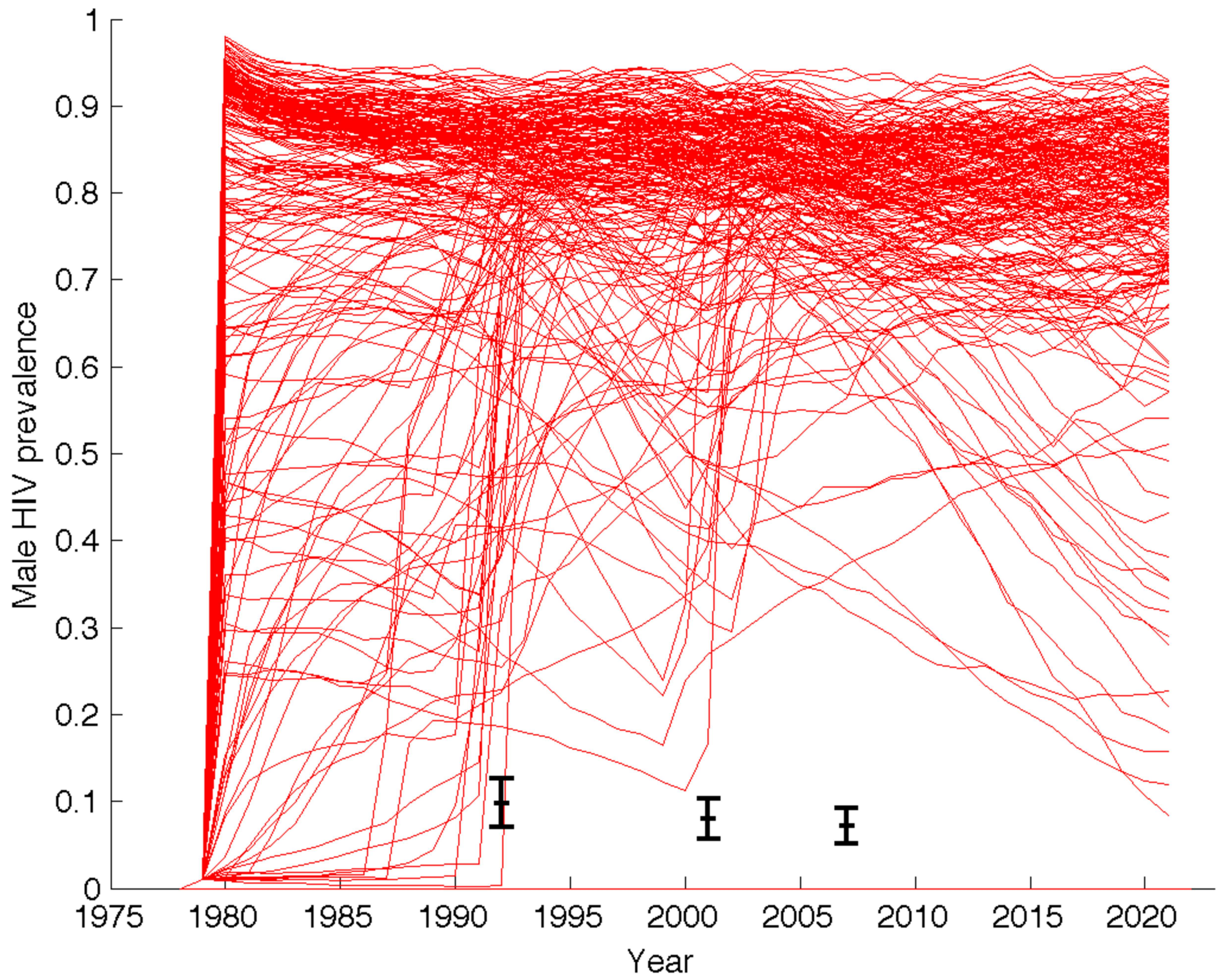
Mukwano Output: Male HIV Prevalence (3 Runs)



Mukwano Output: Male HIV Prevalence (10 Runs)

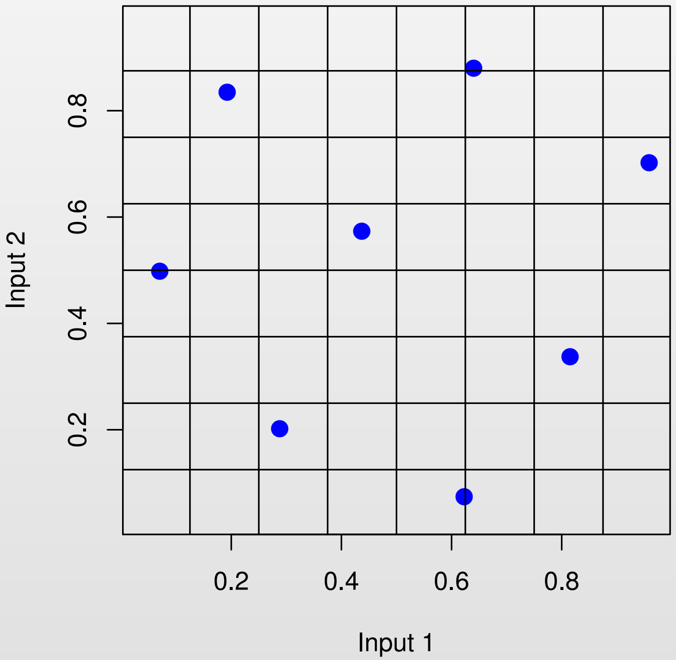


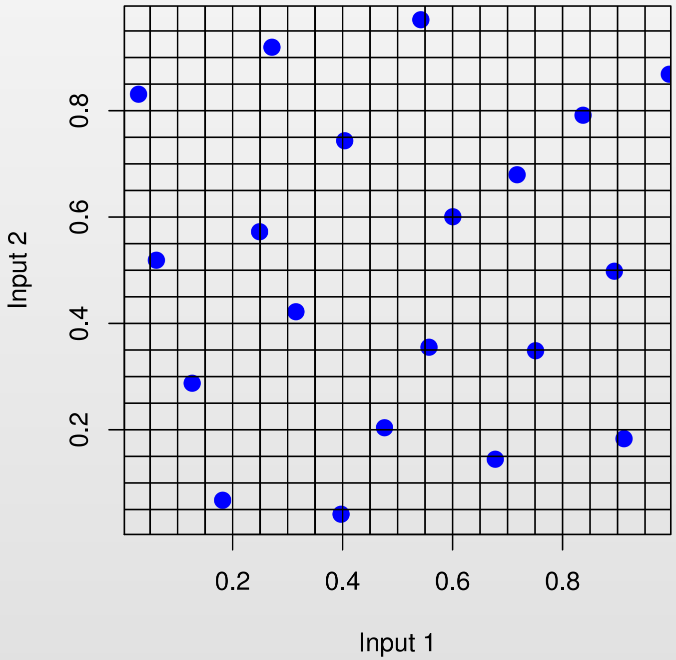
Mukwano Output: Male HIV Prevalence (250 Runs)



Design: Latin Hypercubes

- Design: Construct a batch of runs of the model using a space filling maximin Latin Hypercube design:





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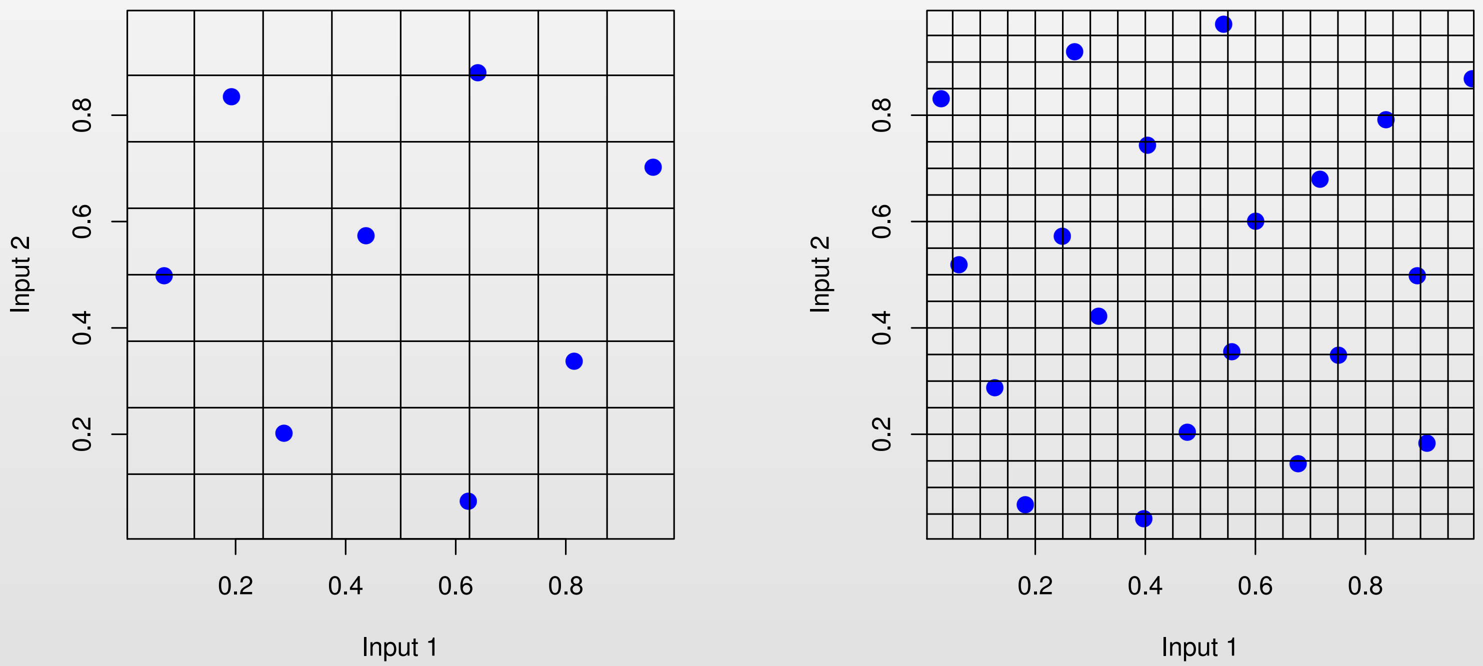

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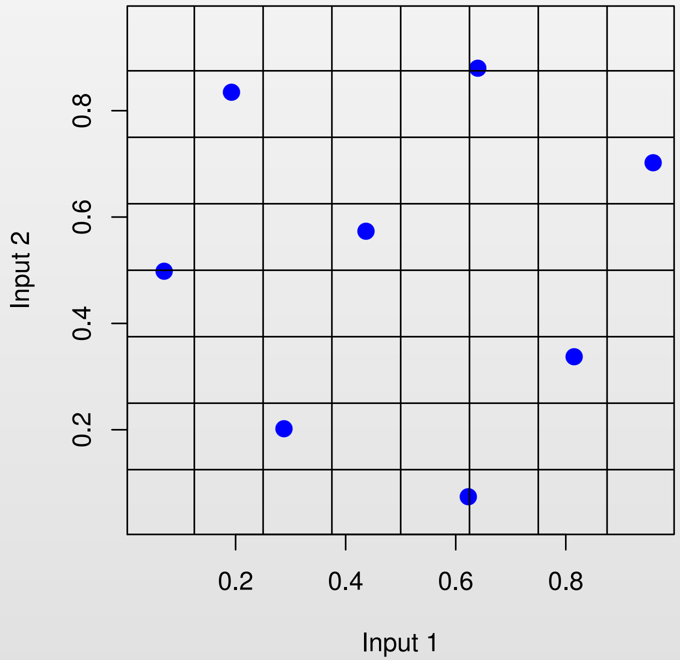

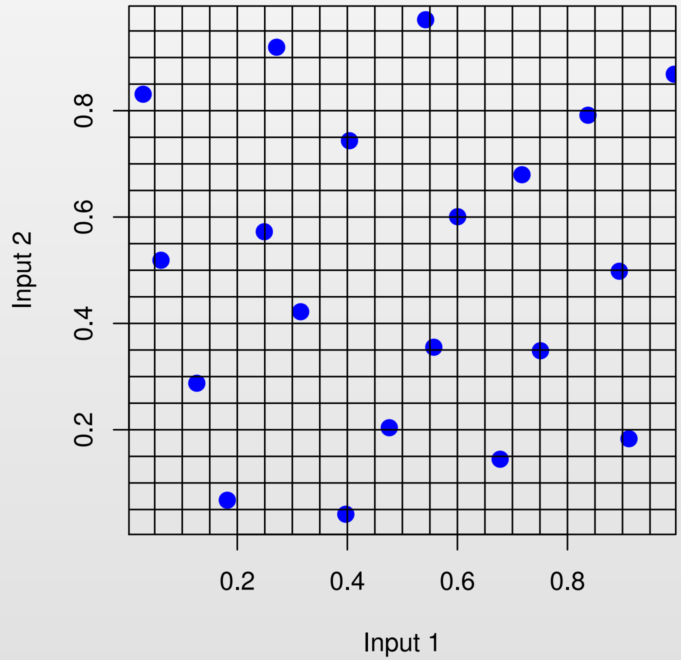

- These designs are both space filling and approximately orthogonal, both desirable features for fitting emulators.
- We evaluated 250 runs of the model for the first Wave.

Observed data: 1D example

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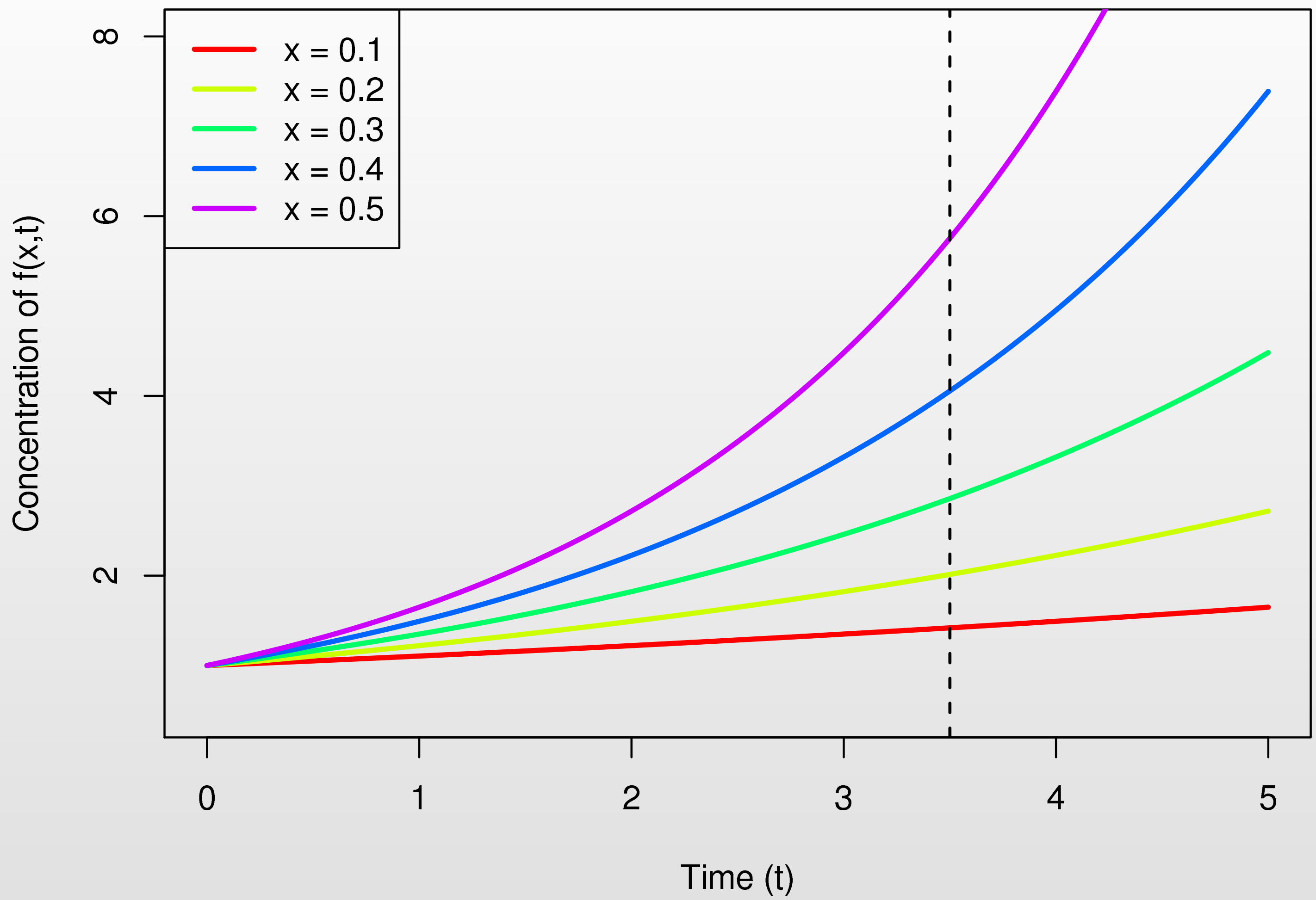

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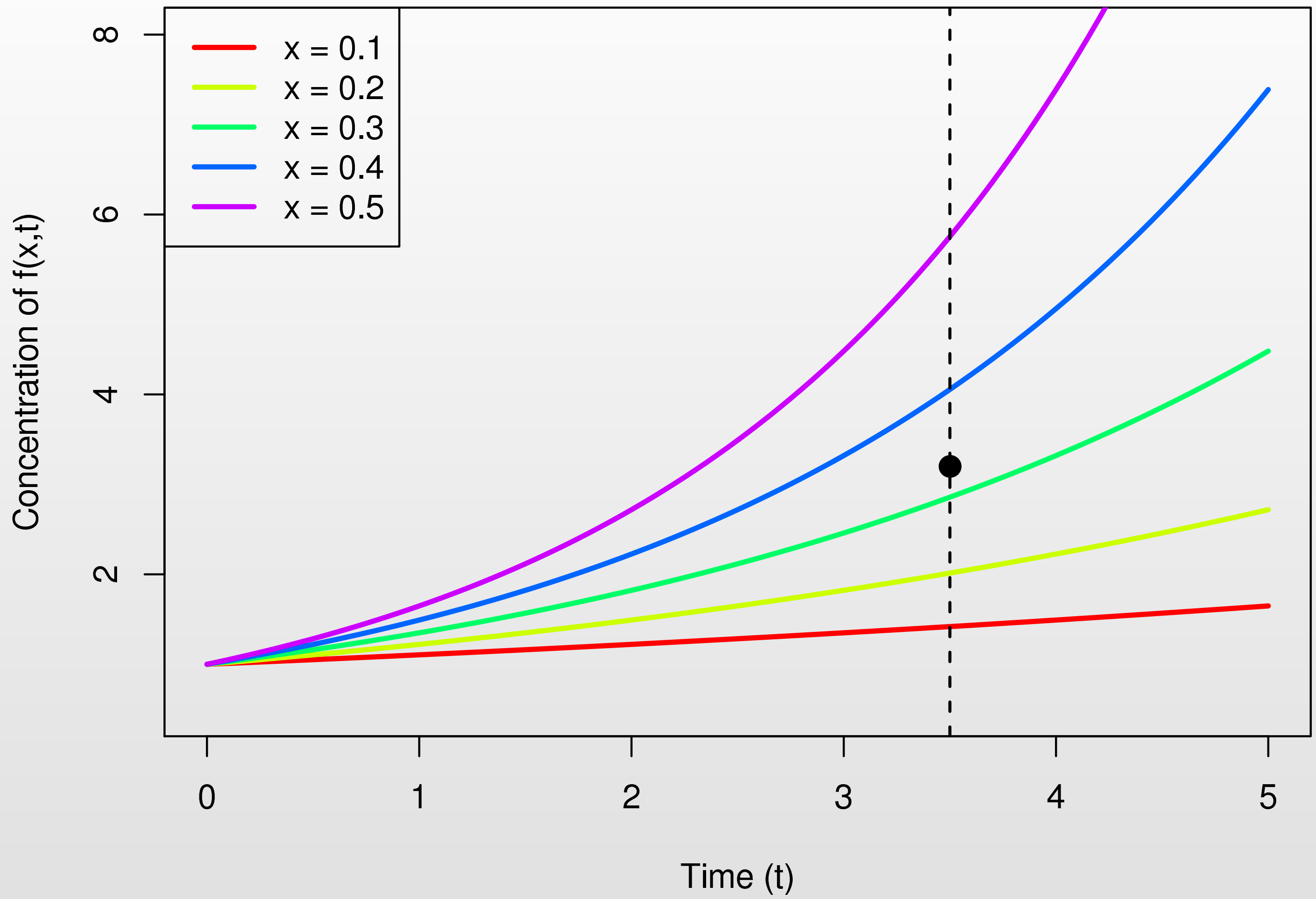

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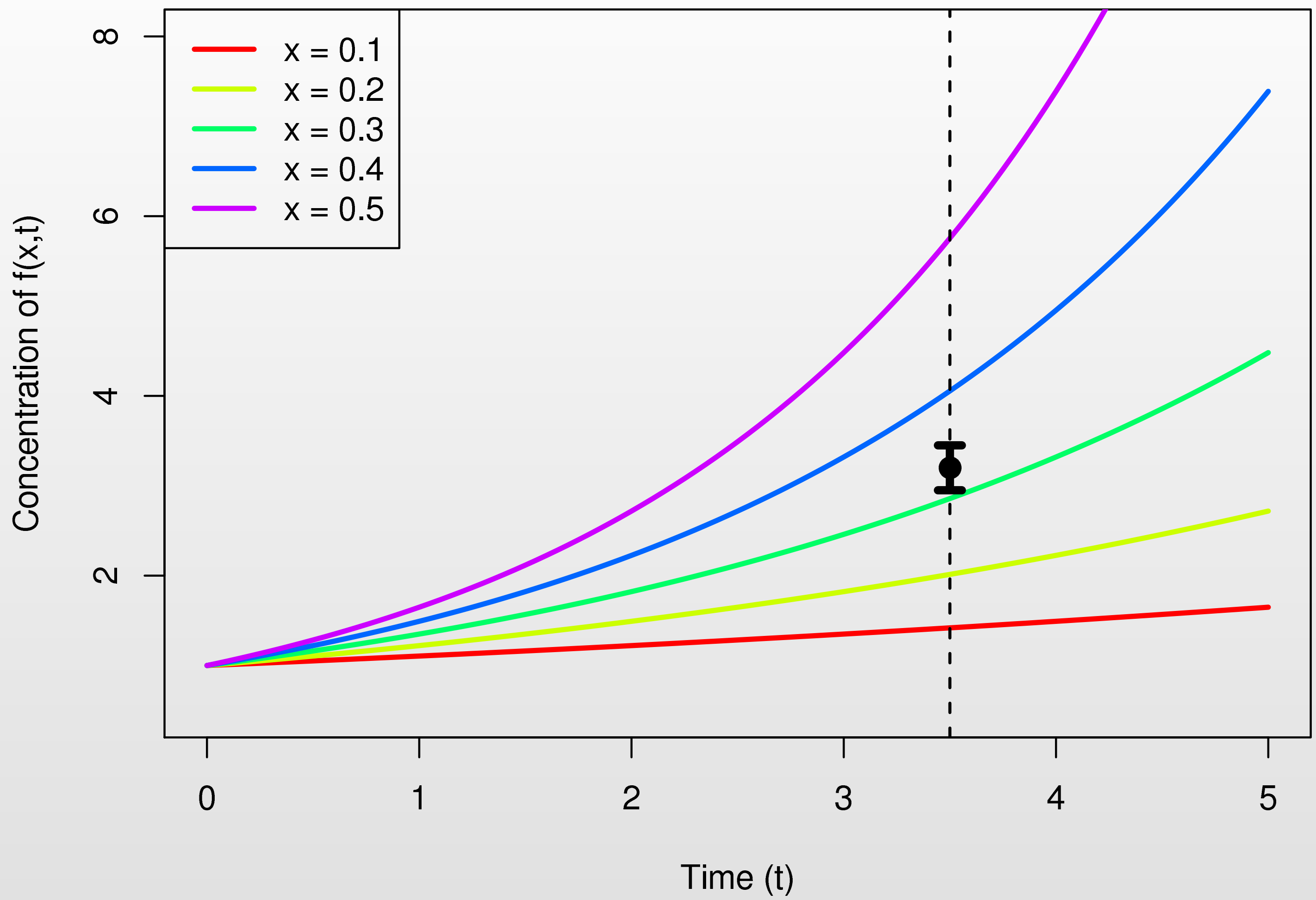

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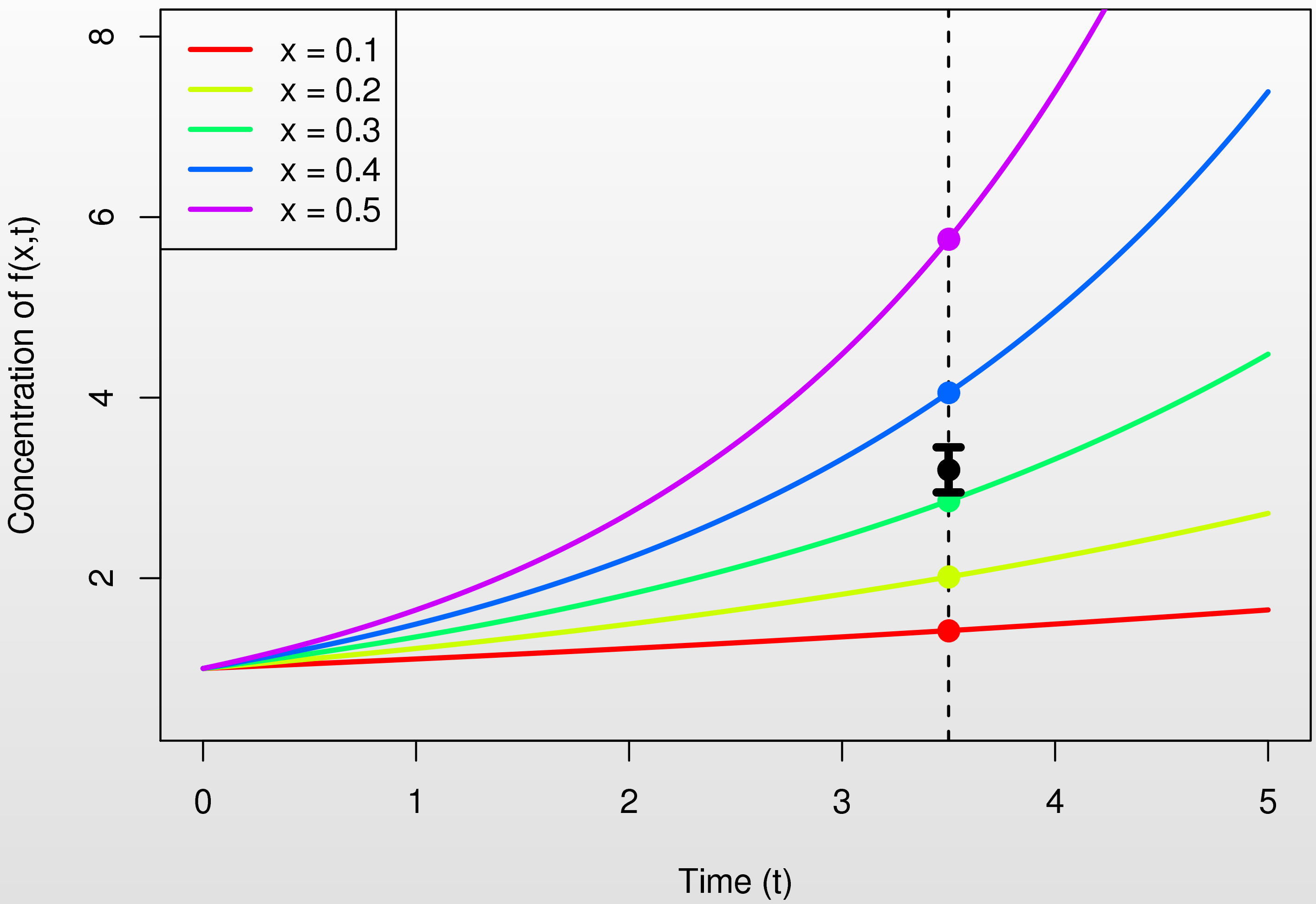

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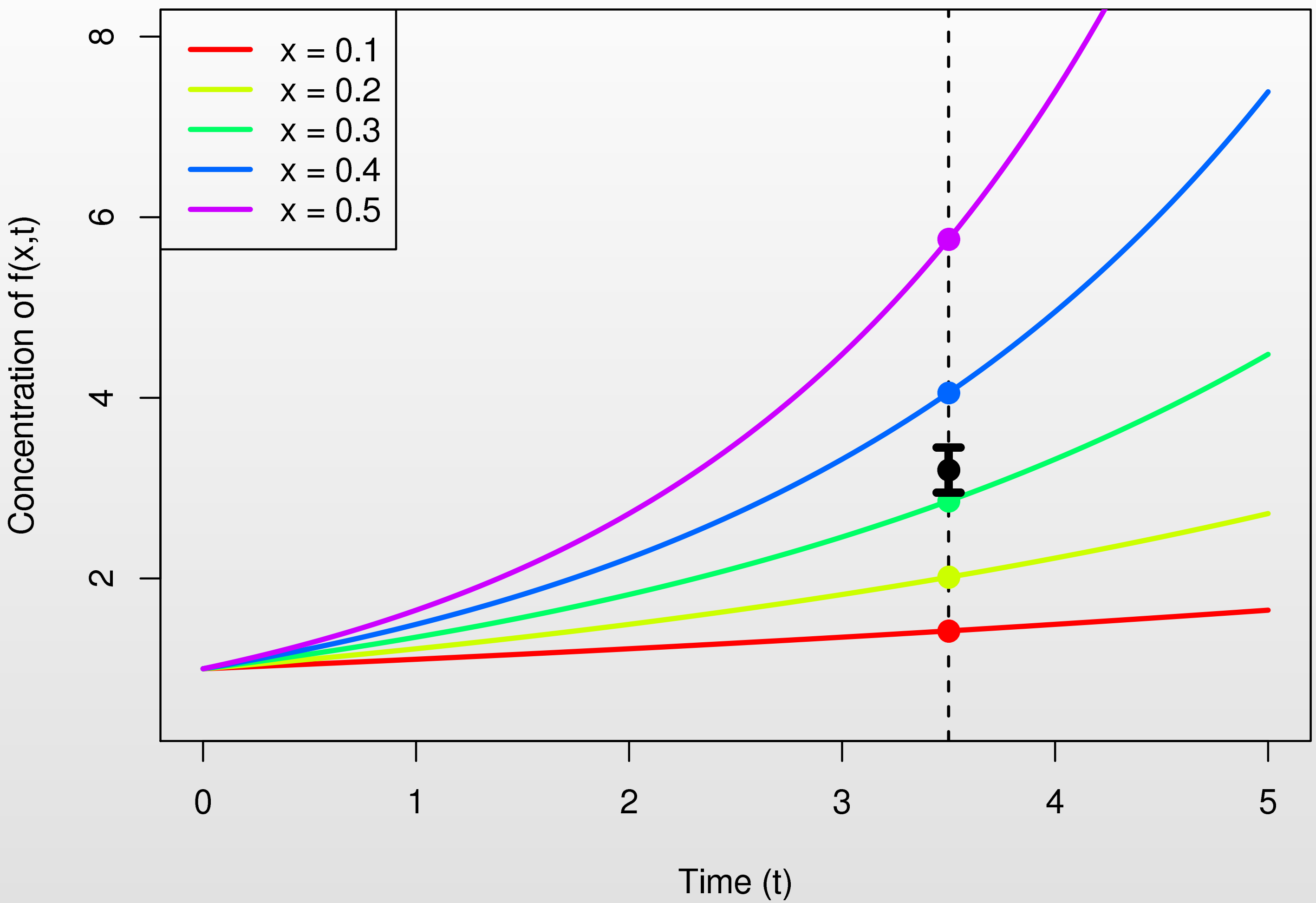

- Major question: which values of x ensure the output $f(x, t = 3.5)$ is consistent with the observations?
- It would seem that x has to be at least between 0.3 and 0.4.

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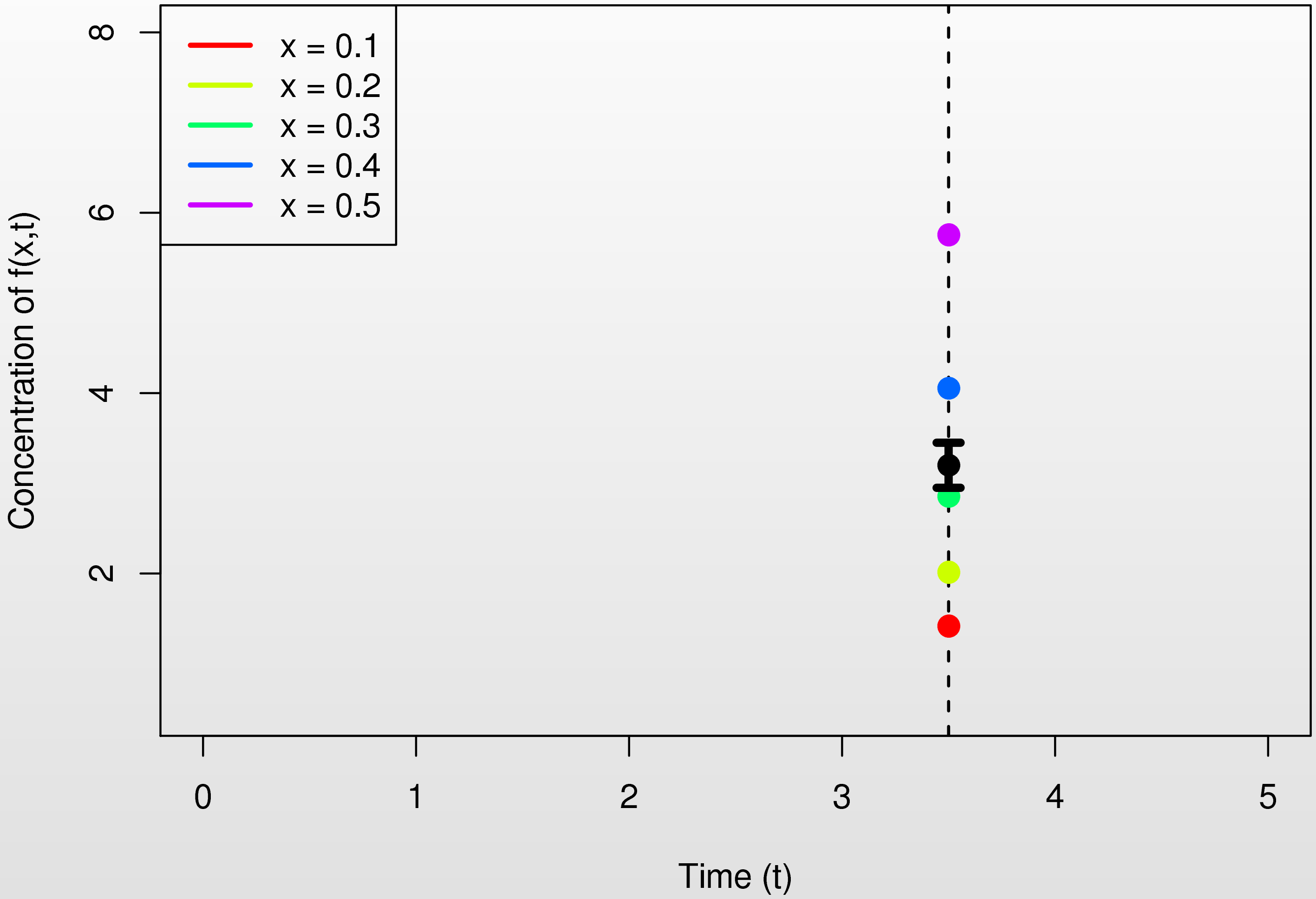

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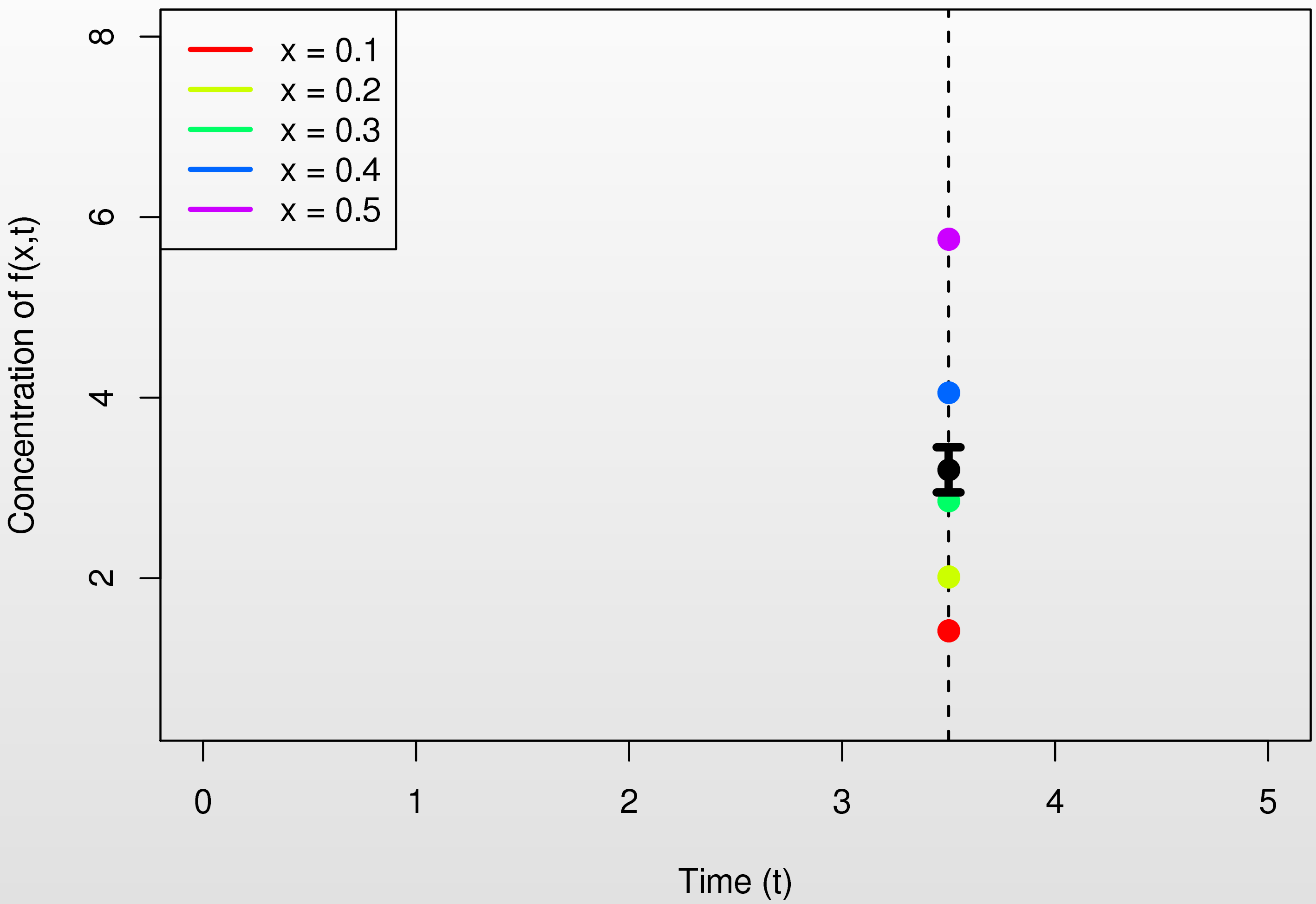
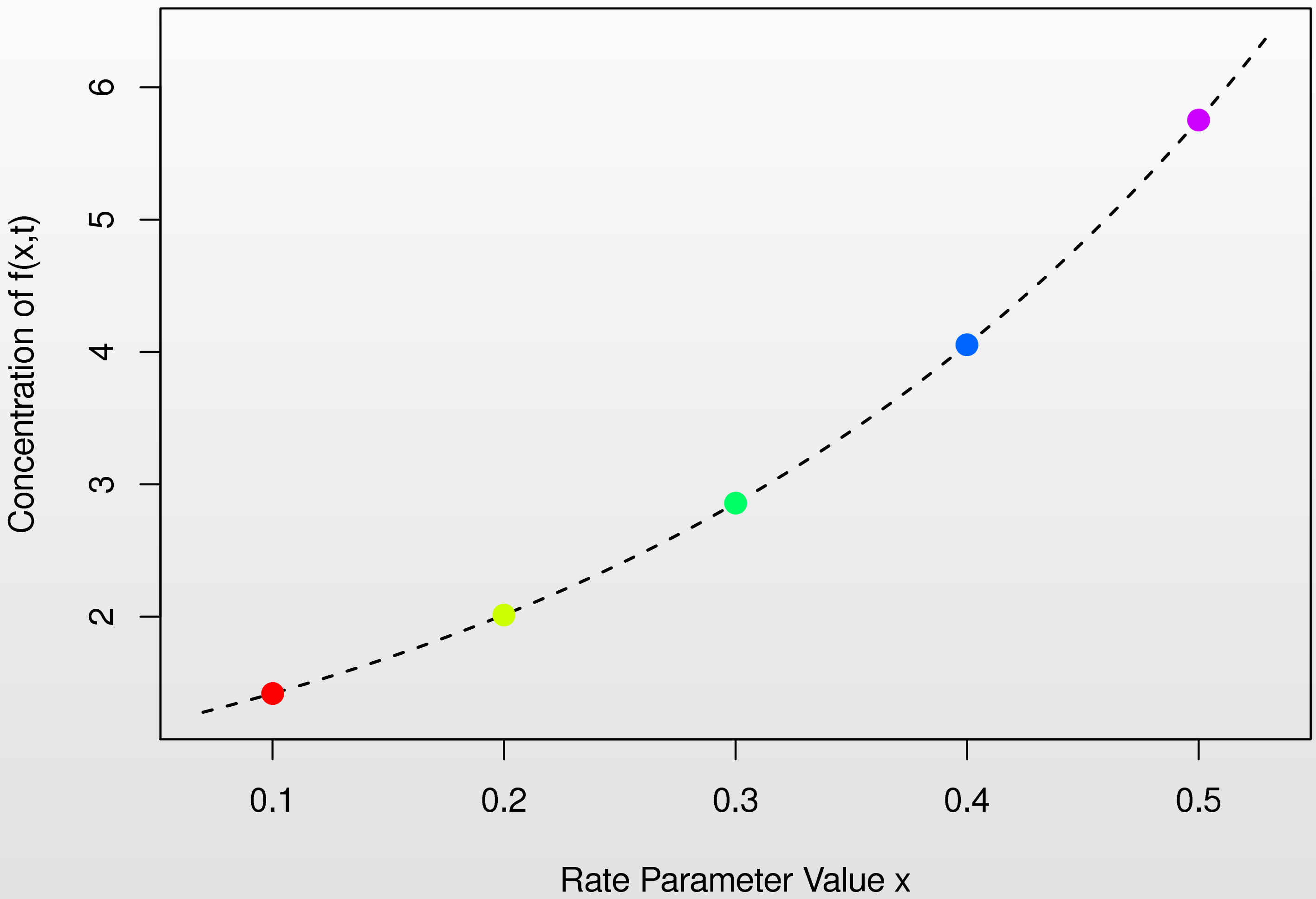


- To answer this, we can now discard other values of $f(x,t)$ and think of $f(x,t=3.5)$ as a function of x only.
- That is take $f(x) \equiv f(x,t=3.5)$

Observed errors and Model Discrepancy: 1D example



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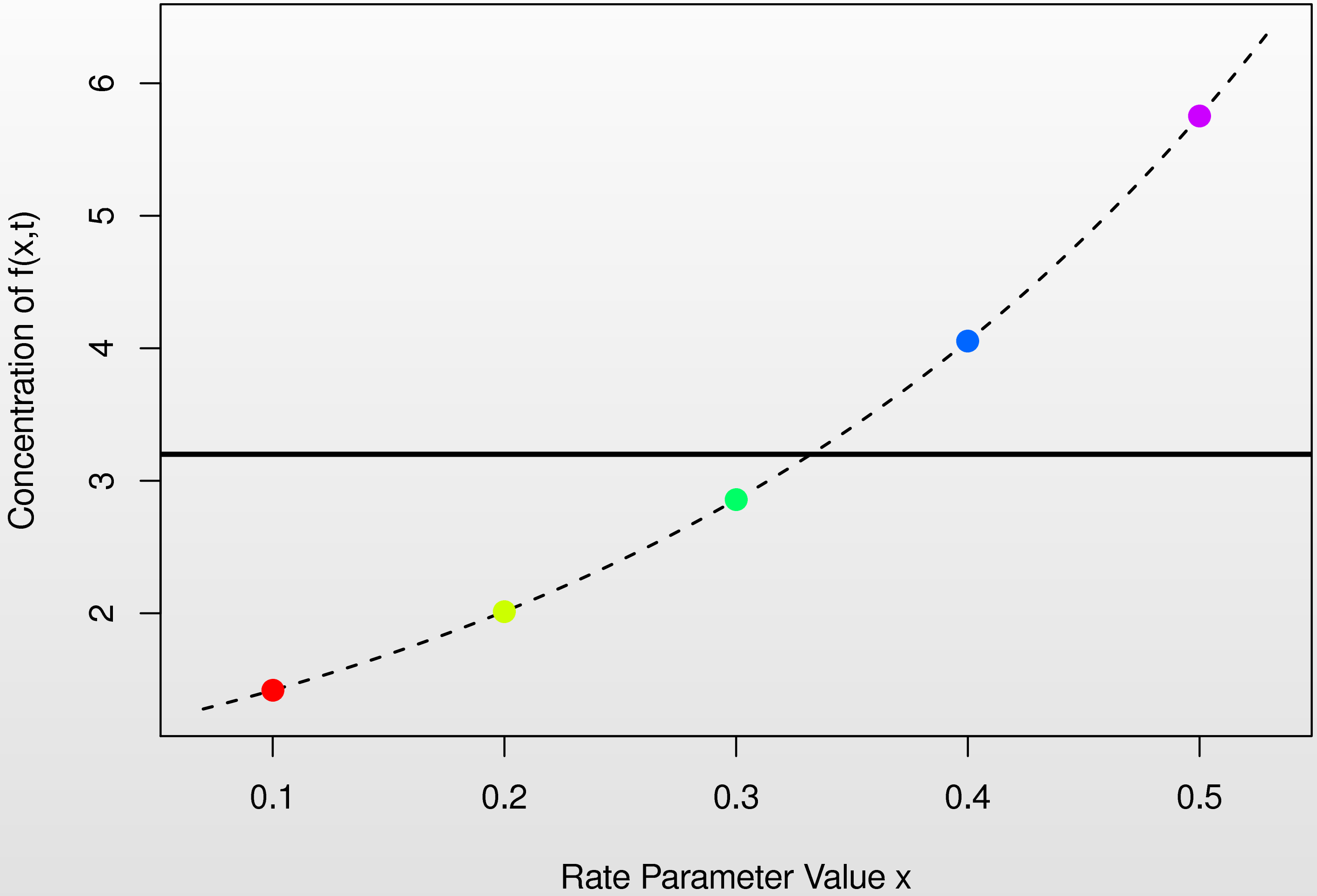

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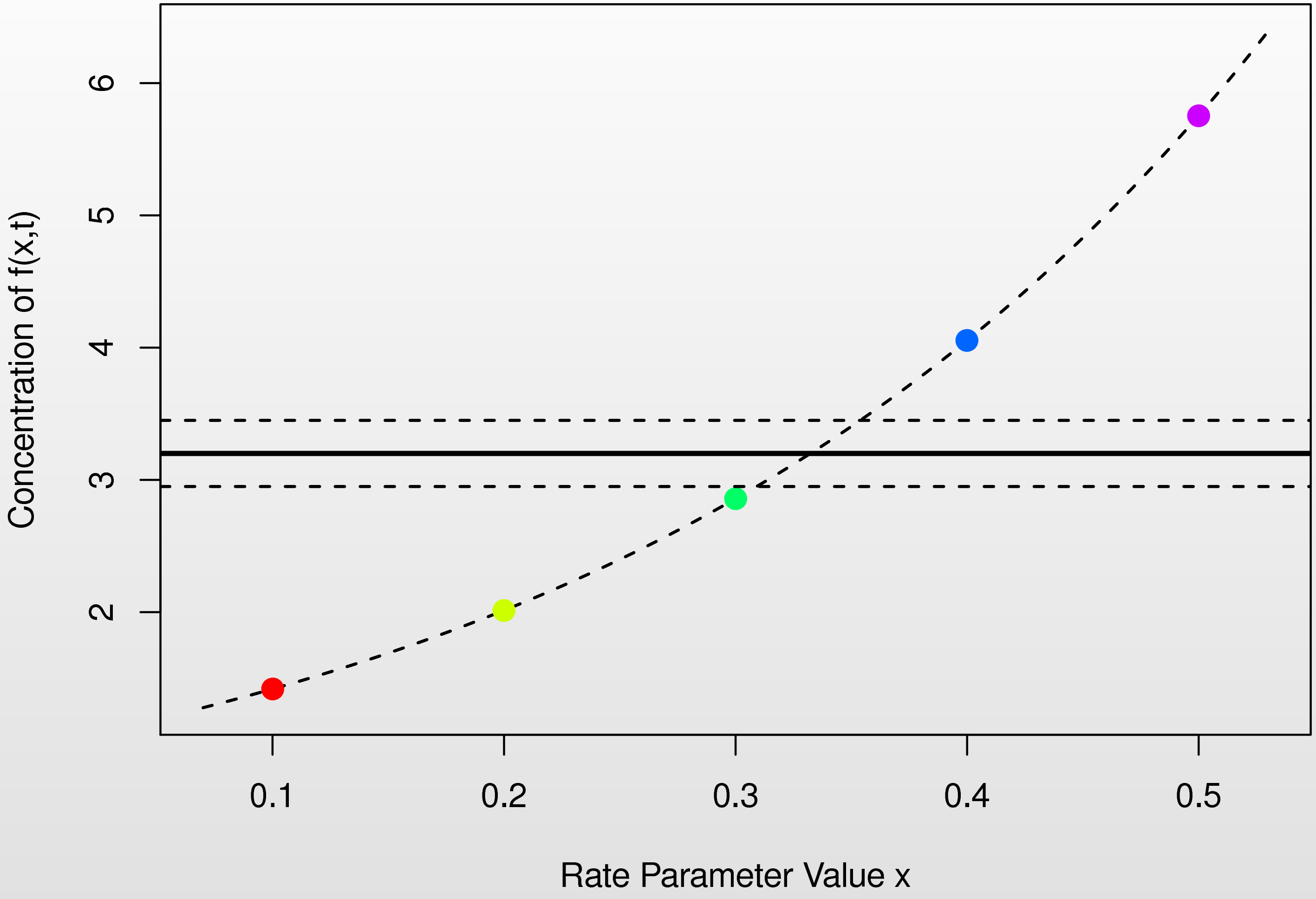

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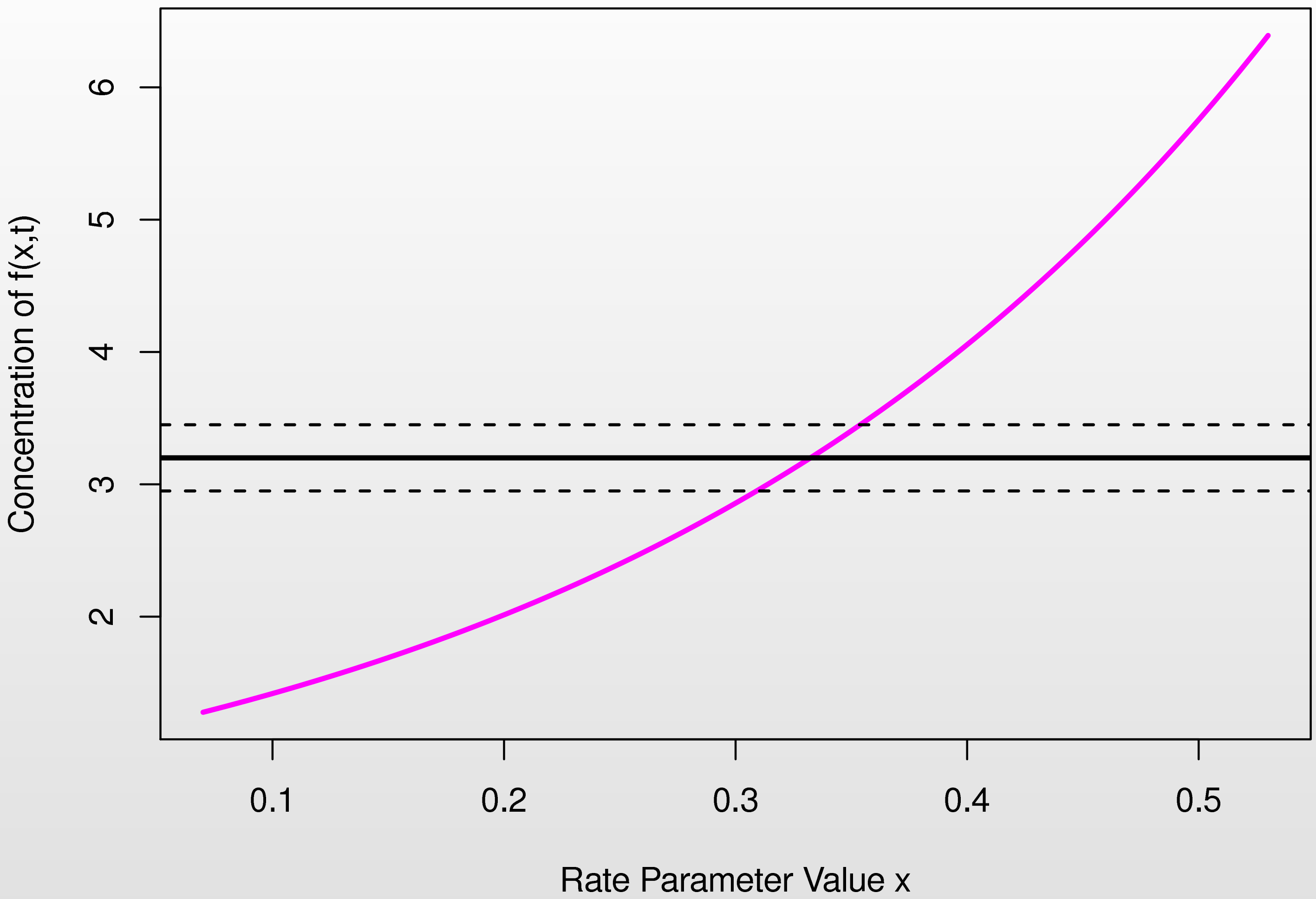

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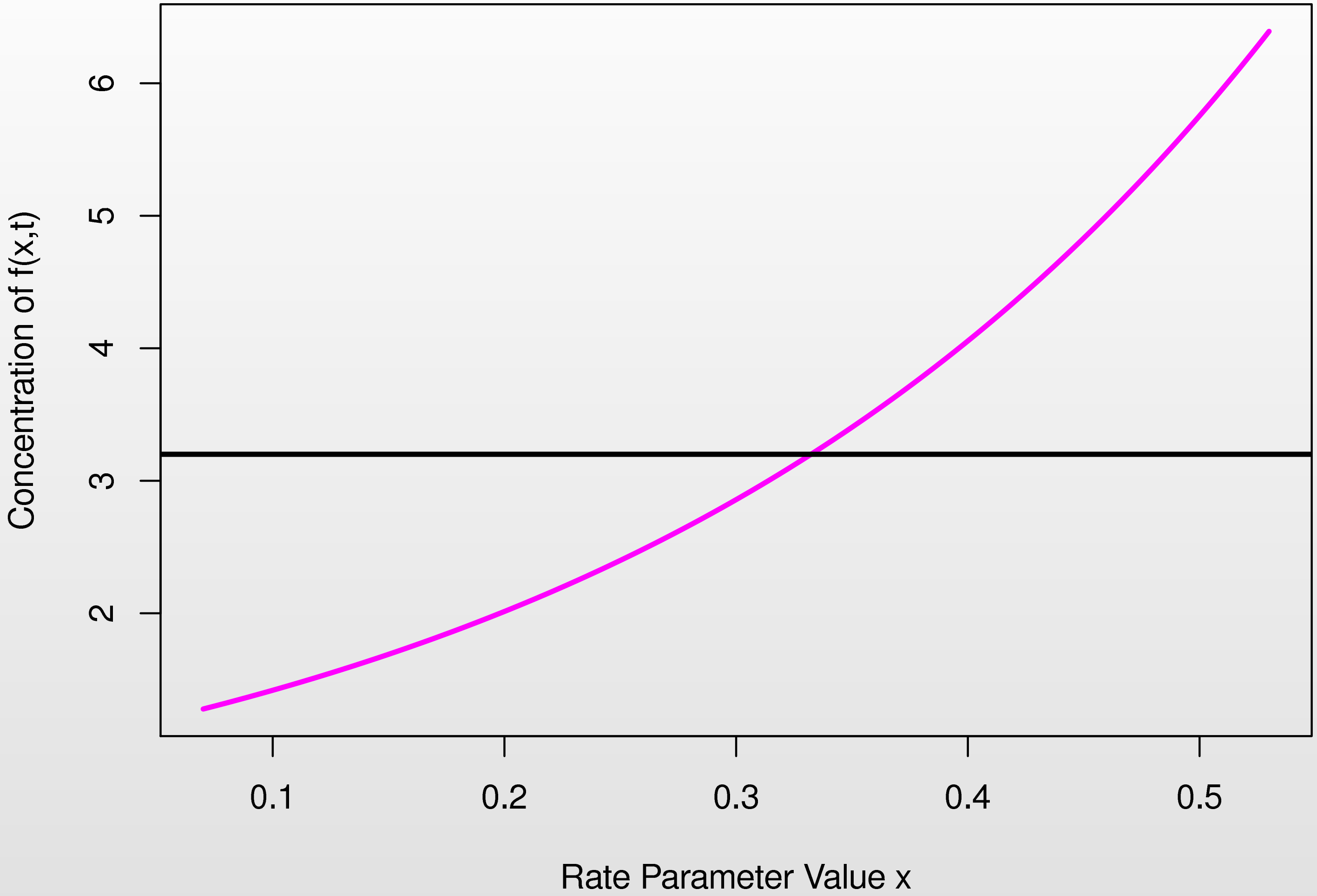

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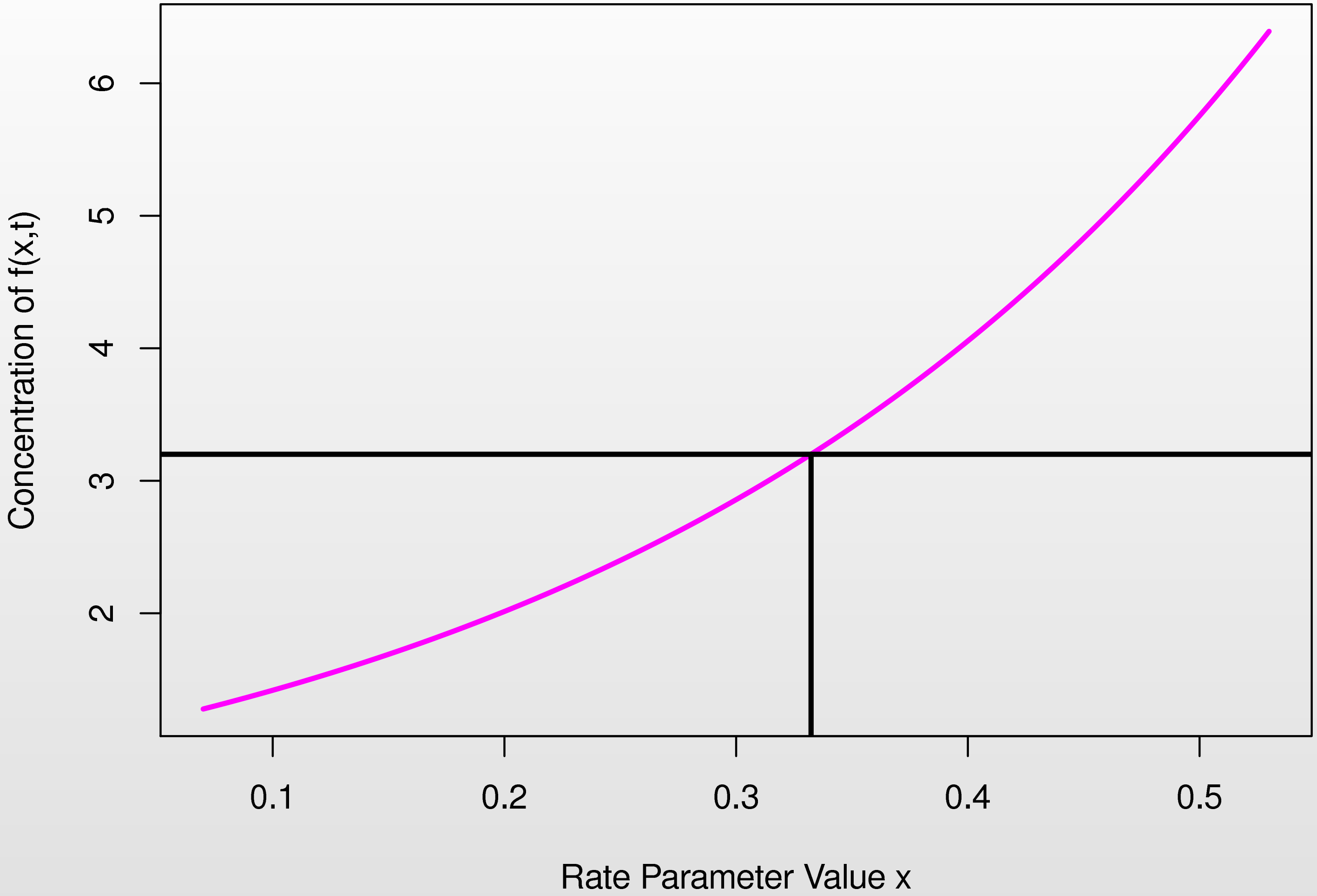

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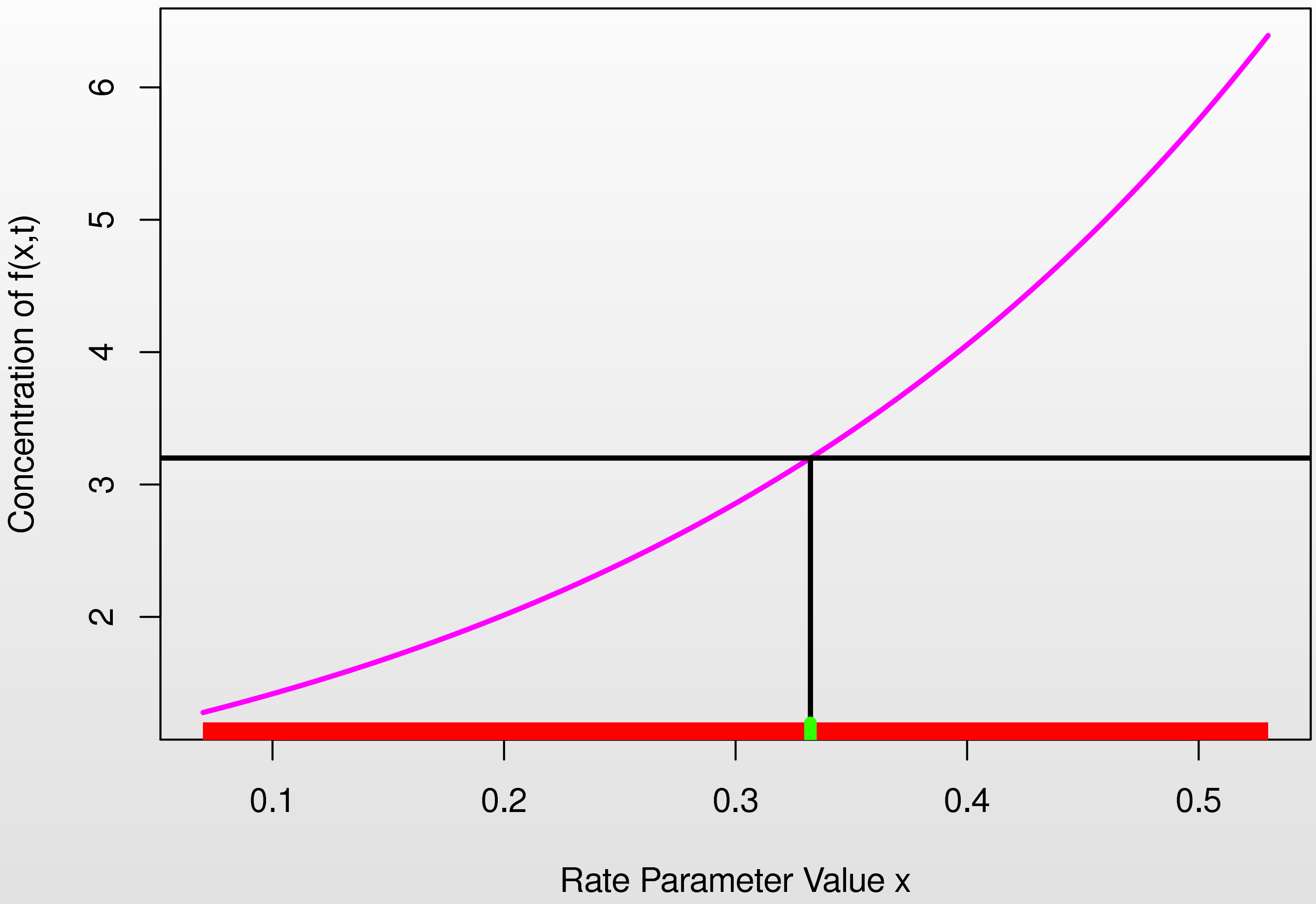

- If we know the analytical expression for $Y(k) = \exp(3.5k)$, then we can identify the values of x of interest.
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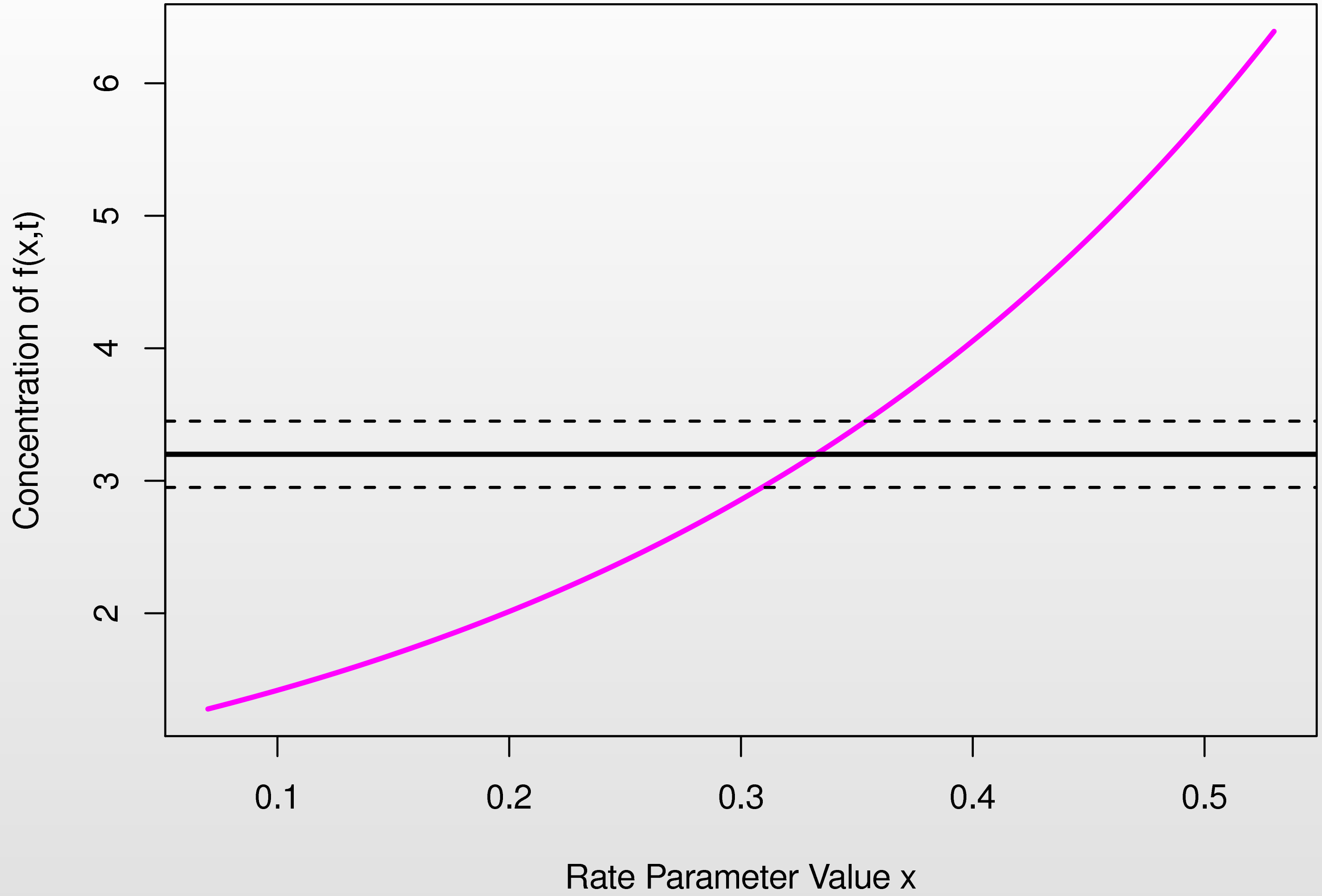

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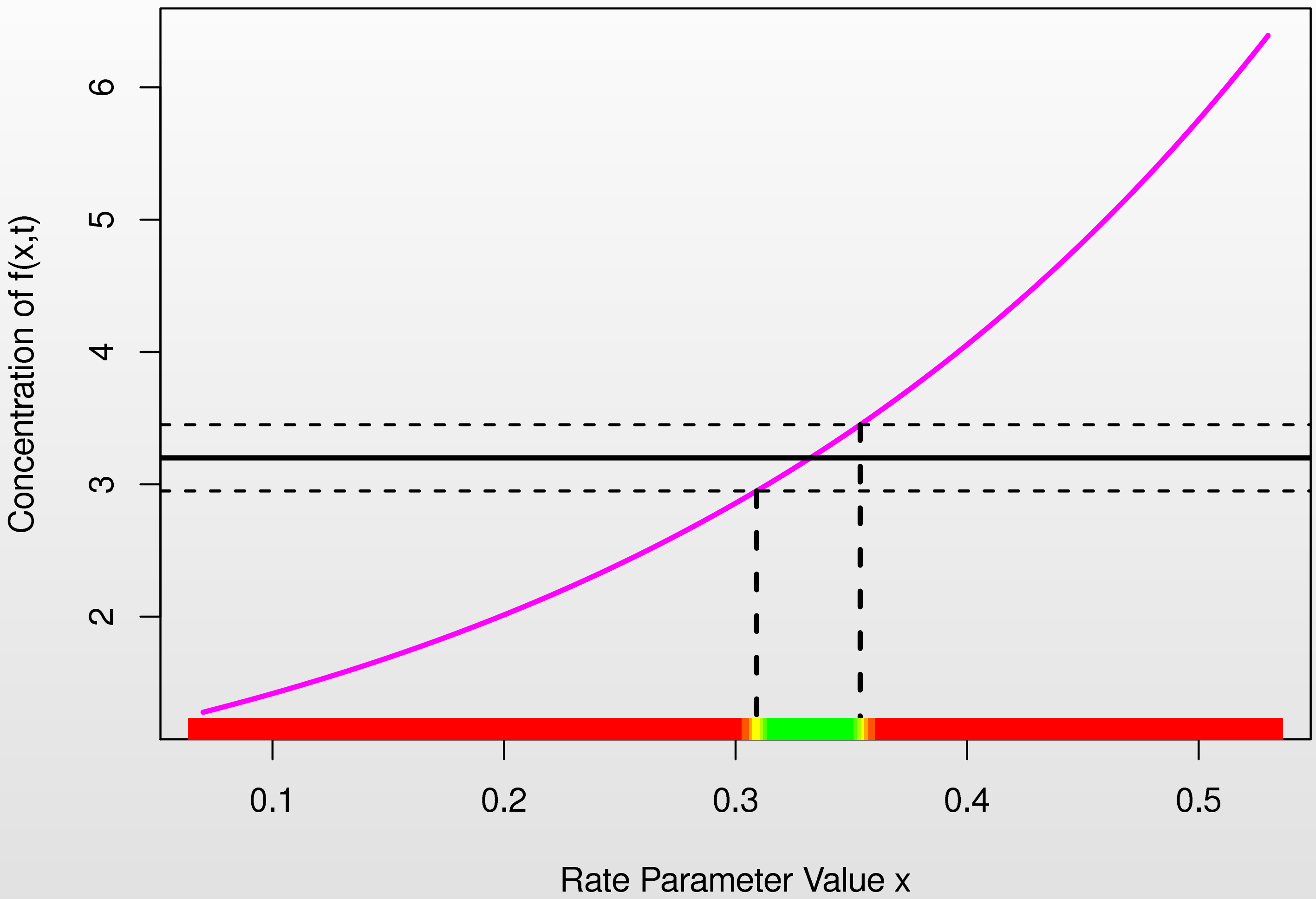

- Uncertainty in the measurement of $f(x,t)$ leads to uncertainty in the inferred values of x.
- Hence we see a range (green/yellow) of possible values of x consistent with the measurements, with all the implausible values of x in red.

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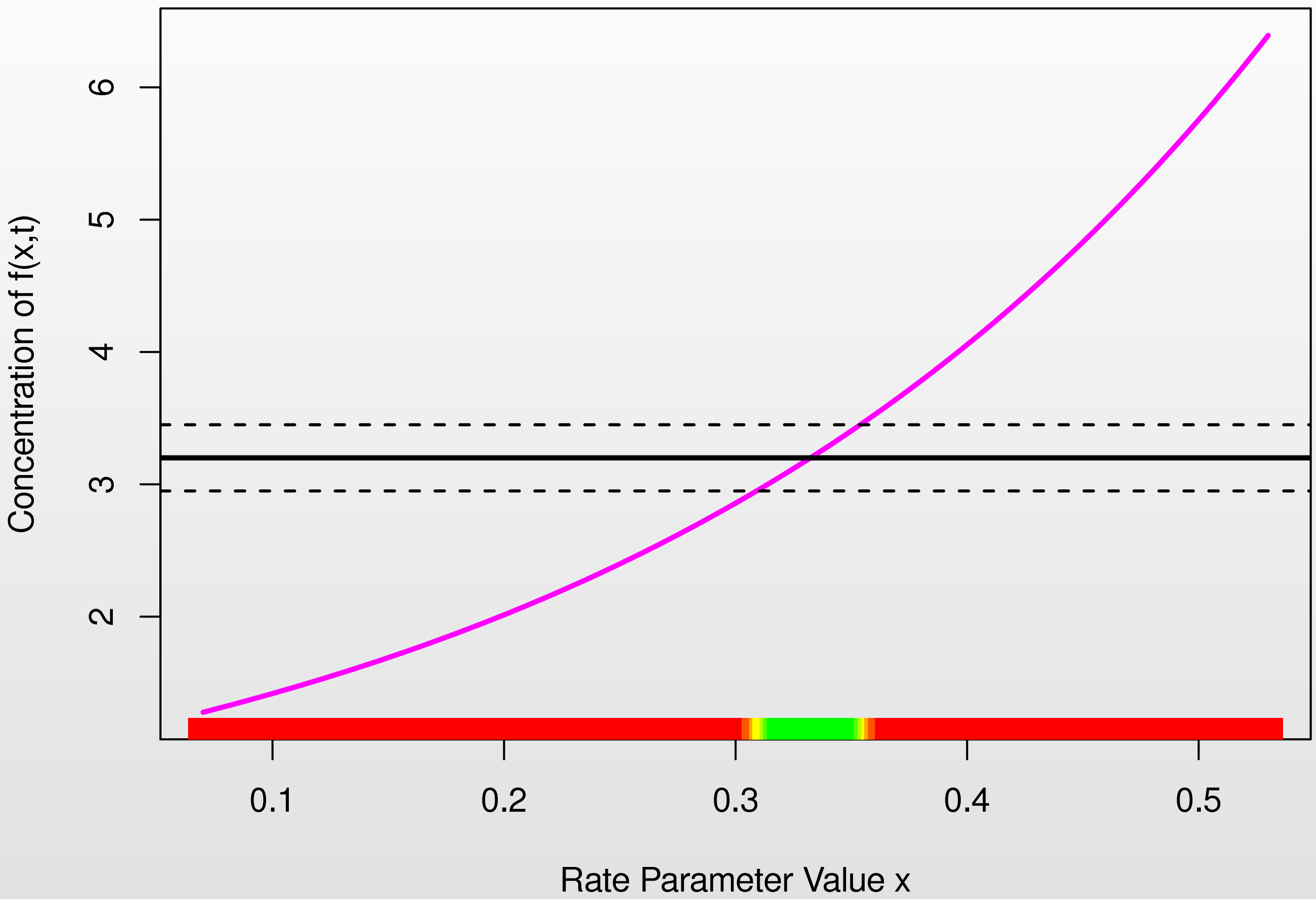

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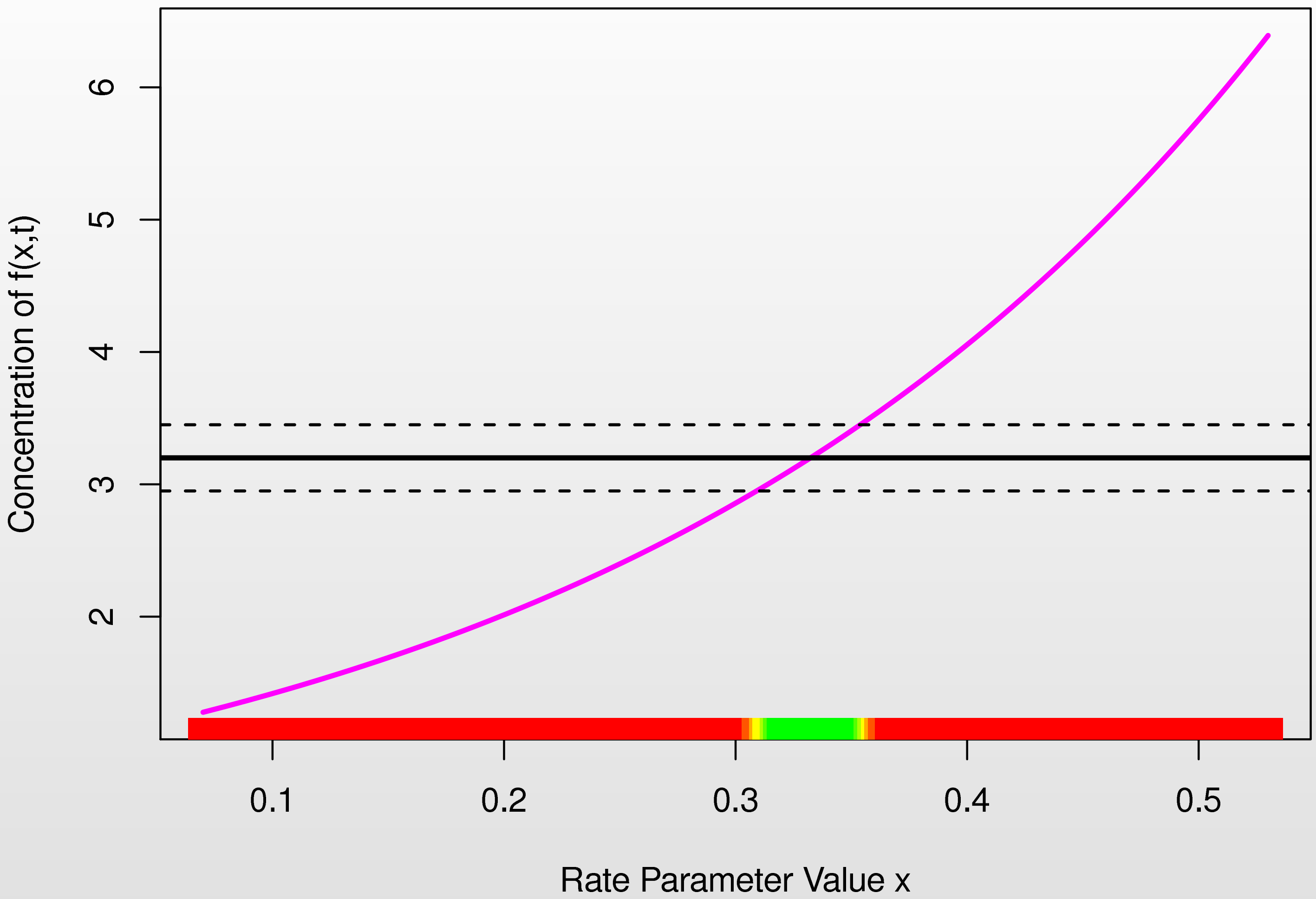

- Another important form of uncertainty is that of model discrepancy related to how accurate we believe the model to be.
- This uncertainty arises from many issues: is the form of model appropriate, is the model a simplified description of a more complex system etc?

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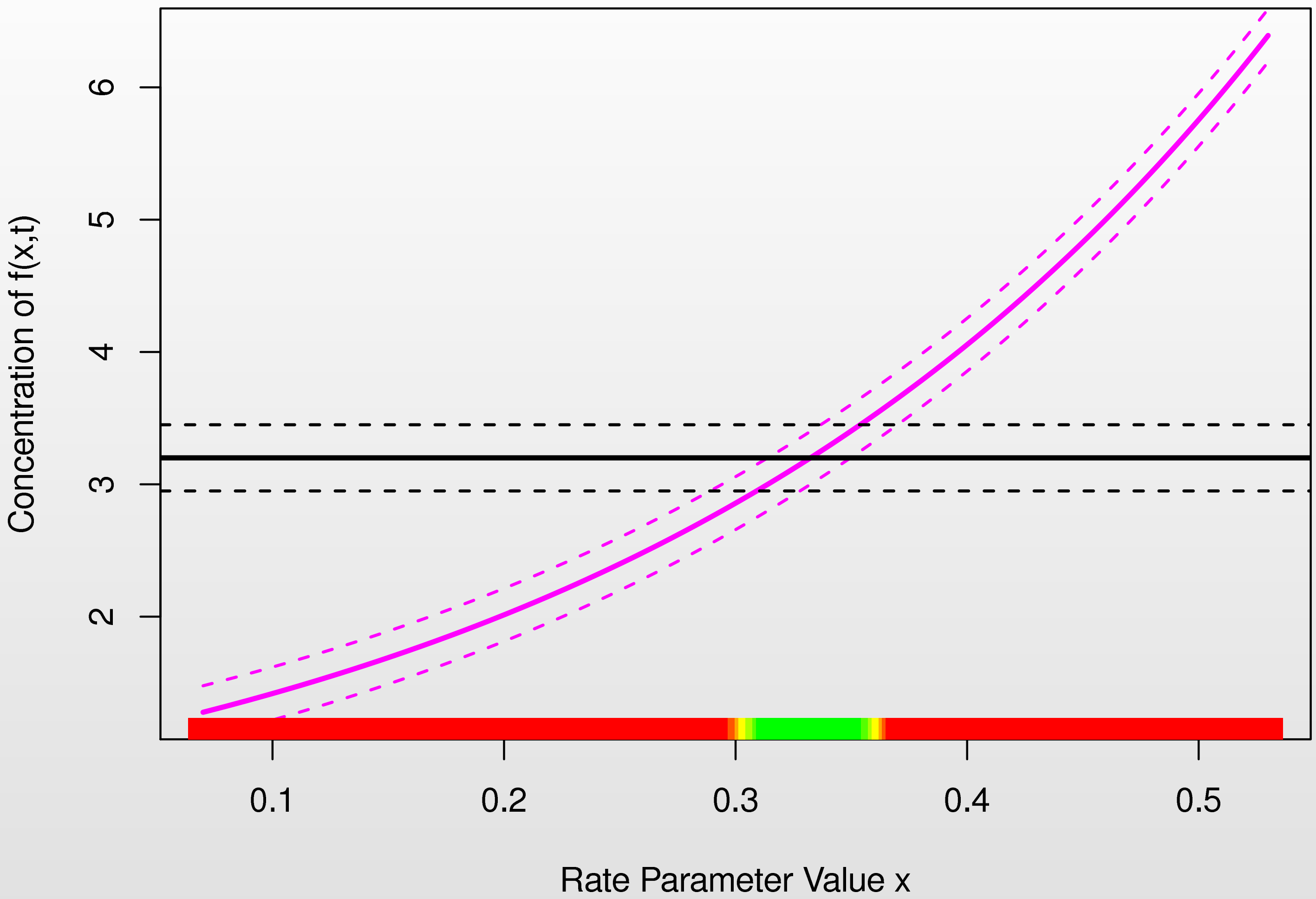

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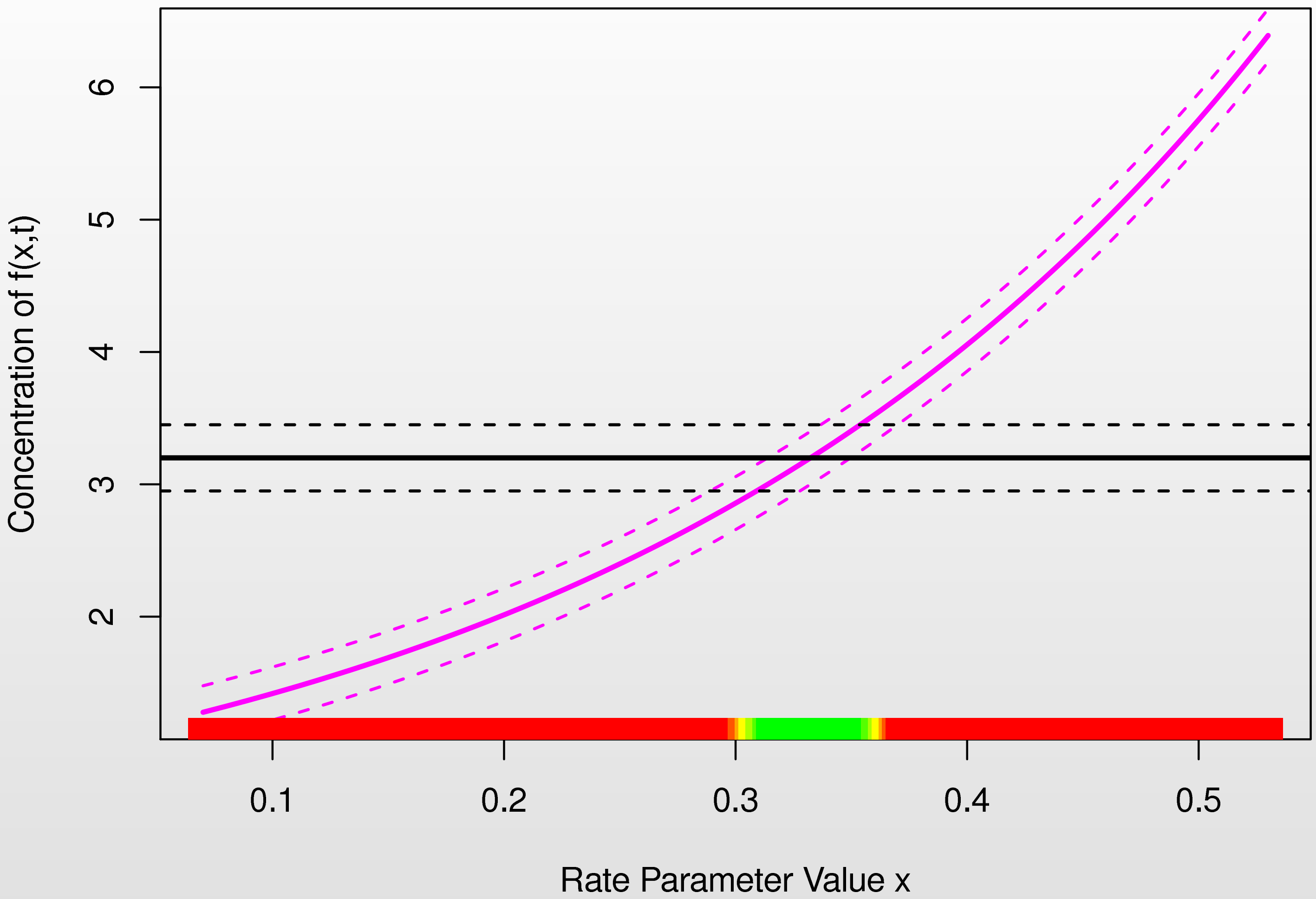

- Model discrepancy is represented as uncertainty around the model output $f(x)$ itself: here the purple dashed lines.
- This results in more uncertainty in x, and hence a larger range of x values.

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- We will use the Bayes Linear methodology, which only involves expectations, variances and covariances.

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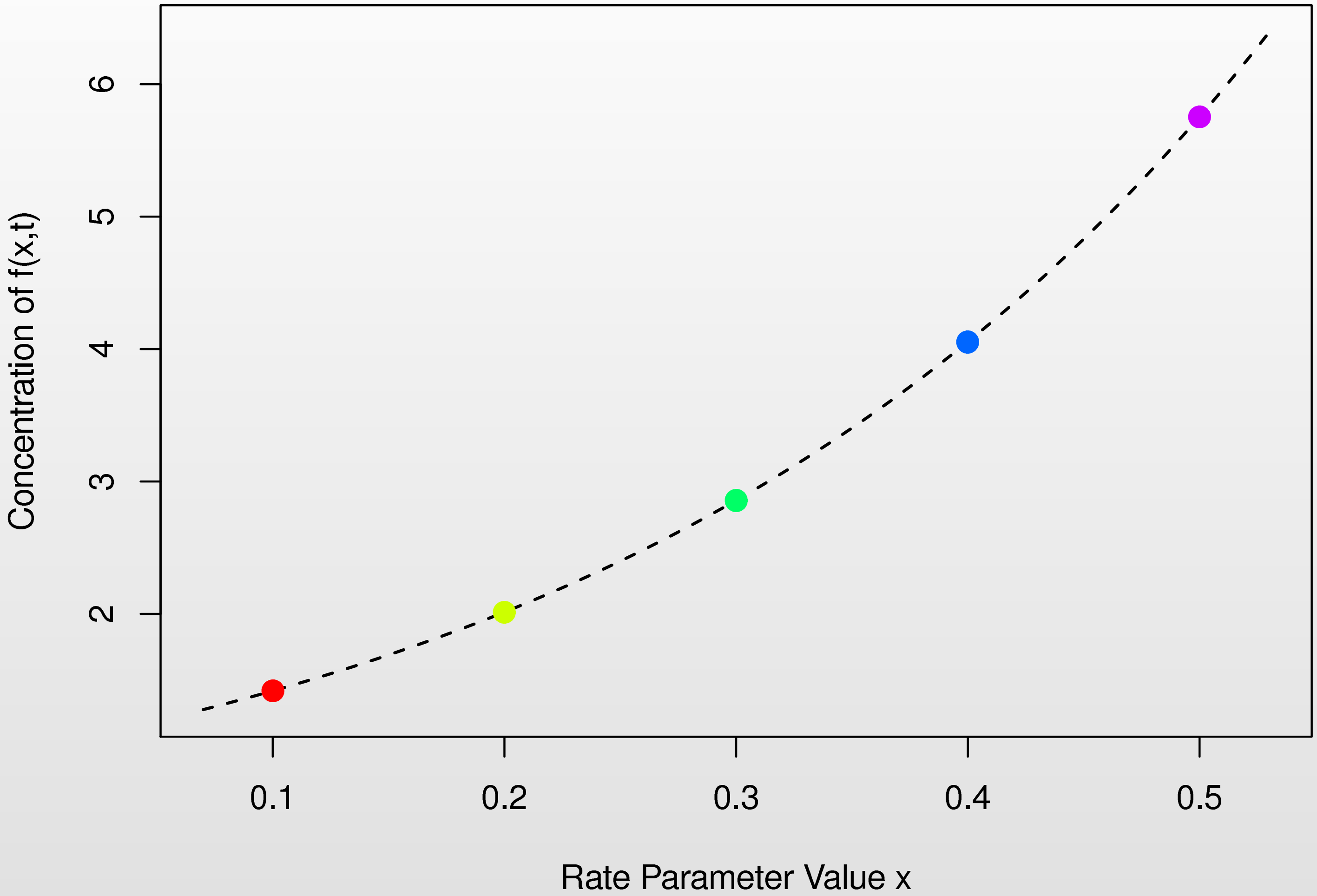
- In our first paper on Mukwano the modellers gave the simple assessment that $3\sqrt{\mathrm{Var}(\epsilon)}$ corresponds to approximately 10% of model output.
- In subsequent work we performed far more detailed assessments of internal and external discrepancy by considering model deficiencies and possible model improvements. In prep, but for a list of simple assessment techniques see:

Goldstein, M., Seheult, A., Vernon, I.: Assessing Model Adequacy. In: Wainwright, J., Mulligan, M. (eds.) Environmental Modelling: Finding Simplicity in Complexity, 2nd edn. John Wiley & Sons, Ltd, Chichester, UK (2013)

Emulation: 1D example



- Consider the graph of $f(x)$: in general we do not have the analytic solution of $f(x)$, here given by the dashed line.

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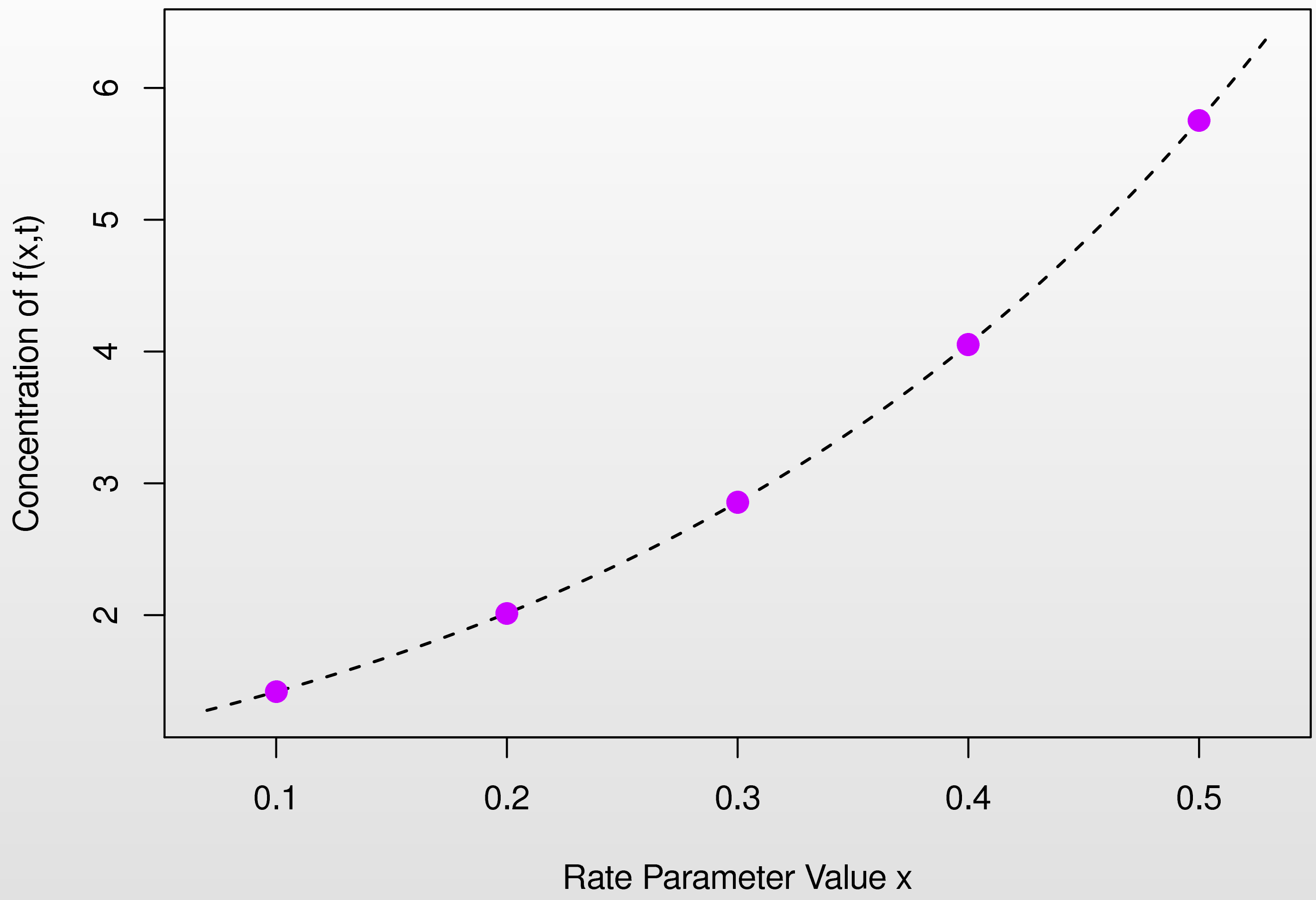

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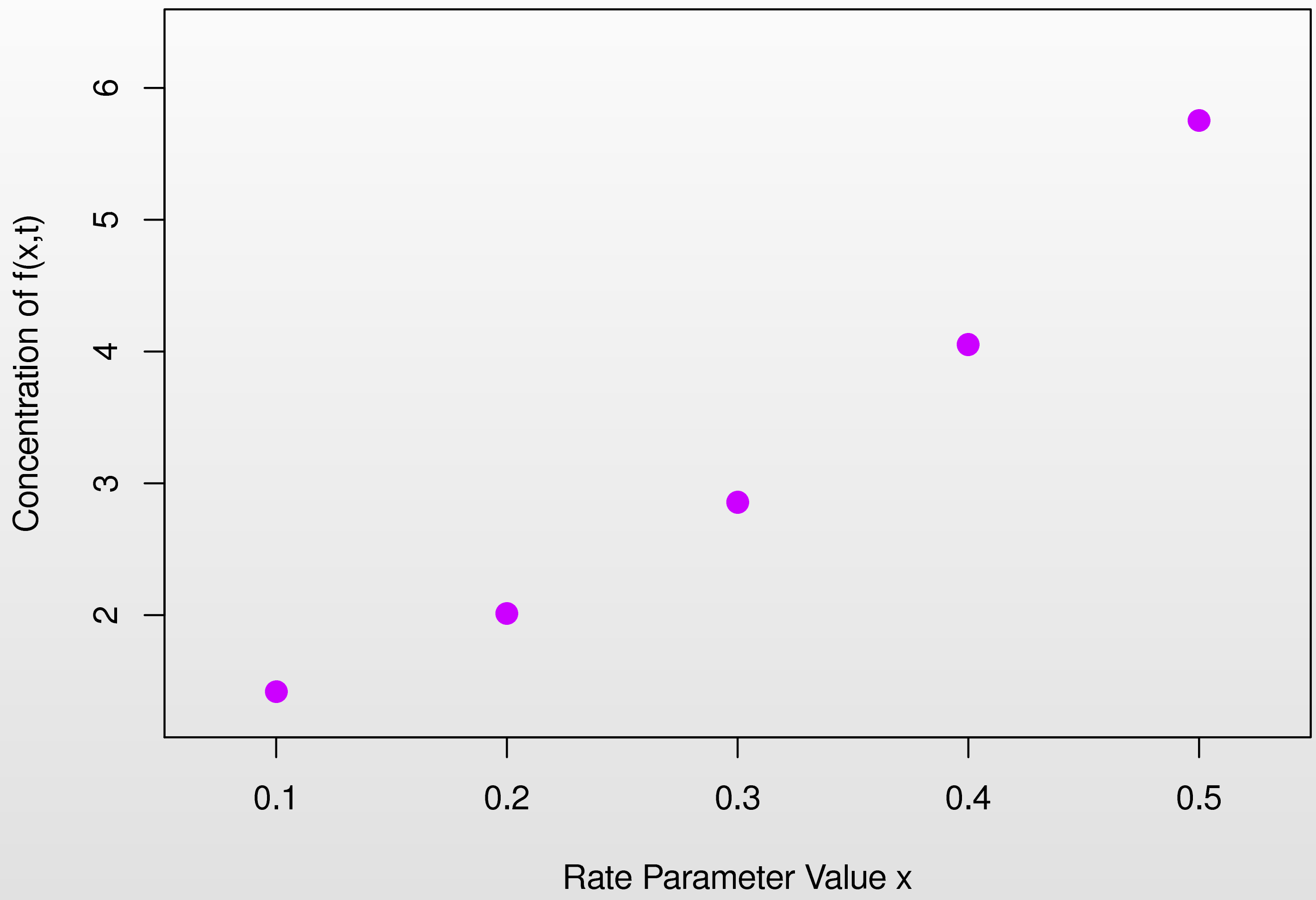

- Consider the graph of $f(x)$: in general we do not have the analytic solution of $f(x)$, here given by the dashed line.
- Instead we only have a finite number of runs of the model, in this case five.

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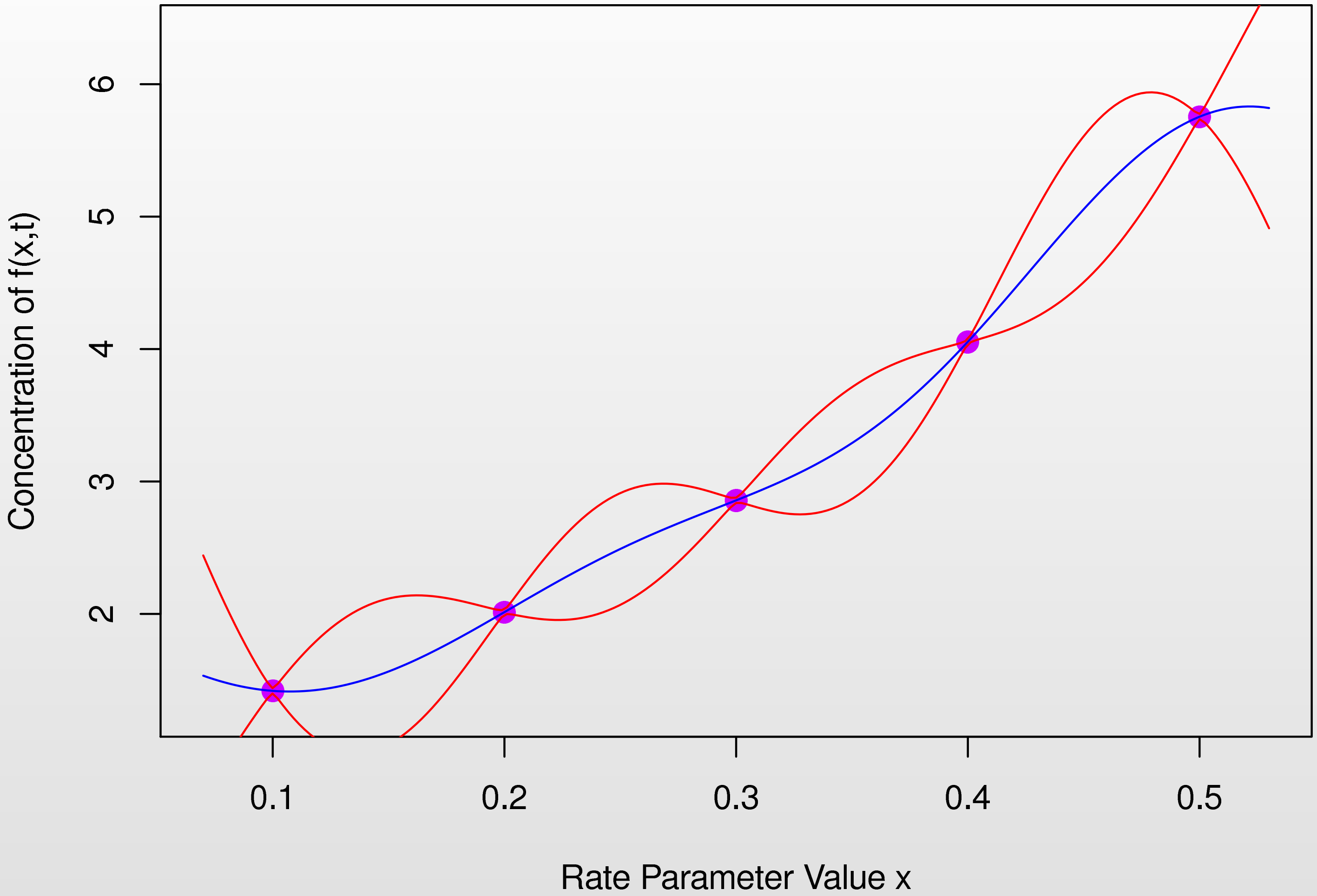

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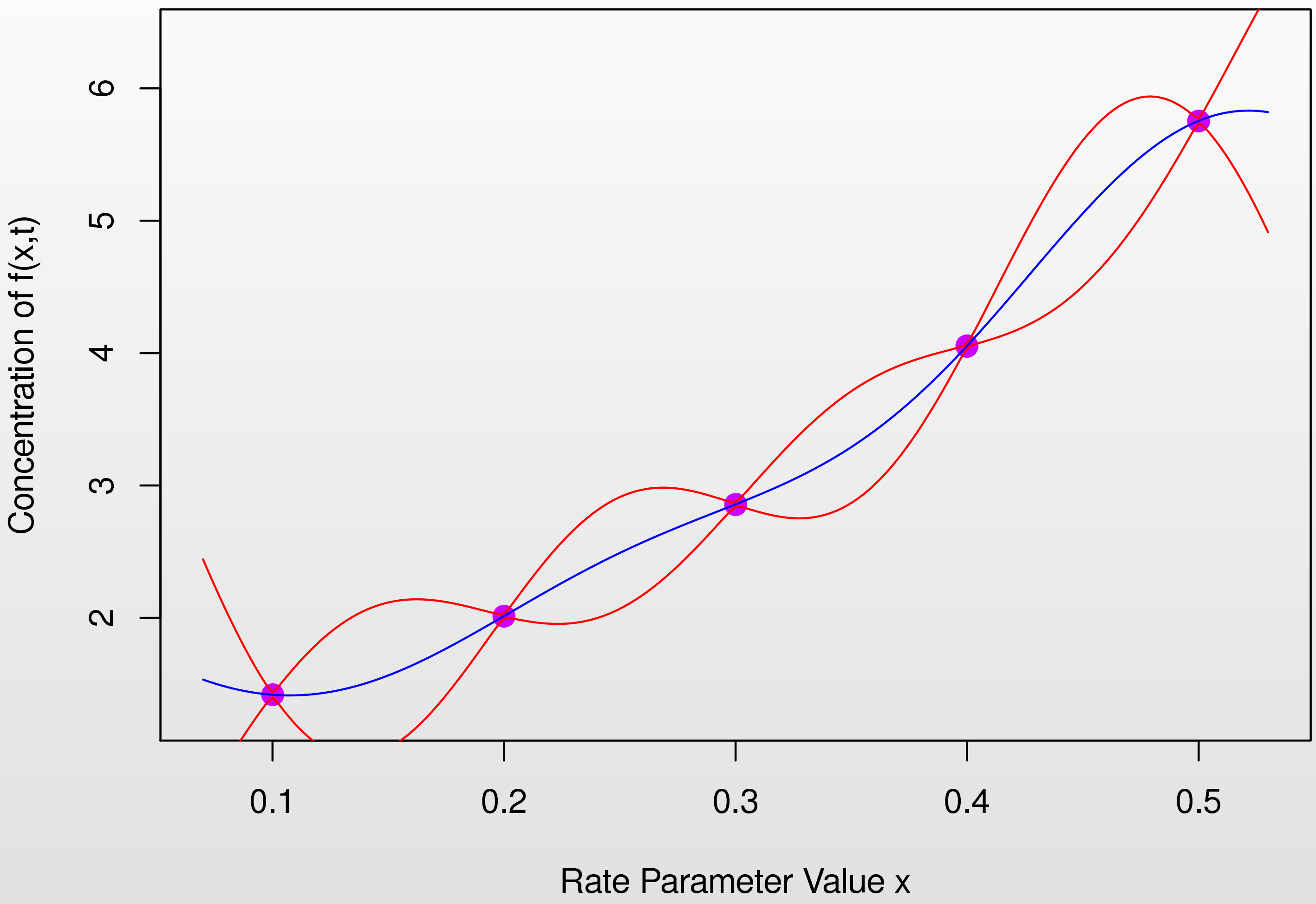

- The emulator can be used to represent our beliefs about the behaviour of the model at untested values of x, and is fast to evaluate.
- Gives the expected value of $f(x)$ (blue line) along with a credible interval for $f(x)$ (red lines) representing the uncertainty about the model's behaviour.

Mukwano: Emulation

- For each of the 18 outputs we pick active variables x^A then emulate univariately (at first) using:

$$f_i(x) = \sum_j \beta_{ij}\, g_{ij}(x^A) + u_i(x^A) + \delta_i(x)$$

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- The Emulators give the expectation $\mathrm{E}[f_i(x)]$ and variance $\mathsf{Var}[f_i(x)]$ at point x for each output given by $i = 1, .., 20$, and are **fast** to evaluate.

Emulation Theory: Bayes Theorem

- We perform an initial wave 1 set of n runs at input locations $x^{(1)}, x^{(2)}, \ldots, x^{(n)}$, using a Latin hypercube design, giving a column vector of model output values

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- This follows the standard Bayesian statistics paradigm, however this involves a detailed, full specification of the joint prior distribution: a complex and difficult task, and is hard to calculate.

Emulation Theory: Bayes Linear Methods

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- Instead of Bayes Theorem we use the Bayes linear update:

$$\begin{aligned} \mathrm{E}_{D_i}(f_i(x)) &= \mathrm{E}(f_i(x)) + \mathrm{Cov}(f_i(x), D_i)\mathrm{Var}(D_i)^{-1}(D_i - \mathrm{E}(D_i)) \\ \mathrm{Var}_{D_i}(f_i(x)) &= \mathrm{Var}(f_i(x)) - \mathrm{Cov}(f_i(x), D_i)\mathrm{Var}(D_i)^{-1}\mathrm{Cov}(D_i, f_i(x)) \end{aligned}$$

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- For a step by step guide to emulation see the tutorial paper:
  "Bayesian uncertainty analysis for complex systems biology models: emulation, global parameter searches and evaluation of gene functions.", Vernon, I, Goldstein, M, Rowe, J, Liu, J and Lindsey, K, BMC Systems Biology, in submission, arXiv:1607.06358.

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- We can (try to) emulate any feature of interest of the distribution of $f(x)$.

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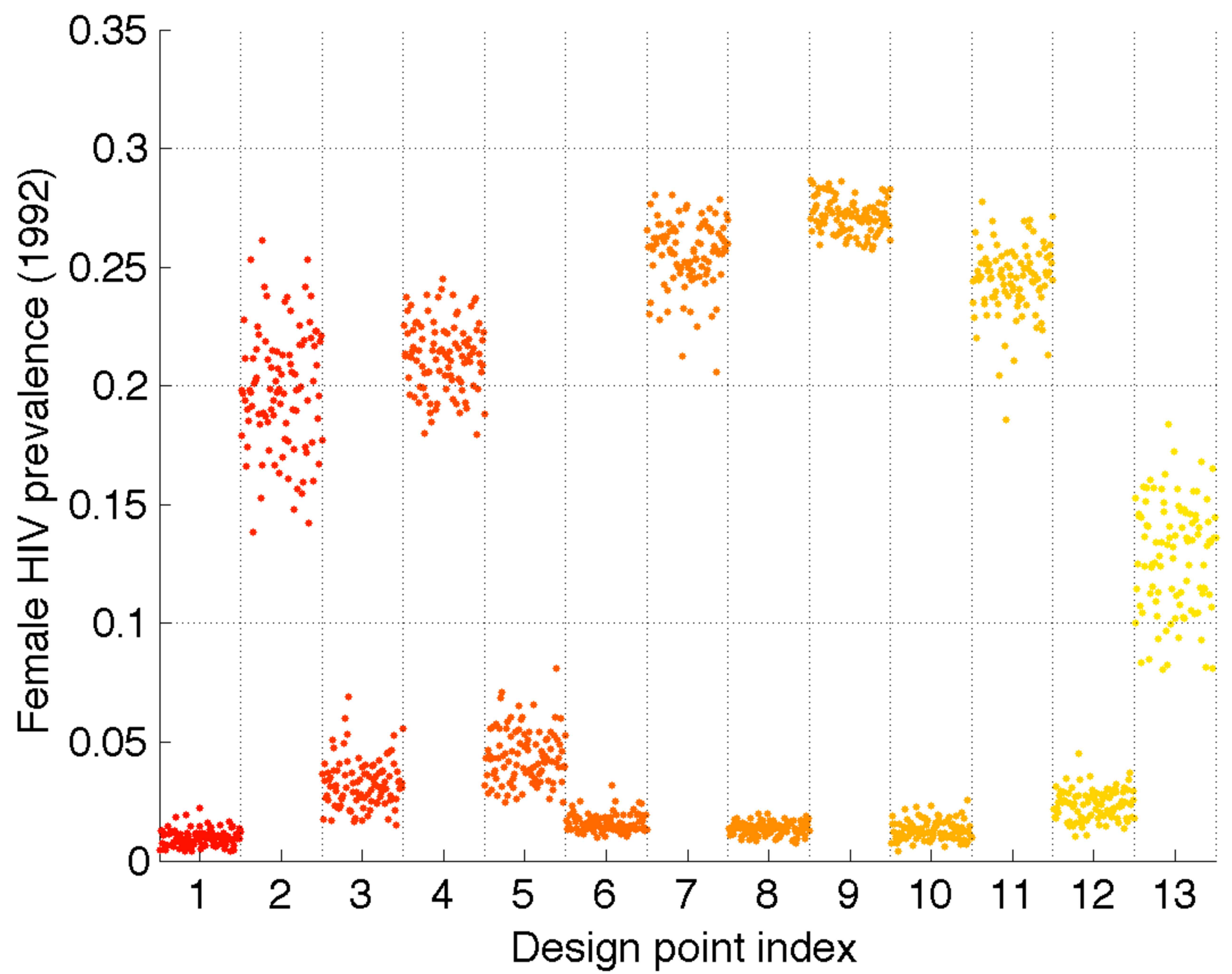

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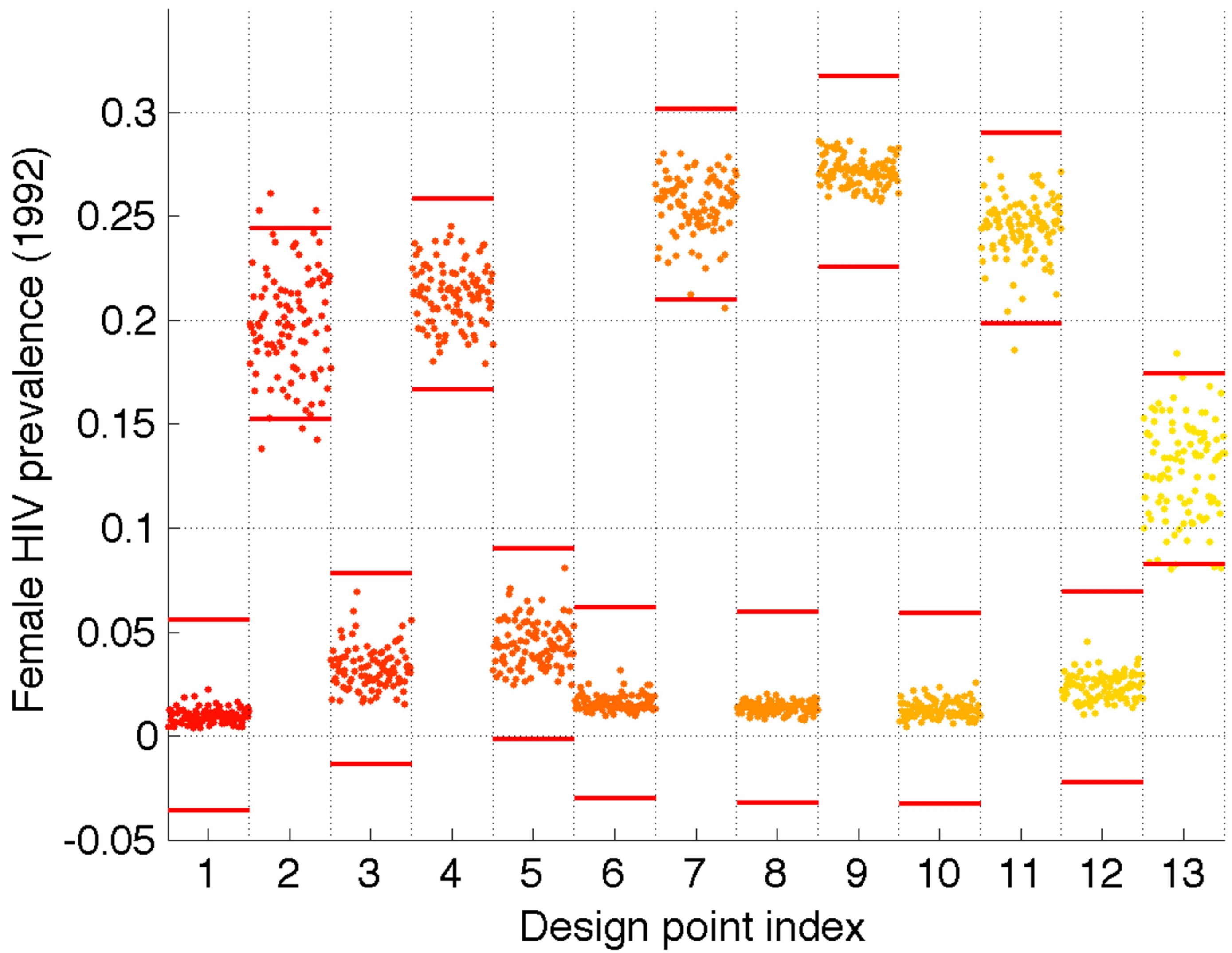

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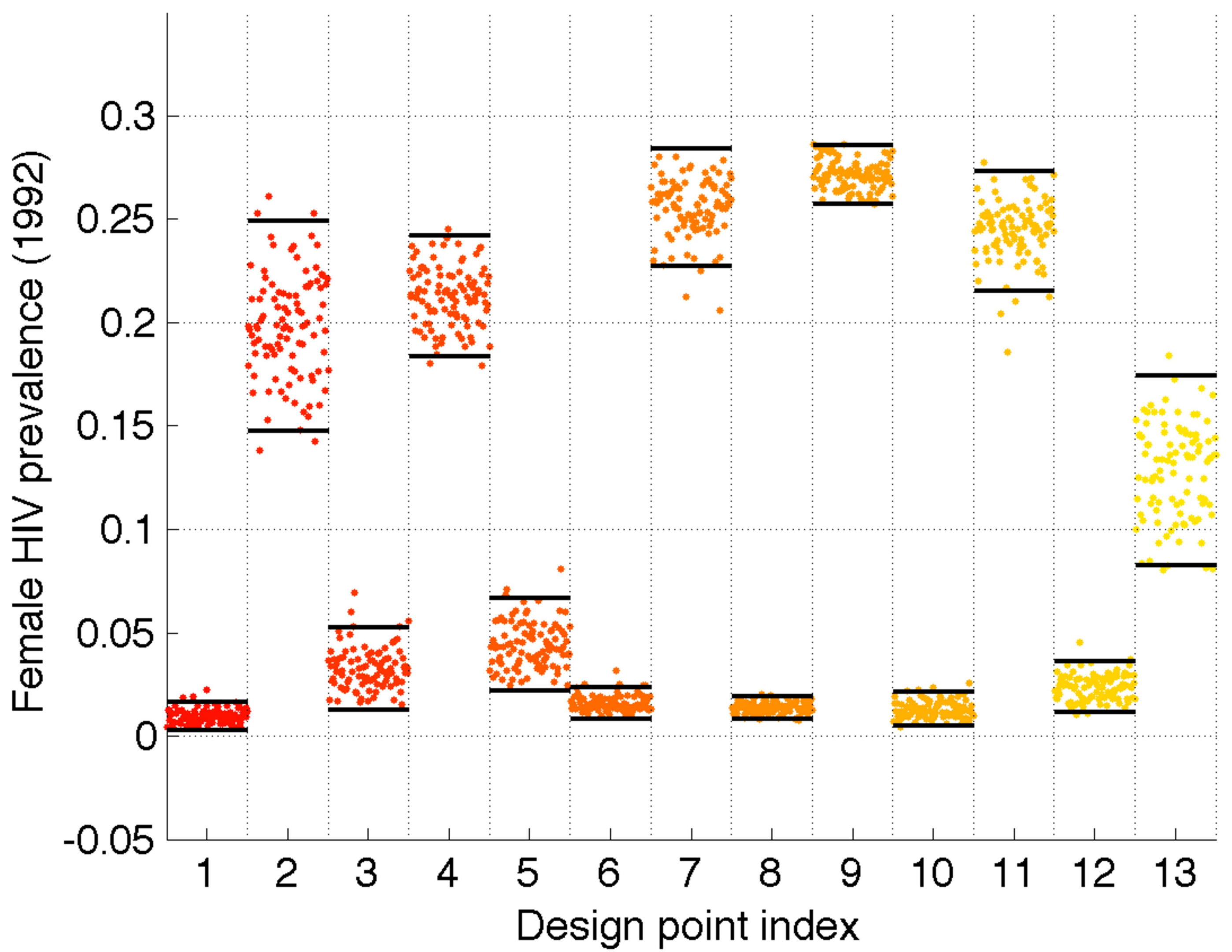
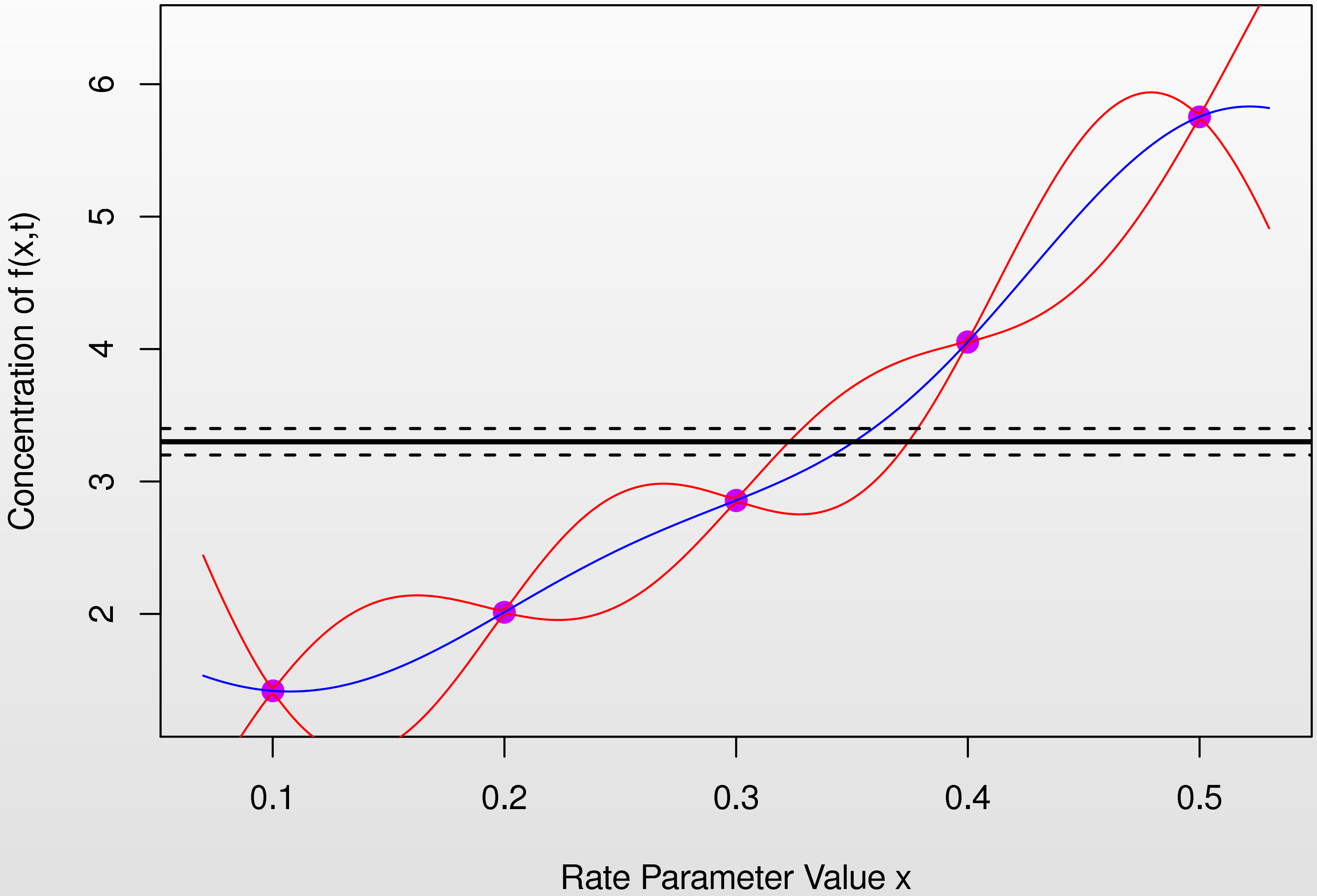


Implausibility Measures: 1D example



- Comparing the emulator to the observed measurement we again identify the set of x values currently consistent with this data (the observed errors here have been reduced for clarity).

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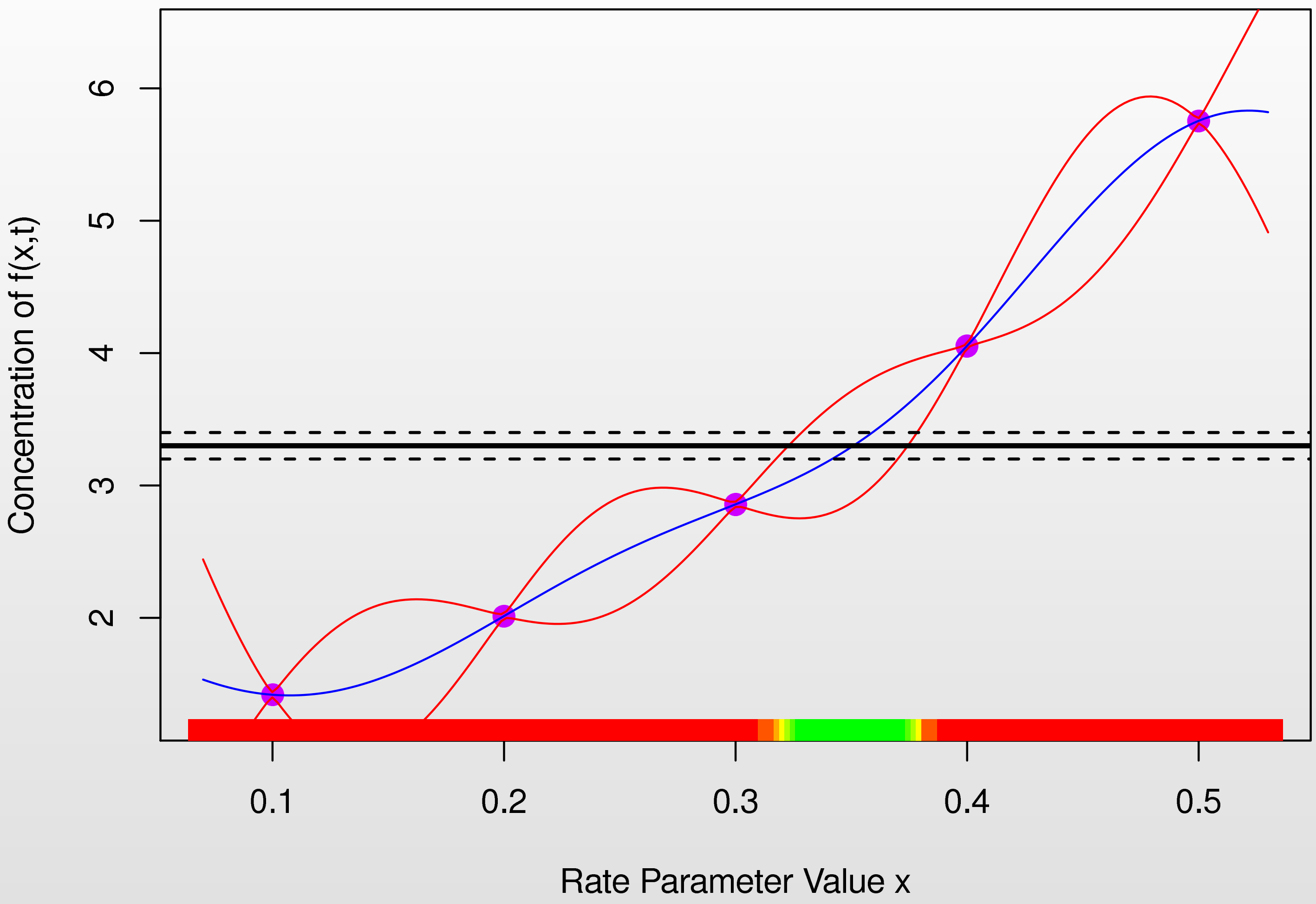

- Comparing the emulator to the observed measurement we again identify the set of x values currently consistent with this data (the observed errors here have been reduced for clarity).
- Note: uncertainty on x now includes uncertainty coming from the emulator.

Implausibility Measures (Univariate)

We can now calculate the Implausibility $I_{(i)}(x)$ at any input parameter point x for each of the $i = 1, .., 11$ outputs. This is given by:

$$I^2_{(i)}(x) = \frac{|\mathrm{E}_{D_i}(f_i(x)) - z_i|^2}{(\mathrm{Var}_{D_i}(f_i(x)) + \mathrm{Var}[\epsilon_i] + \mathrm{Var}[e_i])}$$

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- **Large values** of $I_{(i)}(x)$ imply that we are highly unlikely to obtain acceptable matches between model output and observed data at input x.

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Implausibility Measures (Univariate)

Durham University

We can now calculate the Implausibility $I_{(i)}(x)$ at any input parameter point x for each of the $i = 1, .., 11$ outputs. This is given by:

$$I^2_{(i)}(x) = \frac{|\mathrm{E}_{D_i}(f_i(x)) - z_i|^2}{(\mathrm{Var}_{D_i}(f_i(x)) + \mathrm{Var}[\xi_i] + \mathrm{Var}[\epsilon_i] + \mathrm{Var}[e_i])}$$

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- We may simultaneously employ other choices of implausibility measure: e.g. multivariate, second maximum etc.

Multivariate Implausibility Measure

Durham University

- As we have constructed a multivariate model discrepancy, we can define a multivariate Implausibility measure:

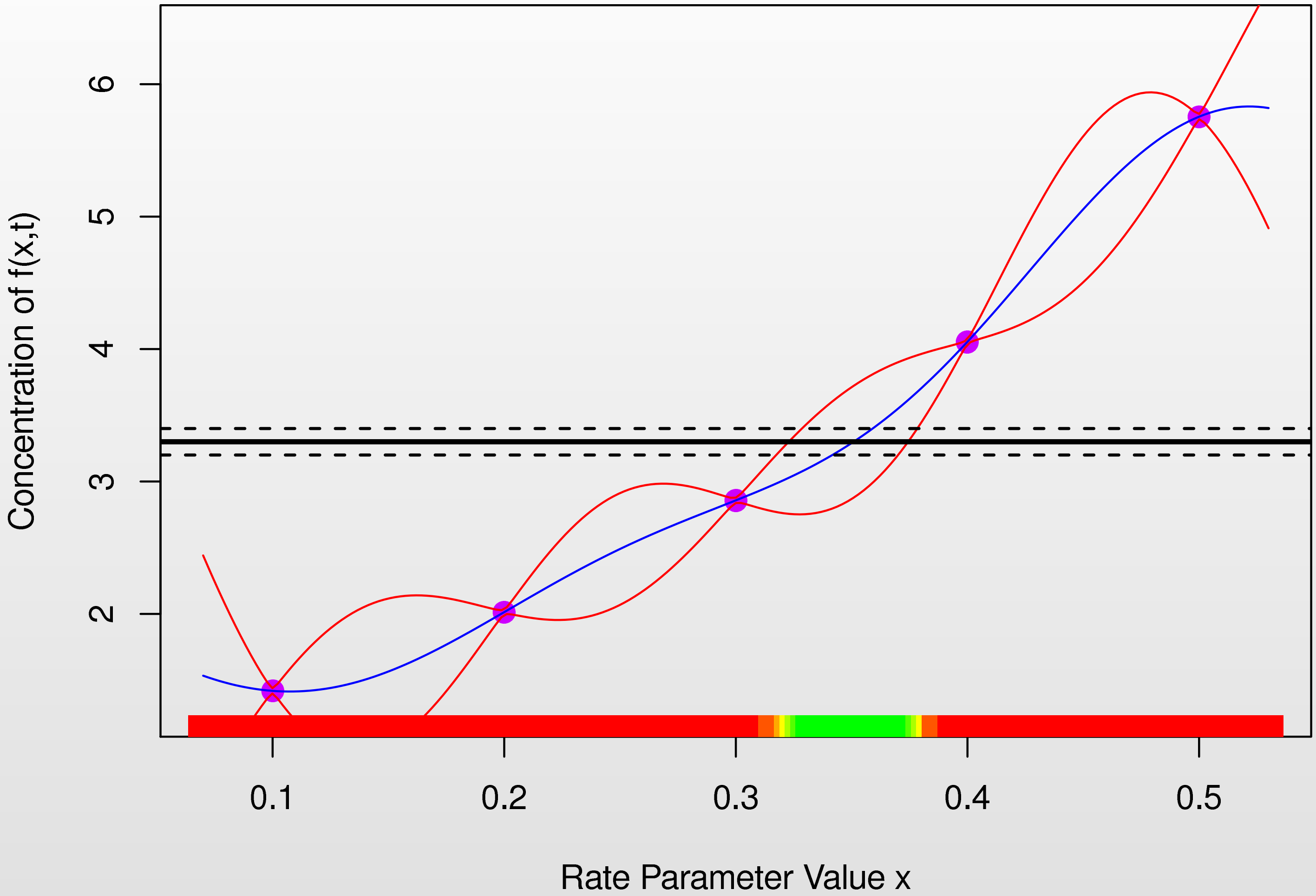
$$I^2(x) = (\mathrm{E}[f(x)] - z)^T \mathrm{Var}[f(x) - z]^{-1} (\mathrm{E}[f(x)] - z),$$

which becomes:

$$I^2(x) = (\mathrm{E}[f(x)] - z)^T (\mathrm{Var}[f(x)] + \mathrm{Var}[\epsilon] + \mathrm{Var}[e])^{-1} (\mathrm{E}[f(x)] - z)$$

- where $\mathrm{Var}[f(x)]$, $\mathrm{Var}[\epsilon]$ and $\mathrm{Var}[e]$ are now the multivariate emulator variance, multivariate model discrepancy and multivariate observational errors respectively (all 18×18 matrices).
- We now have two implausibility measures $I_M(x)$ and $I(x)$ that we can use to reduce the input space.
- We impose suitable cutoffs on each measure to define a smaller set of non-implausible inputs.

Iterative Input Space Reduction: 1D example



- Comparing the emulator to the observed measurement we again identify the set of x values currently consistent with this data (the observed errors here have been reduced for clarity).
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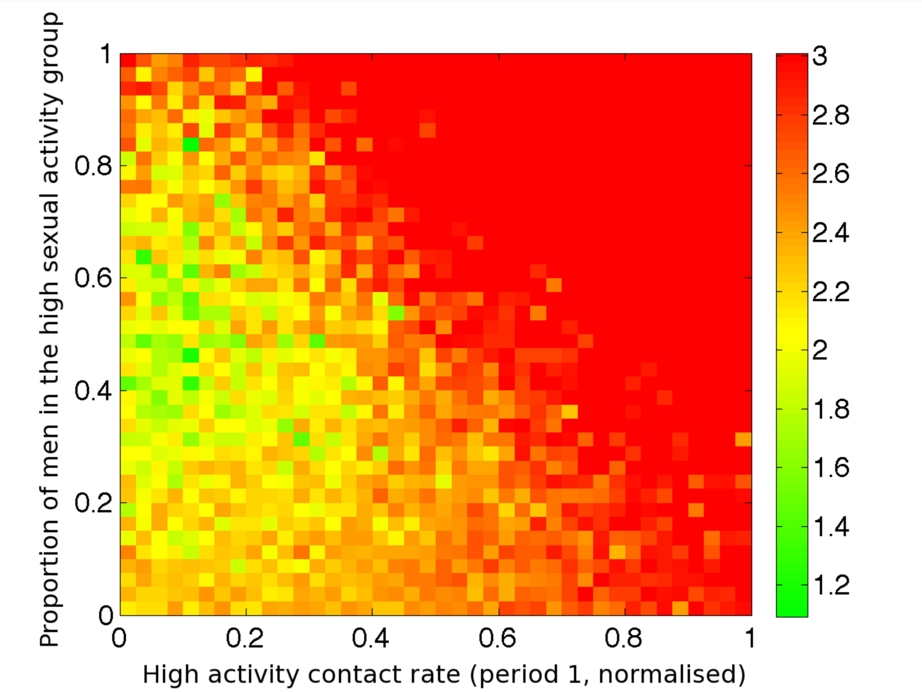
2D Minimised Implausibility Projections: Wave 1



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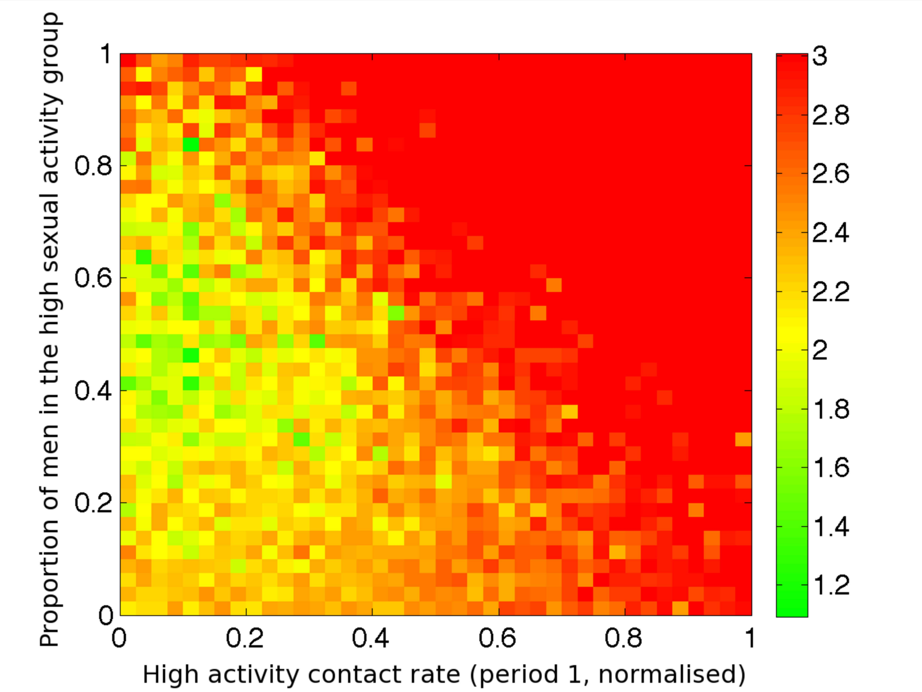

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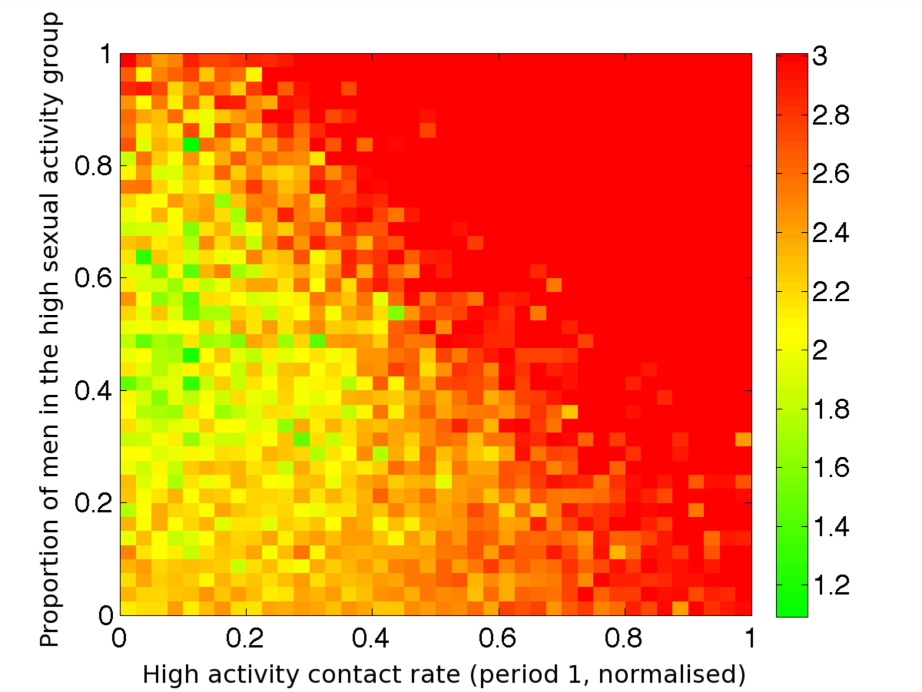
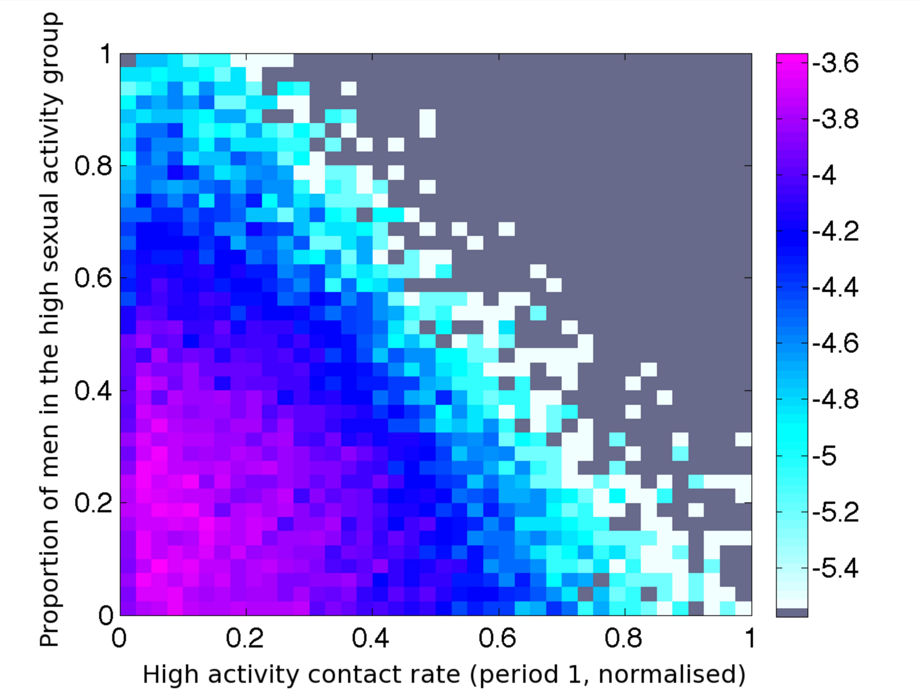


- Minimised Implausibility Projections: at each 2D grid point, minimise the implausibility $I_M(x)$ over a large 20D hypercube.
- If a point on these plots is implausible (coloured red), then it will be implausible for any choice of the 15 other inputs.
- If a point is green, it may or may not prove to be an acceptable input.

2D Optical Depth Plots: Wave 2



- Optical Depth Plots: at each 2D grid point plot the proportion of a large 20D latin hypercube set of points that survive the cutoff $I_M(x) < c_M$.

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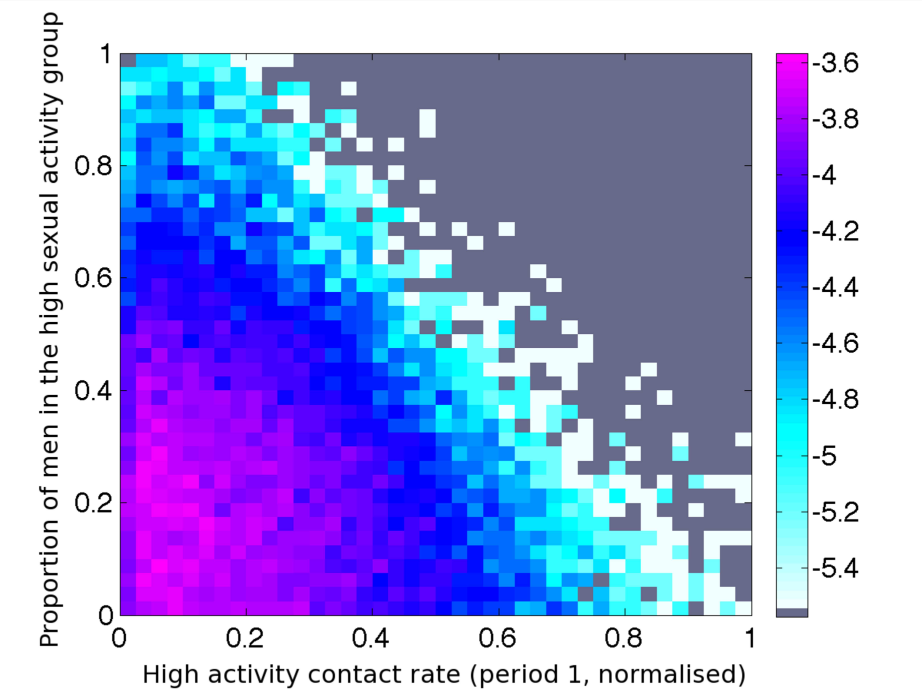

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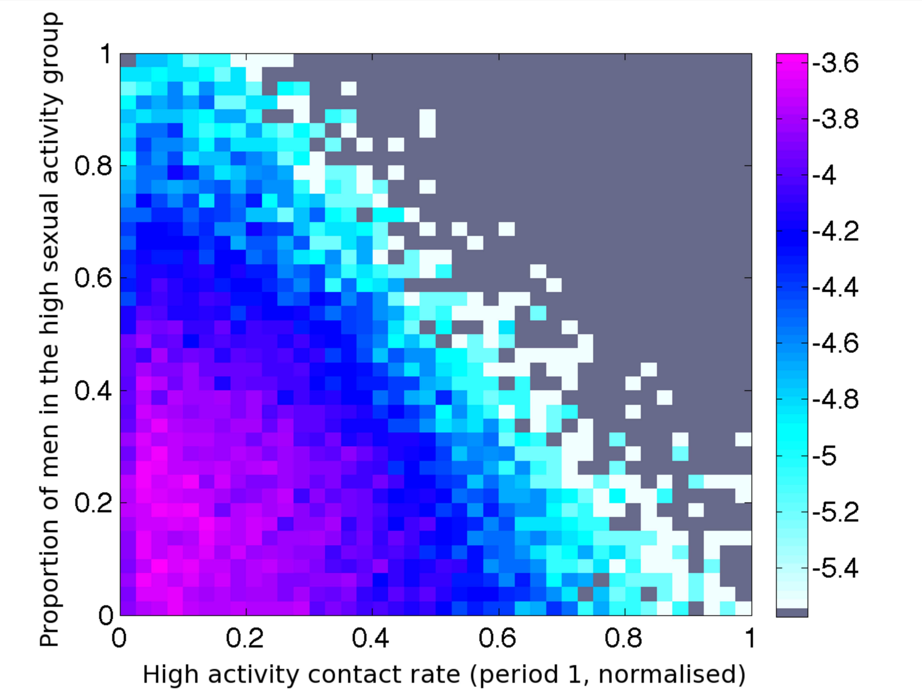

- Optical Depth Plots: at each 2D grid point plot the proportion of a large 20D latin hypercube set of points that survive the cutoff $I_M(x) < c_M$.
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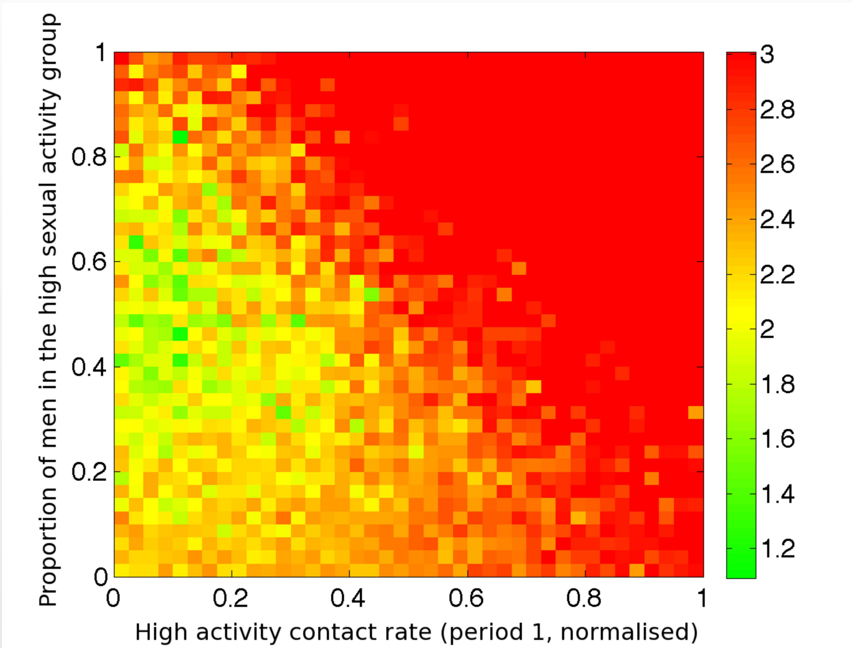
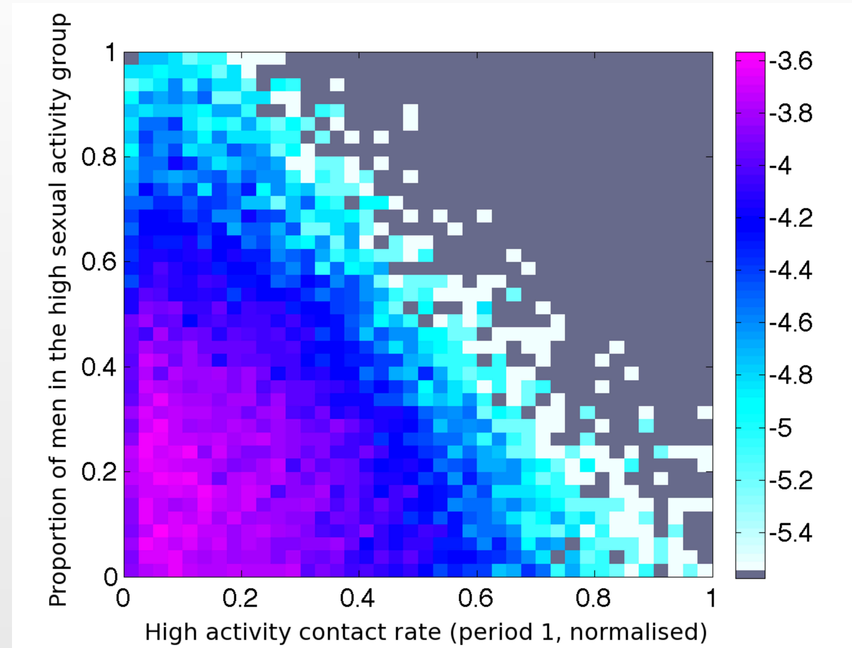
- Shows where the majority of non-implausible points can be found, but not necessarily where the best matches are.

Minimised Implausibility and Depth Plots (NEEDED?)





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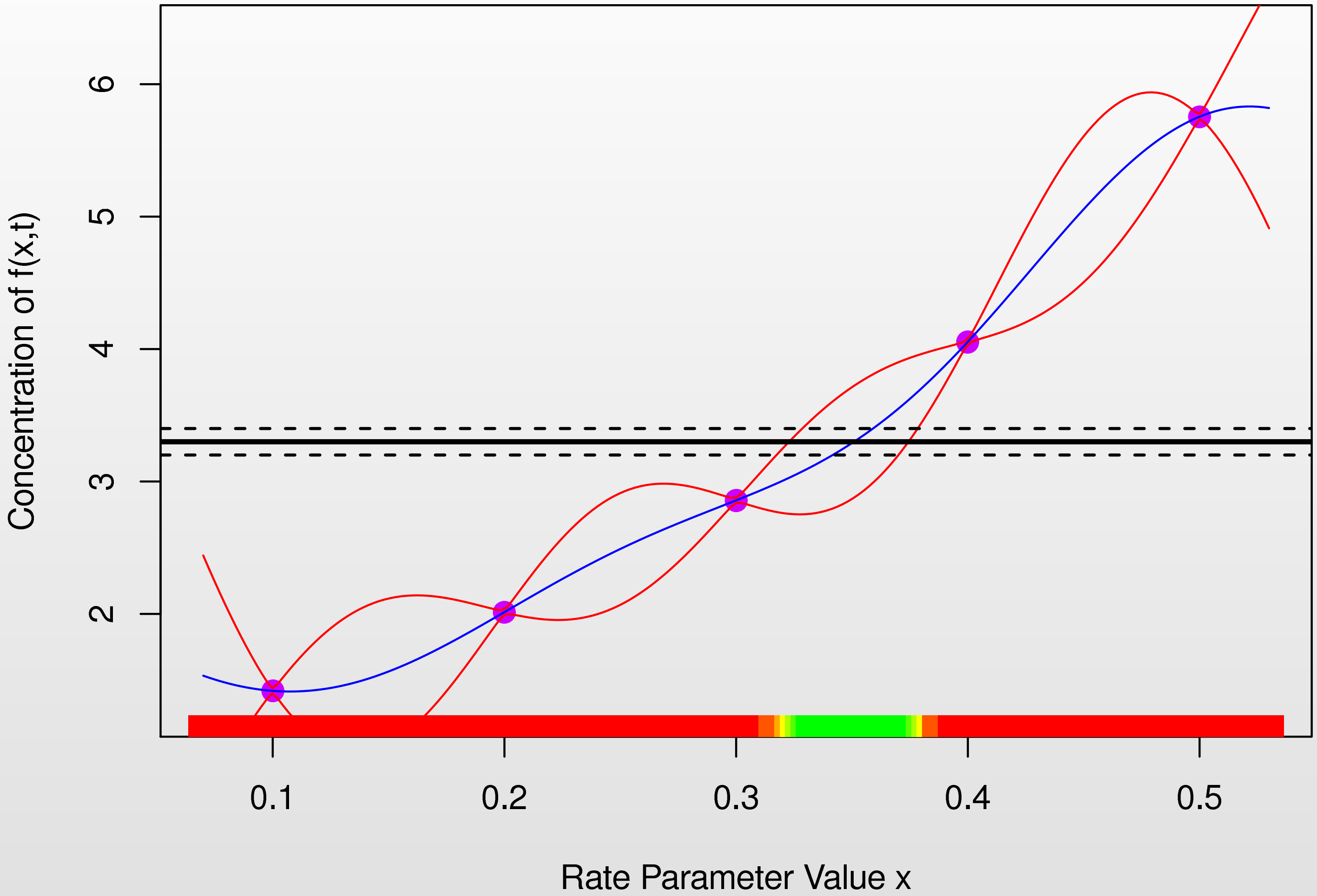

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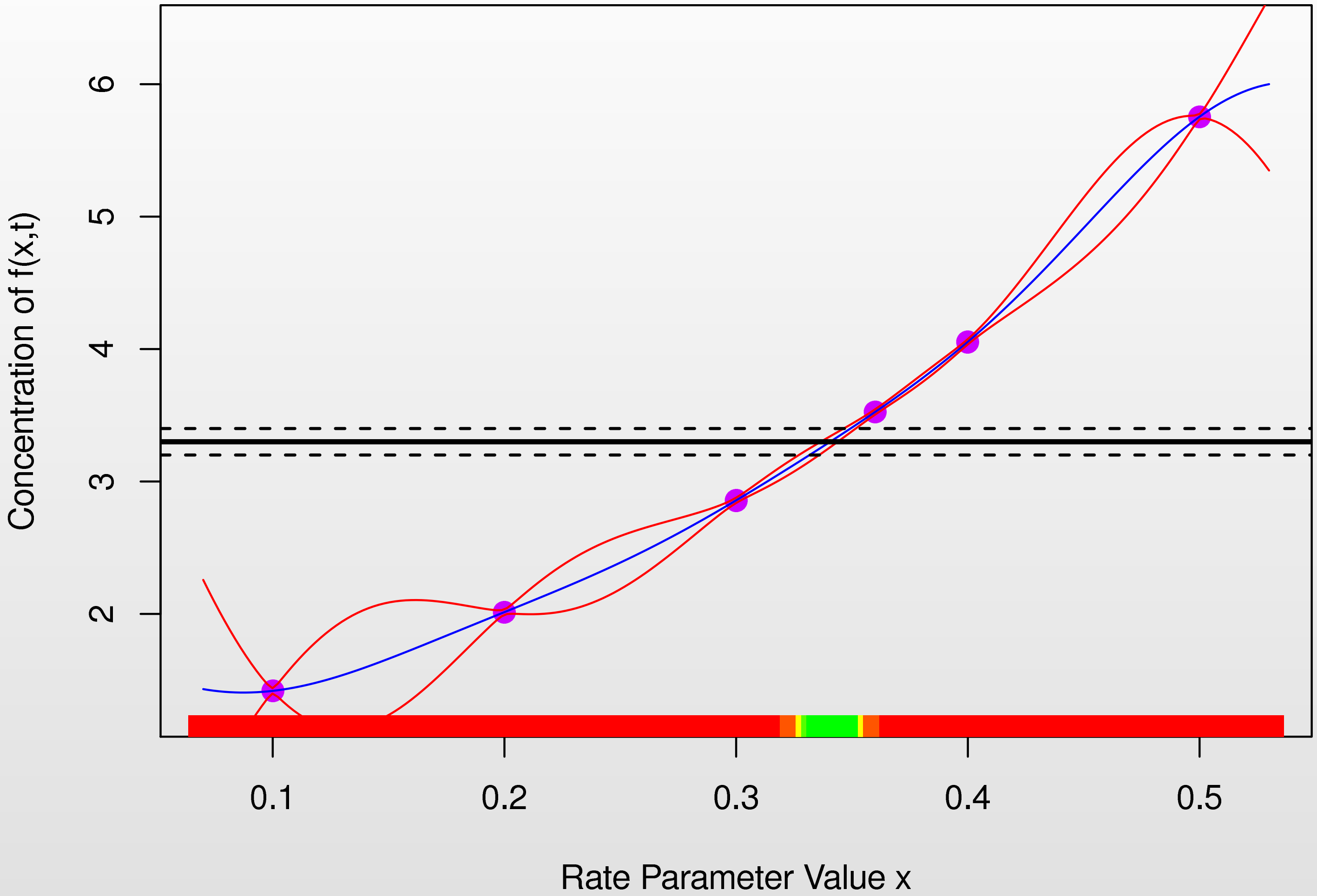

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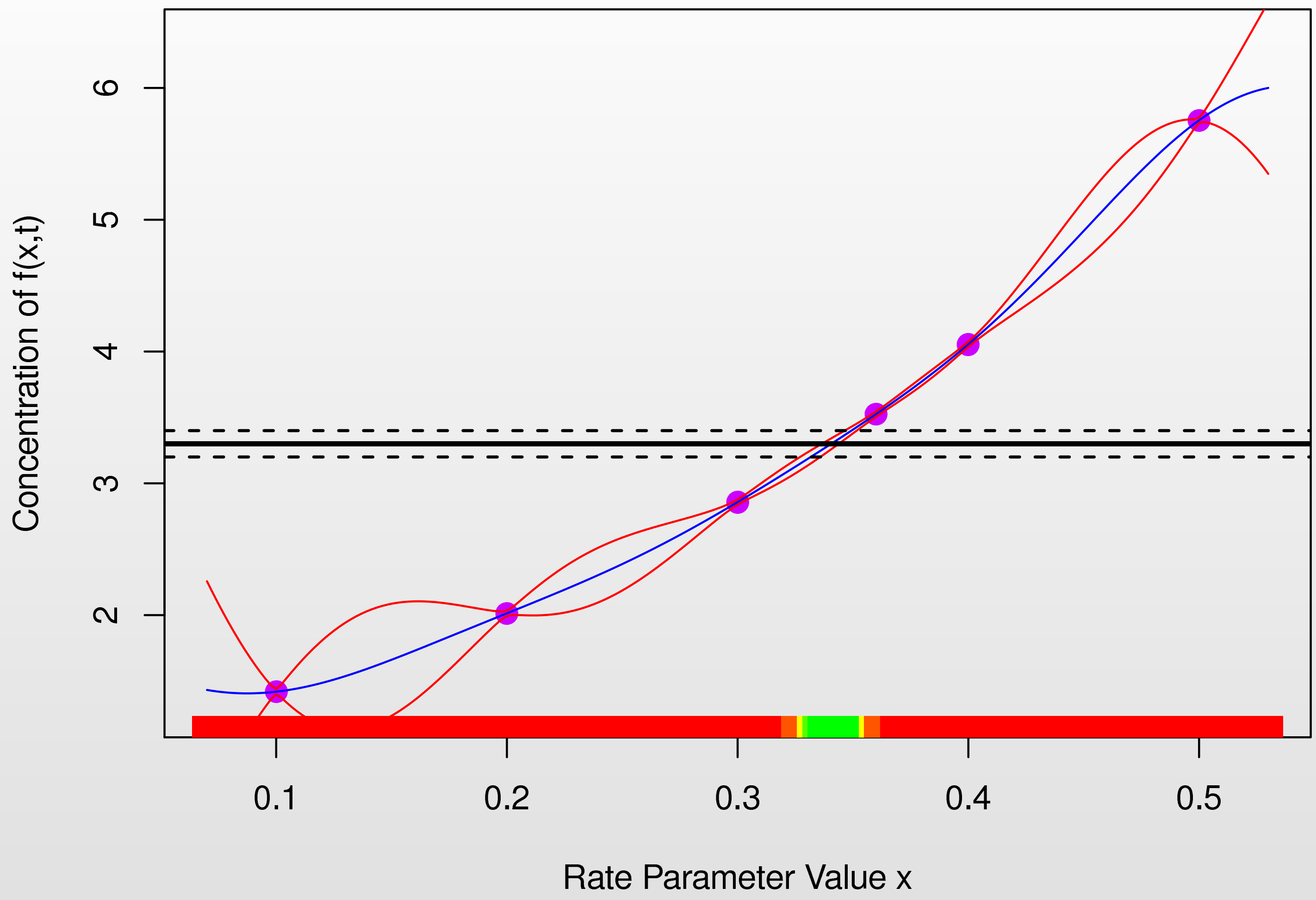

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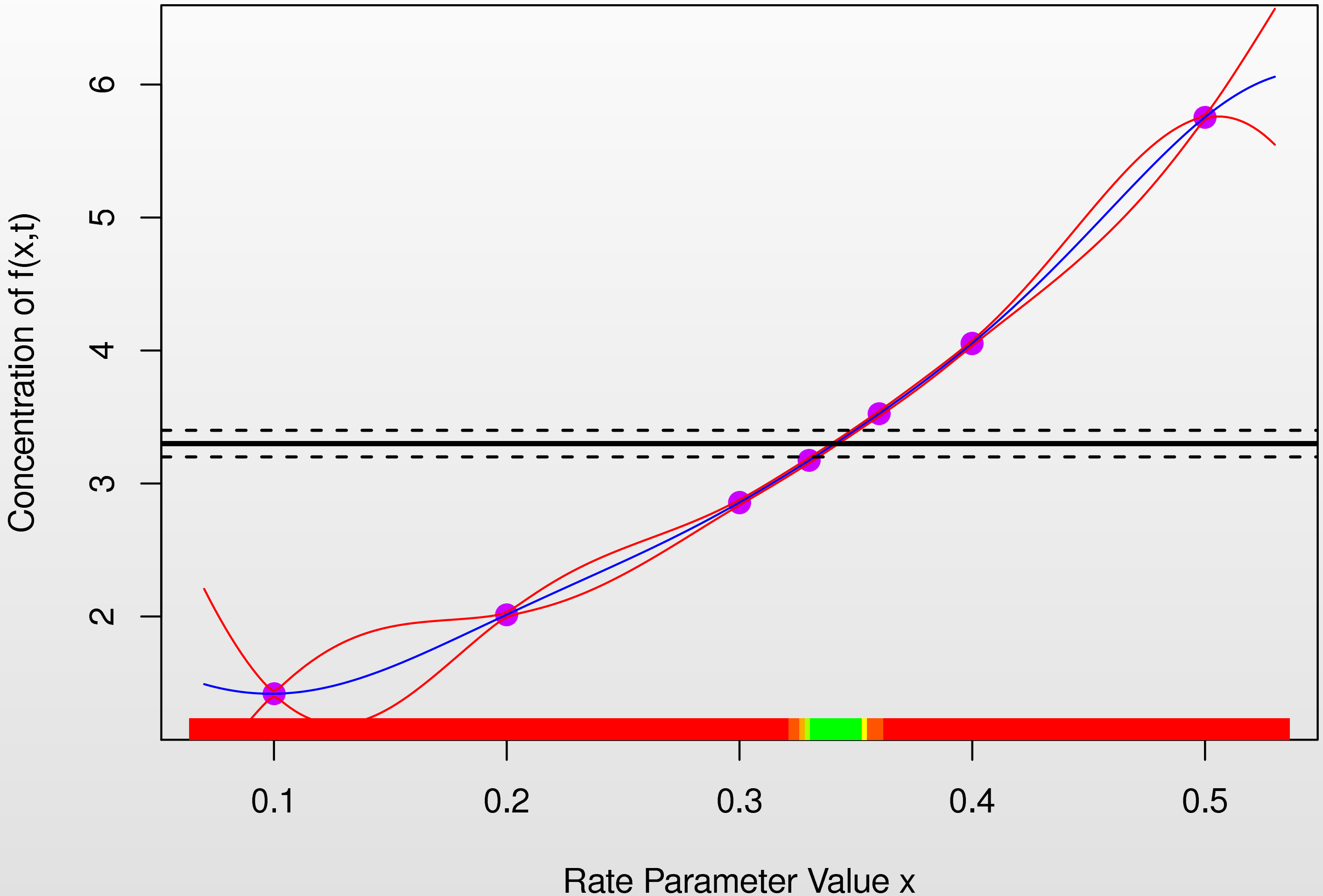
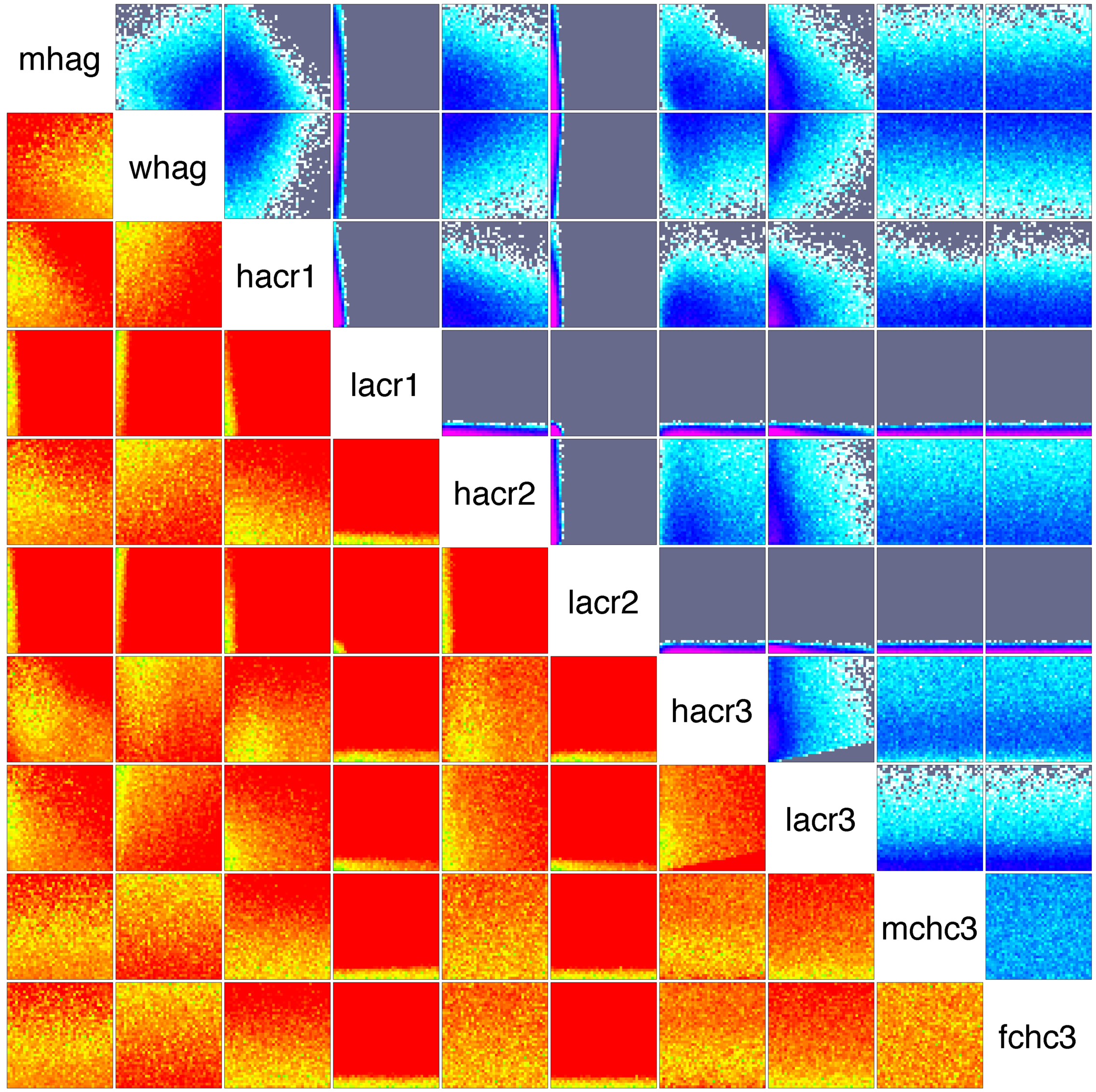
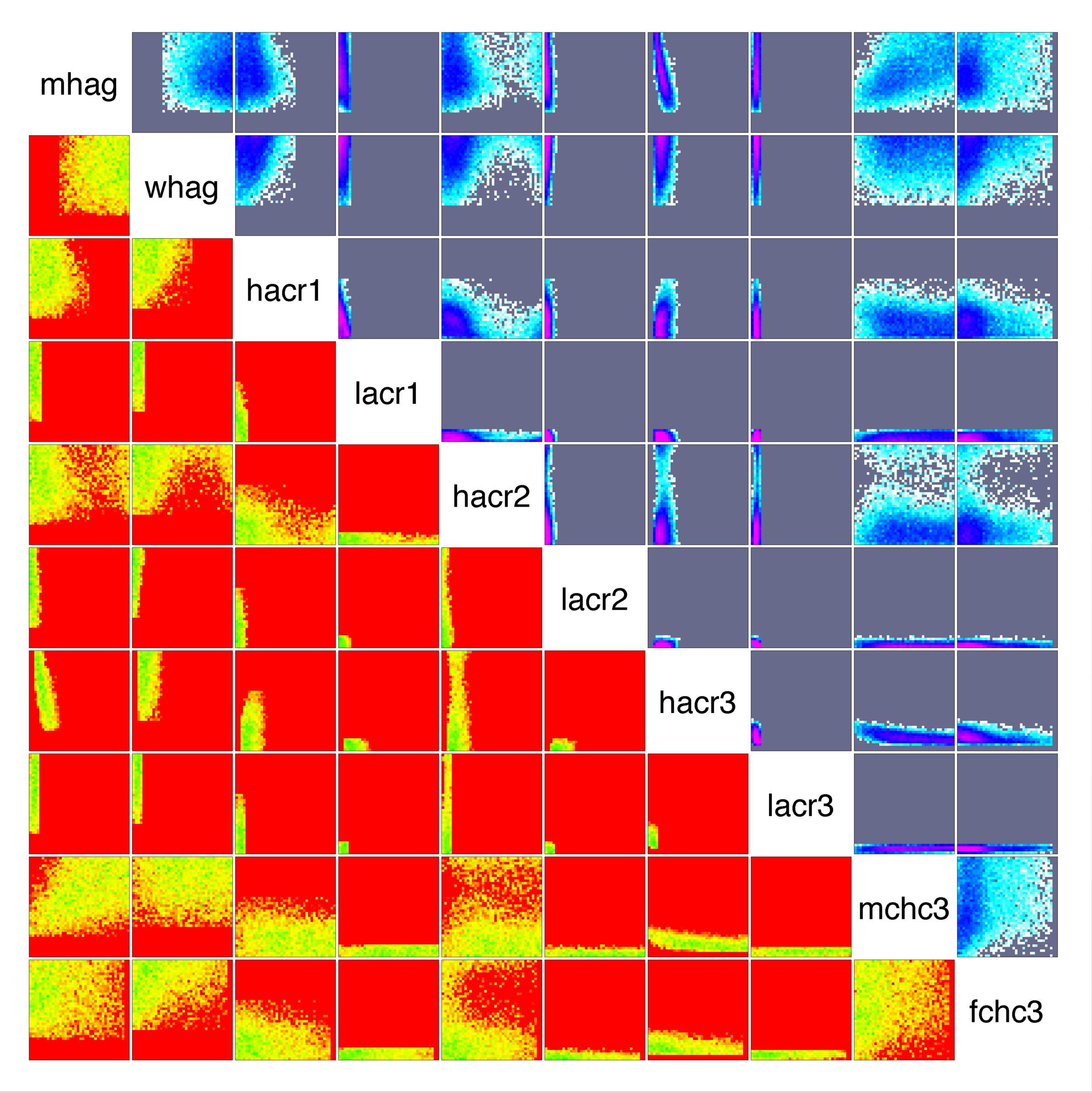


- We perform a 2nd iteration or wave of runs to improve emulator accuracy.
- The runs are located only at non-implausible (green/yellow) points.
- Now the emulator is more accurate than the observations, and we can identify the set of all x values of interest.

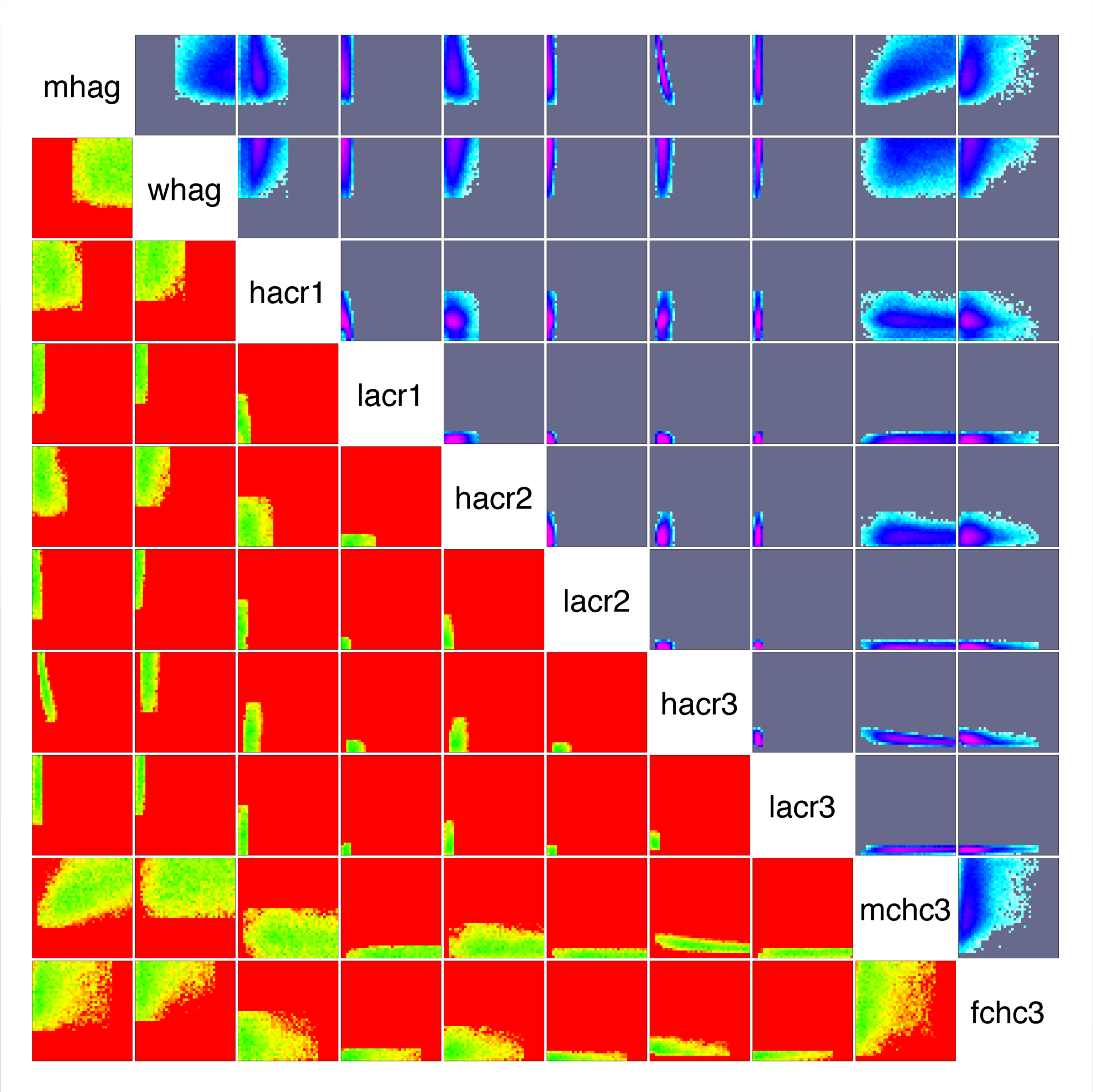
Iterative Input Space Reduction: Mukwano Model Wave 1



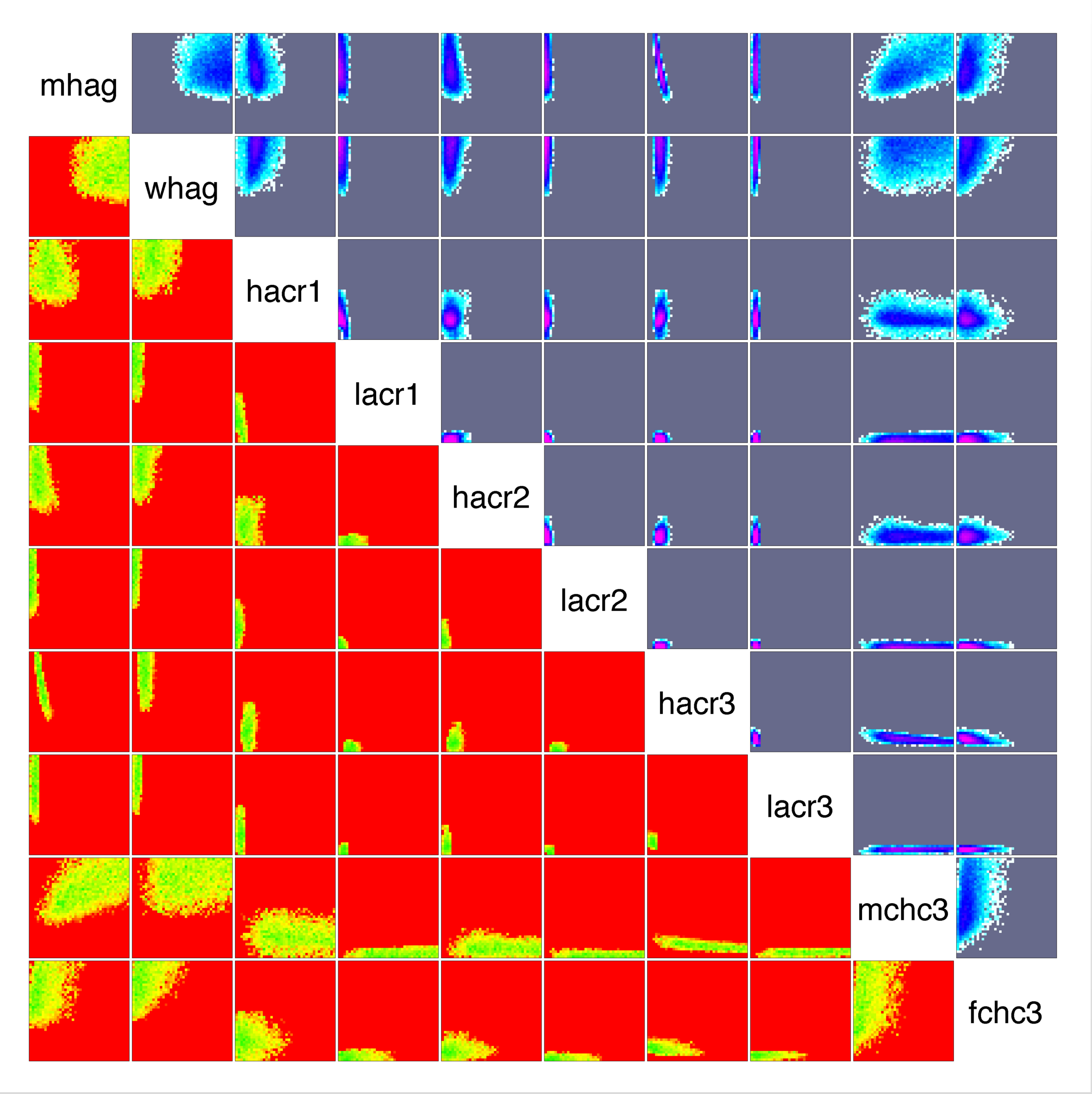
Iterative Input Space Reduction: Mukwano Model Wave 4



Iterative Input Space Reduction: Mukwano Model Wave 7



Iterative Input Space Reduction: Mukwano Model Wave 9



Iterative History Matching for Reducing Input Space.

Durham University

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7. If 6(a) true, generate a large number of acceptable runs from the final non-implausible volume $\mathcal{X}$, with appropriate sampling.

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Why do we reduce space in waves? Why not attempt to do it all at once?

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Why do we reduce space in waves? Why not attempt to do it all at once? Because this requires an accurate emulator valid over whole input space.

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- This is a major strength of the History Matching approach.

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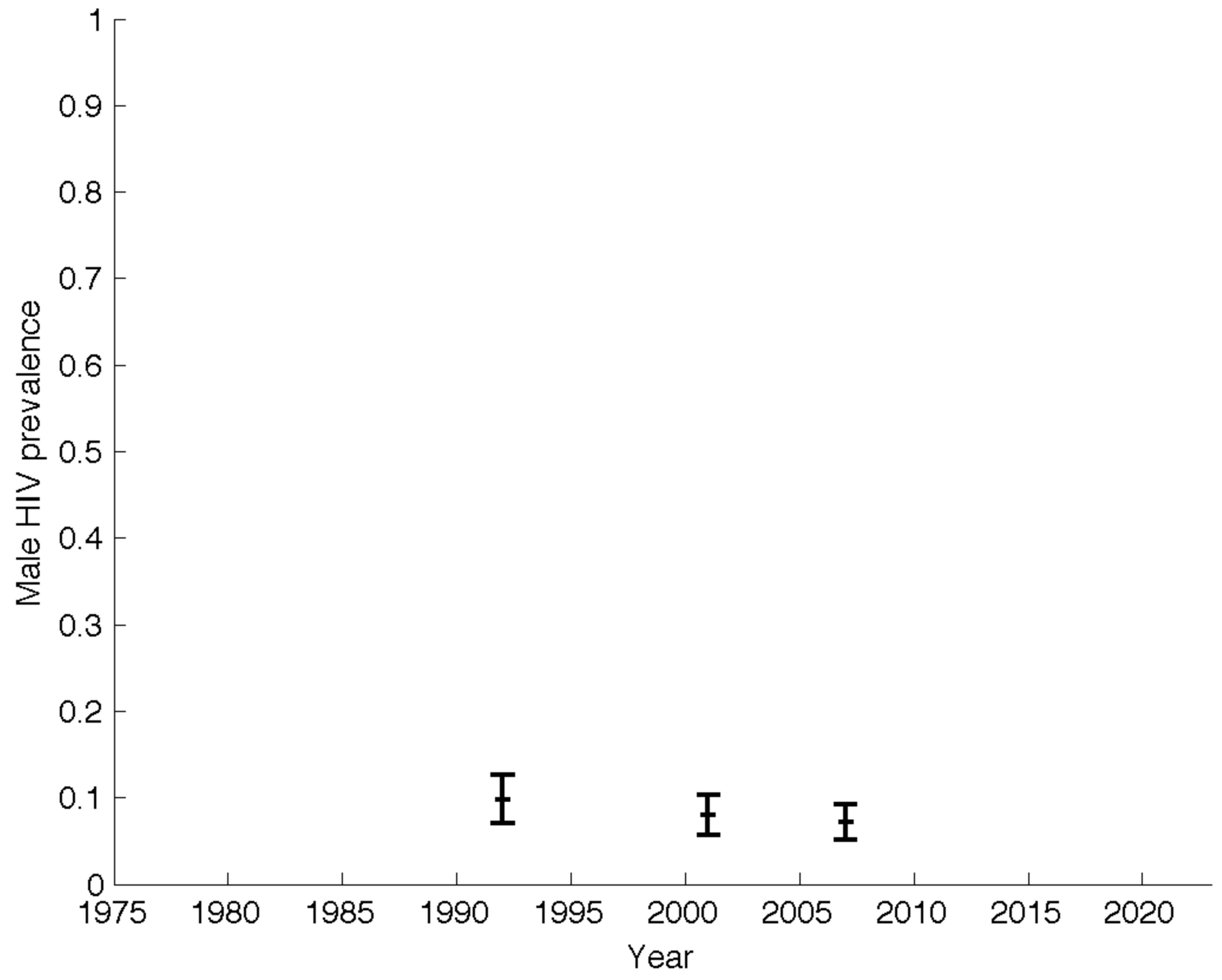

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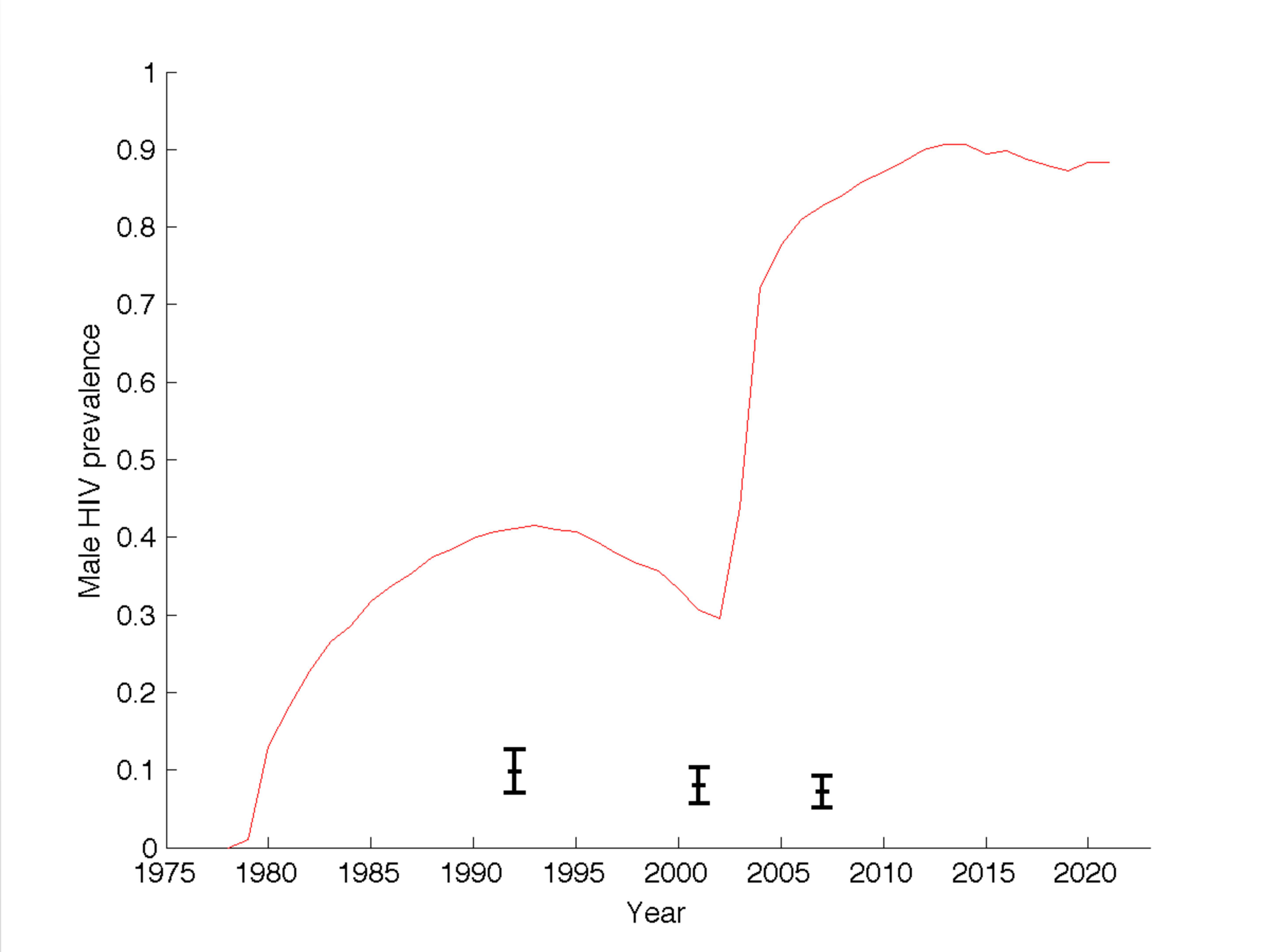

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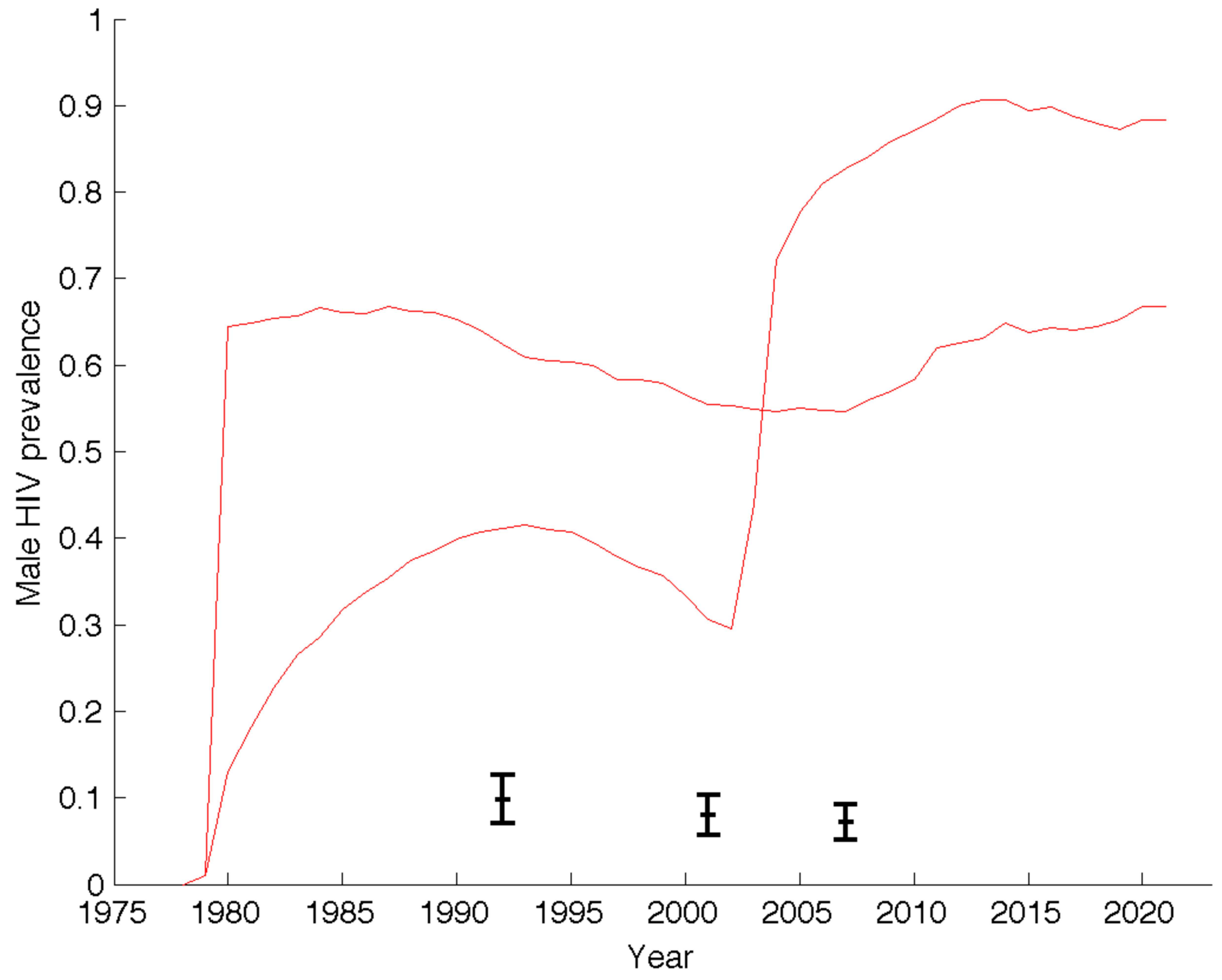
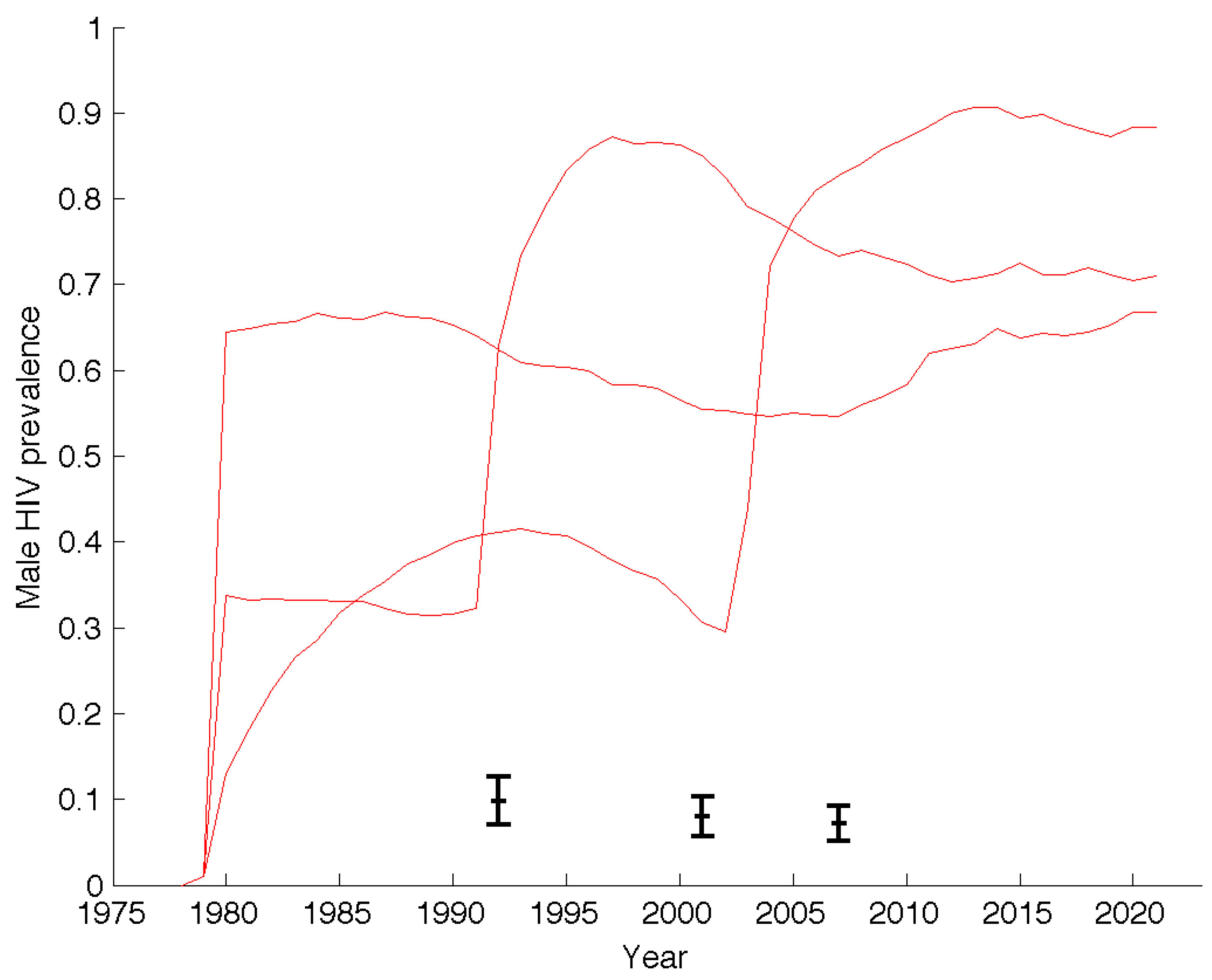
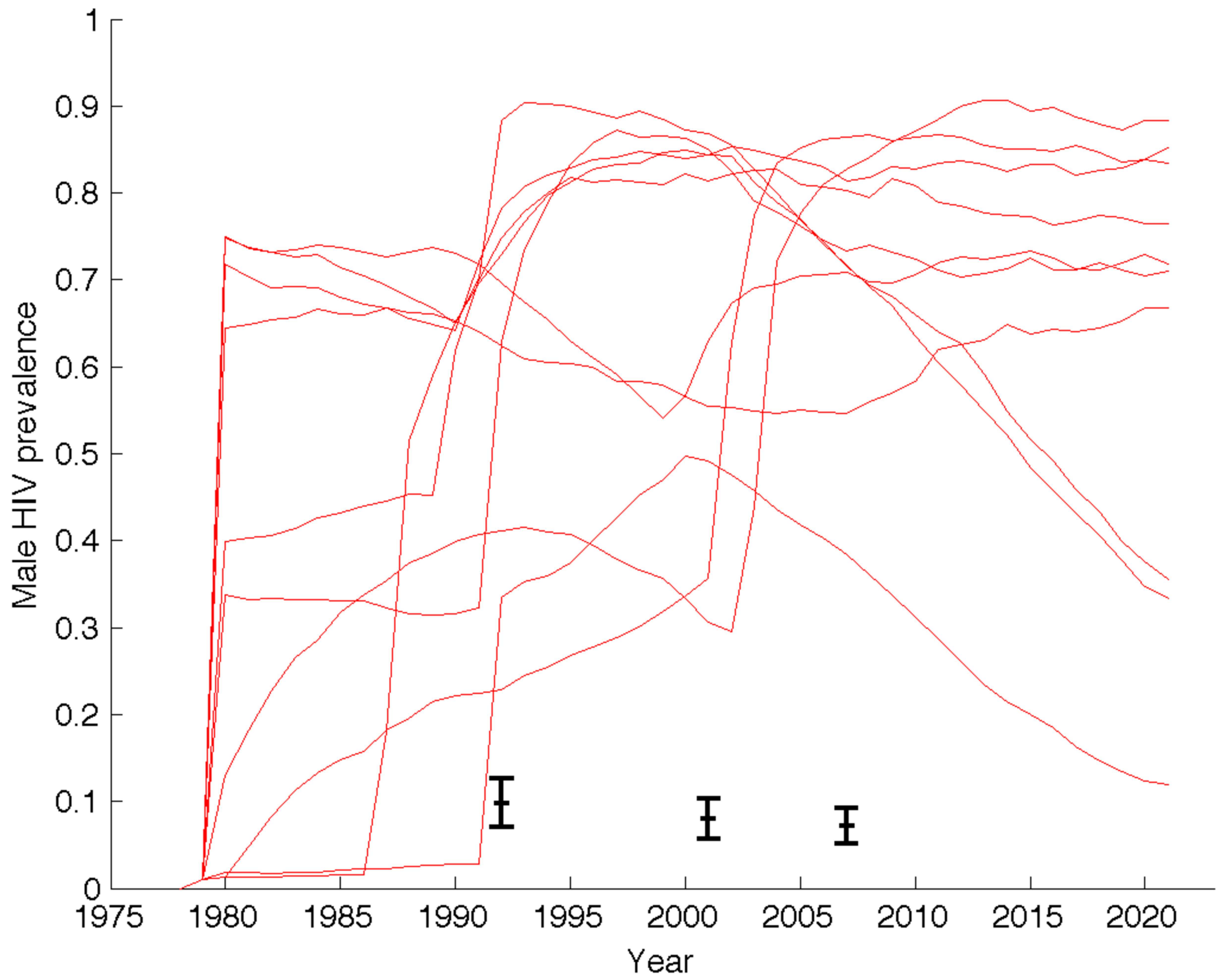


Mukwano Output: Male HIV Prevalence (3 Runs)



Mukwano Output: Male HIV Prevalence (10 Runs)



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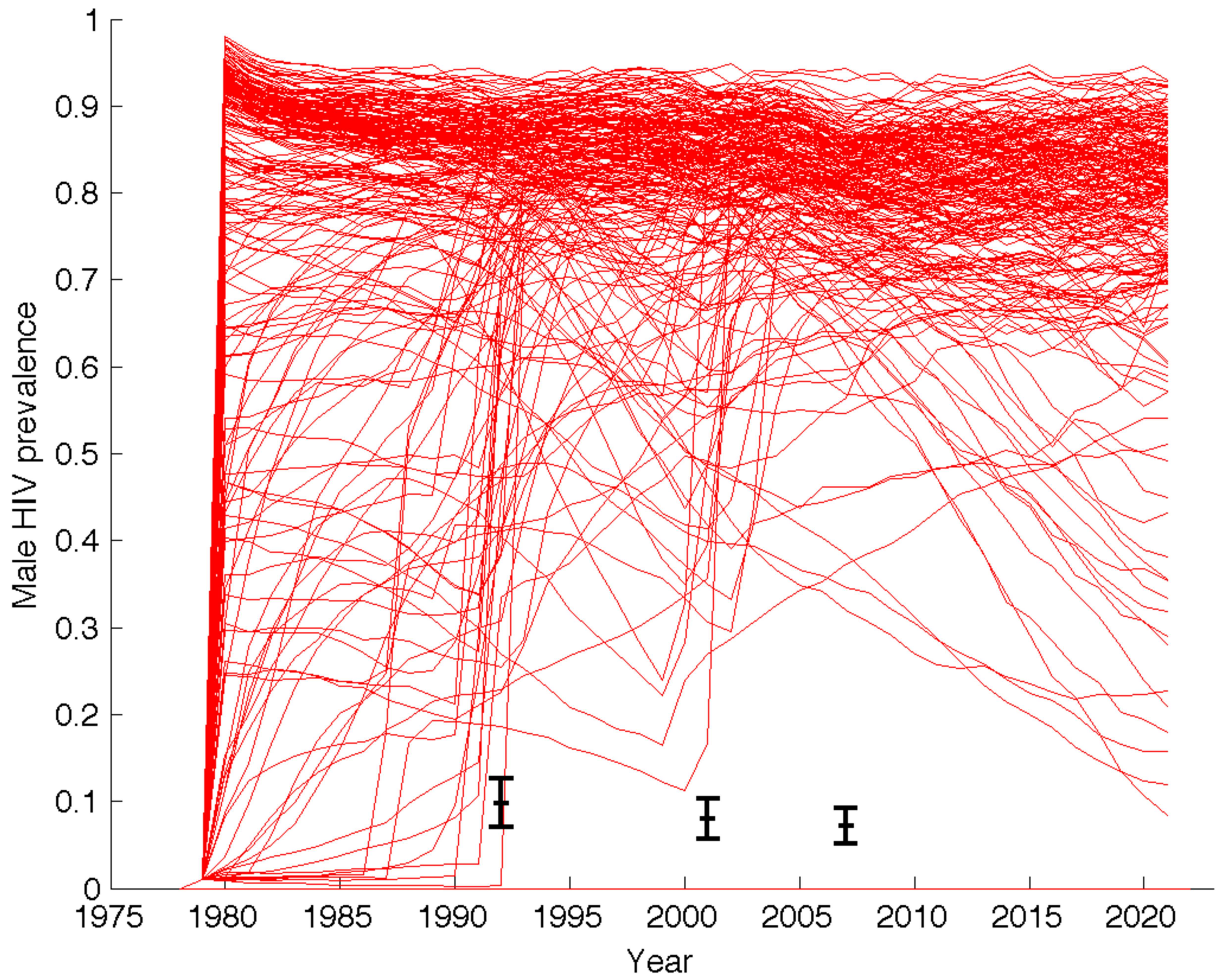

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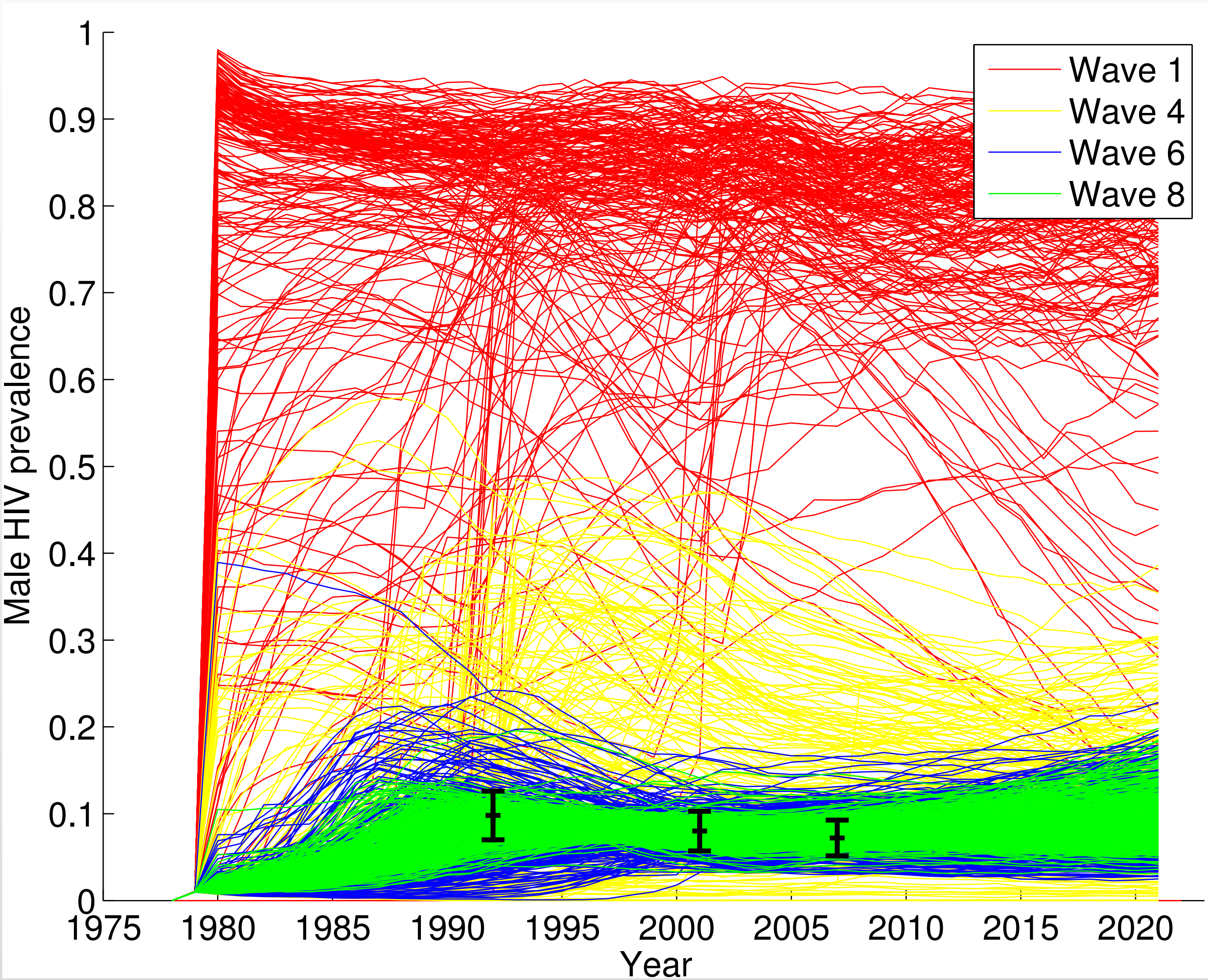

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Mukwano: Sensitivity Analysis re Uncertainties

- Final non-implausible volume: 1.3×10^{-11} of the original.
- We can perform a sensitivity analysis on the volume of the non-implausible region, by decreasing the size of each of the four main uncertainty contributions.

Decrease	Observation Error	Emulator Uncertainty	Model Discrepancy	Stochastic Variability
50%	19.8	11.8	10.7	54.8
90%	45.4	24.9	21.9	91.4

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- Simulates HIV transmission under various ART treatment strategies.
- Predicts the effects of ART on mortality and transmission over the next 15-20 years.
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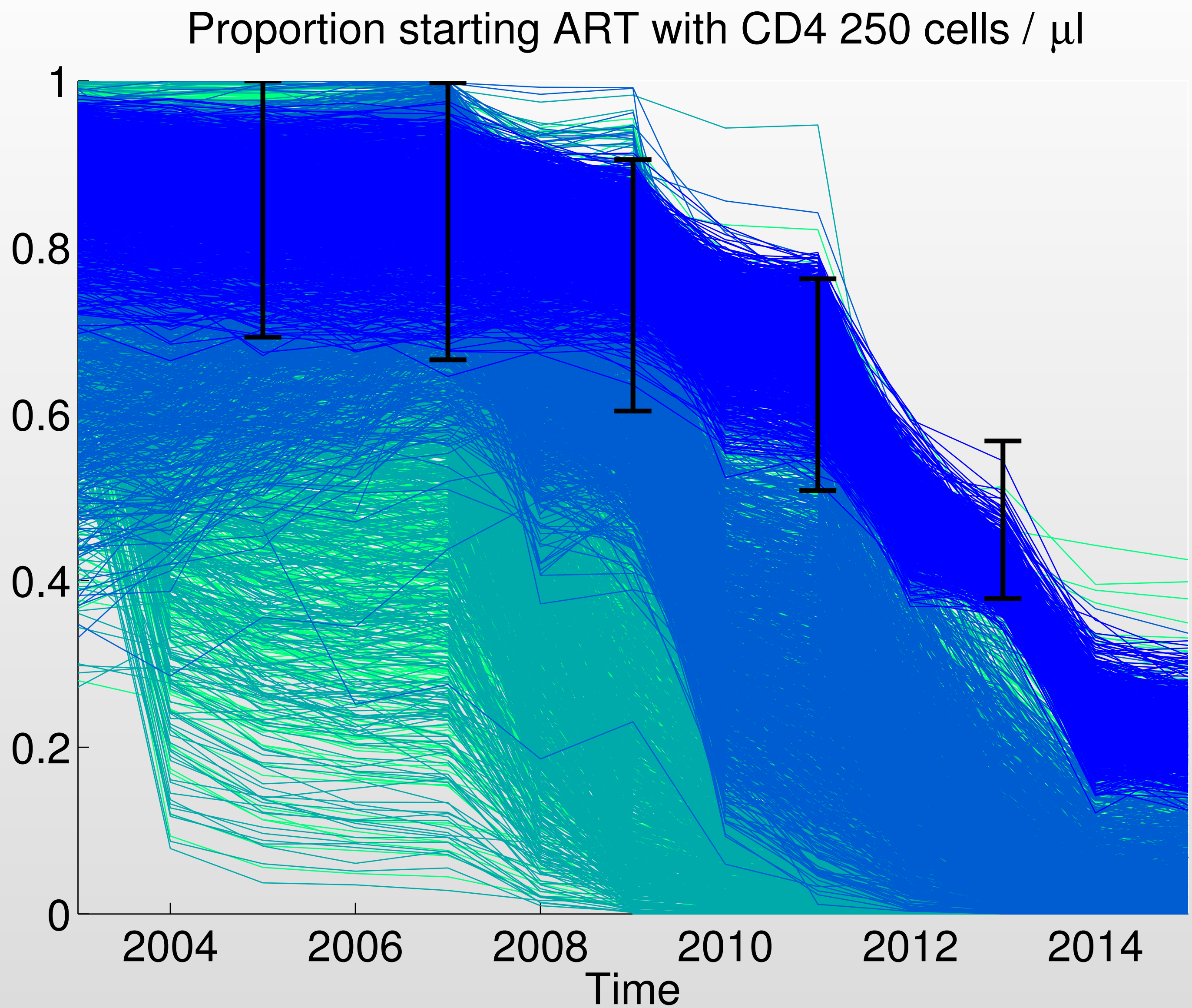
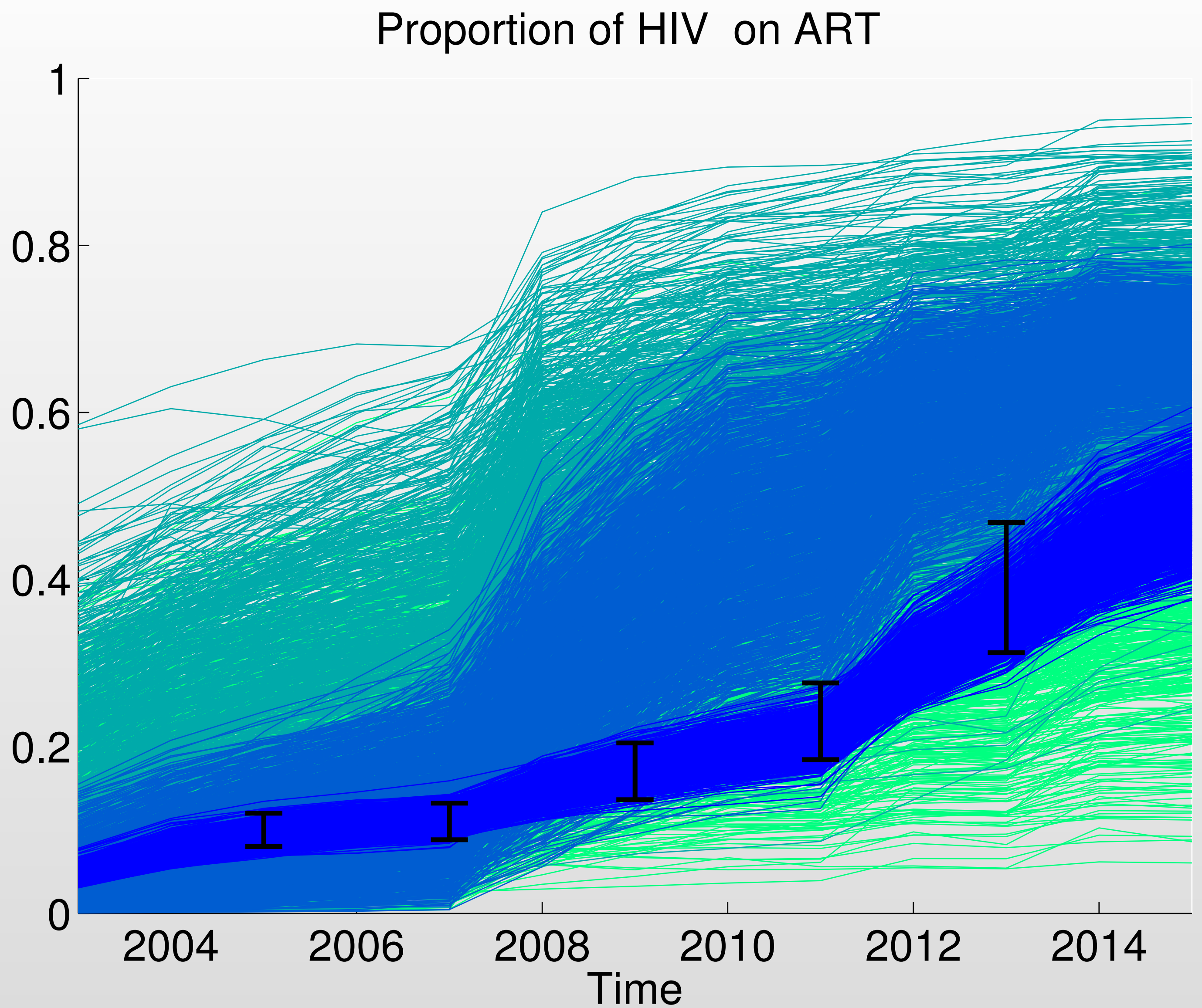
Mukwano 2.0



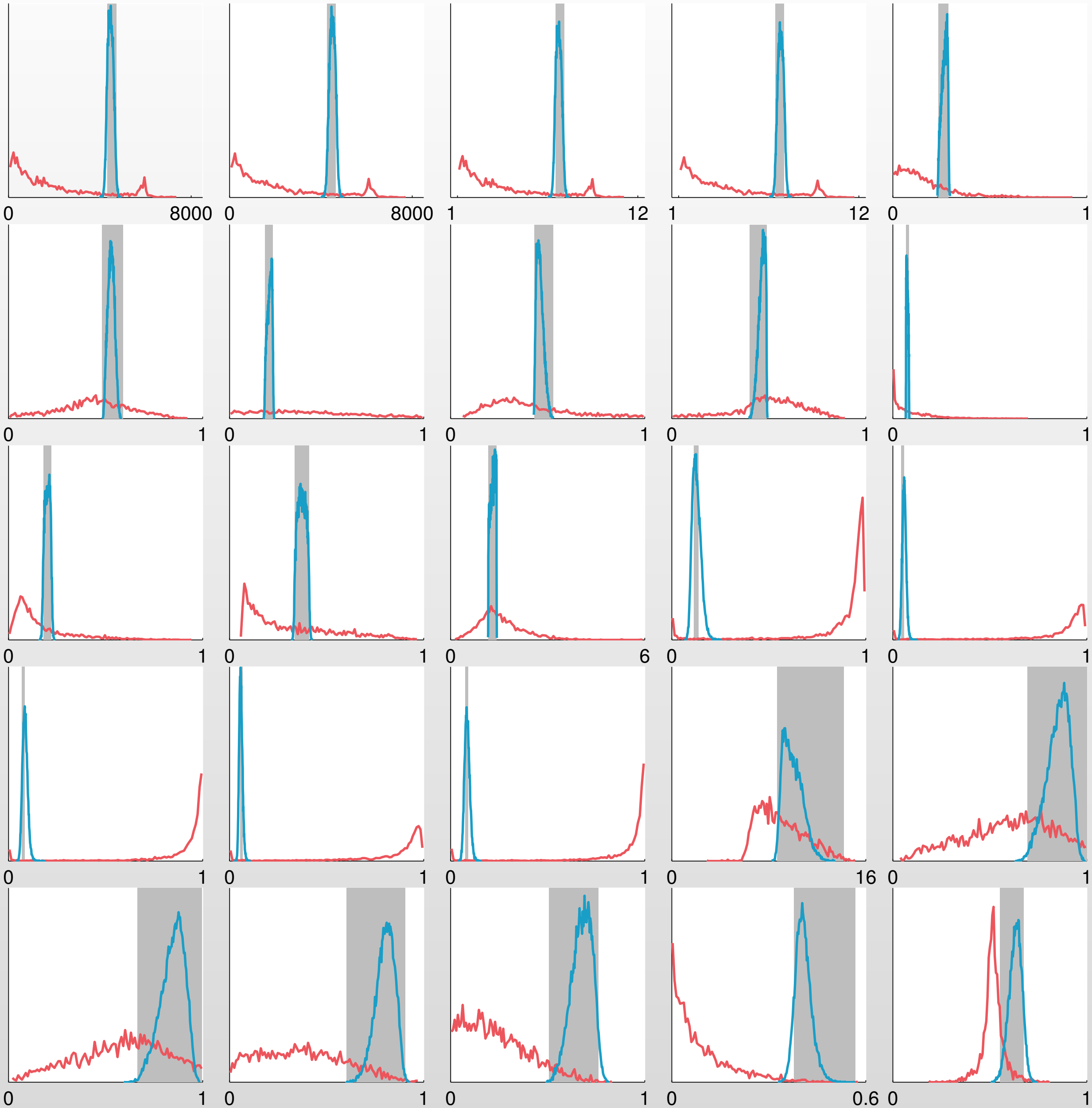
Proportion starting ART with CD4 250 cells / µl
1
0.8
0.6
0.4
0.2
0
2004
2006
2008
2010
2012
2014
Time

Mukwano 2.0



Proportion of HIV on ART
1
0.8
0.6
0.4
0.2
0
2004
2006
2008
2010
2012
2014
Time

Mukwano 2.0



0
8000
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8000
1
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1
0
1
0
6
0
1
0
1
0
1
0
1
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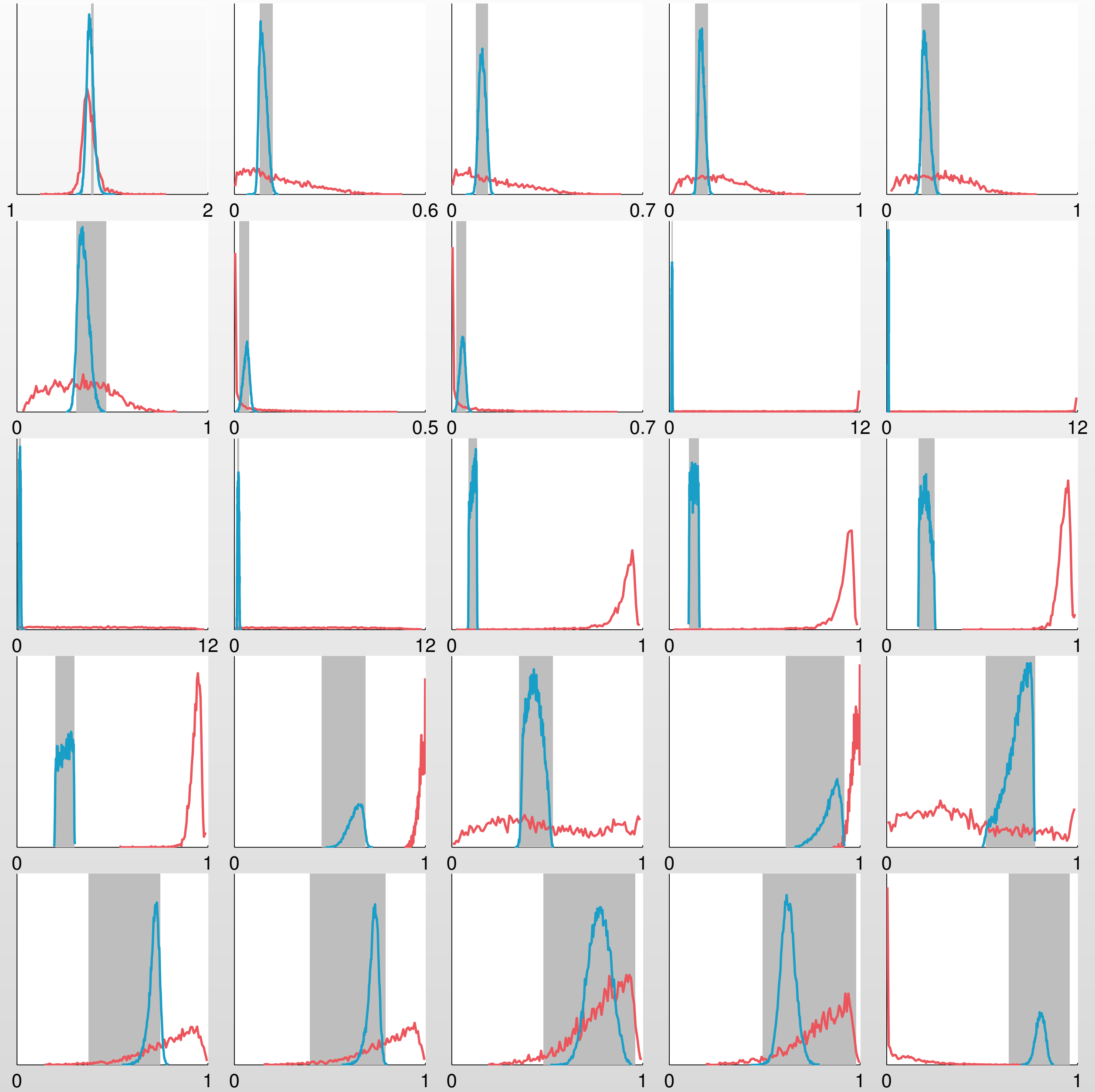
1
0
16
0
1
0
1
0
1
0
1
0
0.6
0
1

Mukwano 2.0



1 2
0 0.6
0 0.7
0 1
0 1
0 1
0 0.5
0 0.7
0 12
0 12
0 12
0 12
0 1
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0 1
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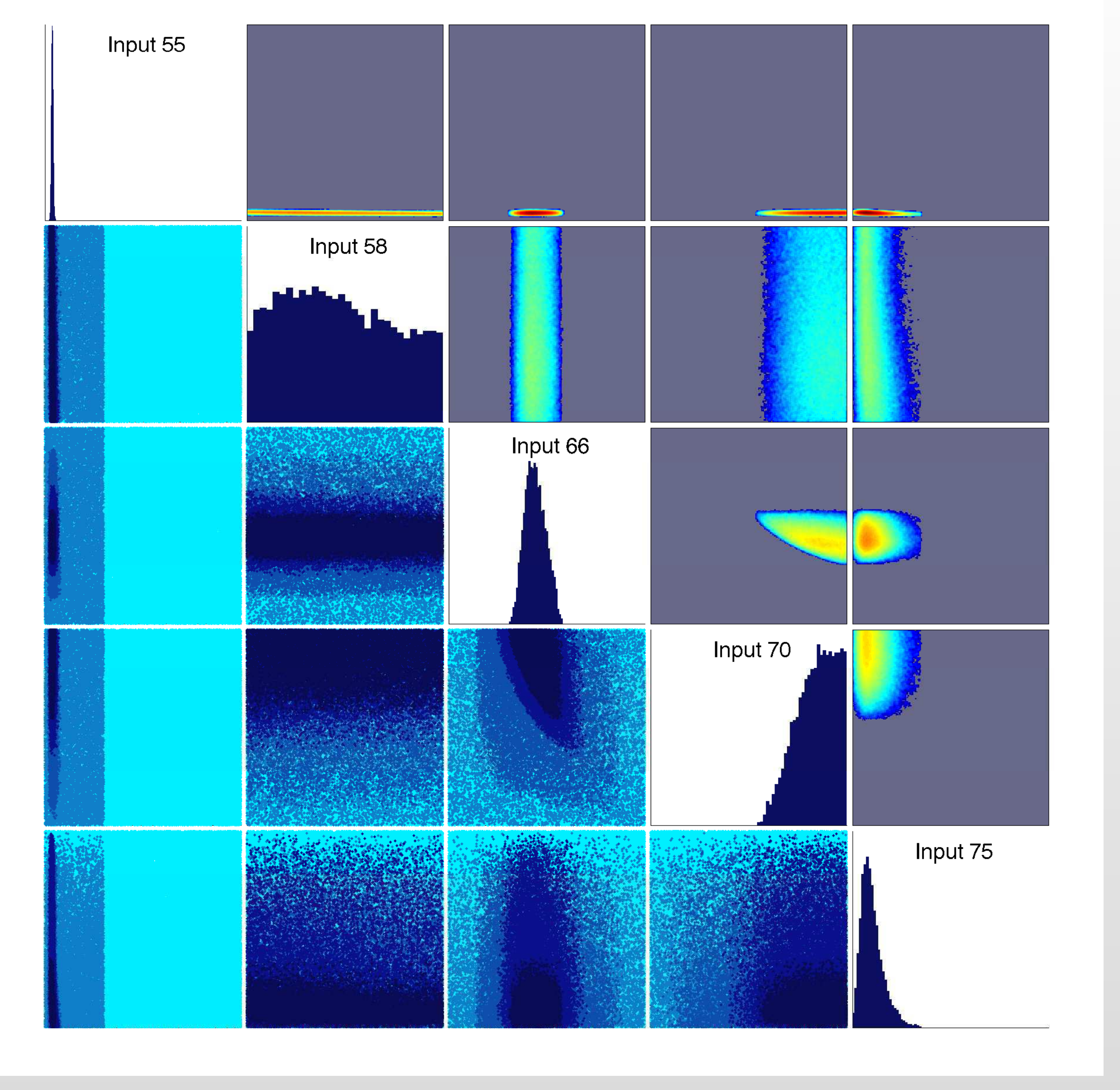
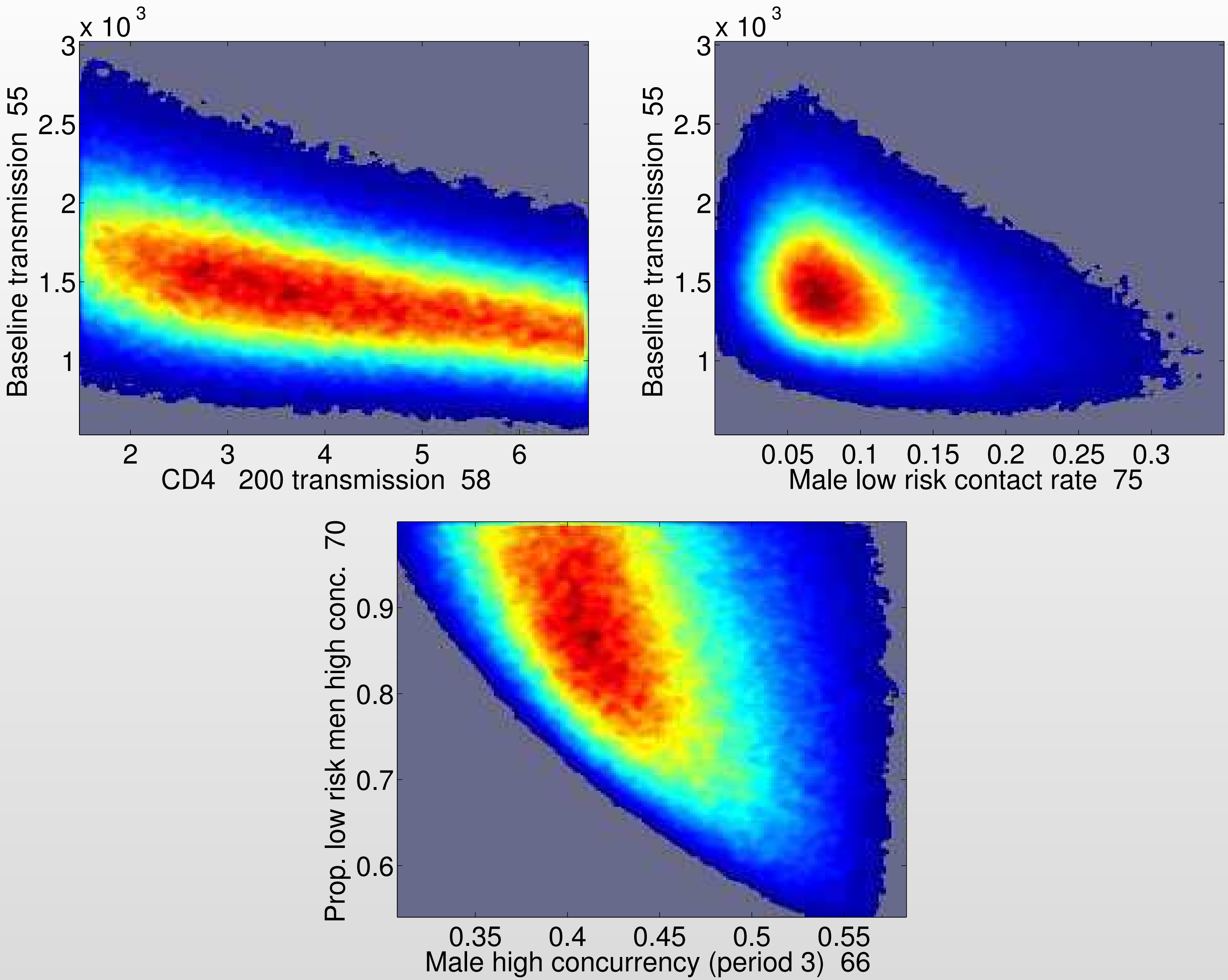
0 1
0 1

Optical Depth Plots



Final non-implausible volume: 2.4×10^{-45} of the original.

Minimised Implausibility and Depth Plots



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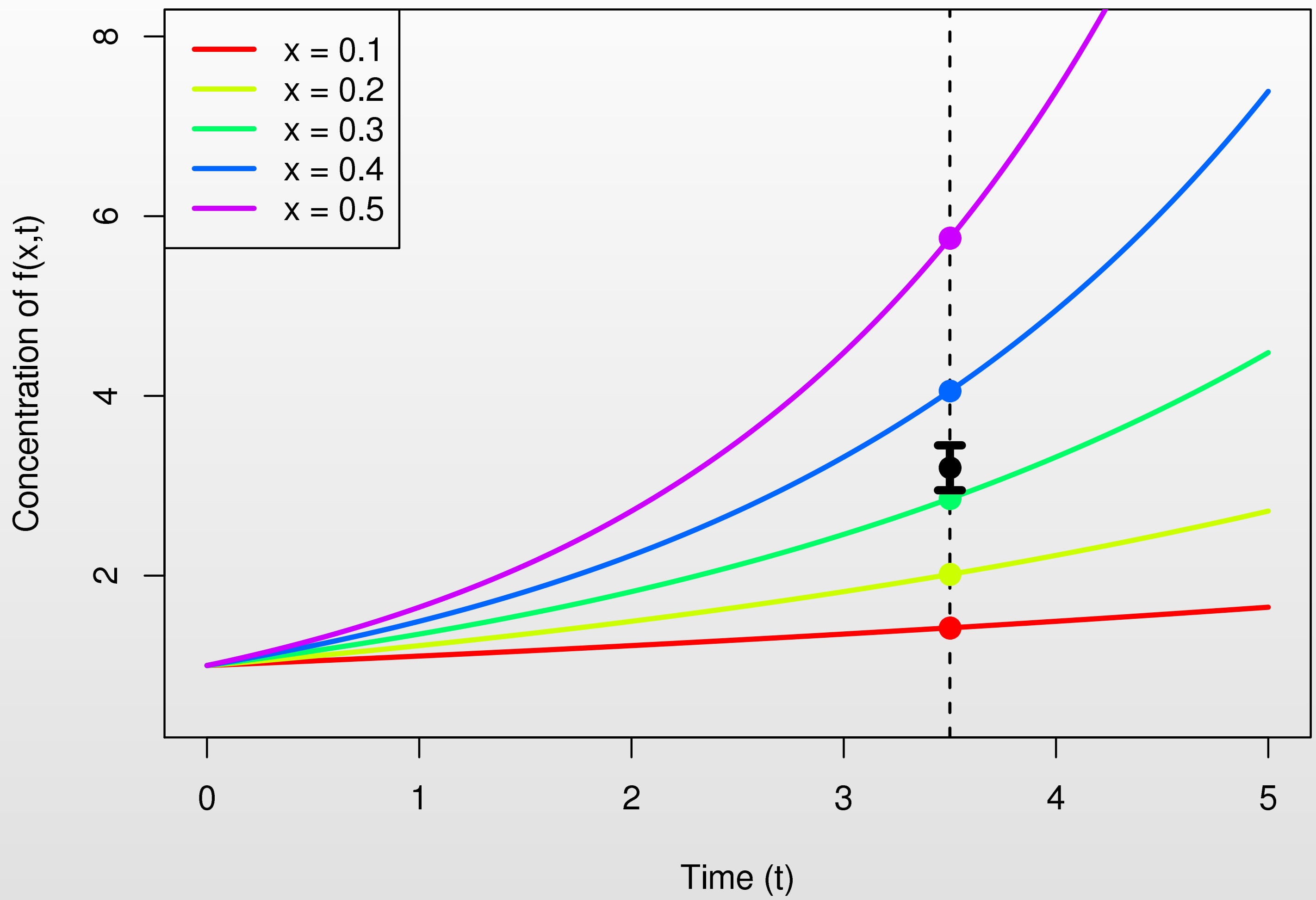
- The results feed into a number of other research projects that quantify the effect of different ART deployment strategies, costs, etc.
- We can hence use the above approach to make decisions about the most effective intervention, but also to design the most efficient data collection campaign.

Designing new experiment: 1D example



- Using the emulator we can choose several values of x consistent with the measurement of $f(x, t)$ at $t = 3.5$, and perform corresponding runs of the model.

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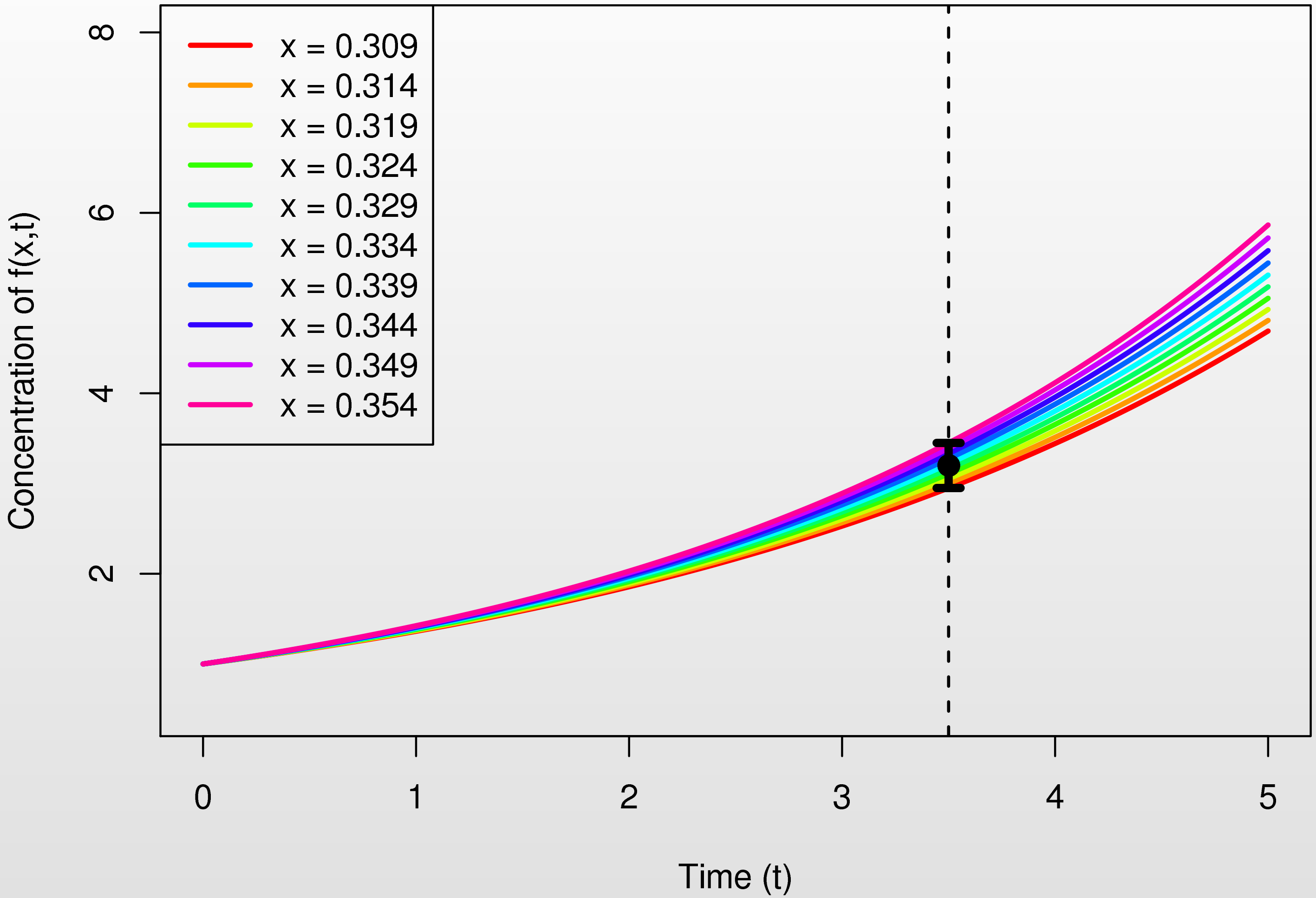

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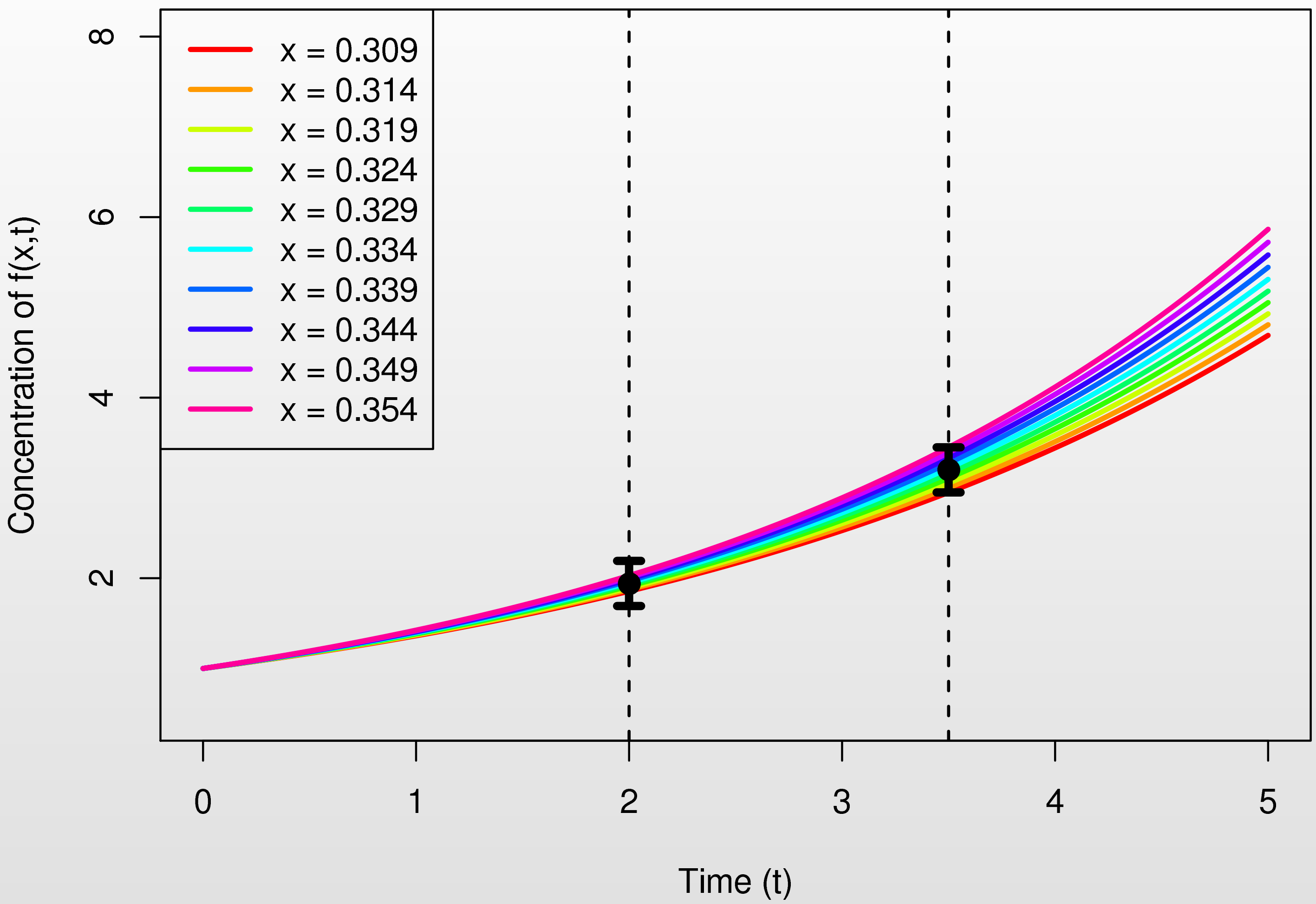
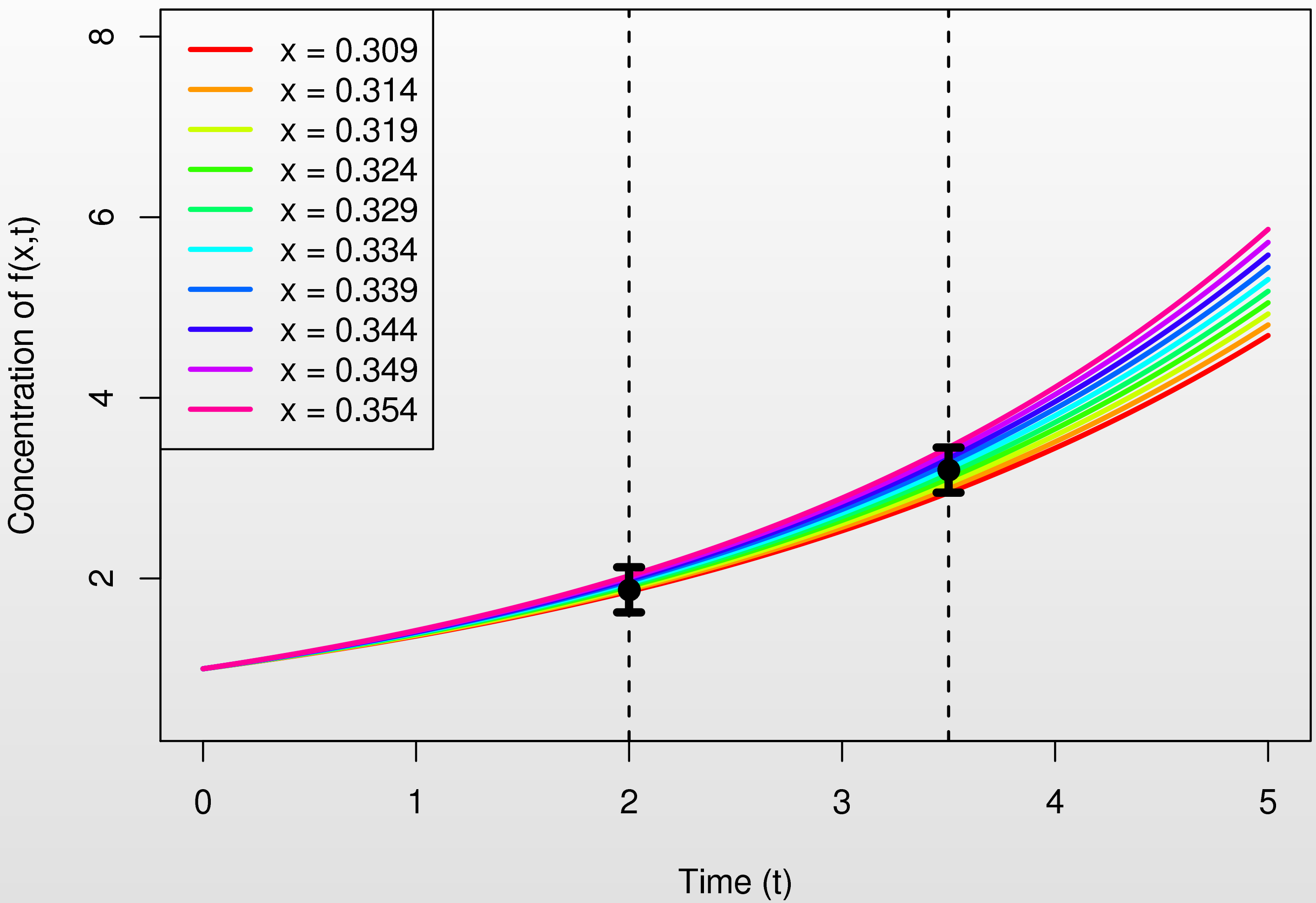


- Using the emulator we can choose several values of x consistent with the measurement of $f(x,t)$ at $t = 3.5$, and perform corresponding runs of the model.
- We can check the predictions made by these runs for $Y(t = 2)$.

Designing new experiment: 1D example



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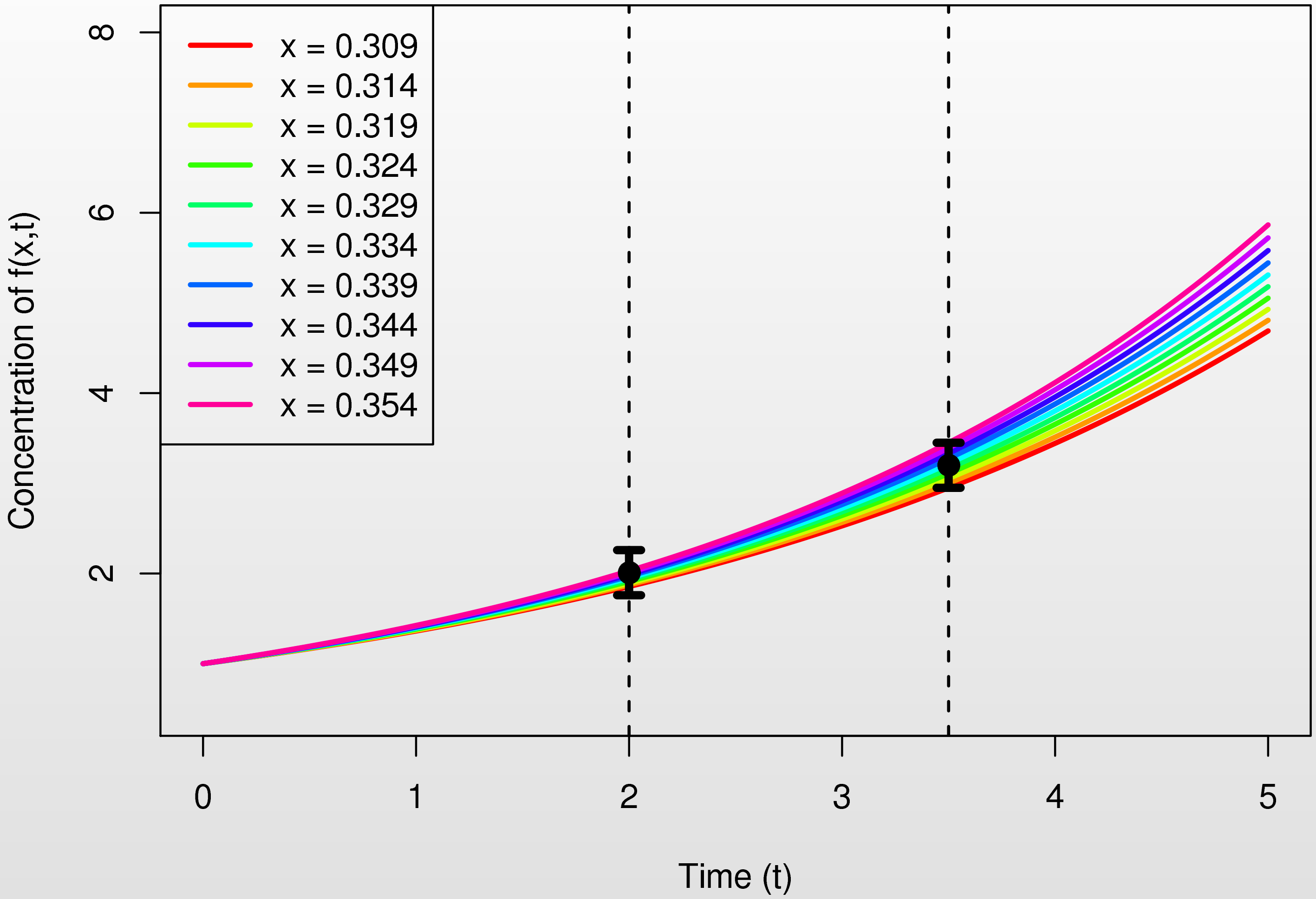
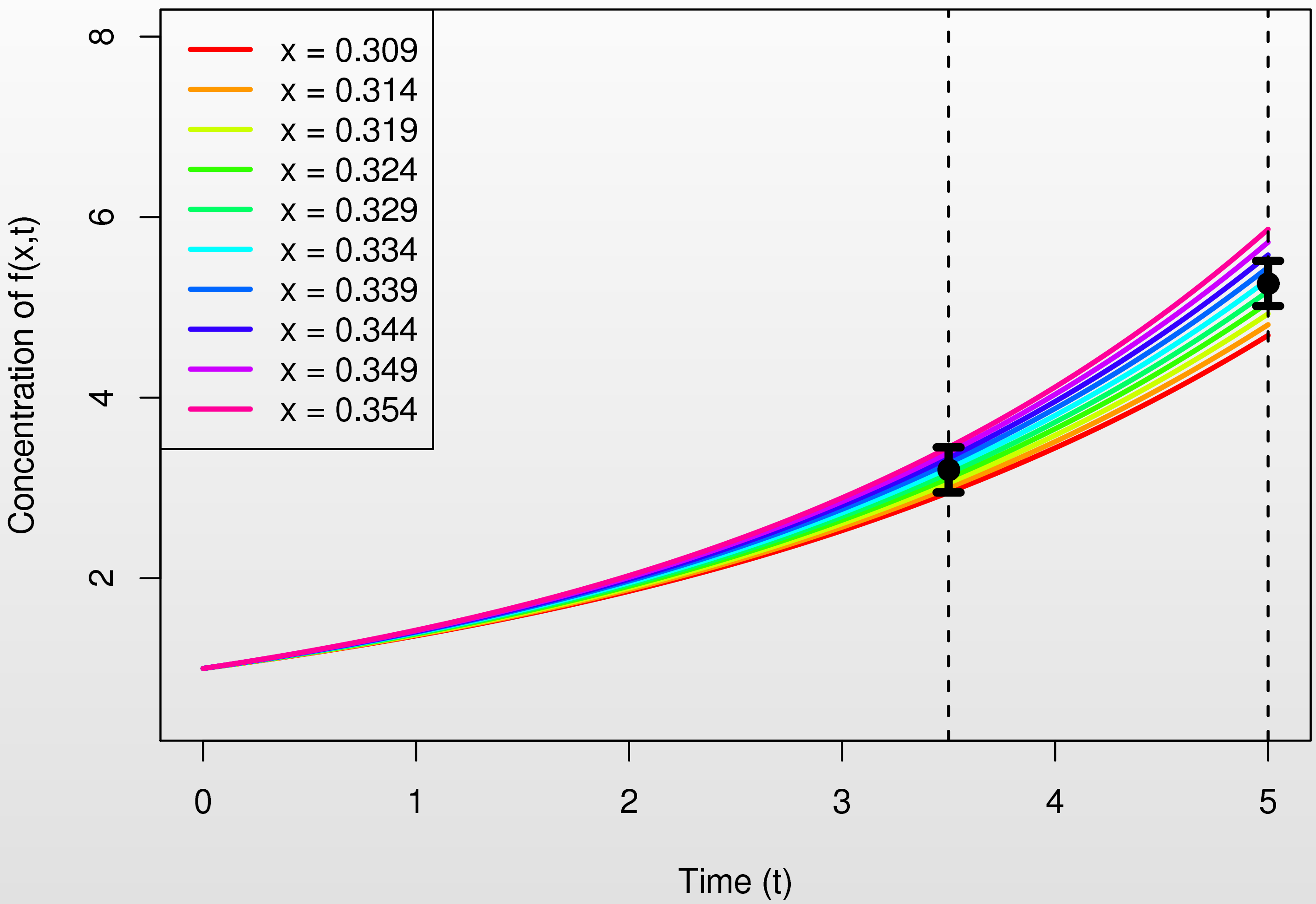


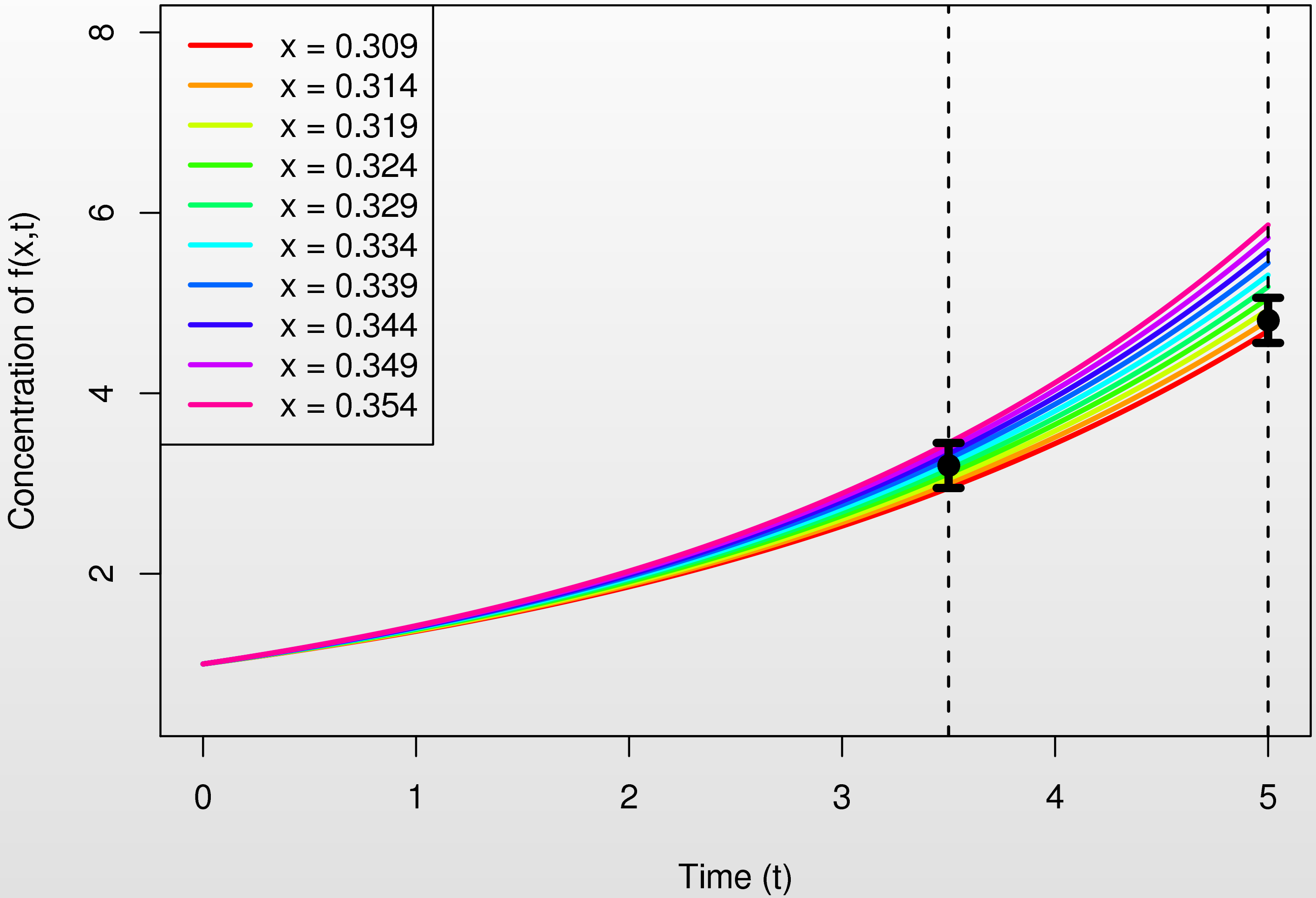
- The predictions imply that any measurement of $Y(t=2)$ is highly unlikely to be informative for x.
- This is due to the measurement errors swamping the signal from the model output $Y(t=2)$.

Designing new experiment: 1D example



- The predictions for $Y(t = 5)$ show a different conclusion.

Designing new experiment: 1D example



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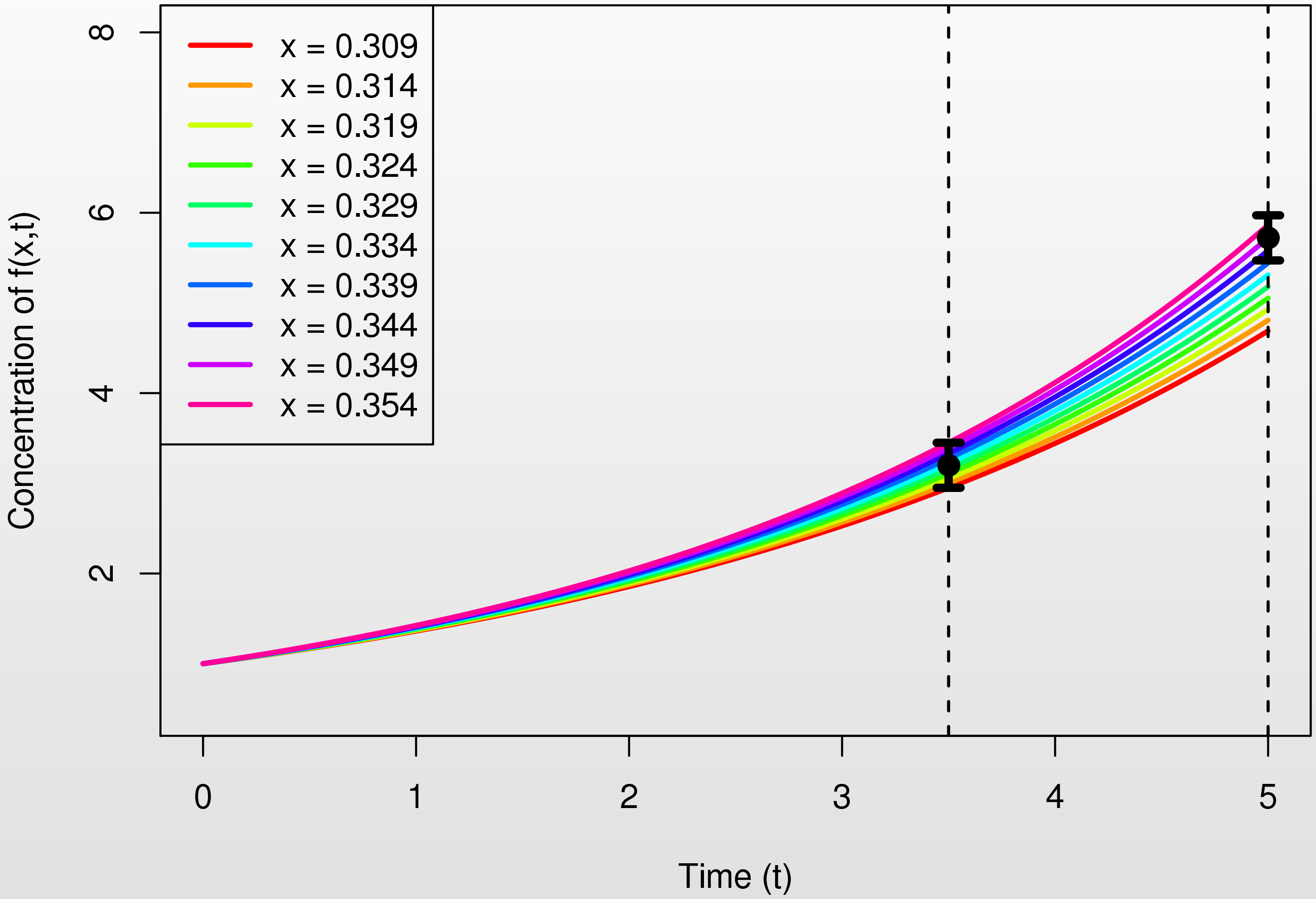
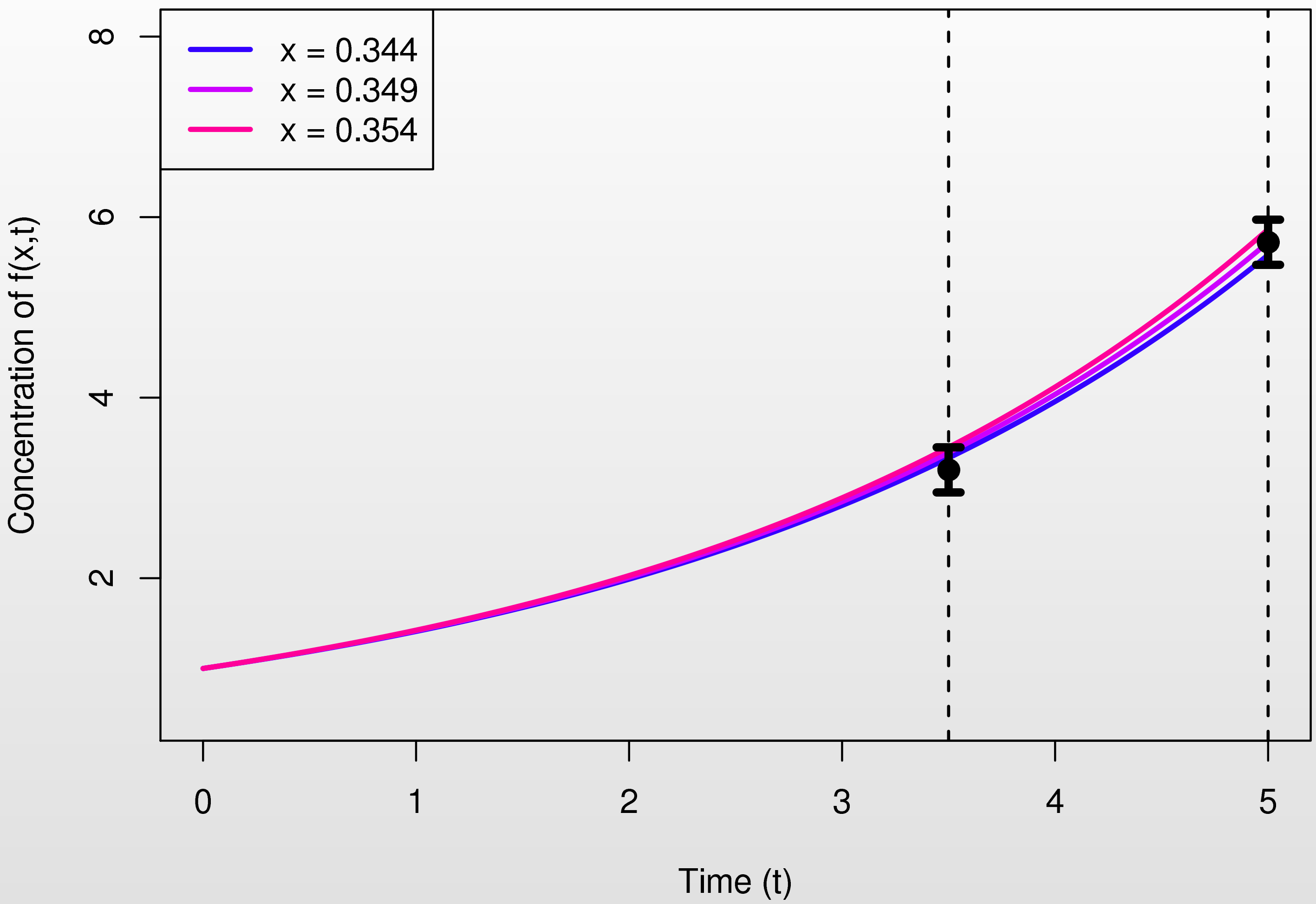


- The predictions for $Y(t = 5)$ show a different conclusion.
- For each possible measurement of $Y(t = 5)$ it is highly likely that we will be able to rule out several more values of x as implausible.

Designing new experiment: 1D example



- For one possible measurement, see that non-implausible values of x would lie between 0.344 and 0.354, ruling out 70% of the possible values of x.

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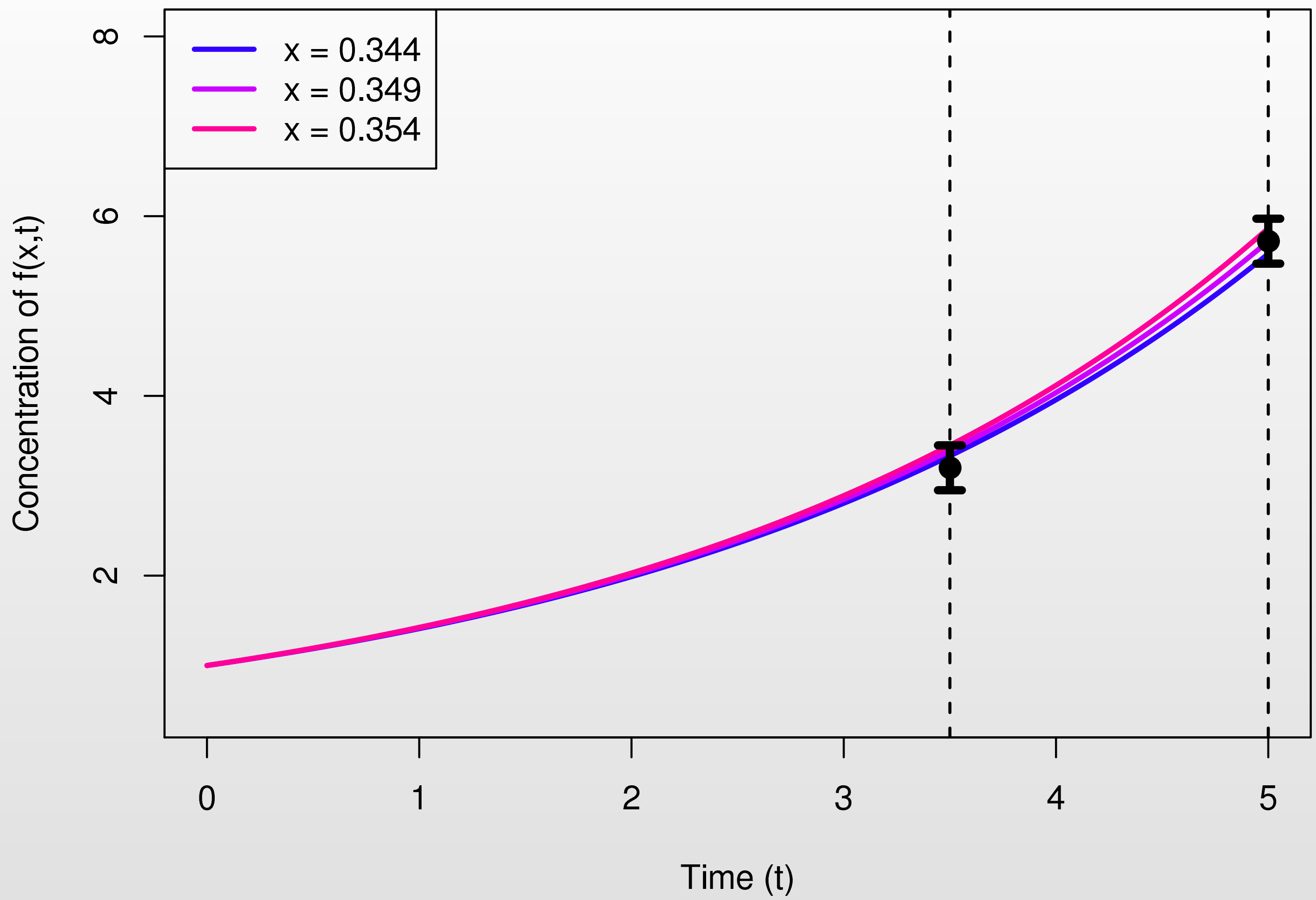

- For one possible measurement, see that non-implausible values of x would lie between 0.344 and 0.354, ruling out 70% of the possible values of x.
- This high expected space reduction in x implies that Experiment B, measuring $f(x,t)$ at $t = 5$, is clearly the best choice.

Final Concluding Comments

- We have a broad methodology for performing full uncertainty analyses on such complex models of disease.

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- The correct treatment of uncertainty is vital: without this, any analysis will be problematic and untrustworthy.
- The emulation methods we describe can be used to exhaustively explore model features (helpful when developing models).
- Due to the need to synthesis many sources of uncertainty within one coherent calculation, a Bayesian approach is ideal.

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