Using Bayesian Approaches to Design New Expensive Experiments

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(with support from an EPSRC Impact award)

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- Bit like a Bayesian posterior over x. (Subtleties here...)

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  - Choose the most efficient experiment based on an Expected Space Reduction criteria and complementary robustness considerations.
- This will result in a design for a new experiment that is expected to be highly informative about the input parameters x of the system (or indeed of any scientific criteria that you care about).

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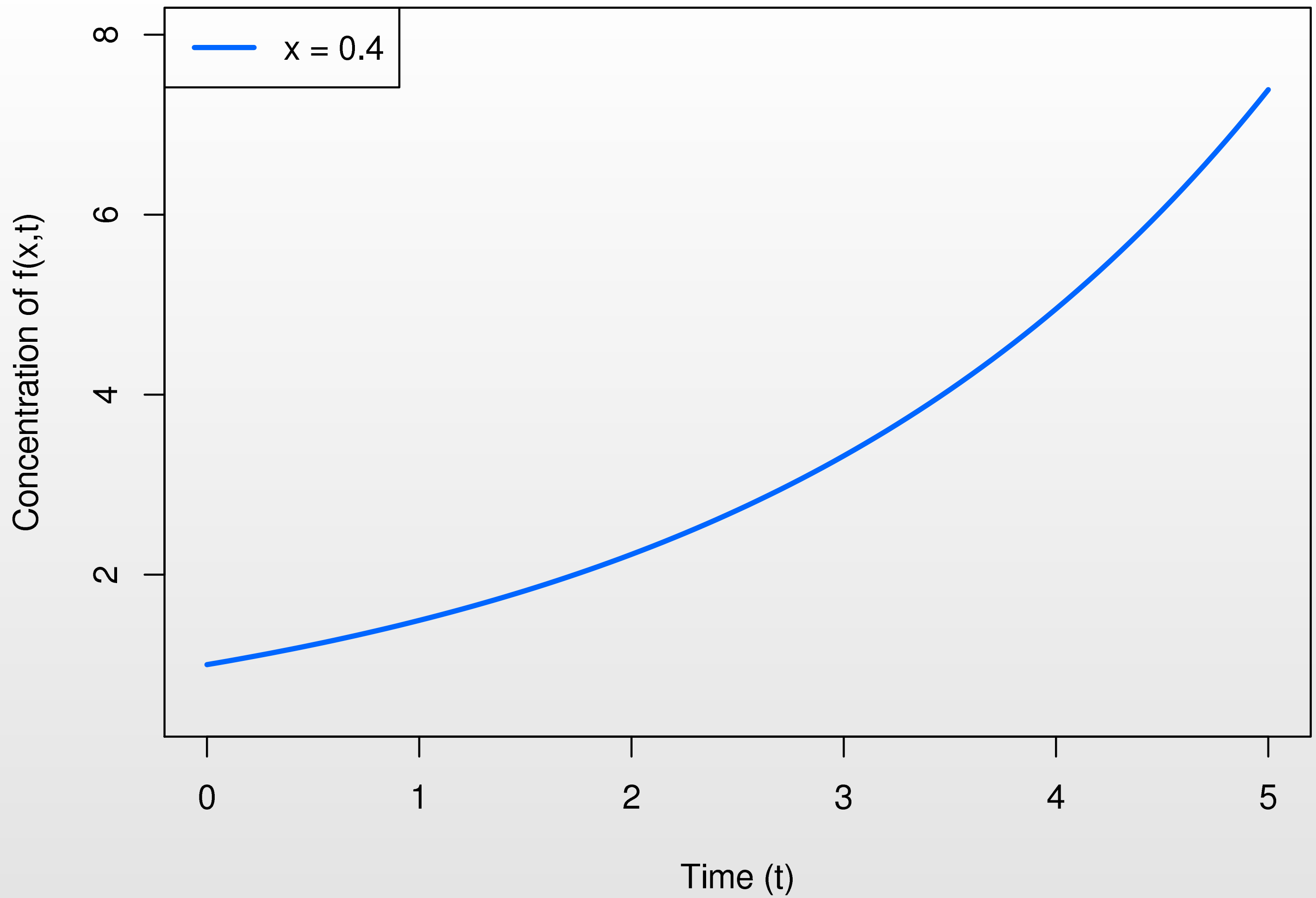
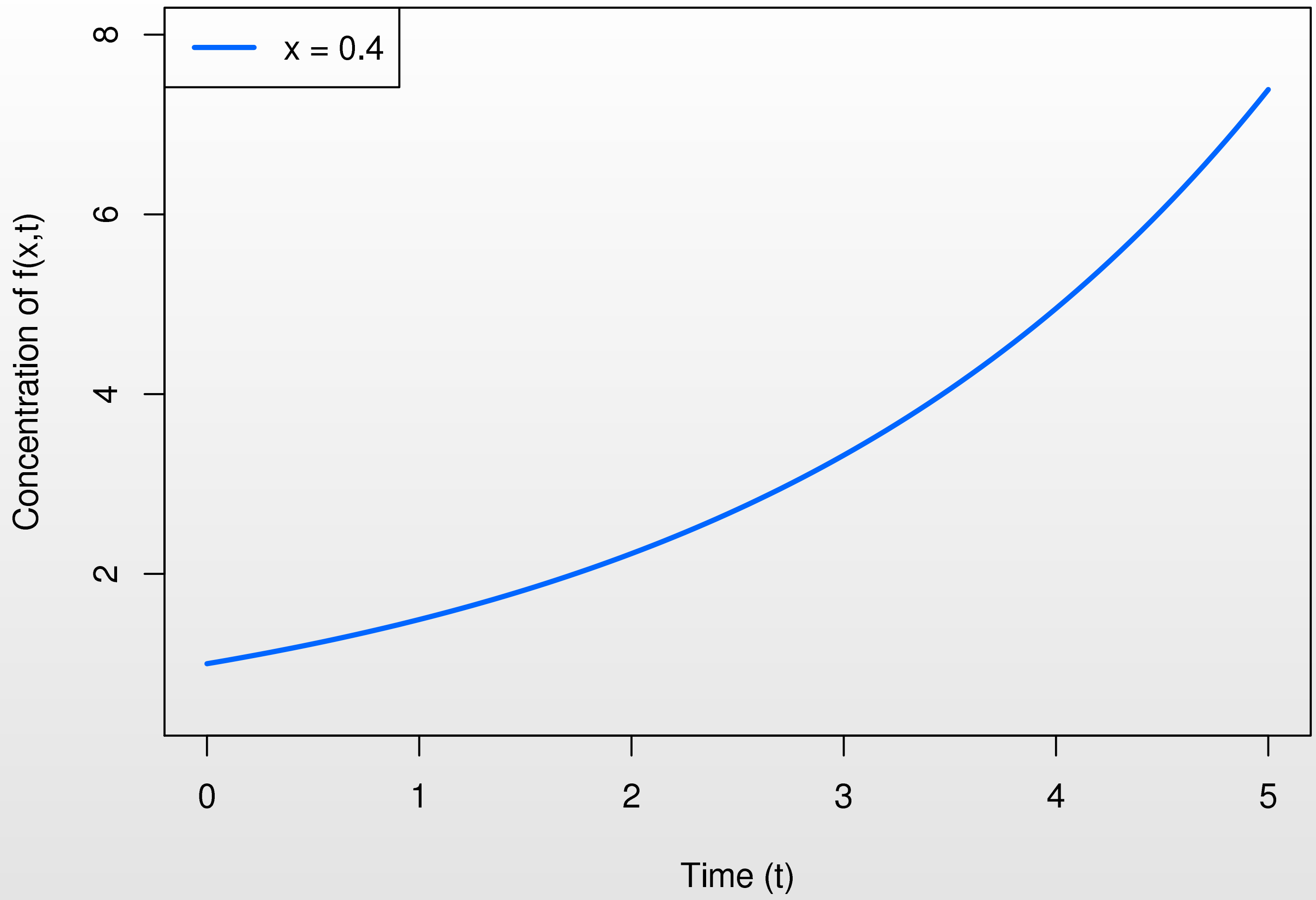
- Model features an input parameter x which we want to learn about.
- Note that normally we would not have the analytic solution for $f(x,t)$.



- One “model run” with the input parameter $x = 0.4$



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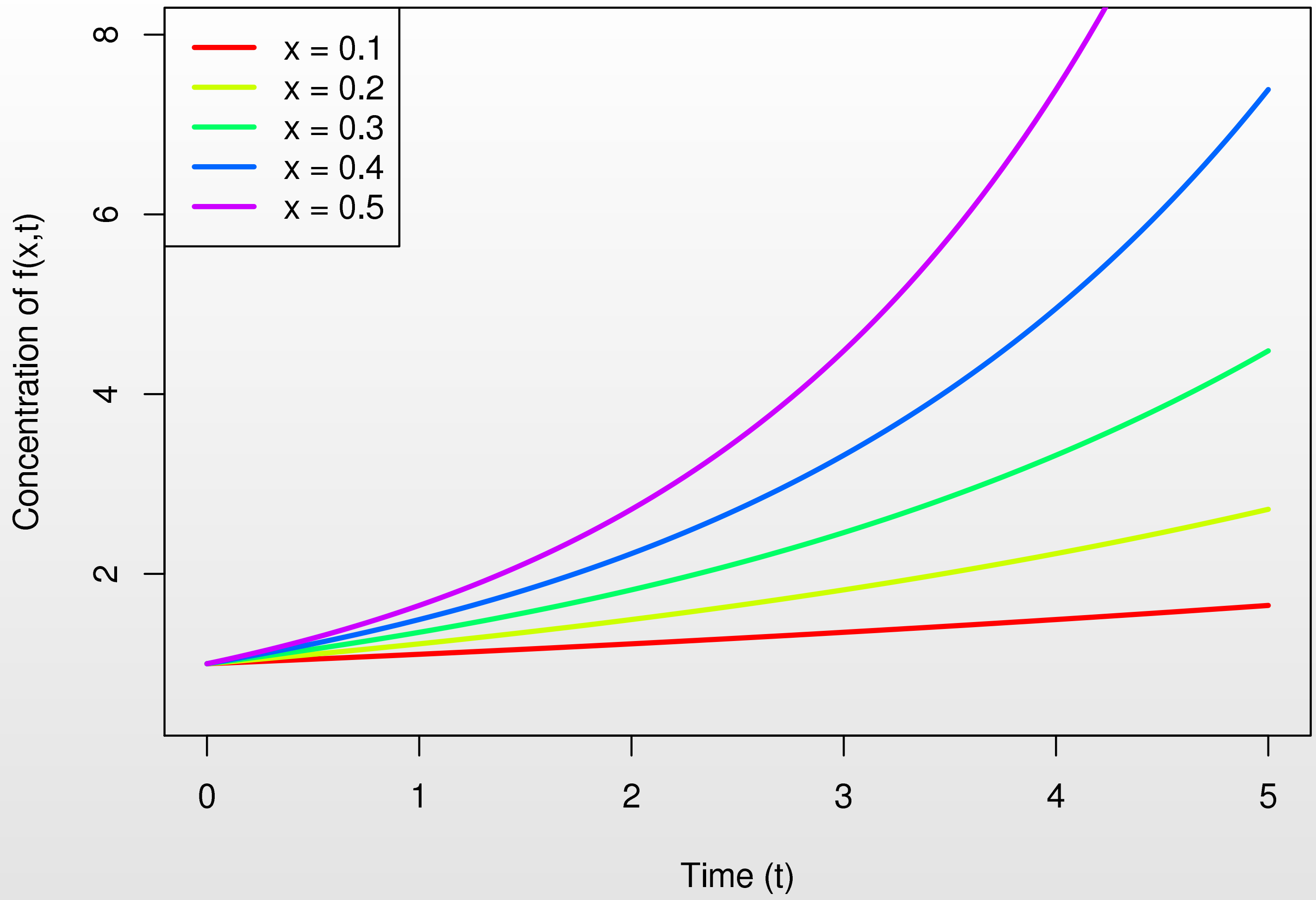
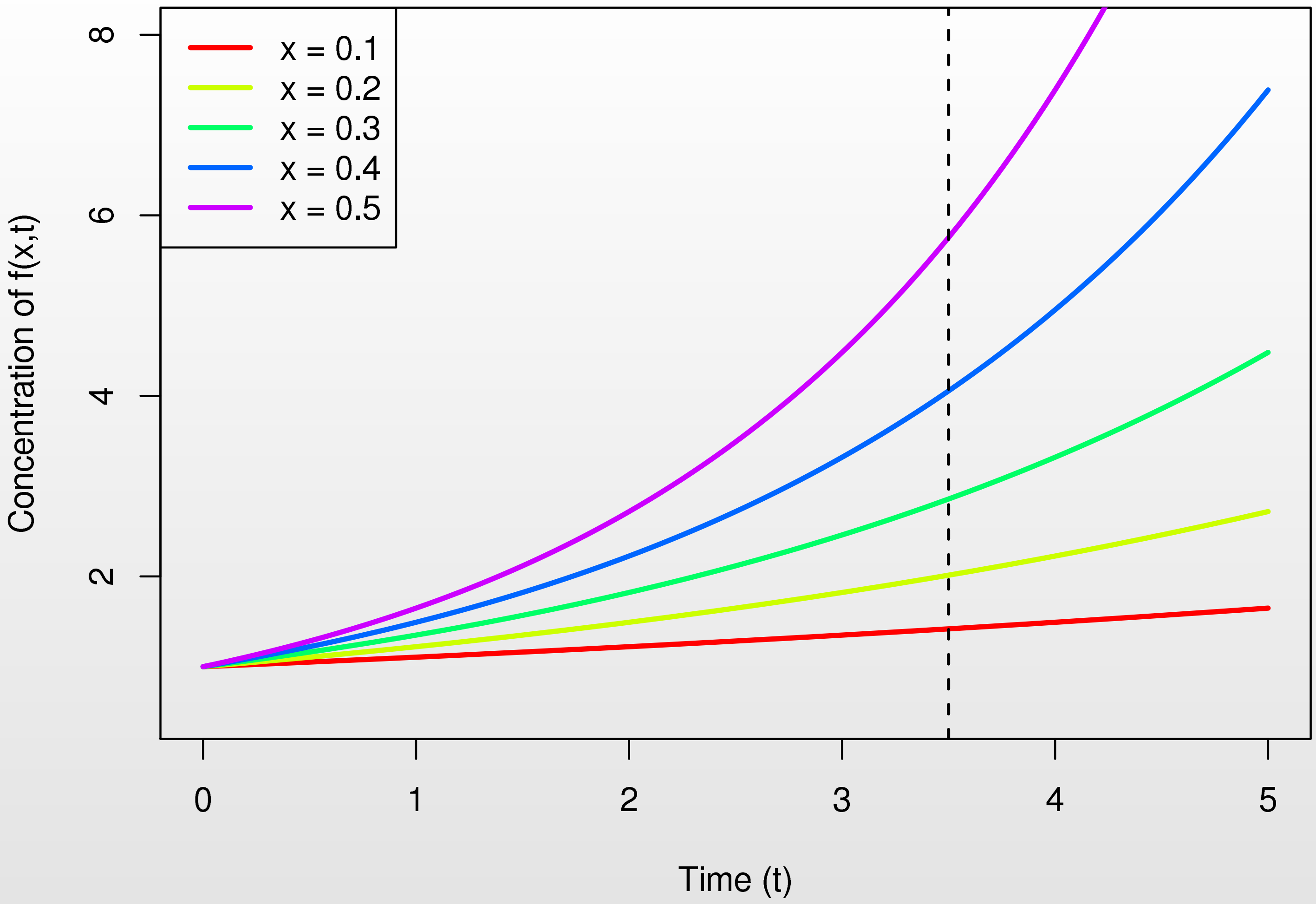
- If we did not know the analytic solution for $f(x,t)$ this would be generated by numerically solving the differential equation.



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



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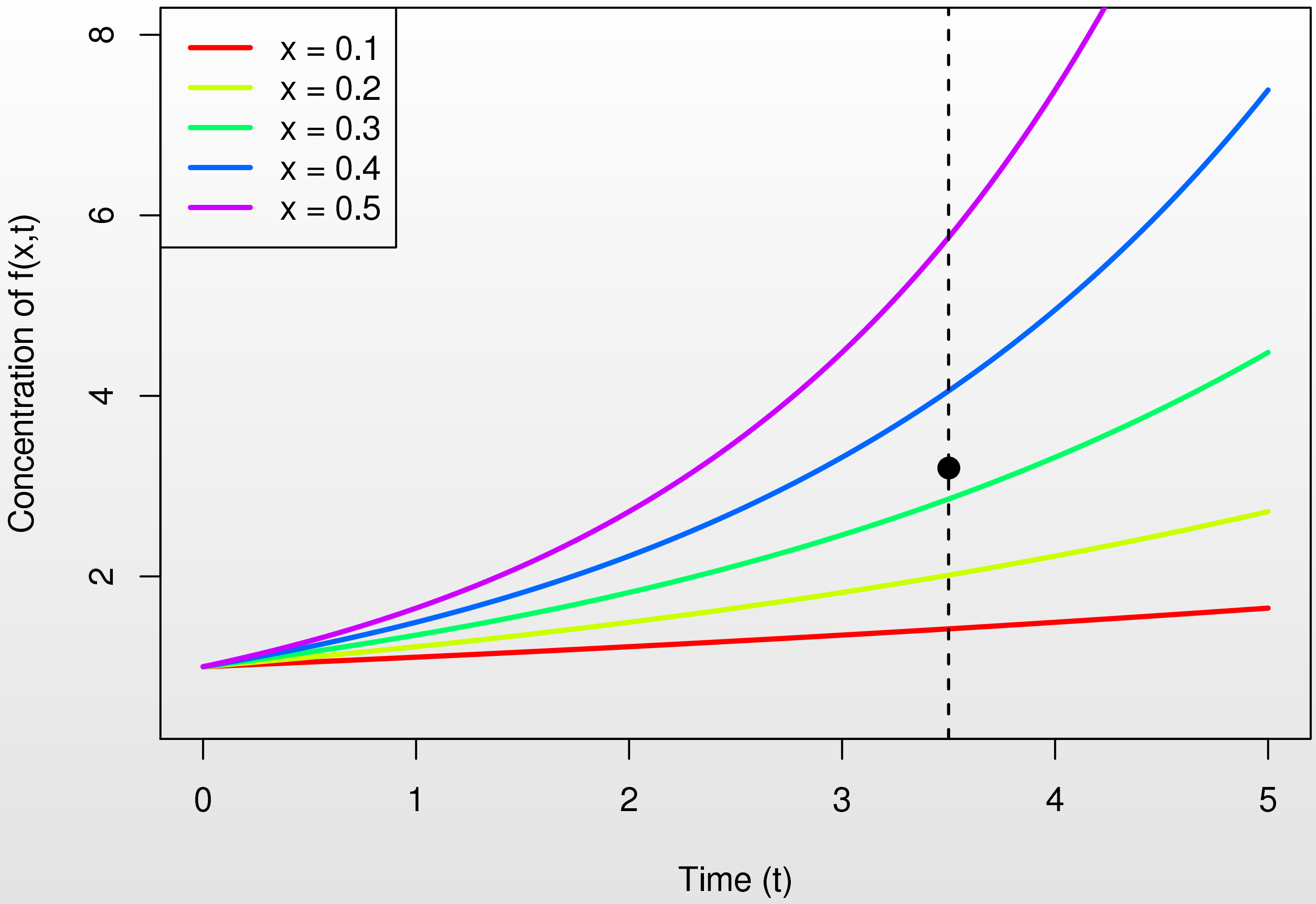

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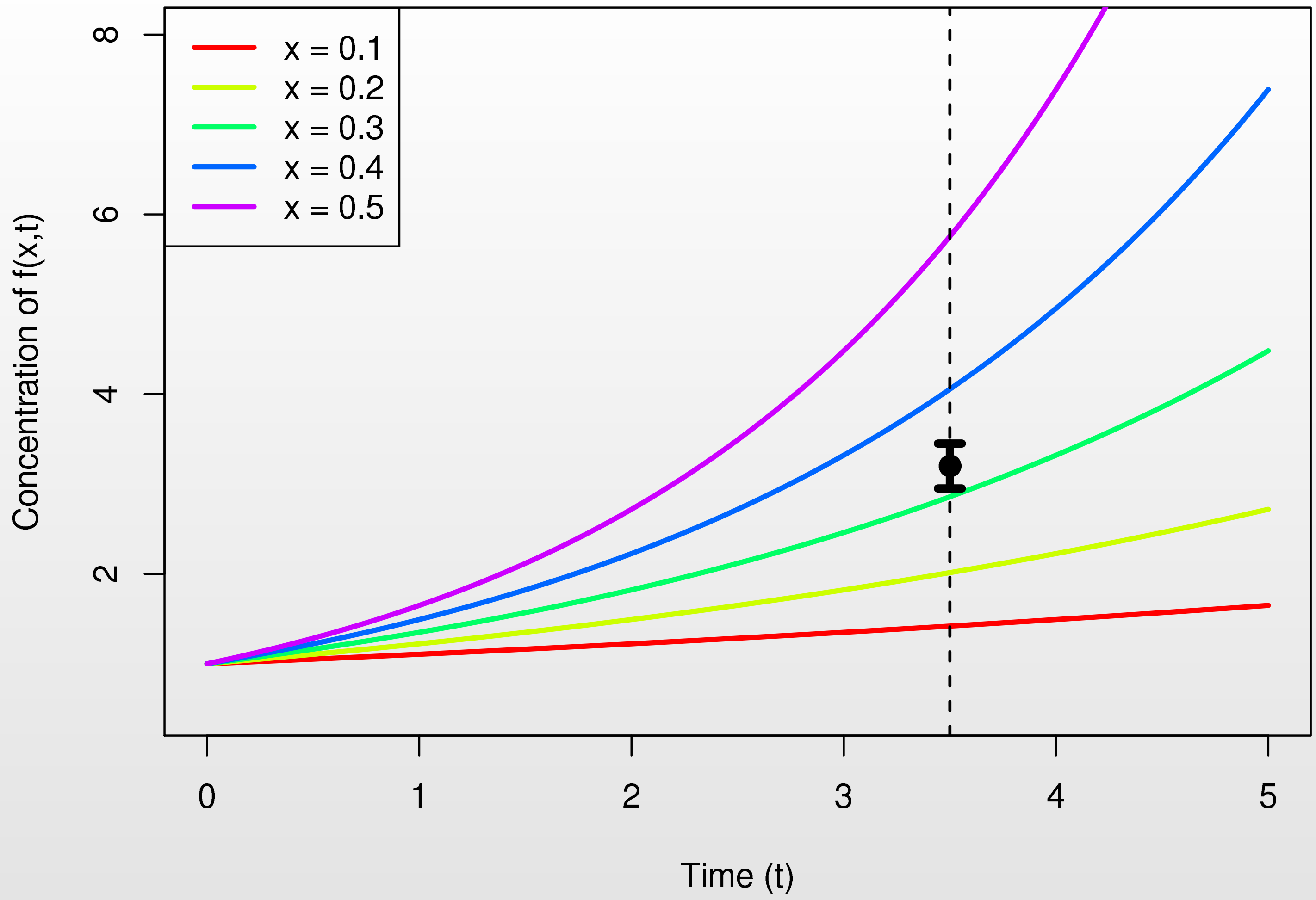

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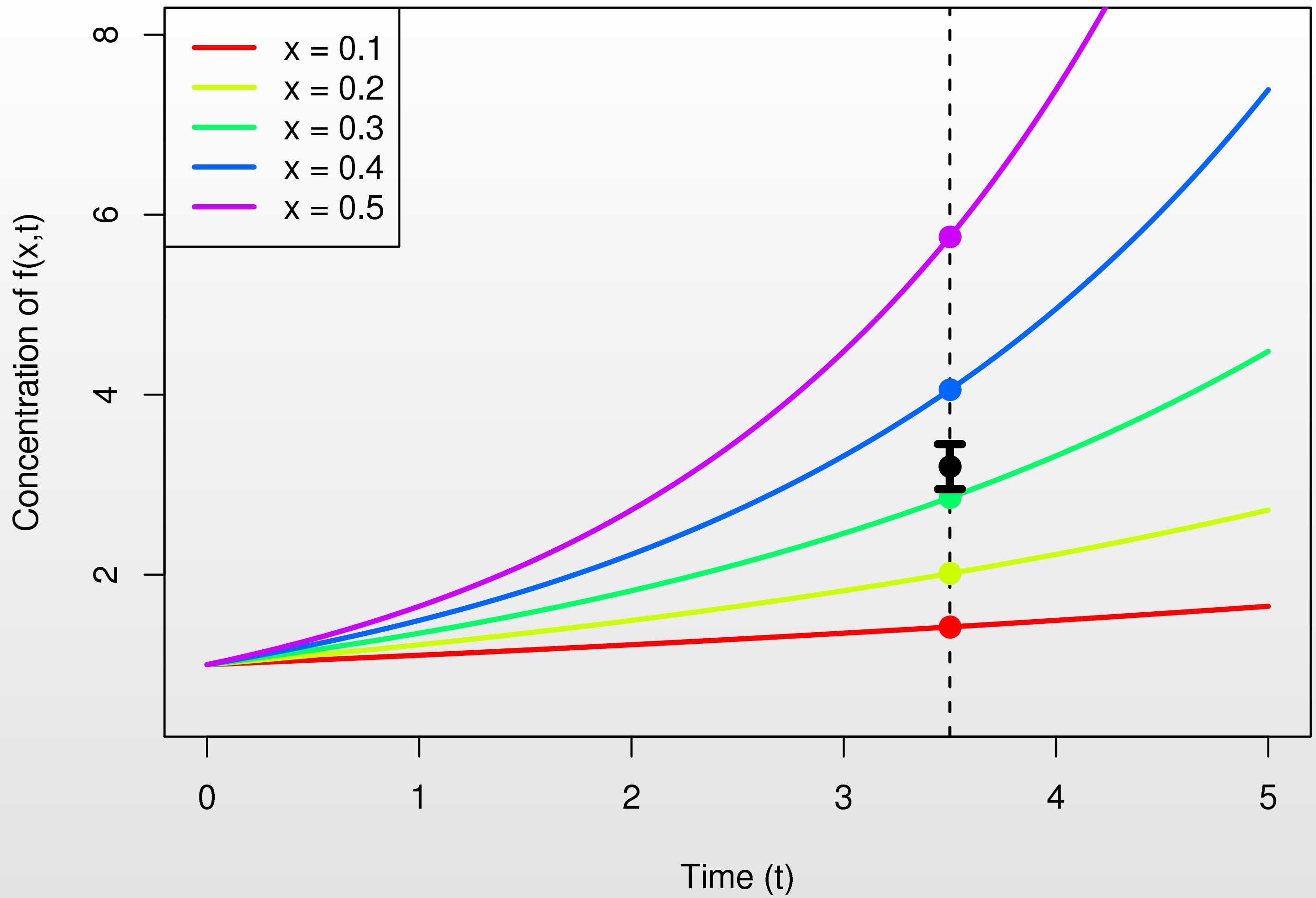
- We are going to measure $f(x,t)$ at $t = 3.5$, giving the value z
- The measurement is not a point but comes with measurement error.



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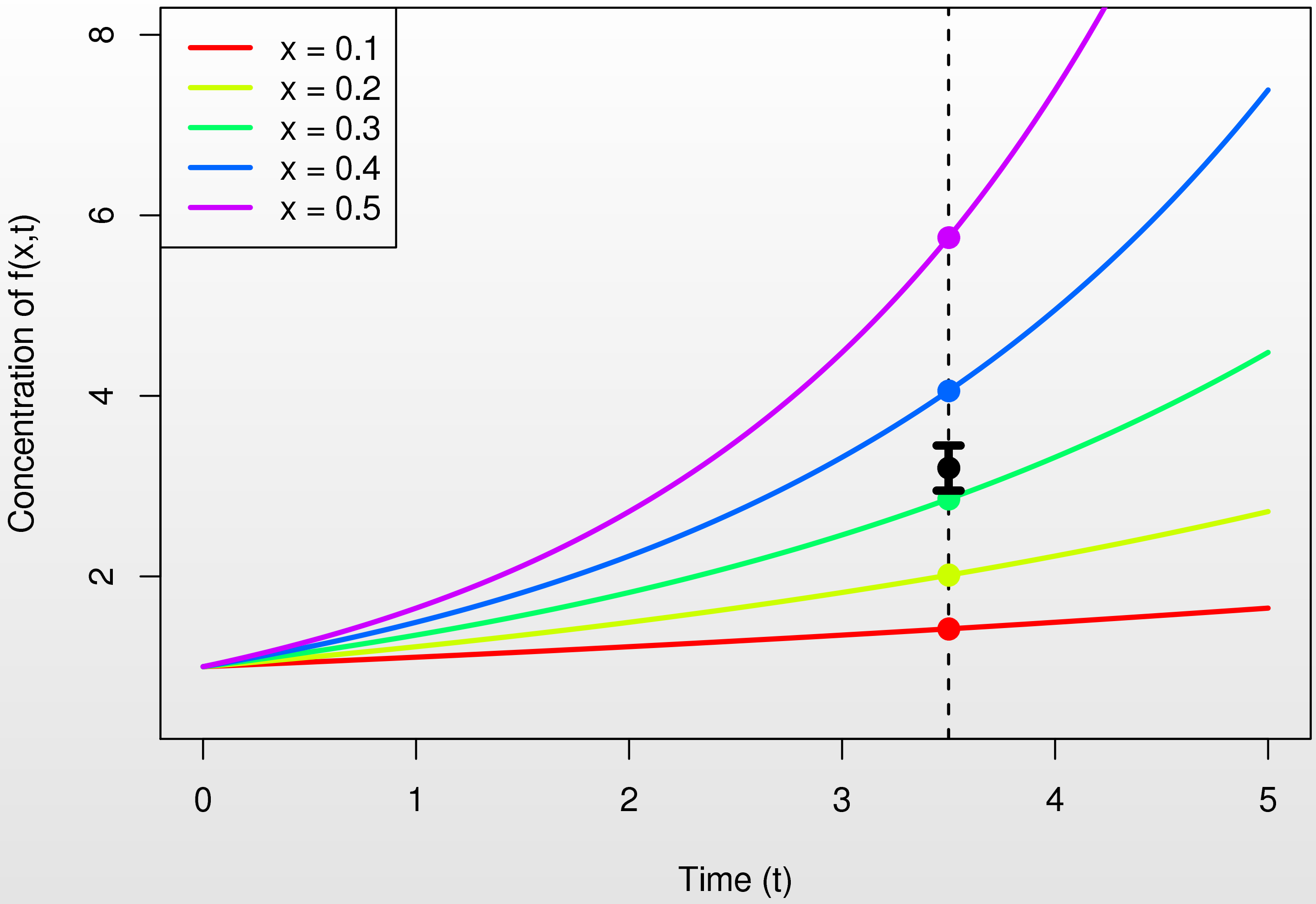

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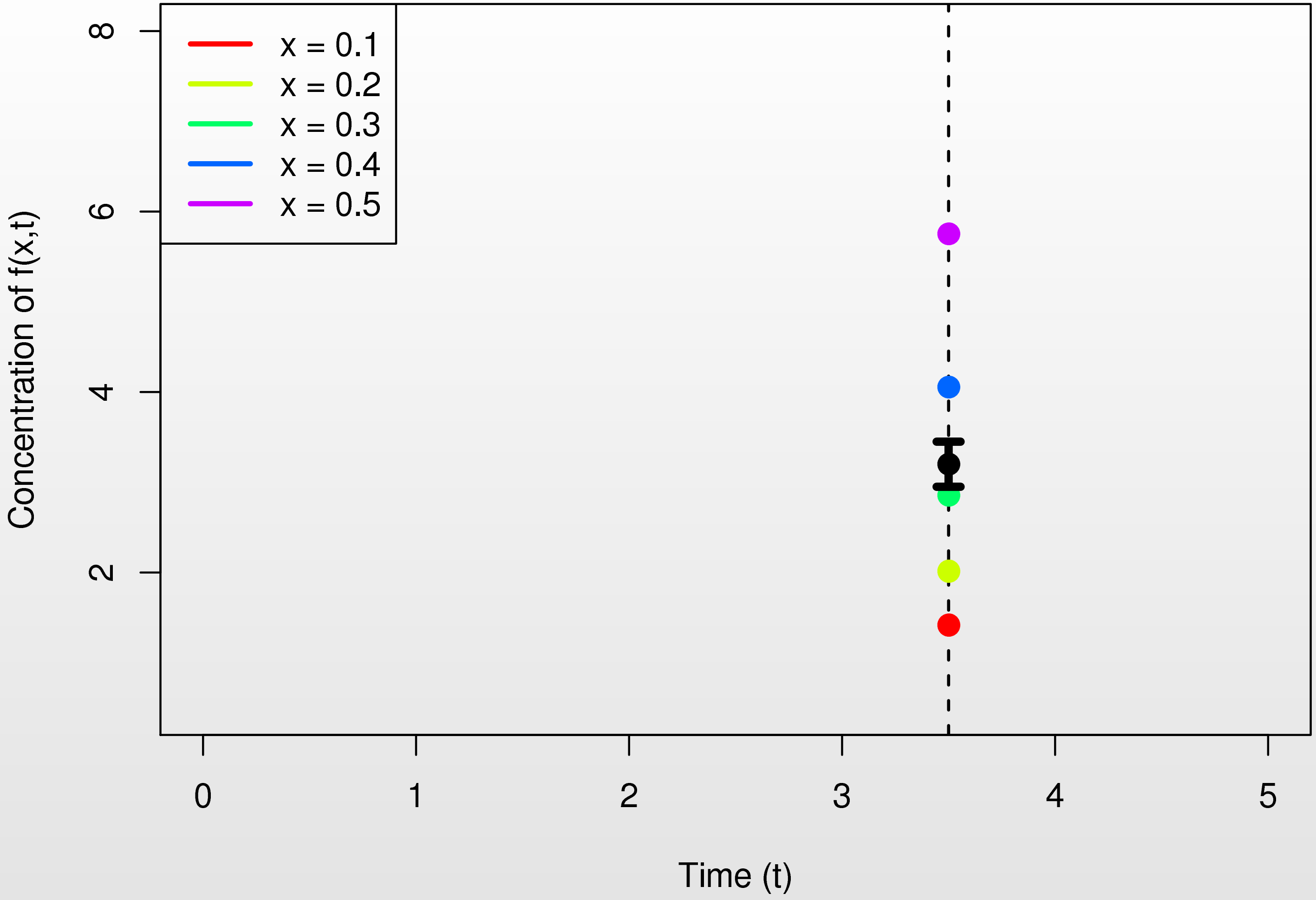
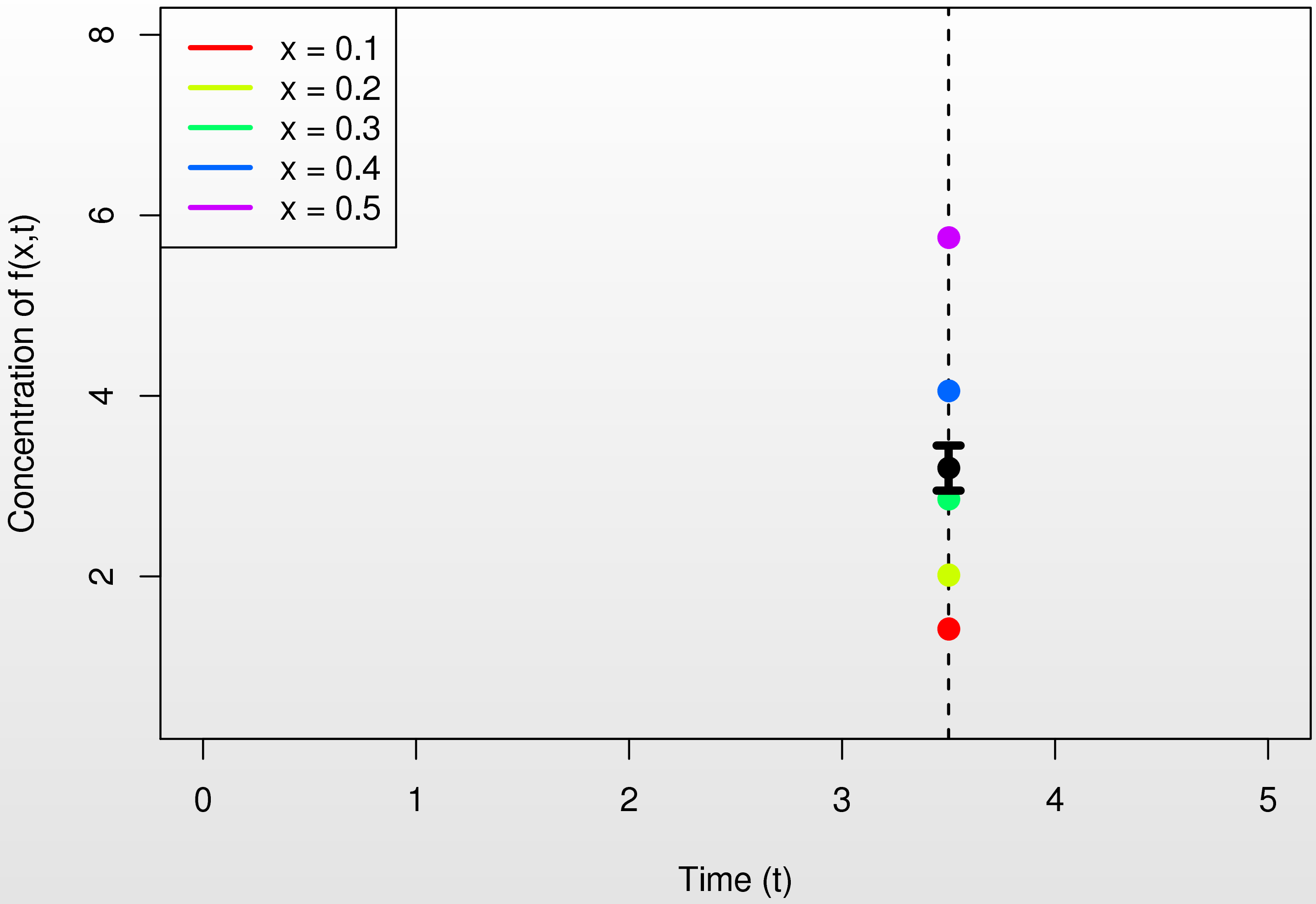
- It would seem that x has to be at least between 0.3 and 0.4.



- 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.



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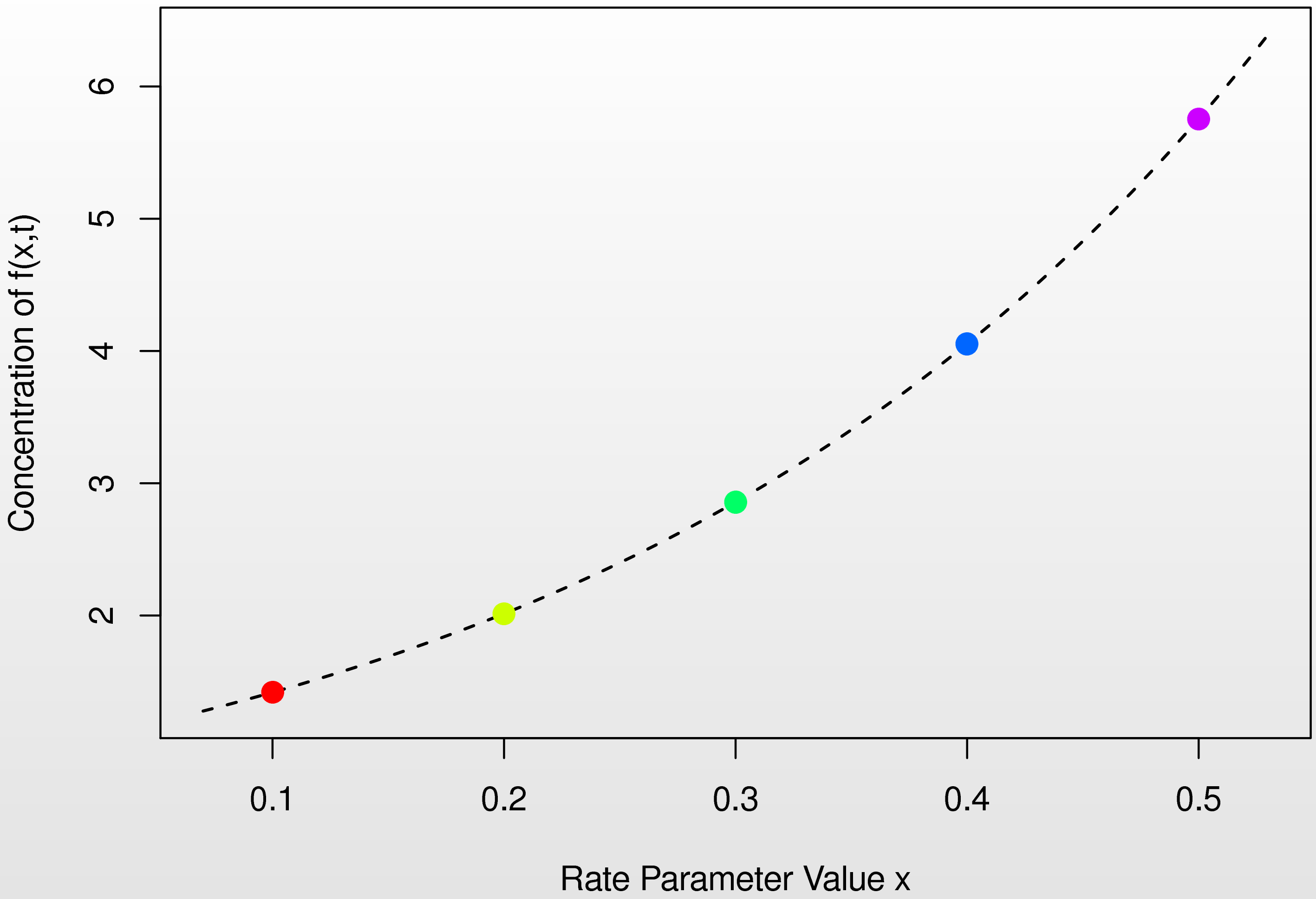
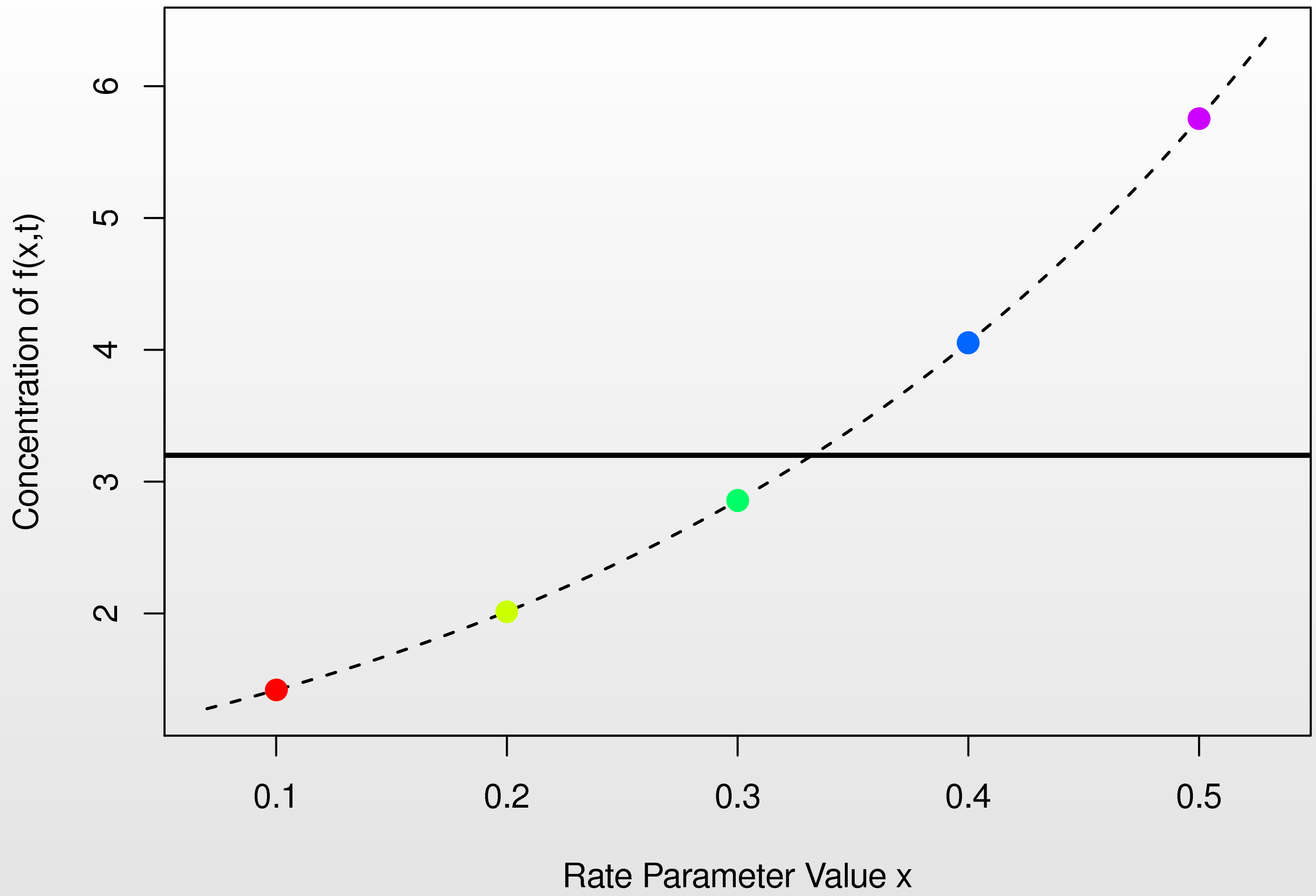
- That is take $f(x) \equiv f(x, t = 3.5)$



- We can now plot the concentration $f(x)$ as a function of the input parameter x.



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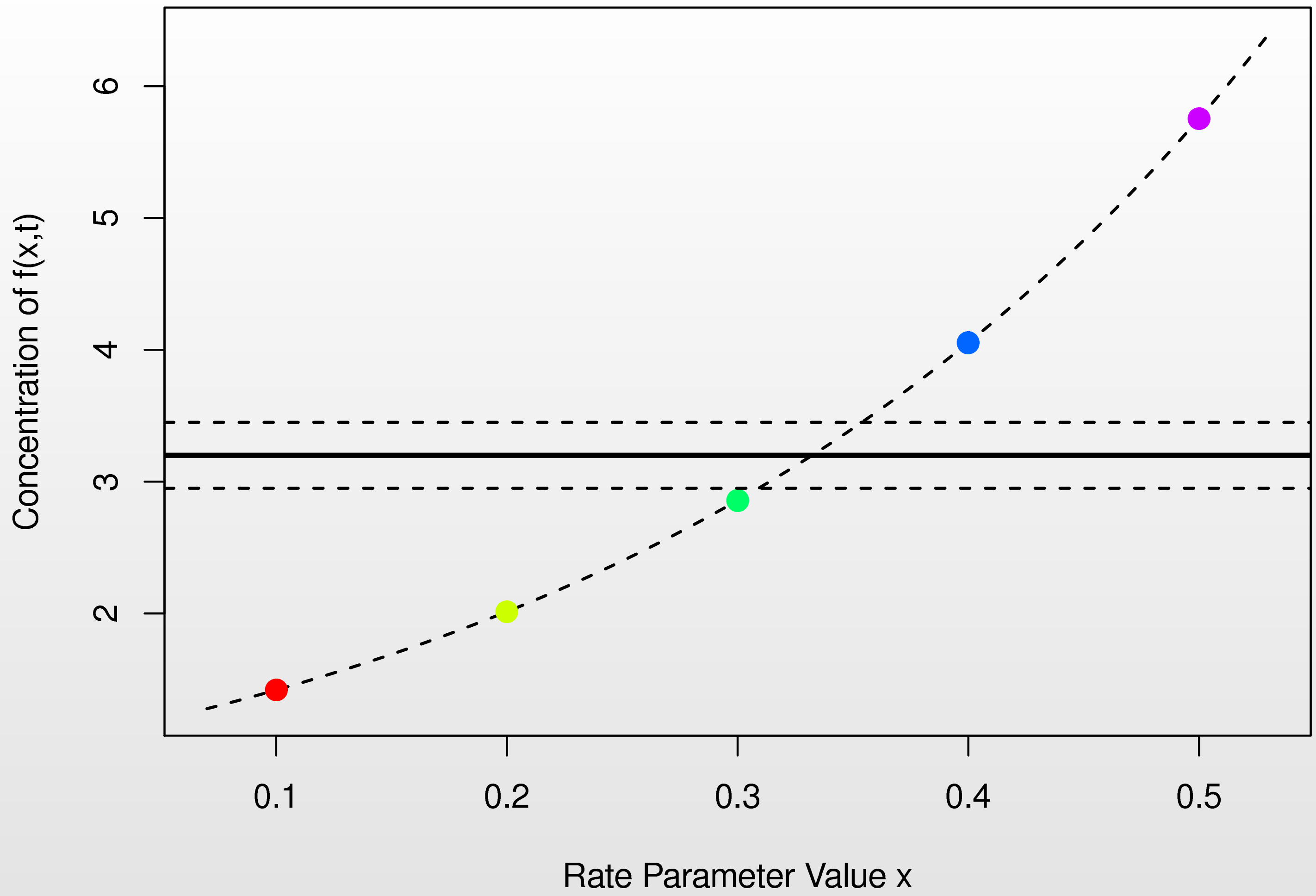

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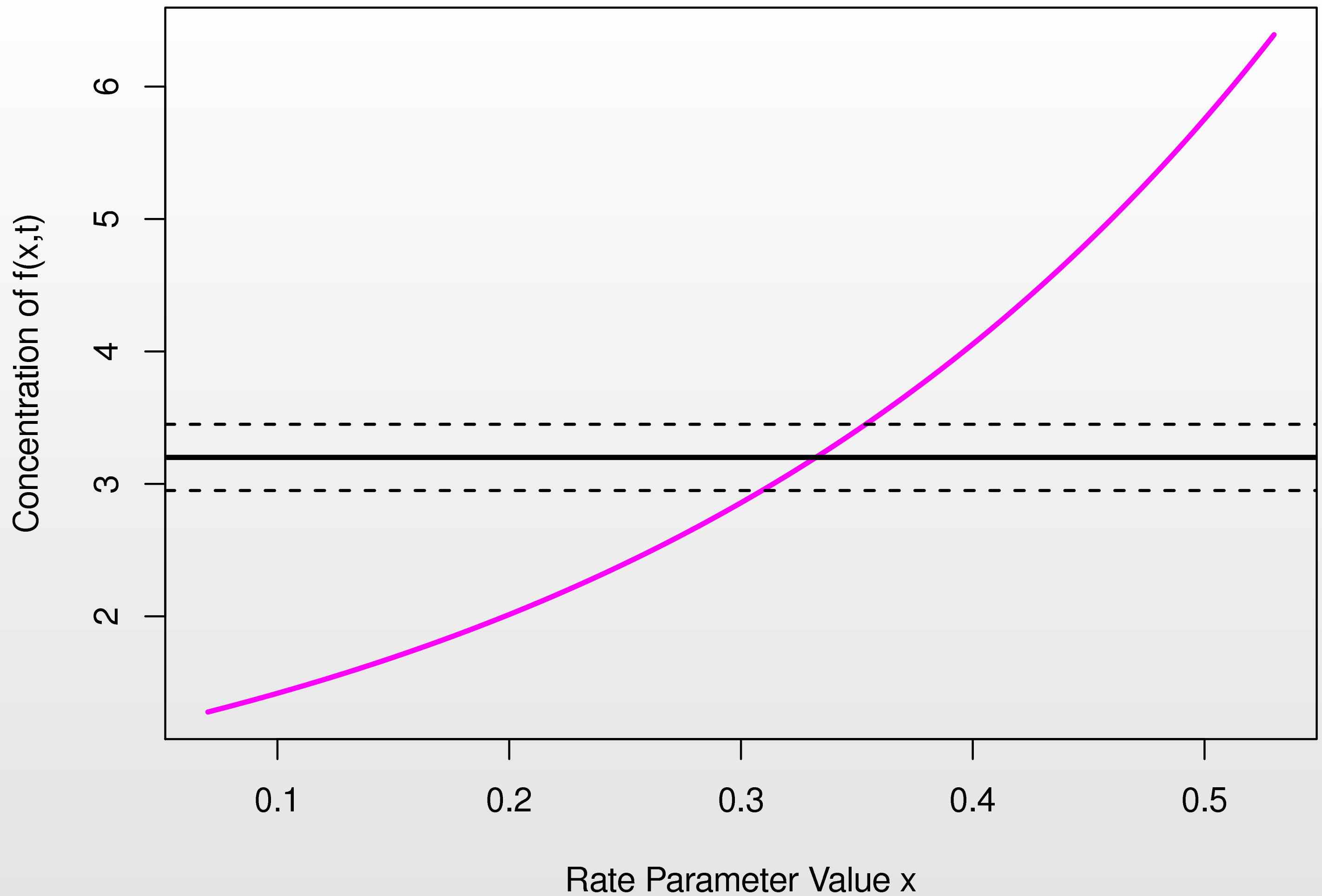
- Black horizontal line: the observed measurement of f
- Dashed horizontal lines: the measurement errors



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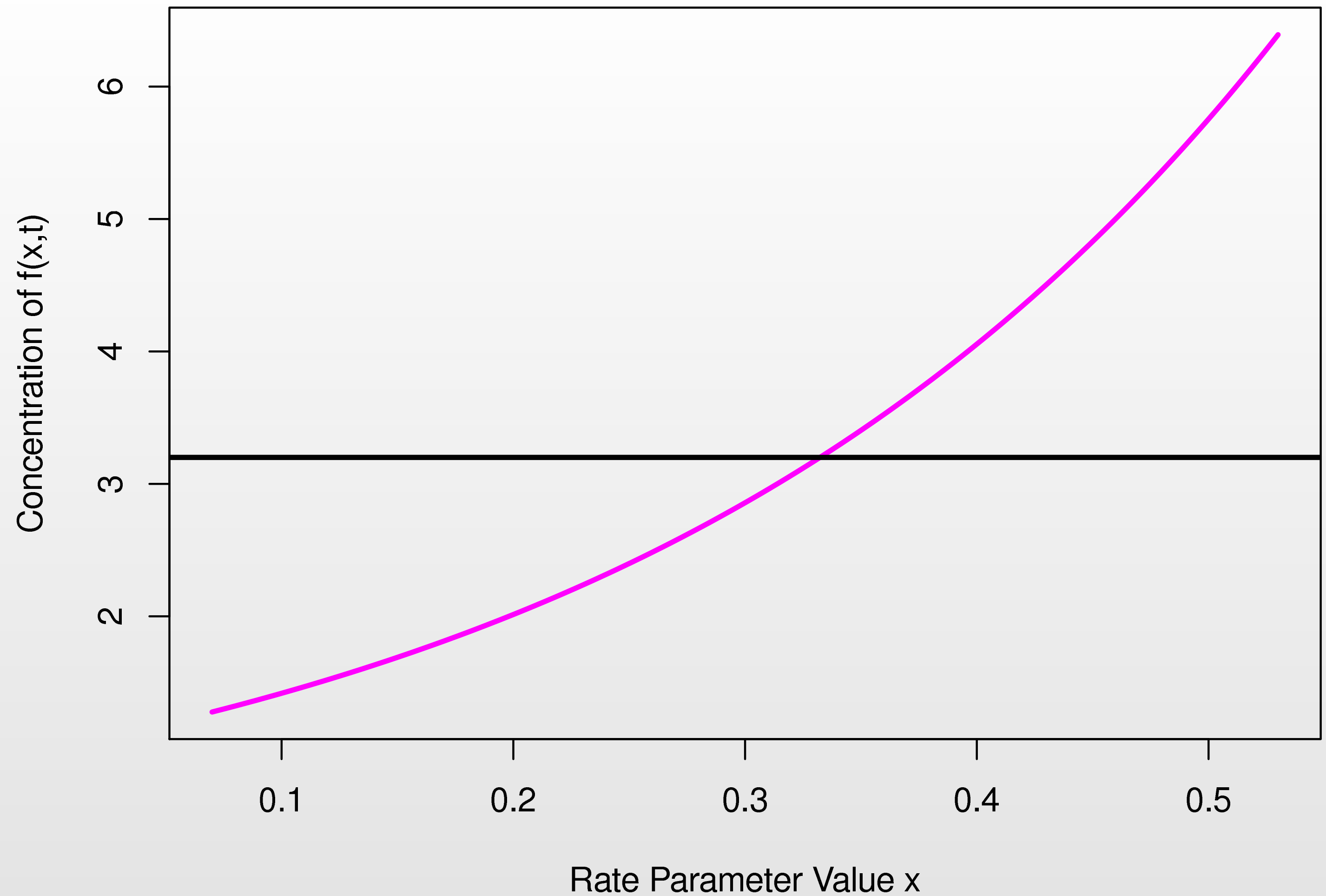

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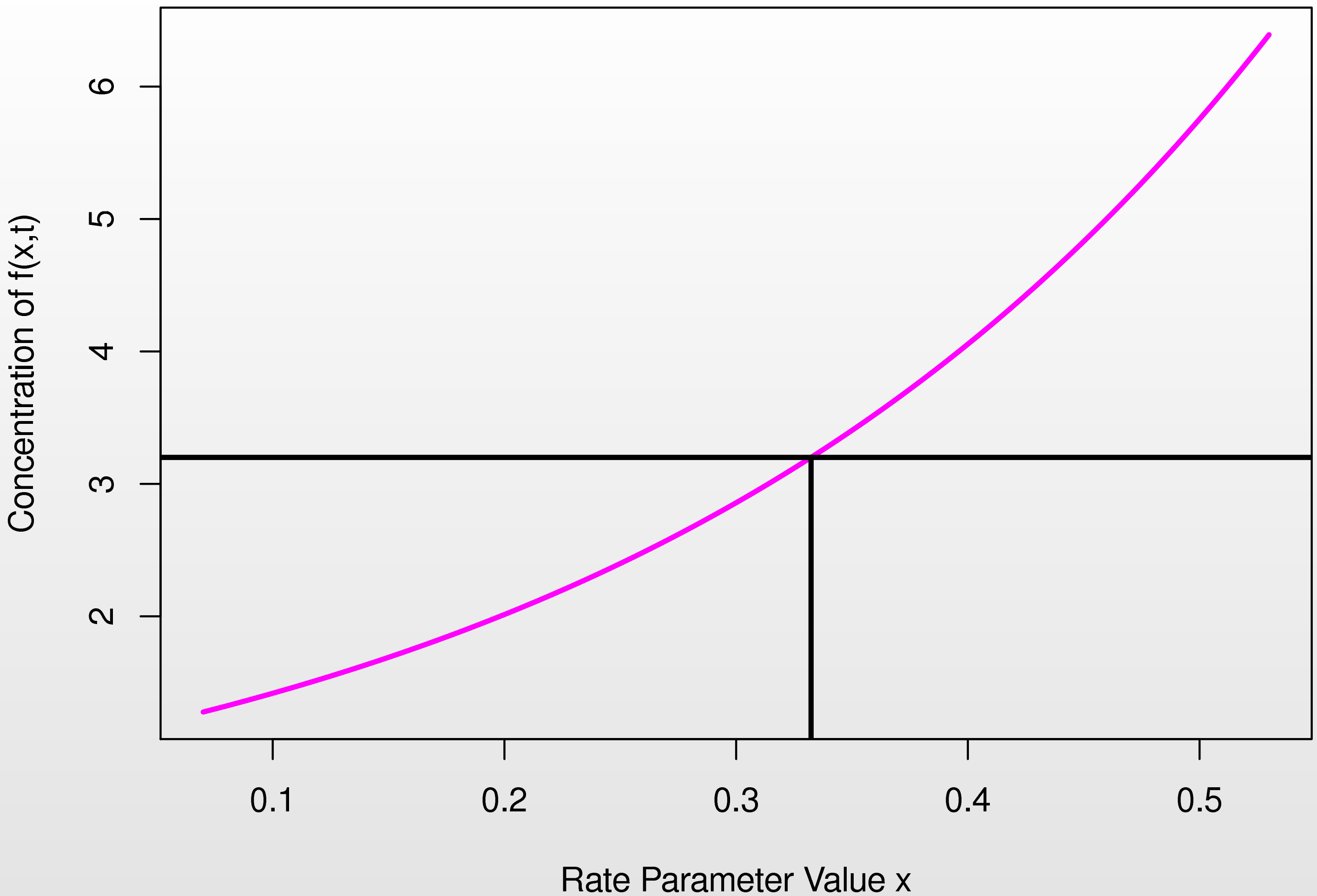
- Ignoring the measurement error would lead to a single value for x but this is incorrect: we have to include the errors.



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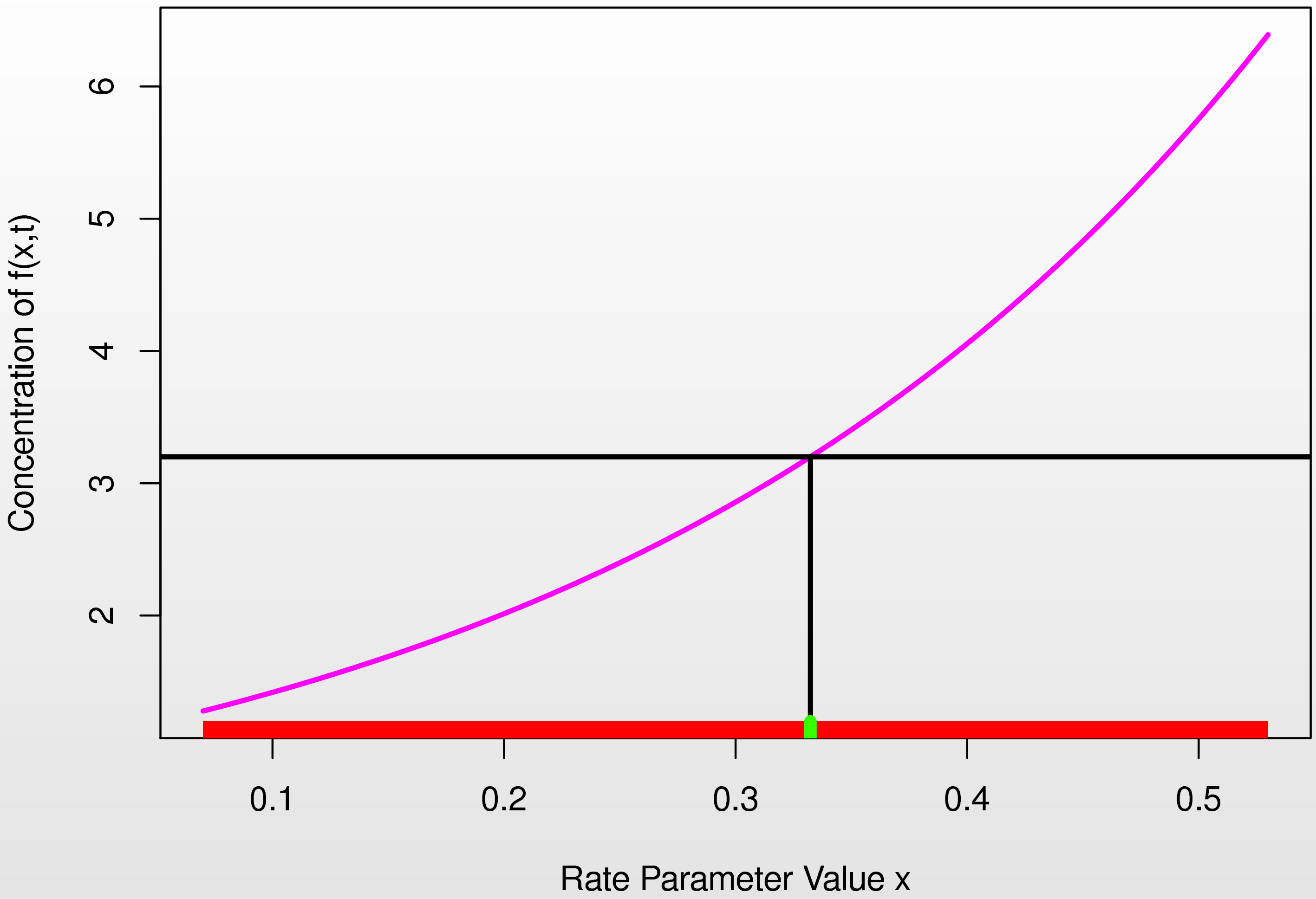

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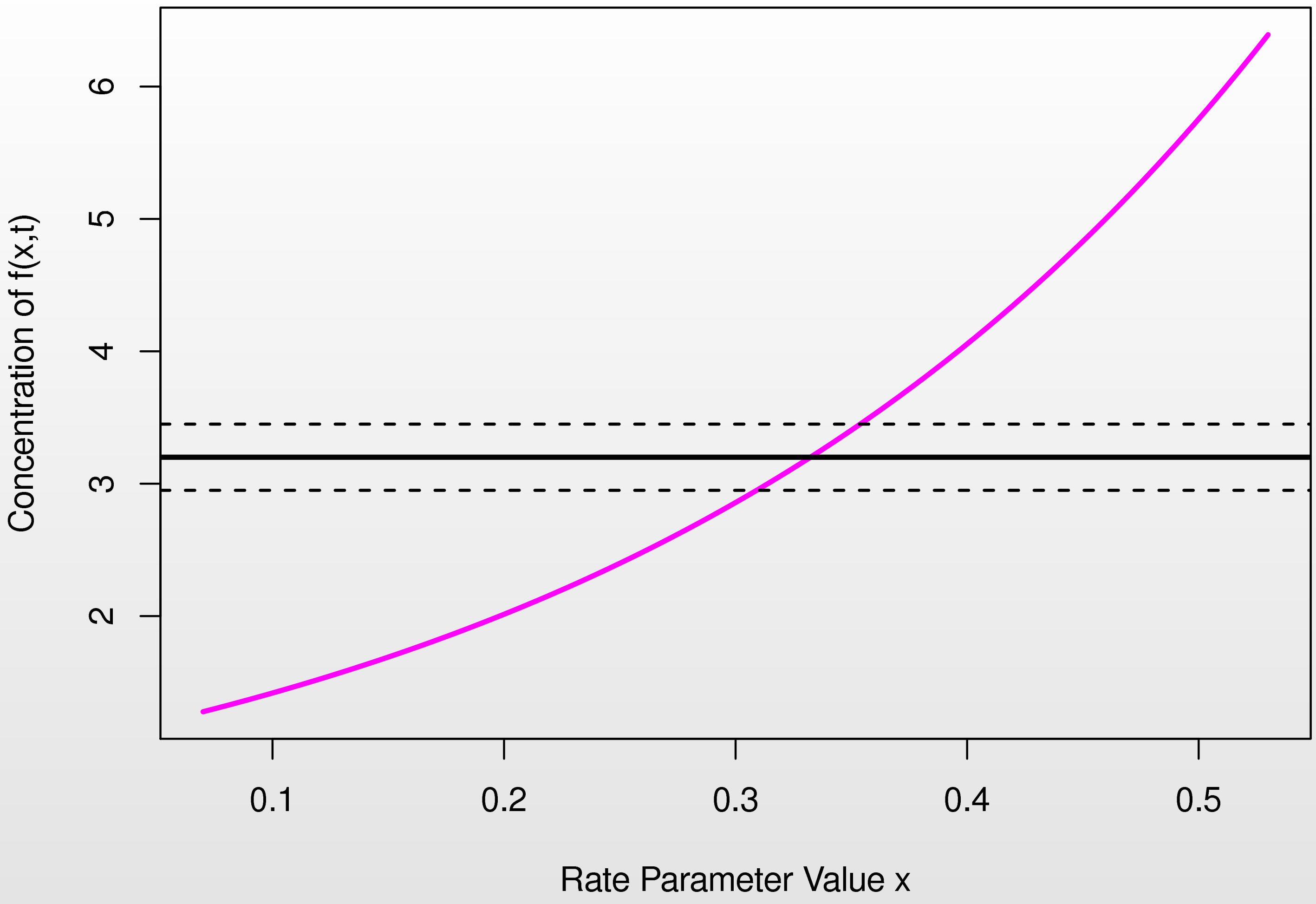

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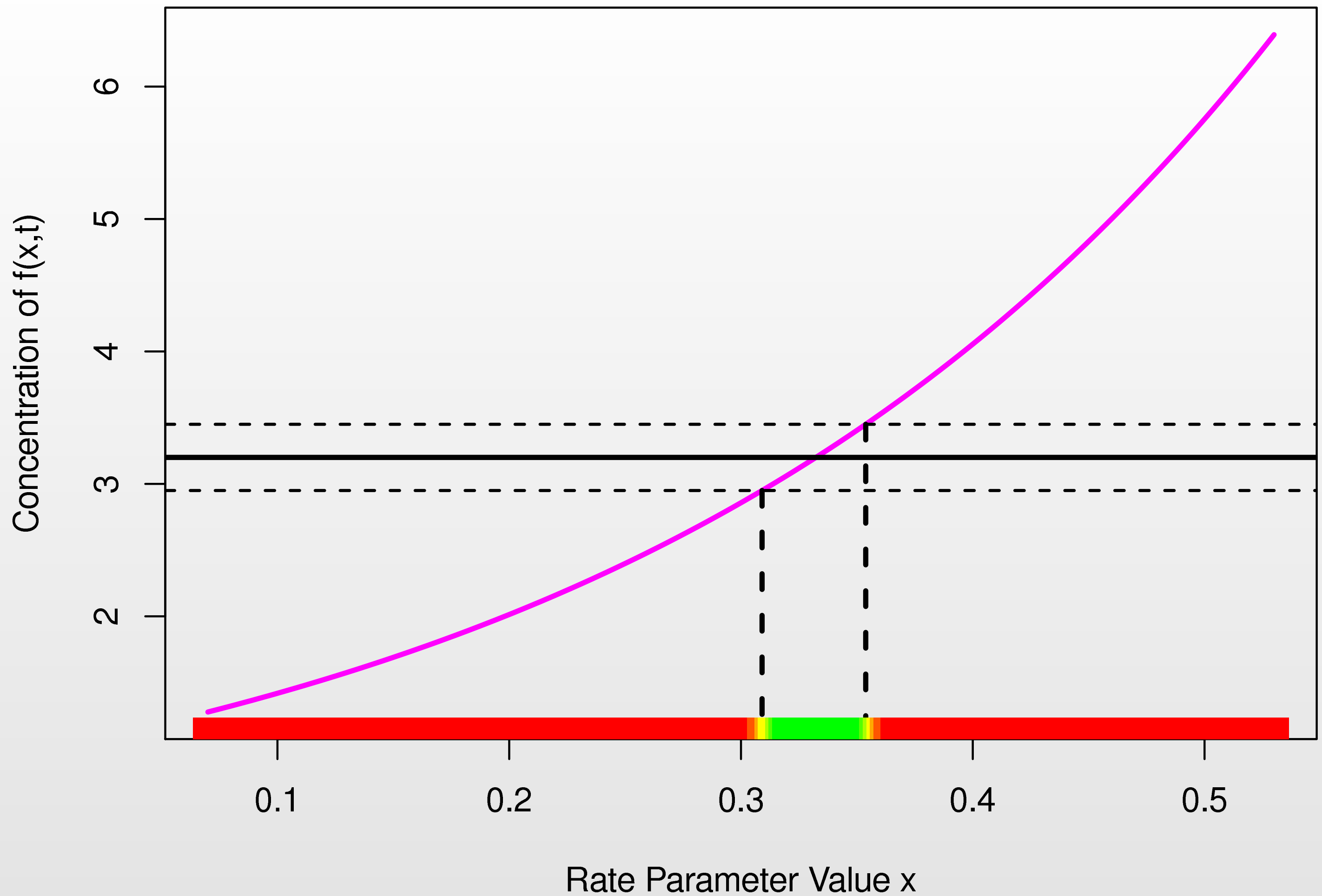
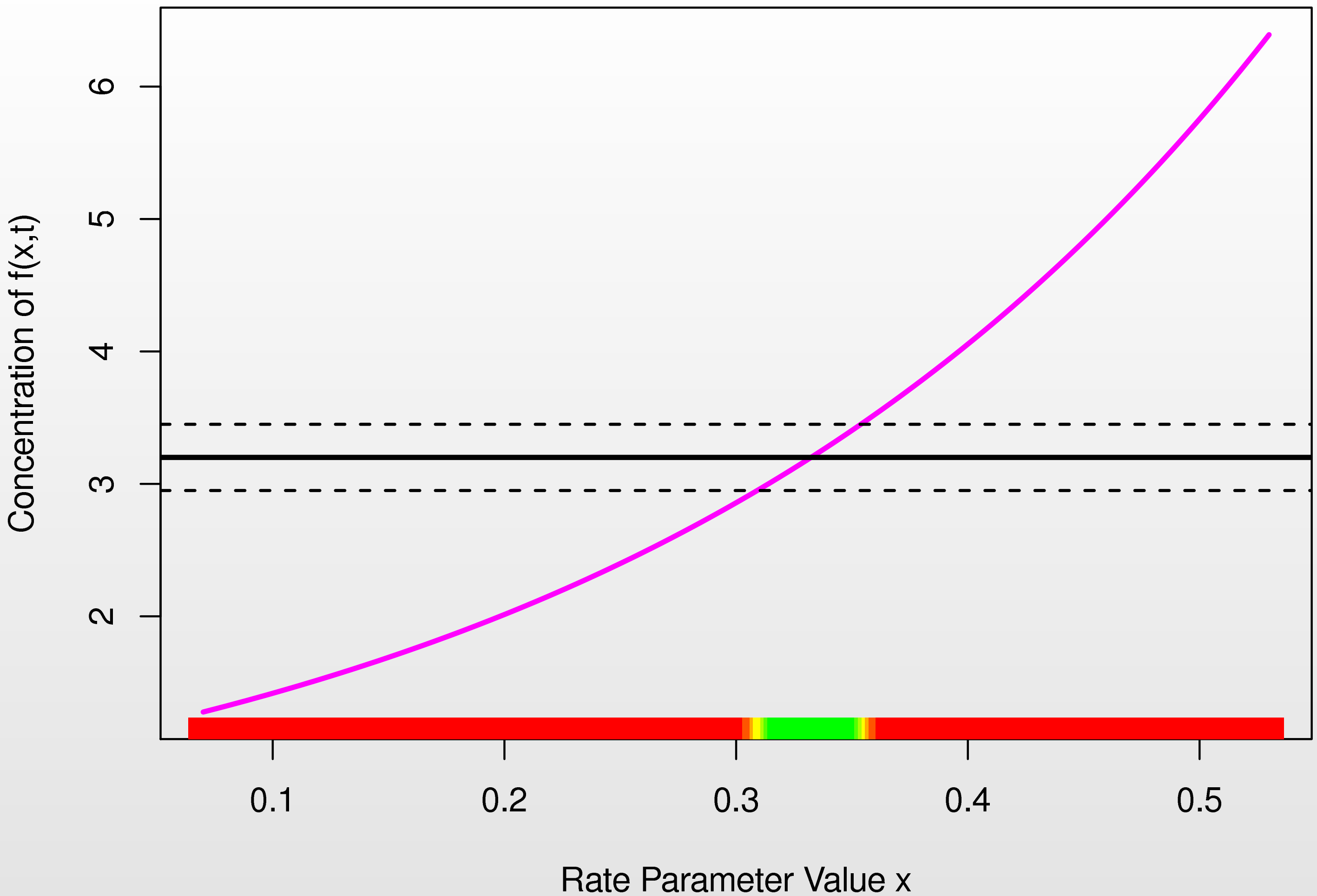
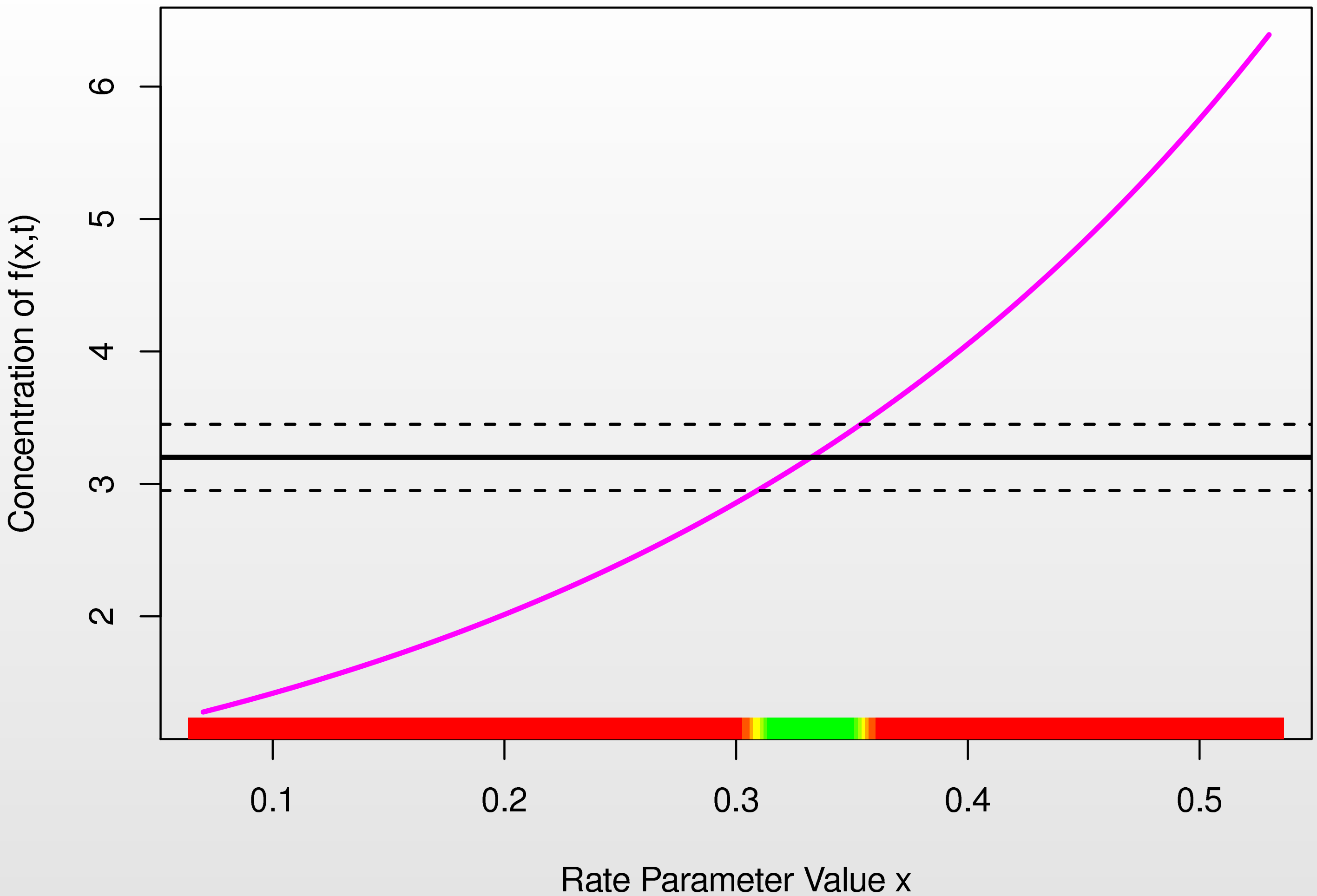


- Uncertainty in the measurement of $f(x, t = 3.5)$ leads to uncertainty in the inferred values of x.
- Hence we see a range (green/yellow) of possible values of x consistent with the measurements, with all the implausible values of x in red.



- Another important form of uncertainty is that of model discrepancy related to how accurate we believe the model to be.



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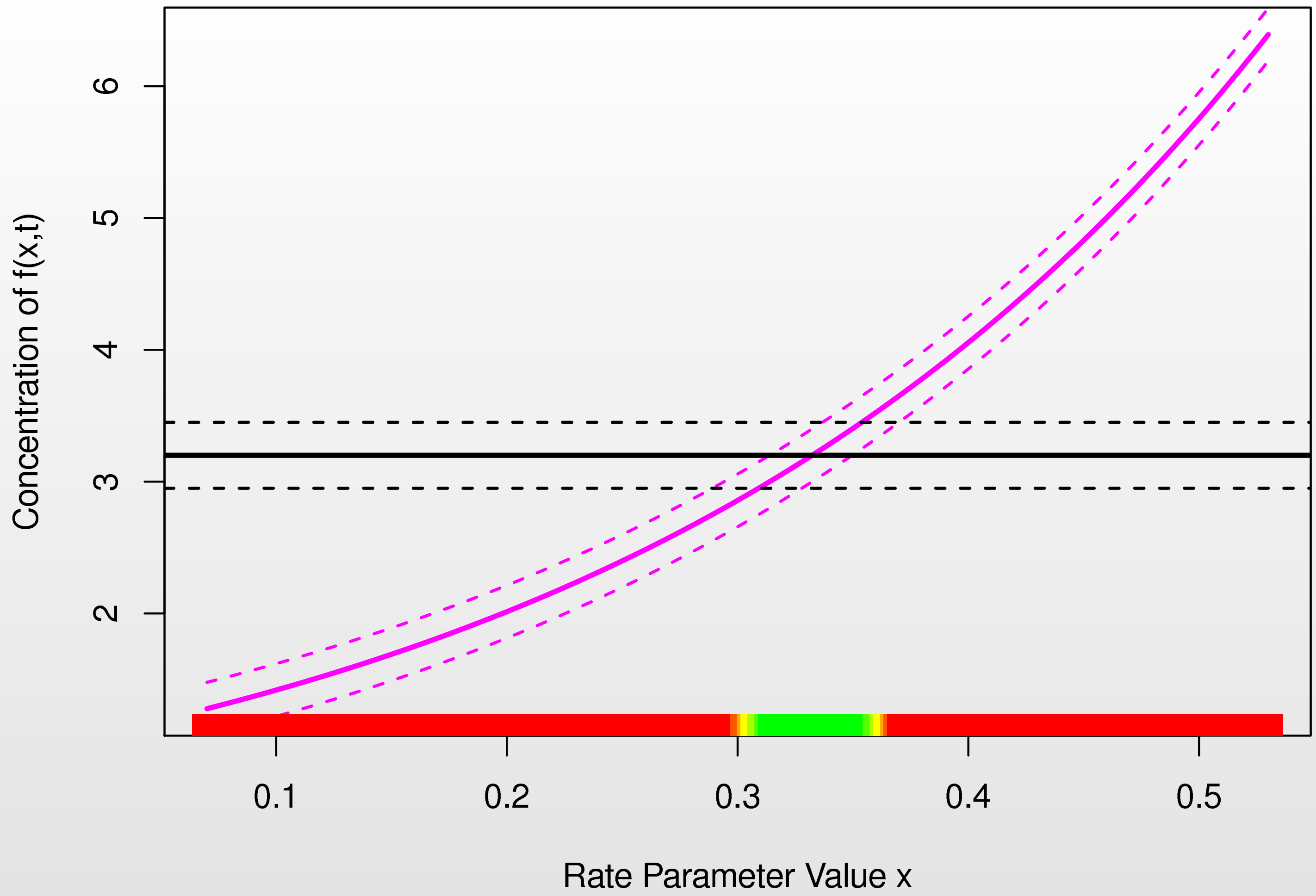
- This uncertainty arises from many issues e.g. is the form of the model (the differential equation) appropriate, is the model a simplified description of a more complex system, is there uncertainty in the initial conditions etc?



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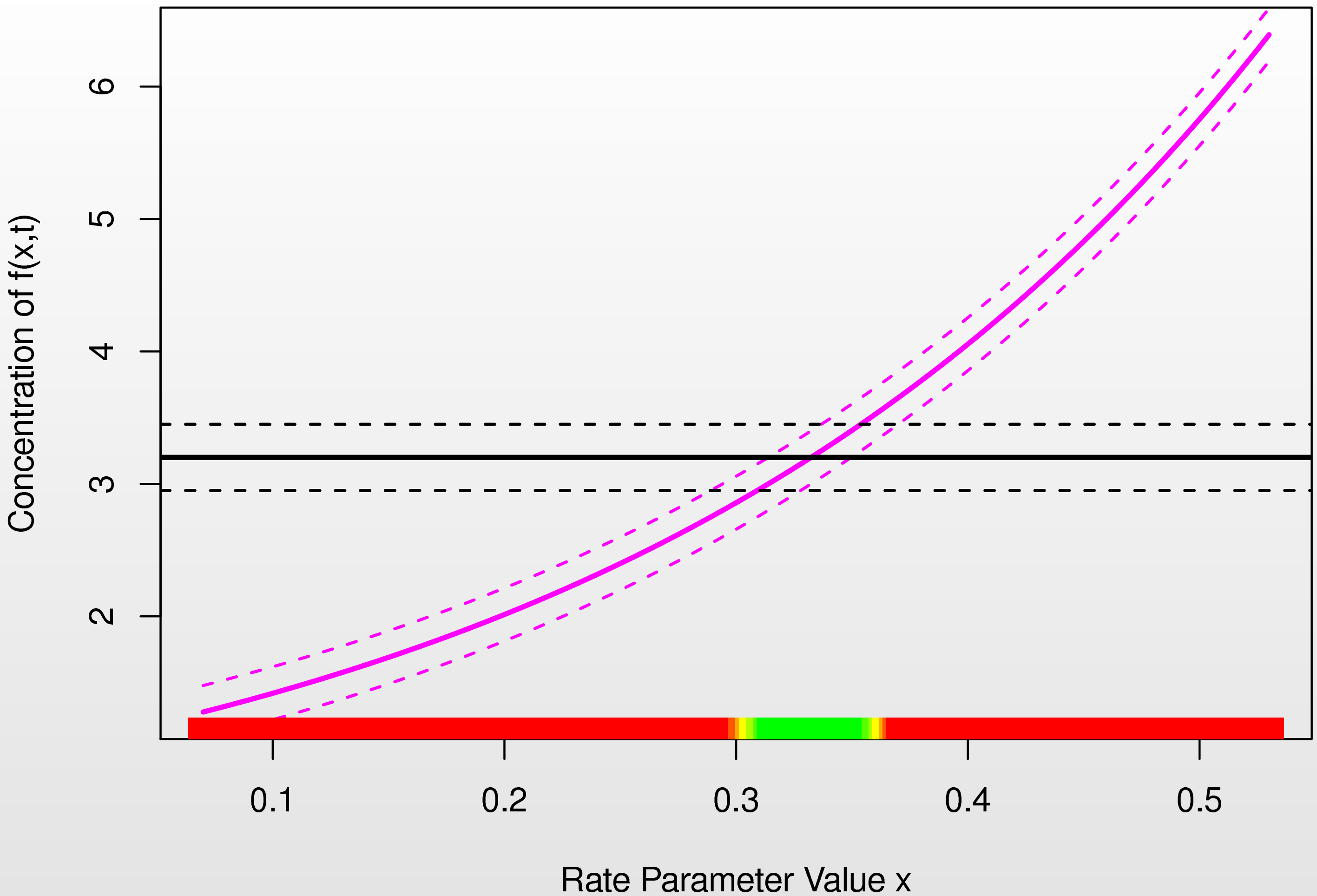

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- This results in more uncertainty in x, and hence a larger range of x values.

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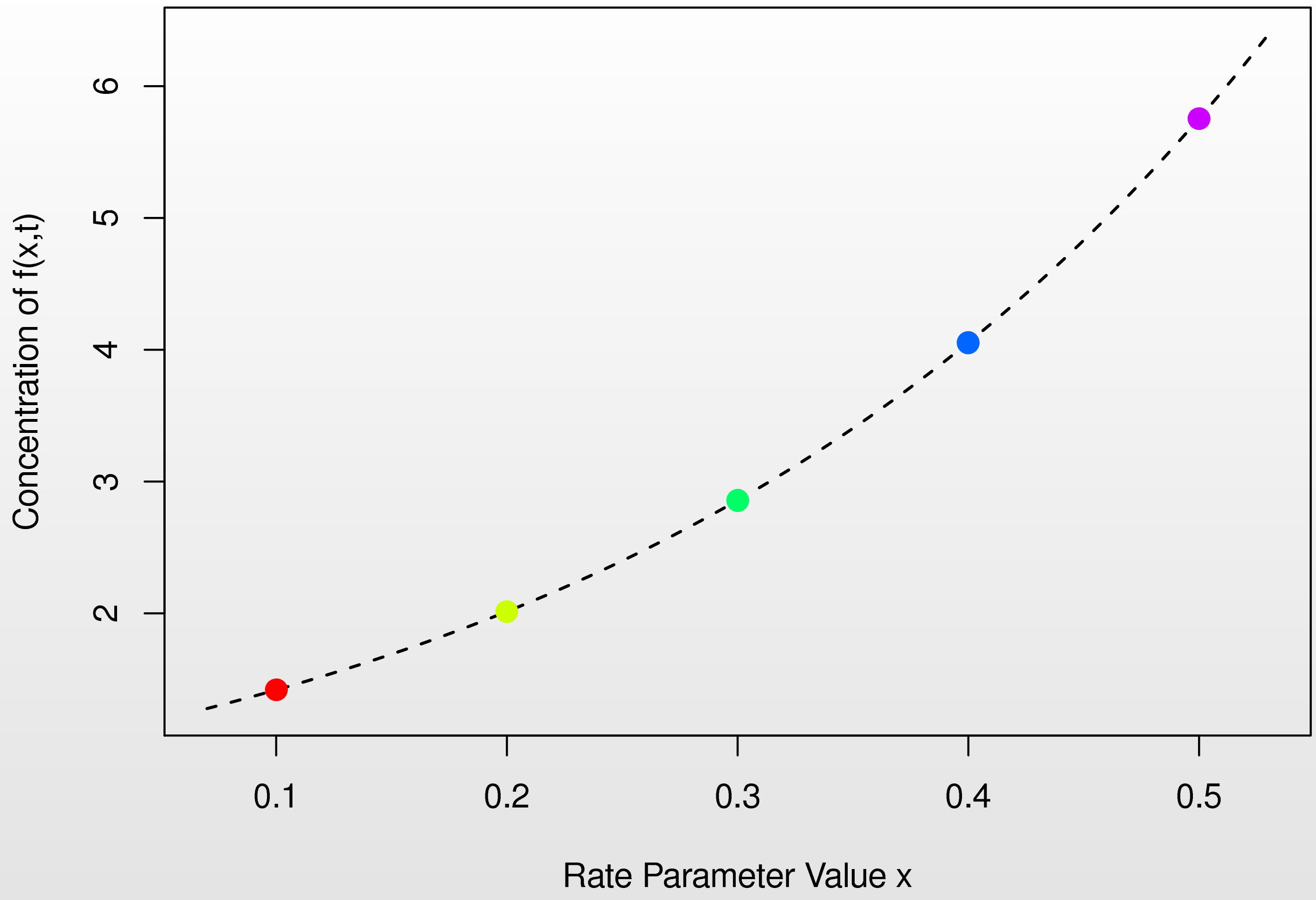
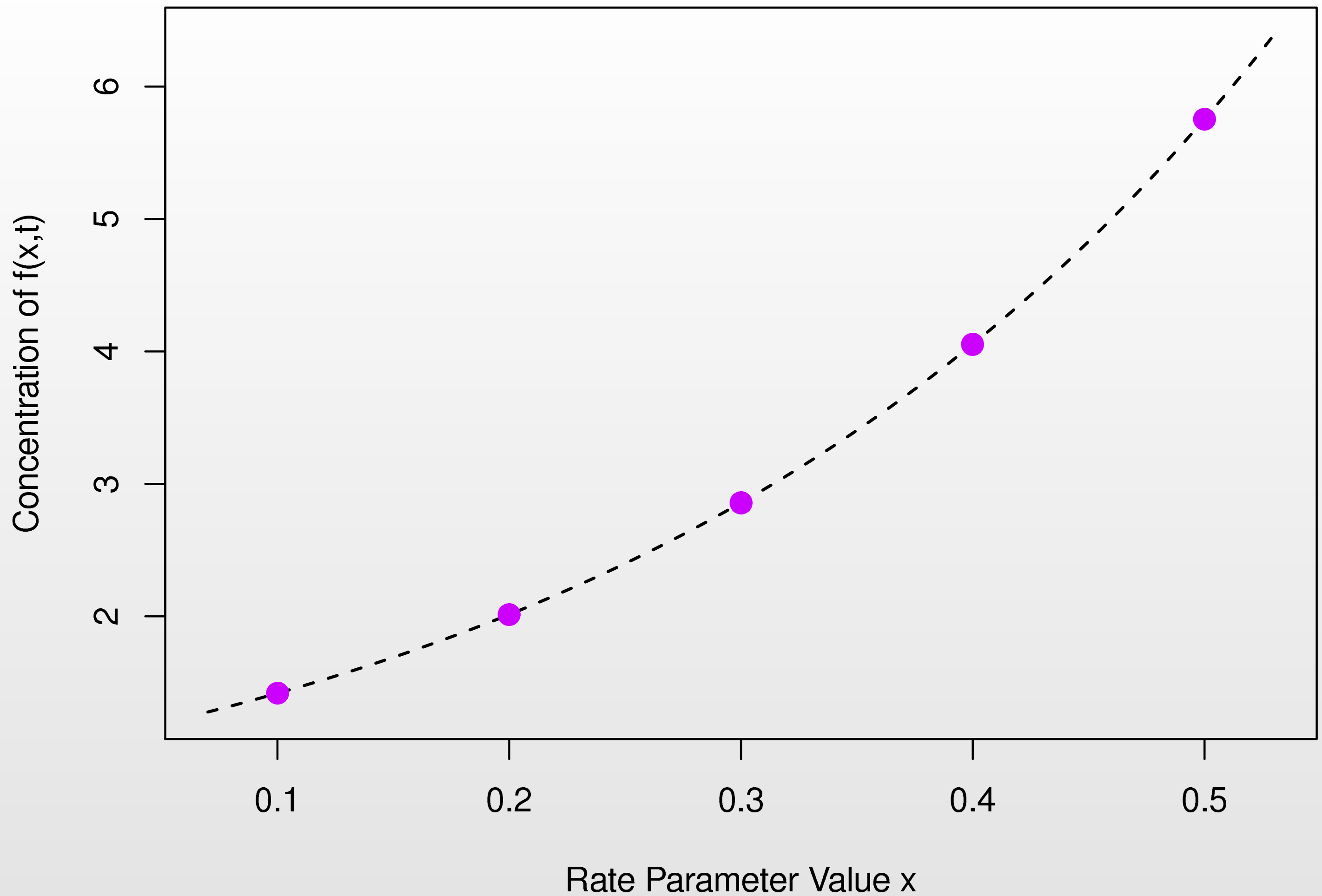
- If x was high dimensional e.g. there were 32 input parameters, then we need a vast number of evaluations of the model to fill this 32 dimensional space: e.g. corners only $2^{32} = 4.3$ billion evaluations.
- A Bayesian GP emulator is a statistical construct that mimics the model, but which is extremely fast to evaluate, often several orders of magnitude faster than the model: use the emulator to learn about x.



- 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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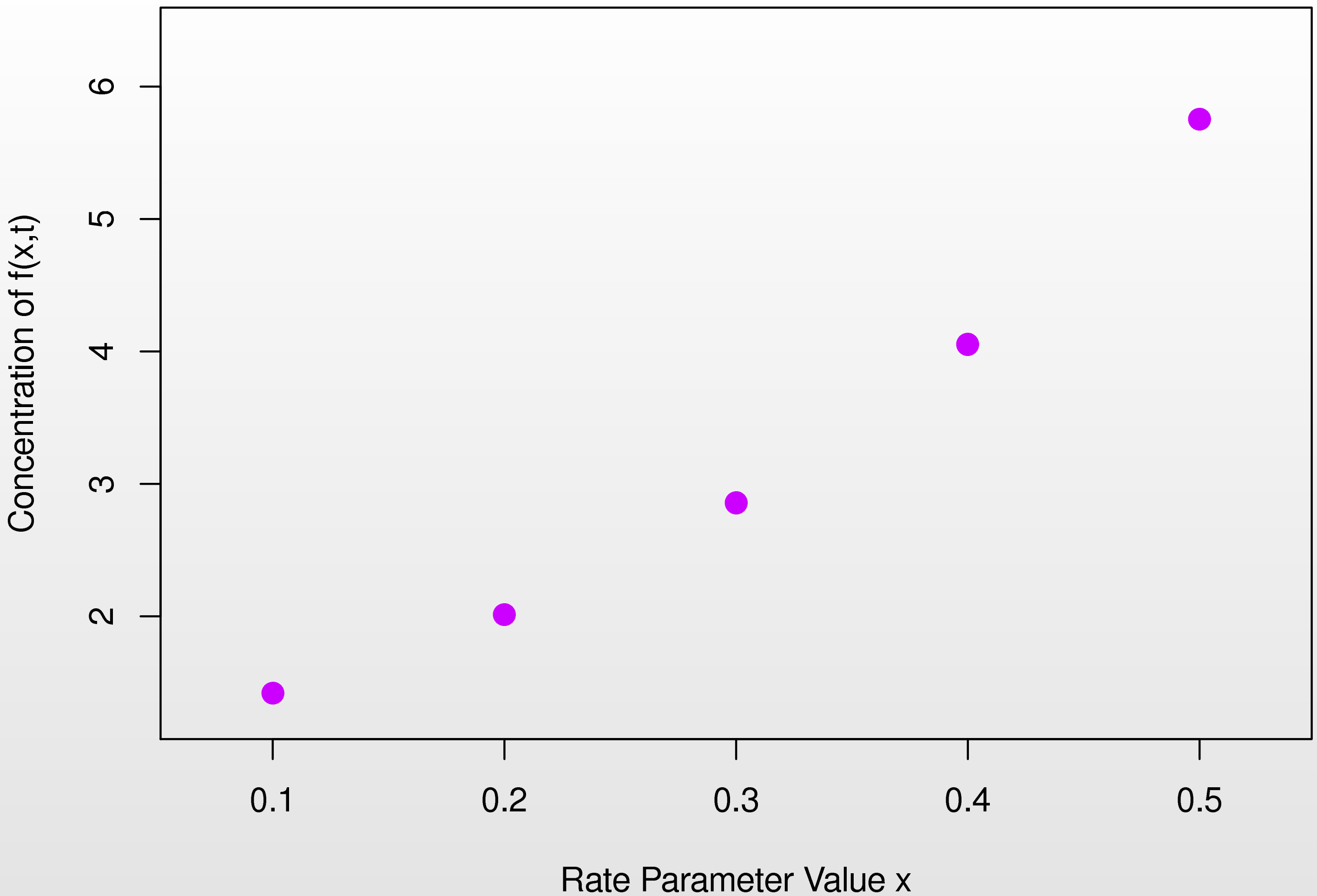

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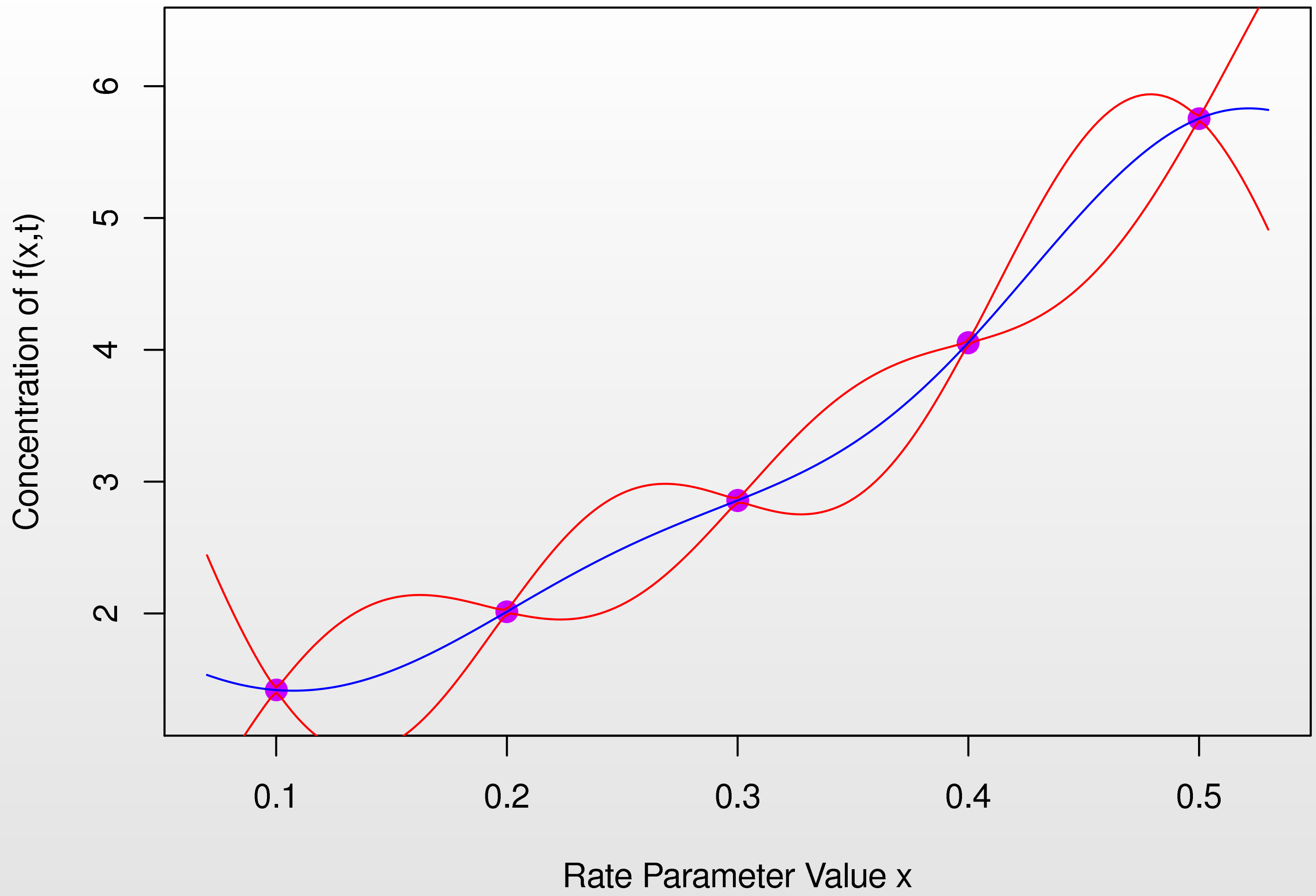
- Instead we only have a finite number of runs of the model, in this case five.



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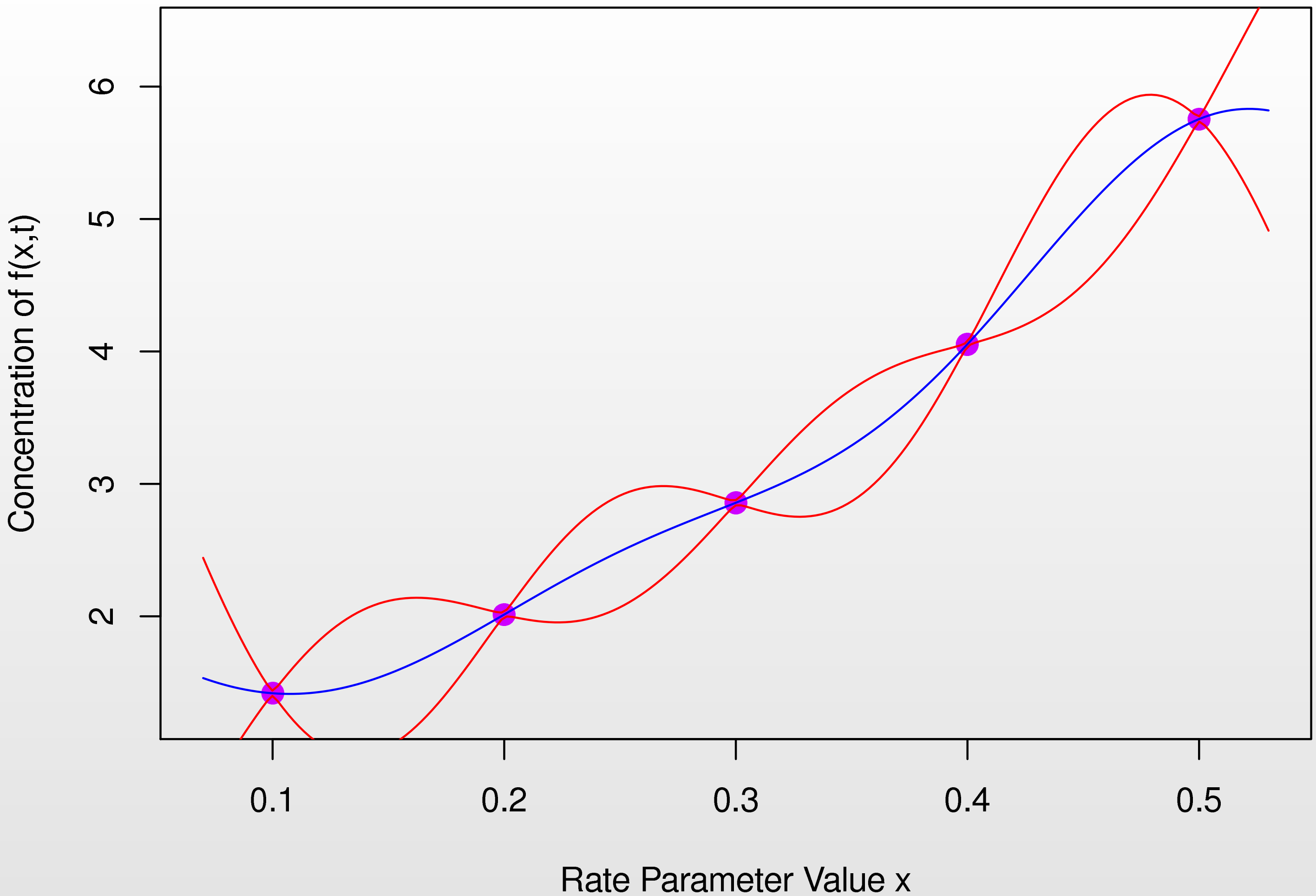
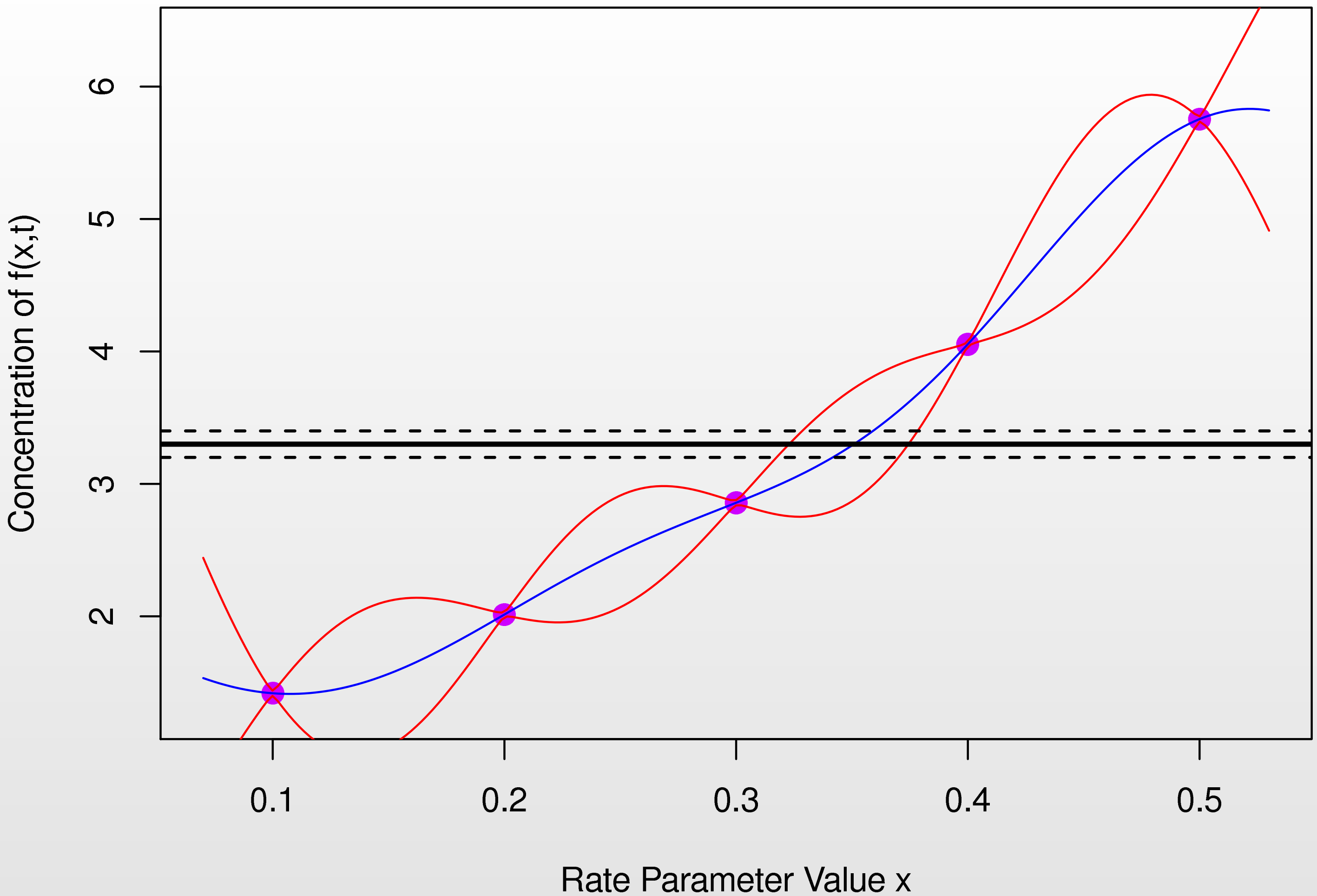
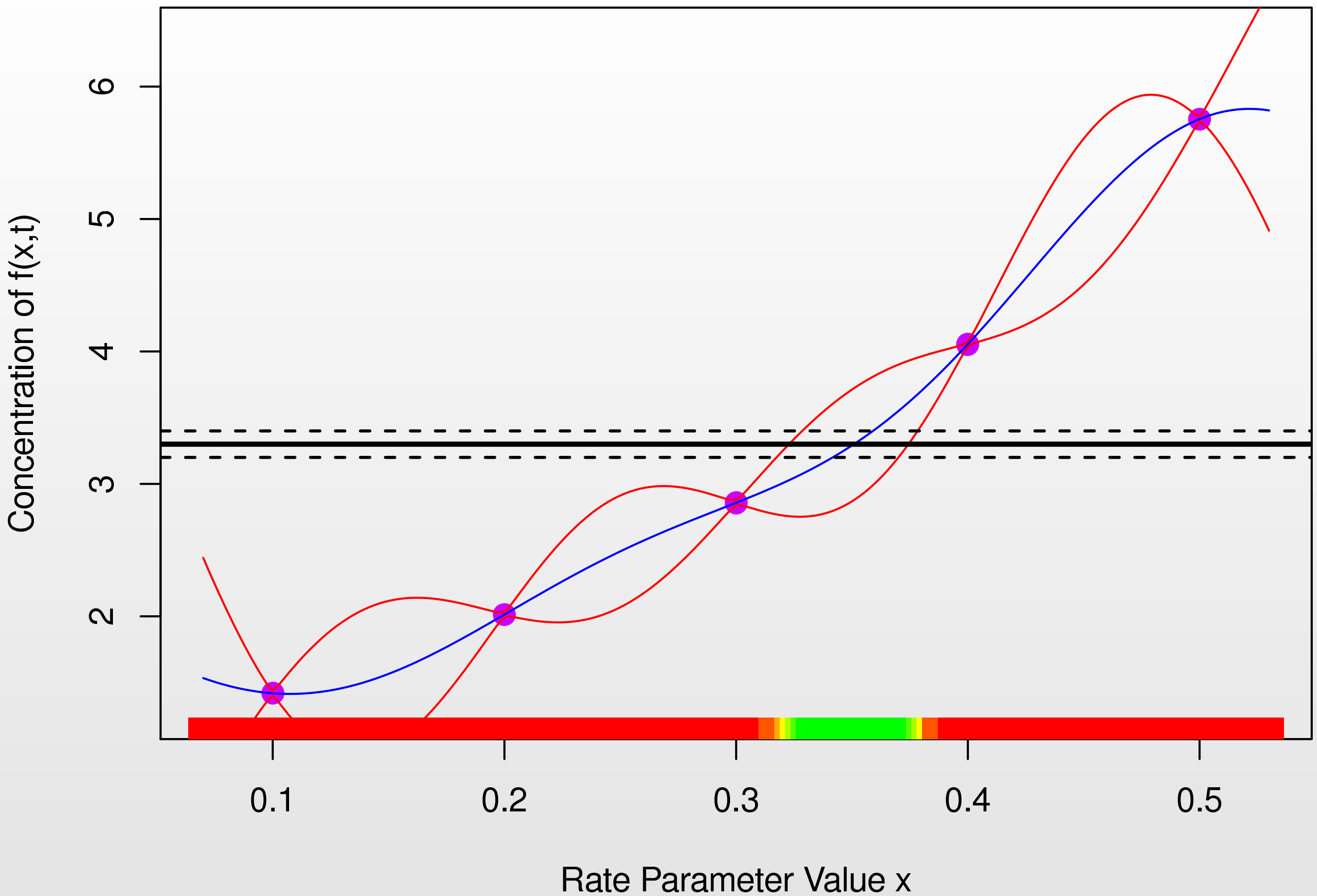


- The emulator can be used to represent our beliefs about the behaviour of the model at untested values of x, and is fast to evaluate.
- It gives both the expected value of $f(x)$ (the blue line) along with a credible interval for $f(x)$ (the red lines) representing the uncertainty about the model's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



- 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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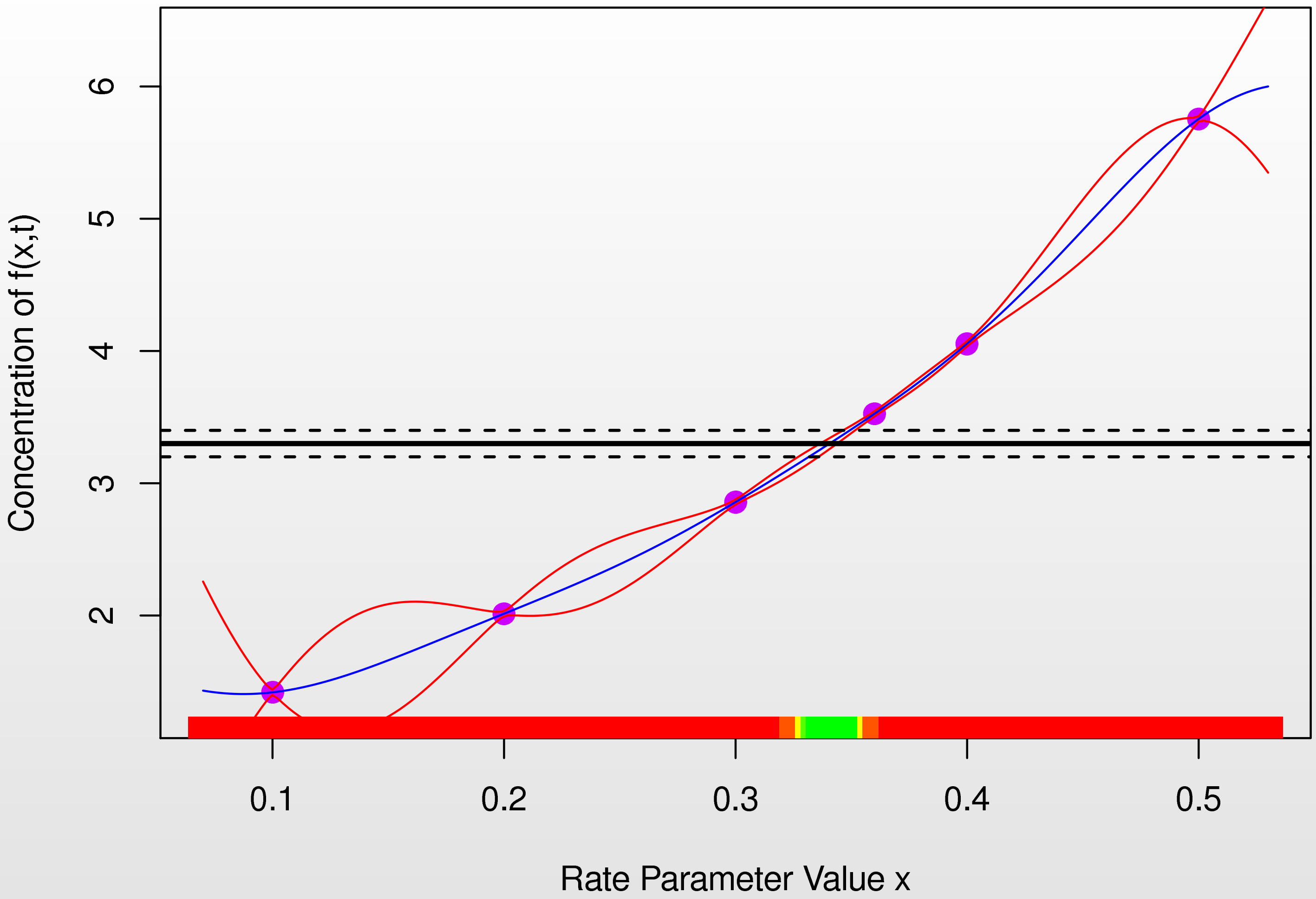
- Note the uncertainty on x now includes uncertainty coming from the emulator.



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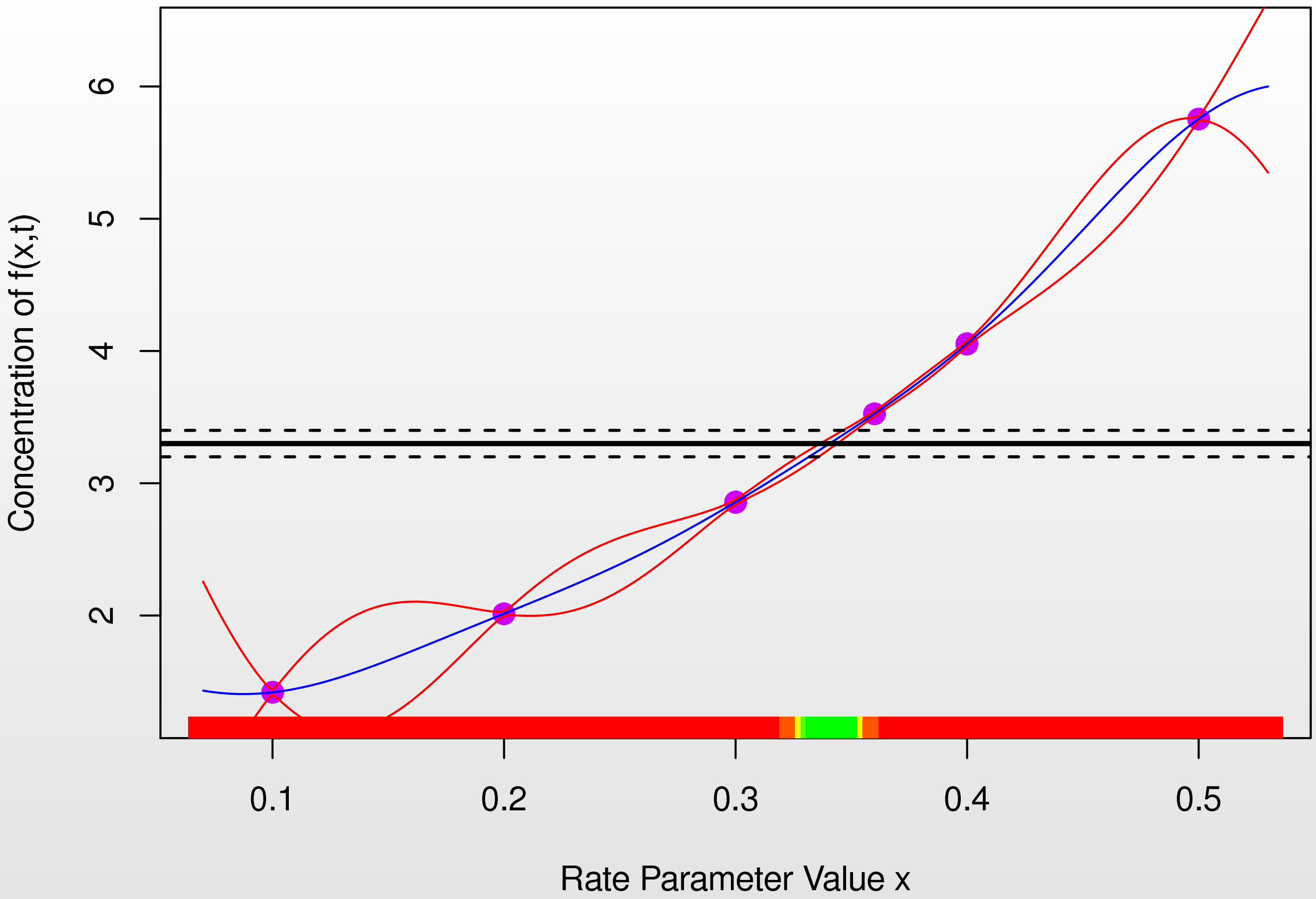

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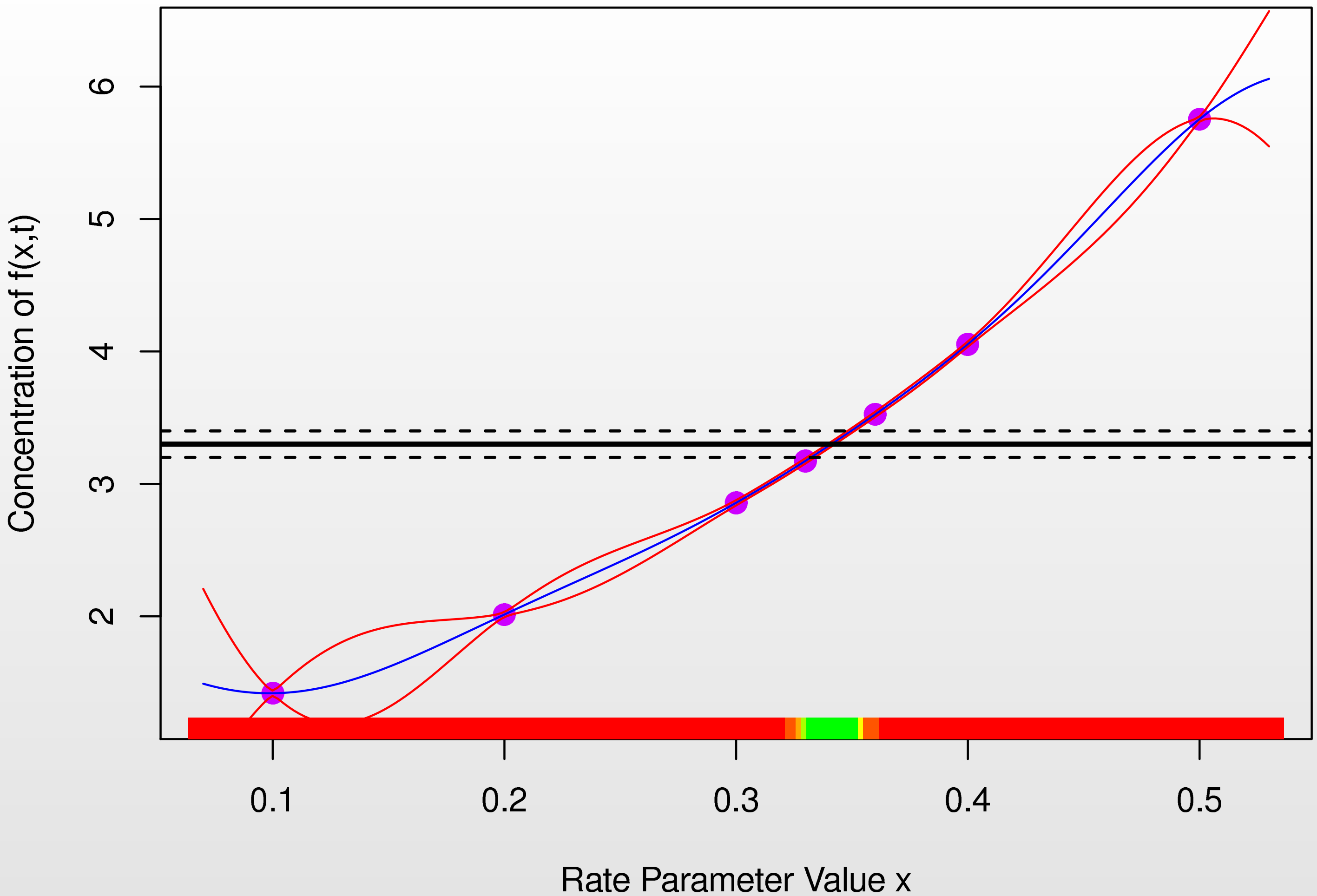

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- Now the emulator is more accurate than the observation, and we can identify the set of all x values of interest.

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Experiment A: Measure $f(x, t)$ at $t = 2$ with same observed error as before.

Experiment B: Measure $f(x, t)$ at $t = 5$ with same observed error as before.

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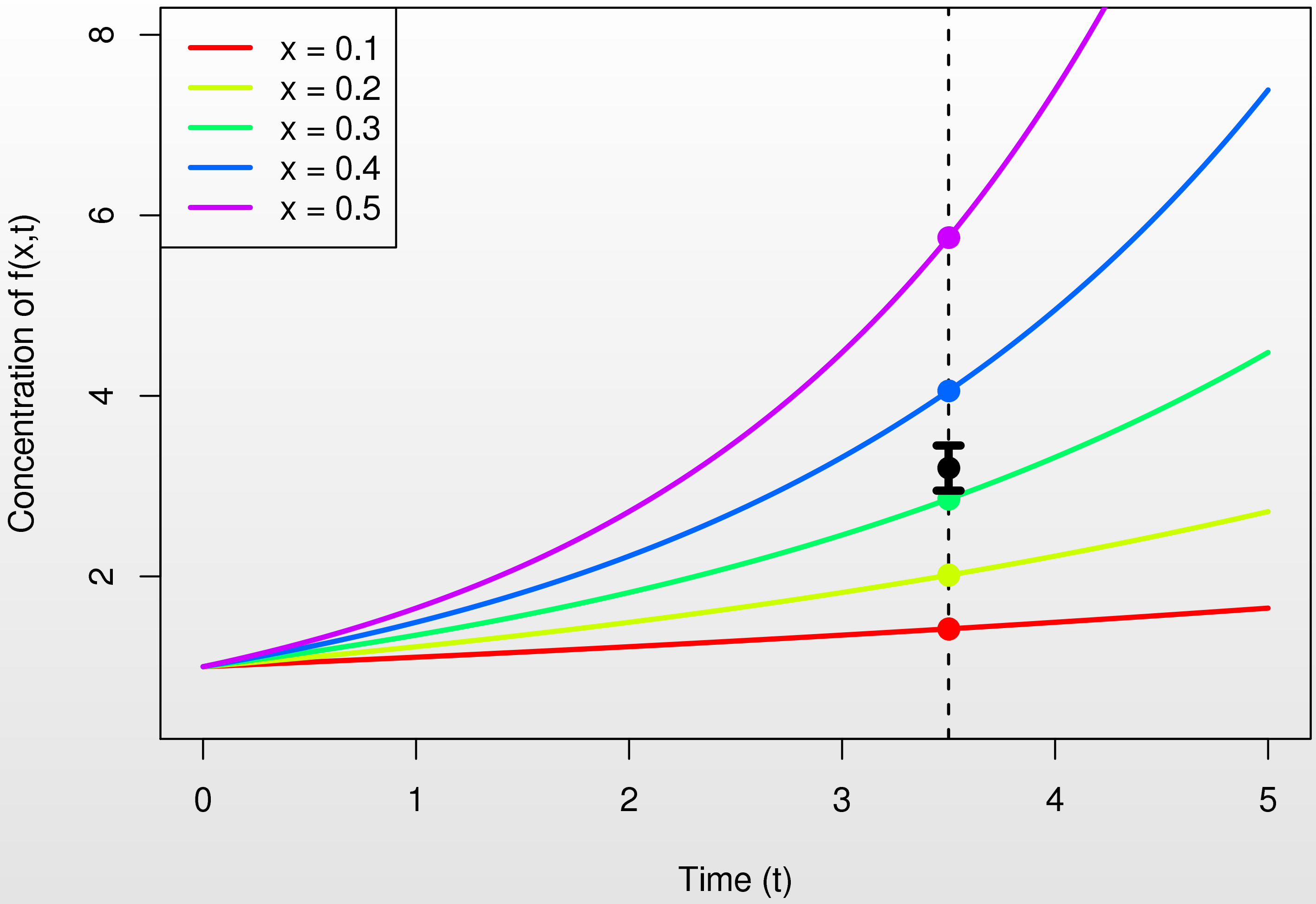
- We can use the model's predictions at $t = 2$ and $t = 5$ to determine which experiment A or B is expected to be most informative about the input parameter x, given our knowledge about $f(x, t)$ at $t = 3.5$.



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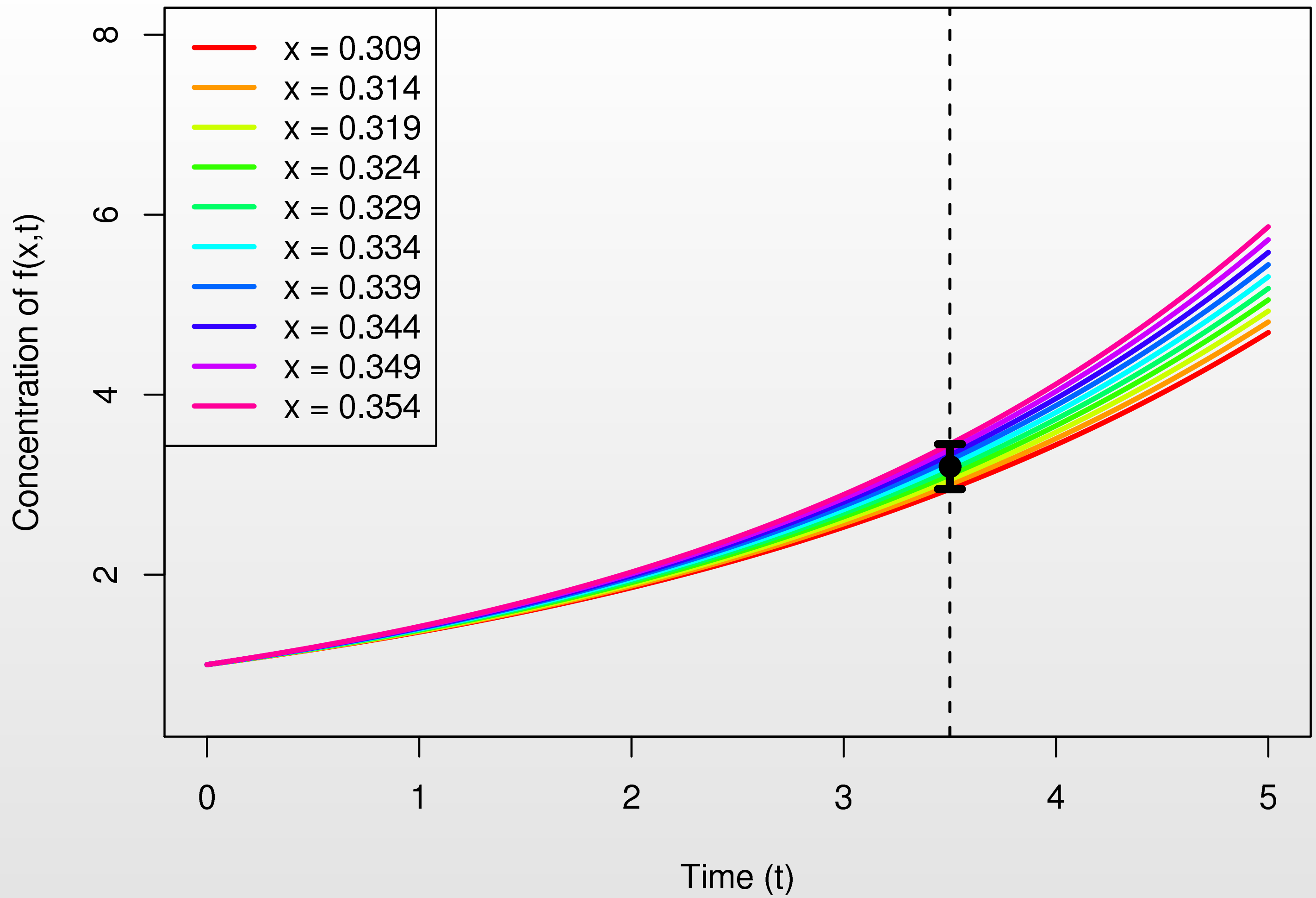

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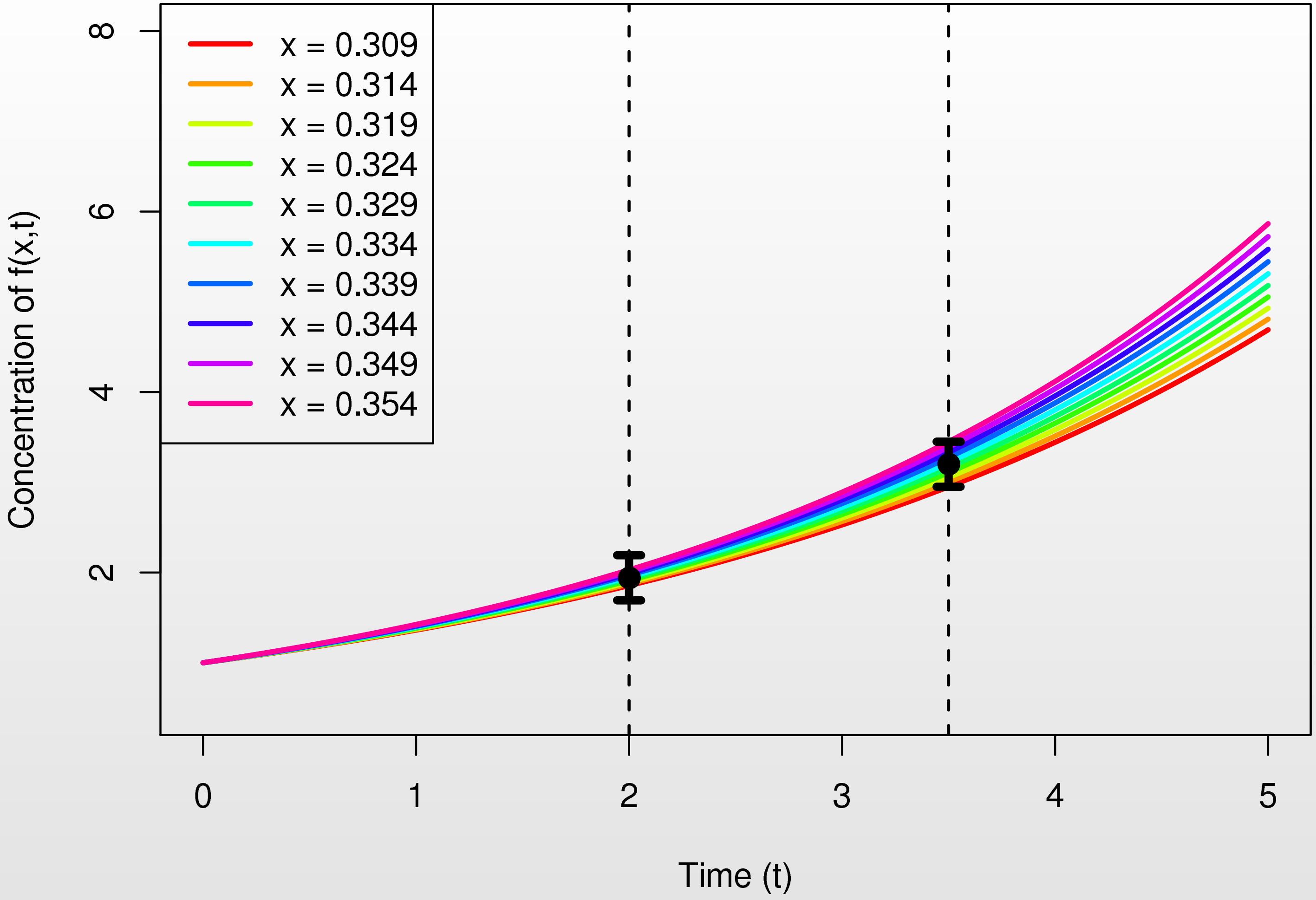

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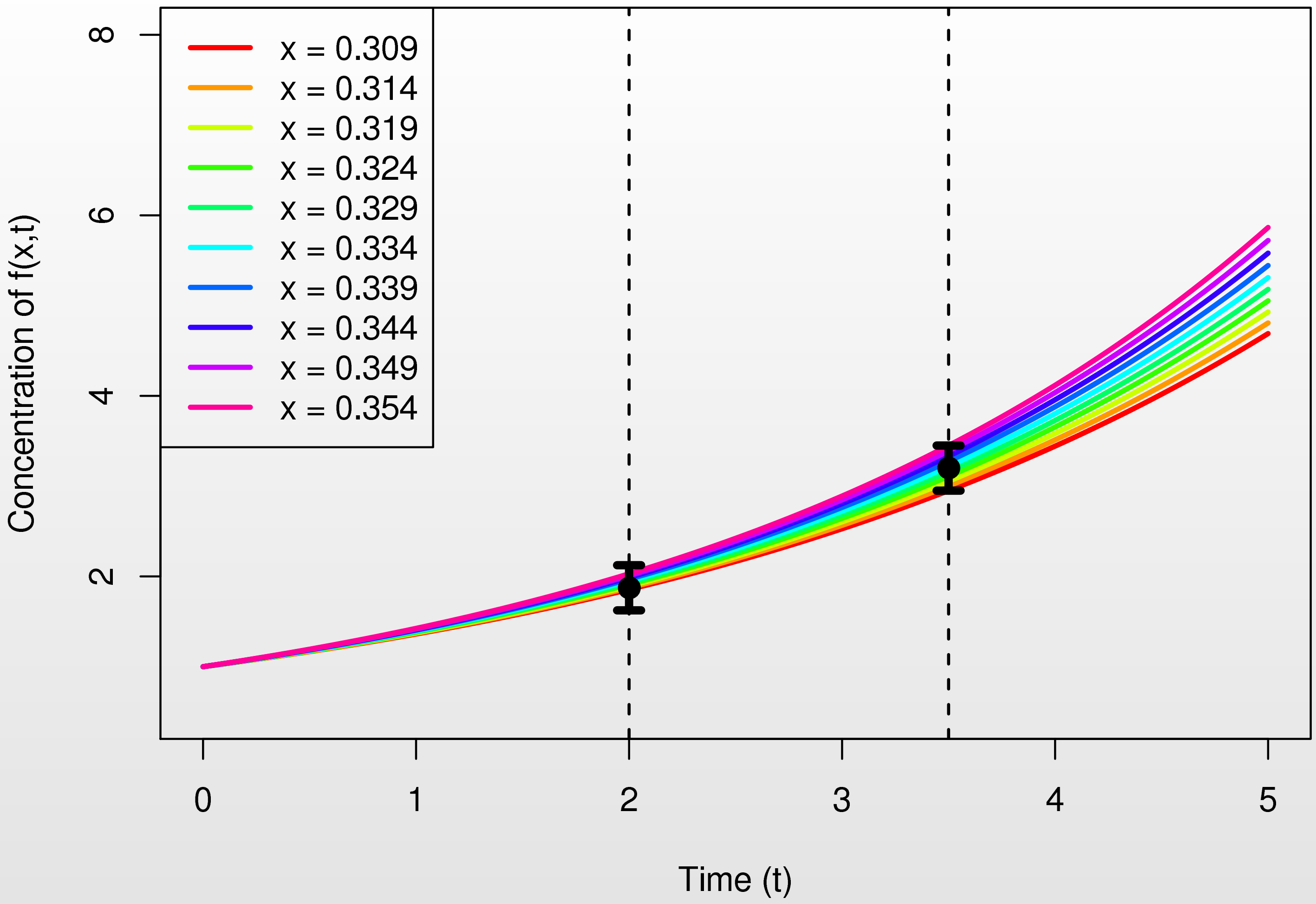

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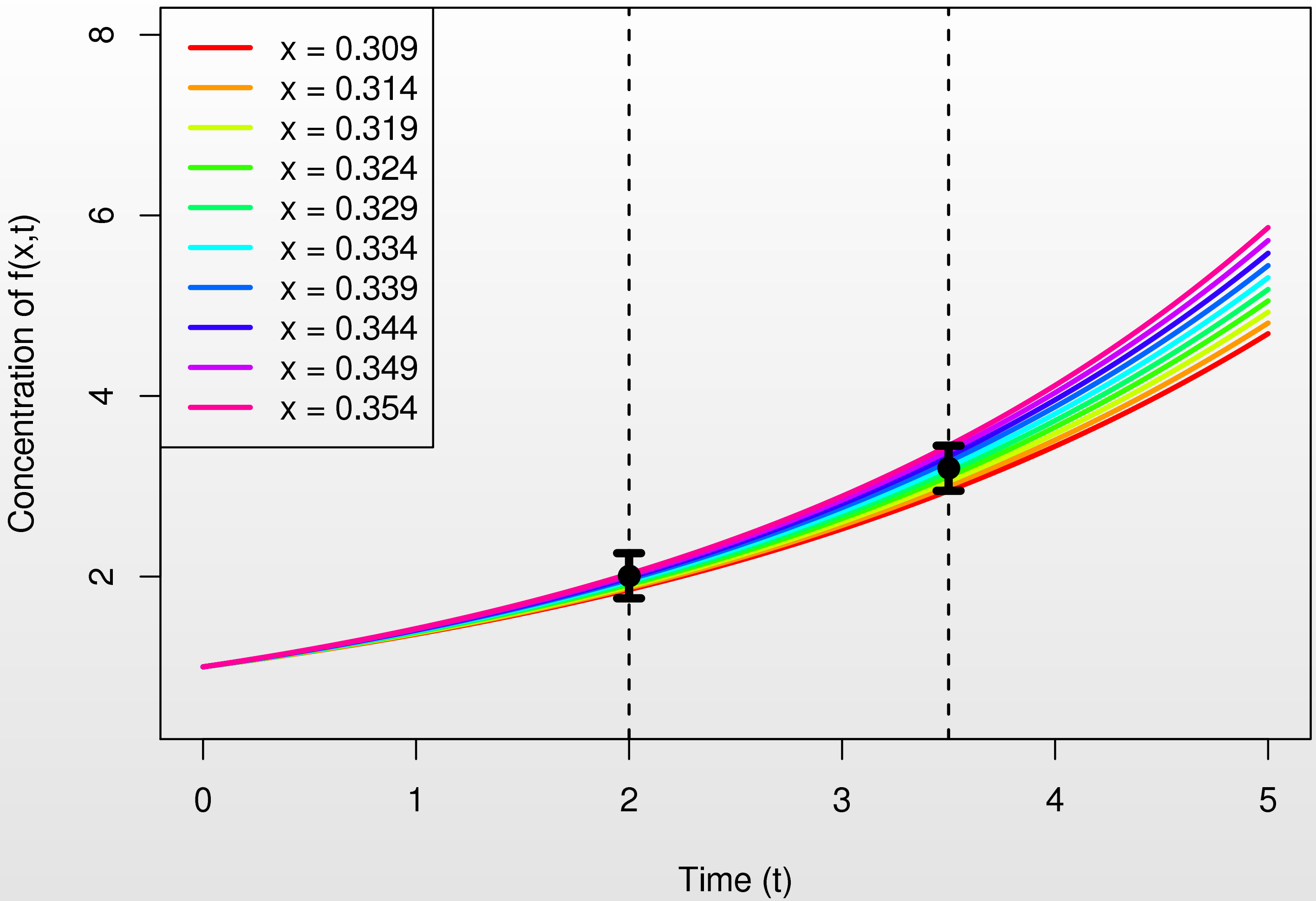
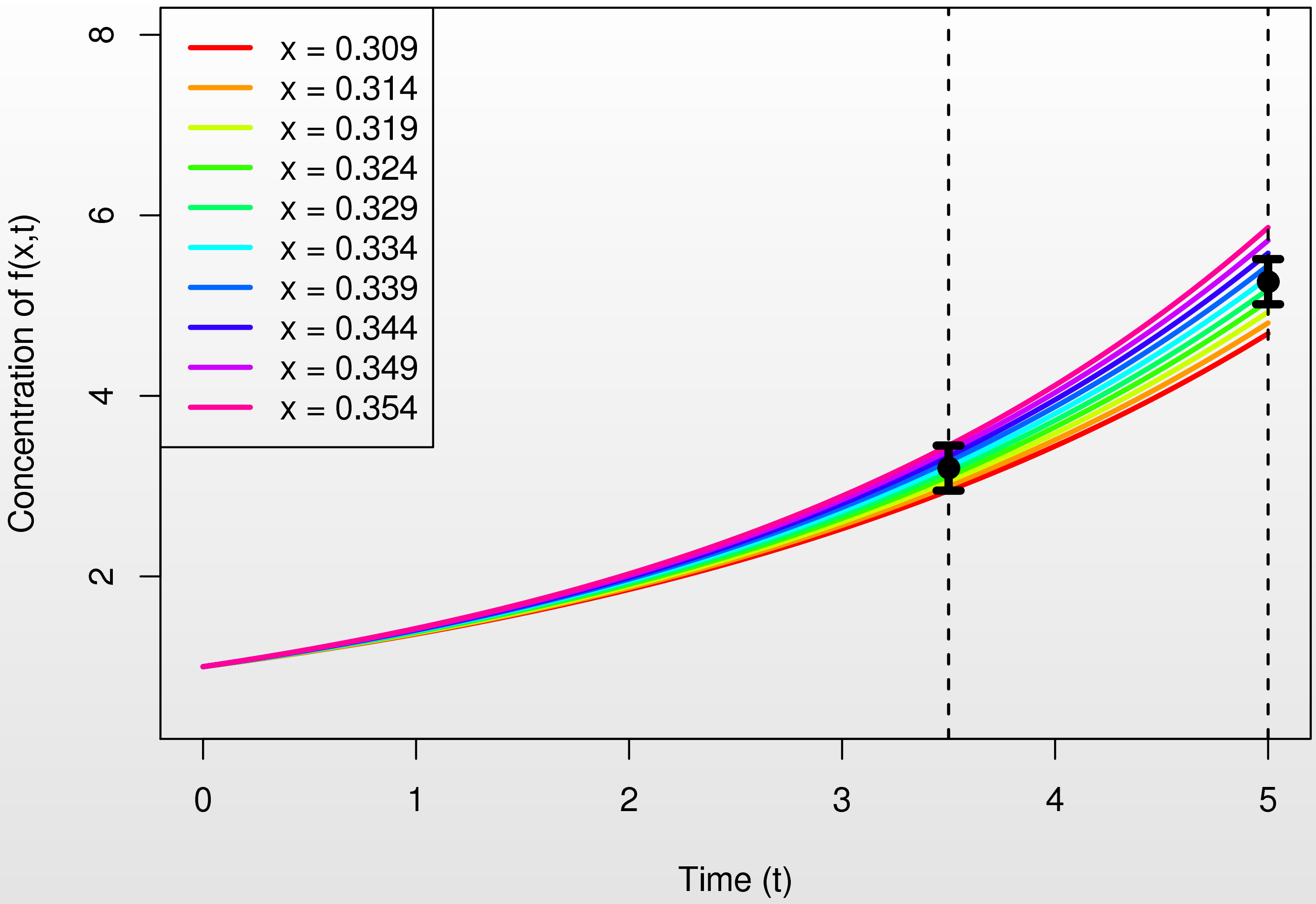
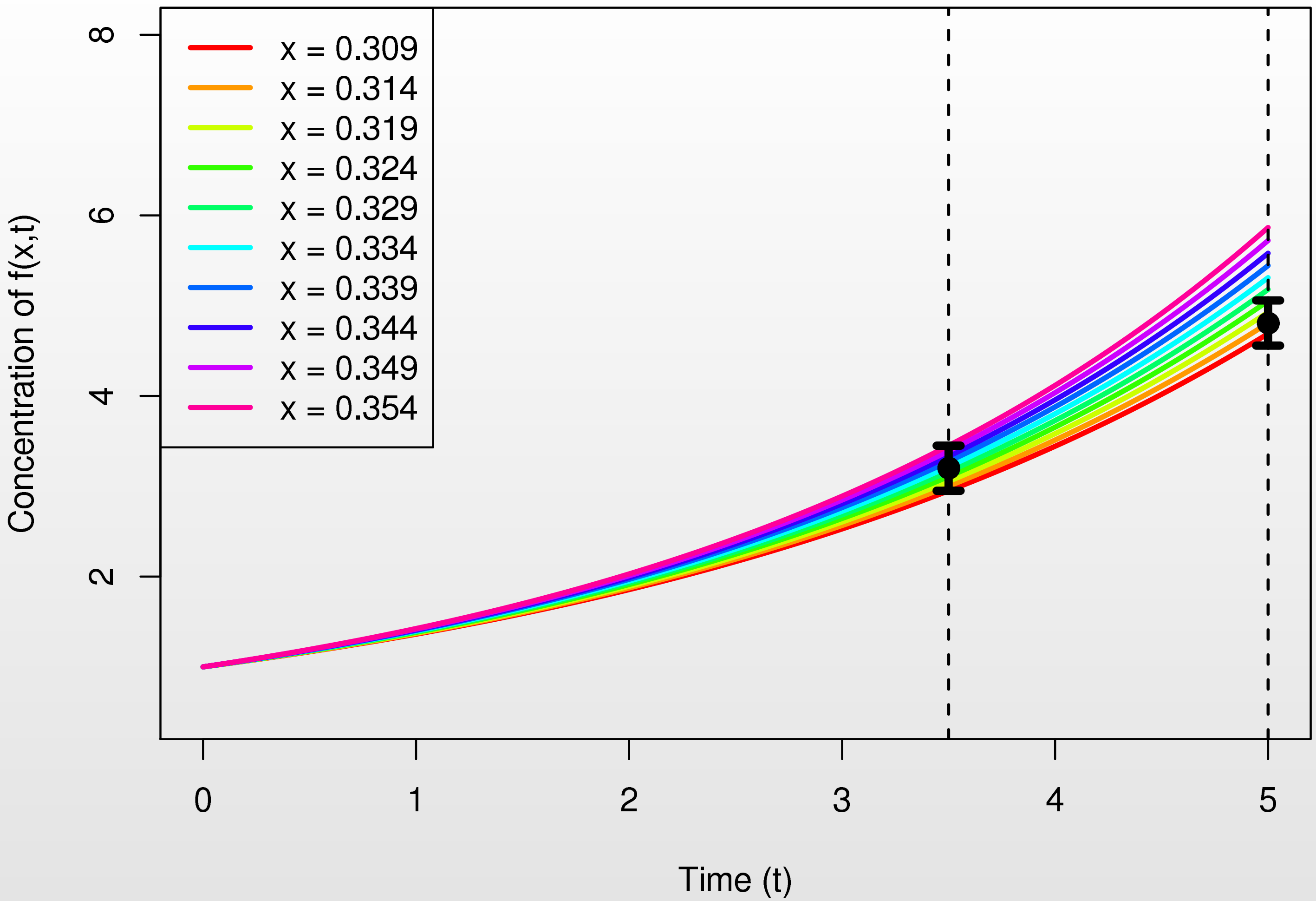


- The predictions imply that any measurement of $f(x, t = 2)$ is highly unlikely to be informative for x.
- This is due to the measurement errors swamping the signal from the model output $f(x, t = 2)$.



- The predictions for $f(x, t = 5)$ show a different conclusion.



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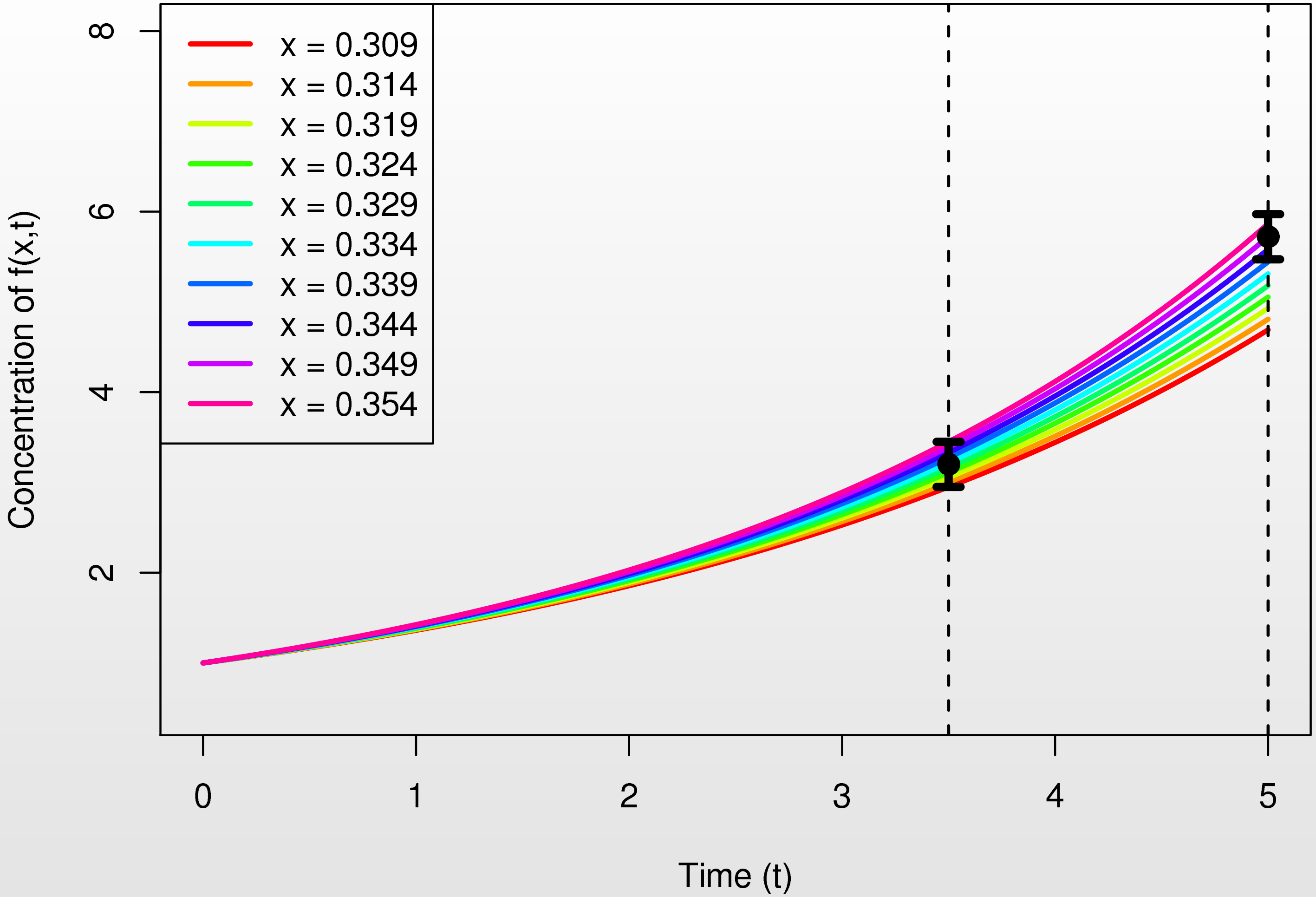
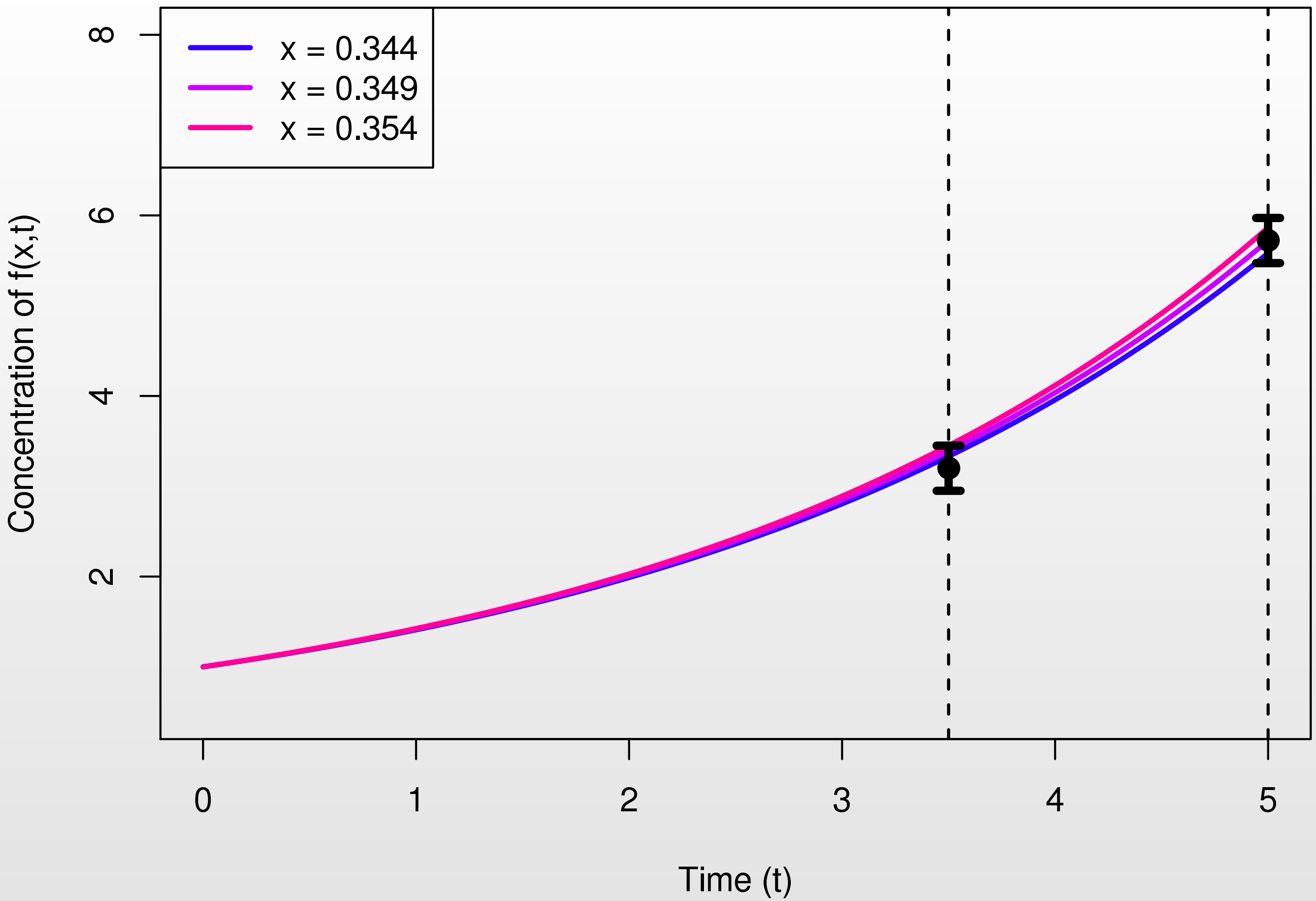
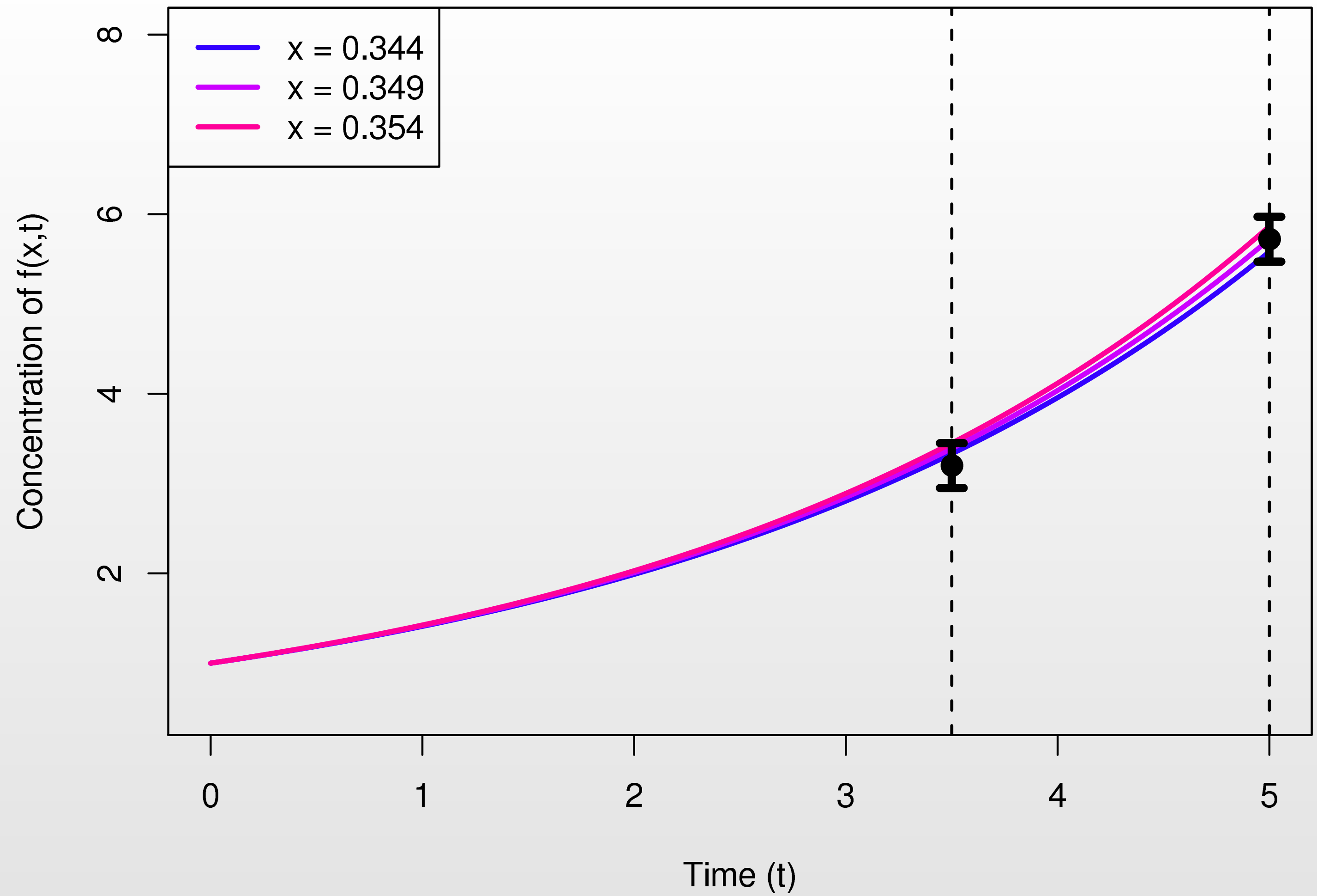


- The predictions for $f(x, t = 5)$ show a different conclusion.
- For each possible measurement of $f(x, t = 5)$ it is highly likely that we will be able to rule out several more values of x as implausible.

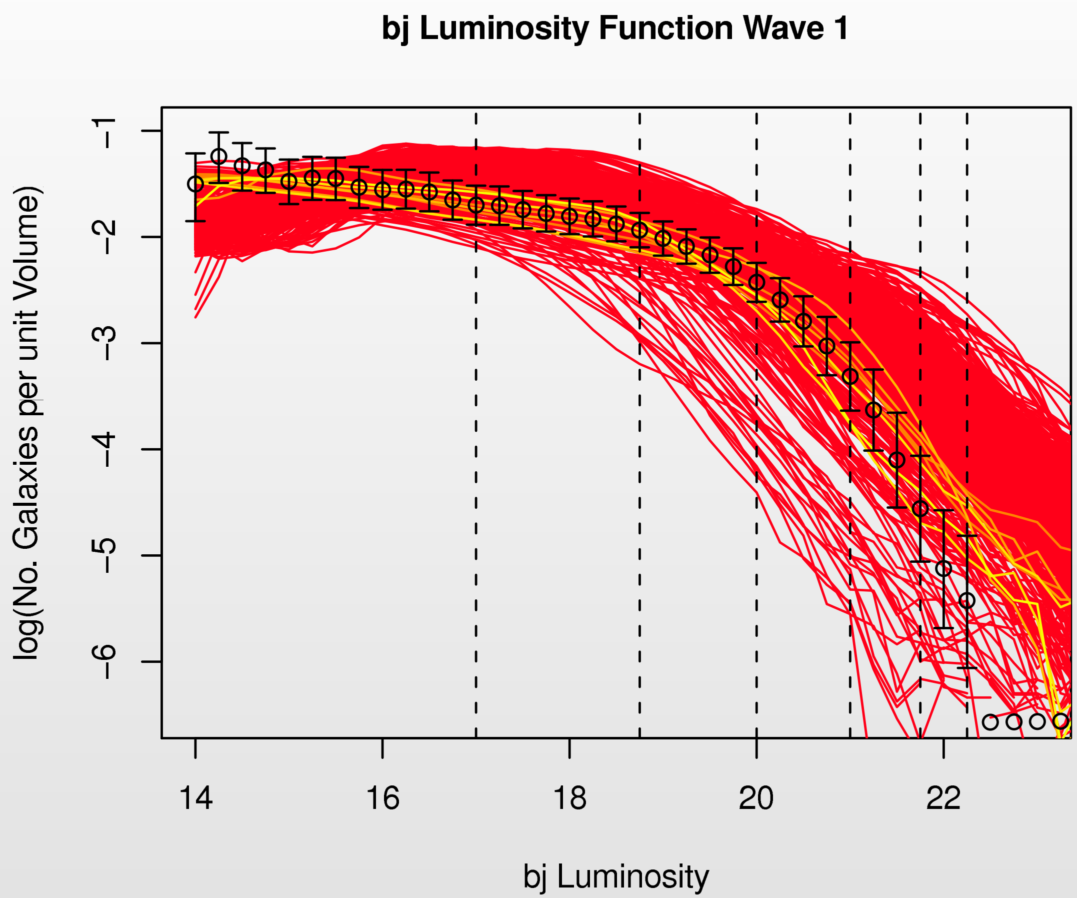


- For one possible measurement, we see that non-implausible values of x would lie approximately between 0.344 and 0.354, ruling out approximately 70% of the possible values of x.



- For one possible measurement, we see that non-implausible values of x would lie approximately between 0.344 and 0.354, ruling out approximately 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. Note no MD.

Quick aside: Galaxy Formation History Match



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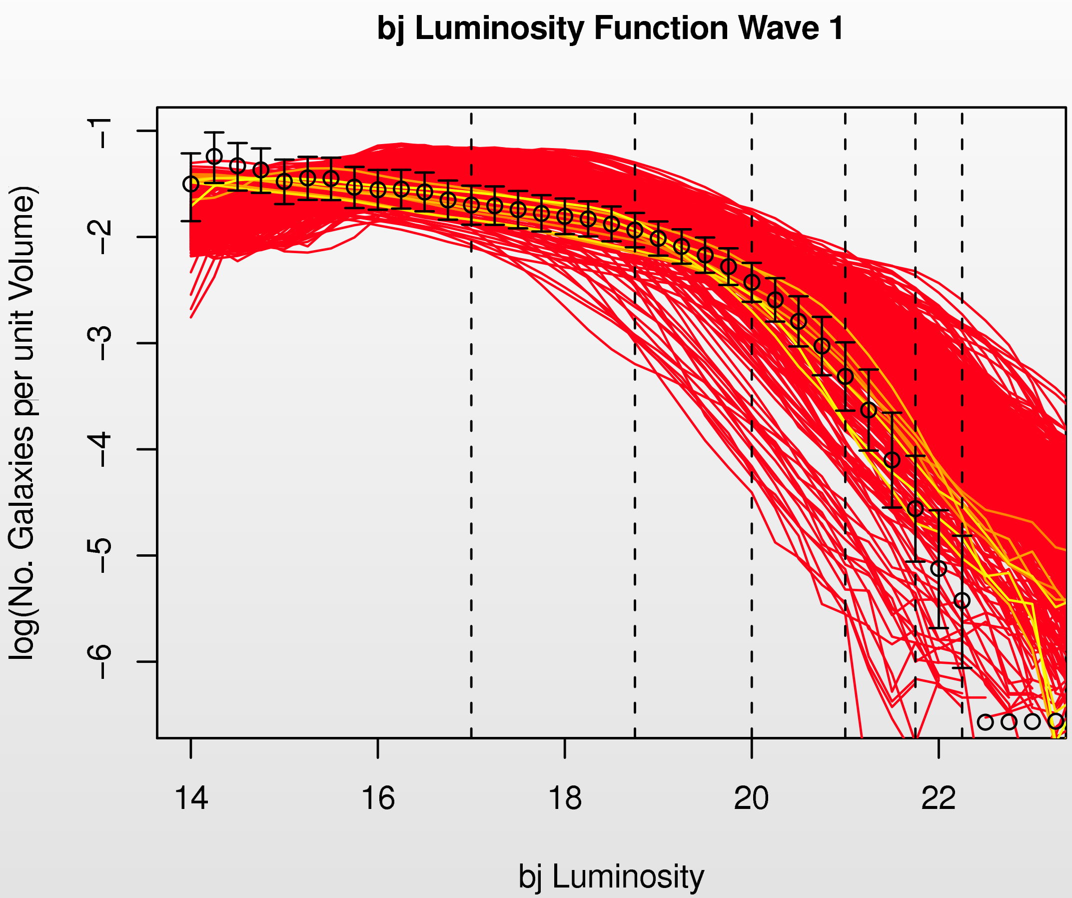

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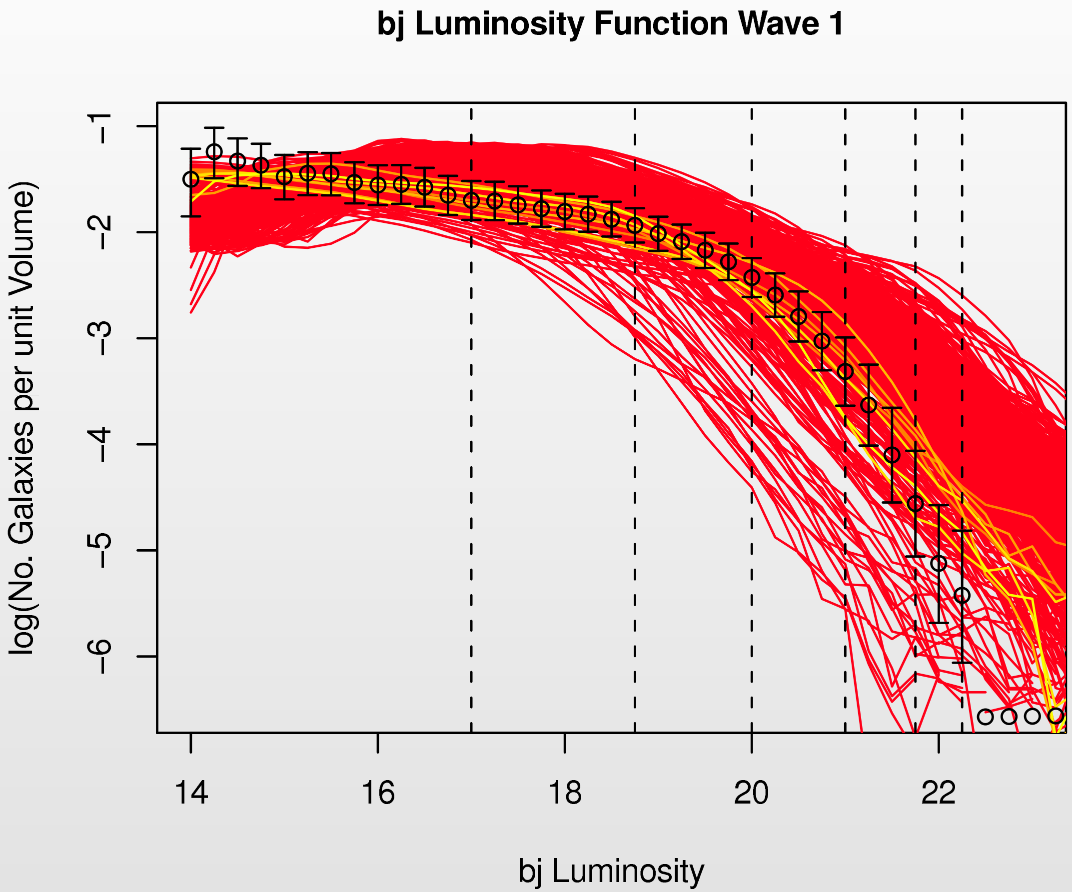

- 17 dimensional input space.
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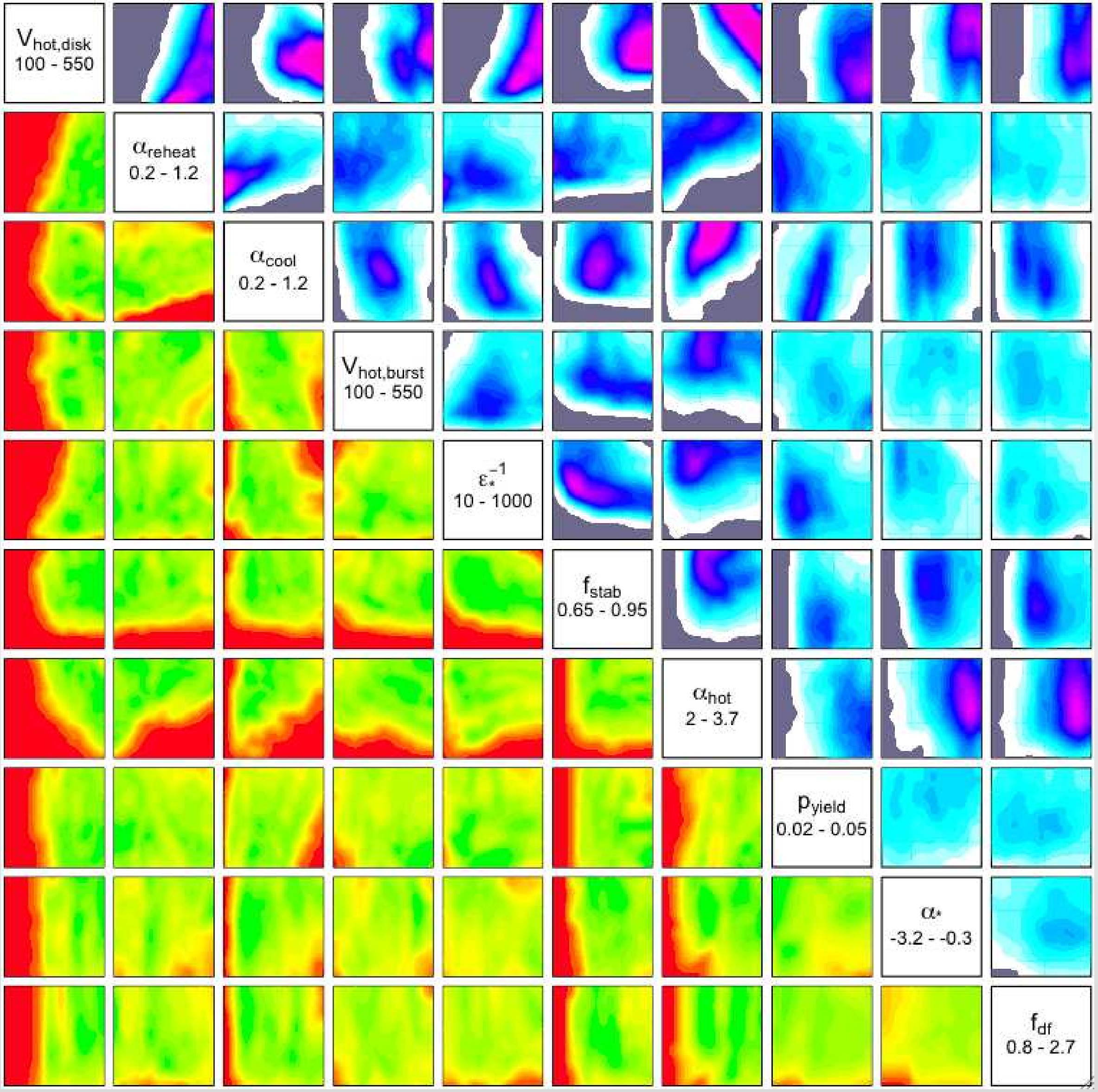
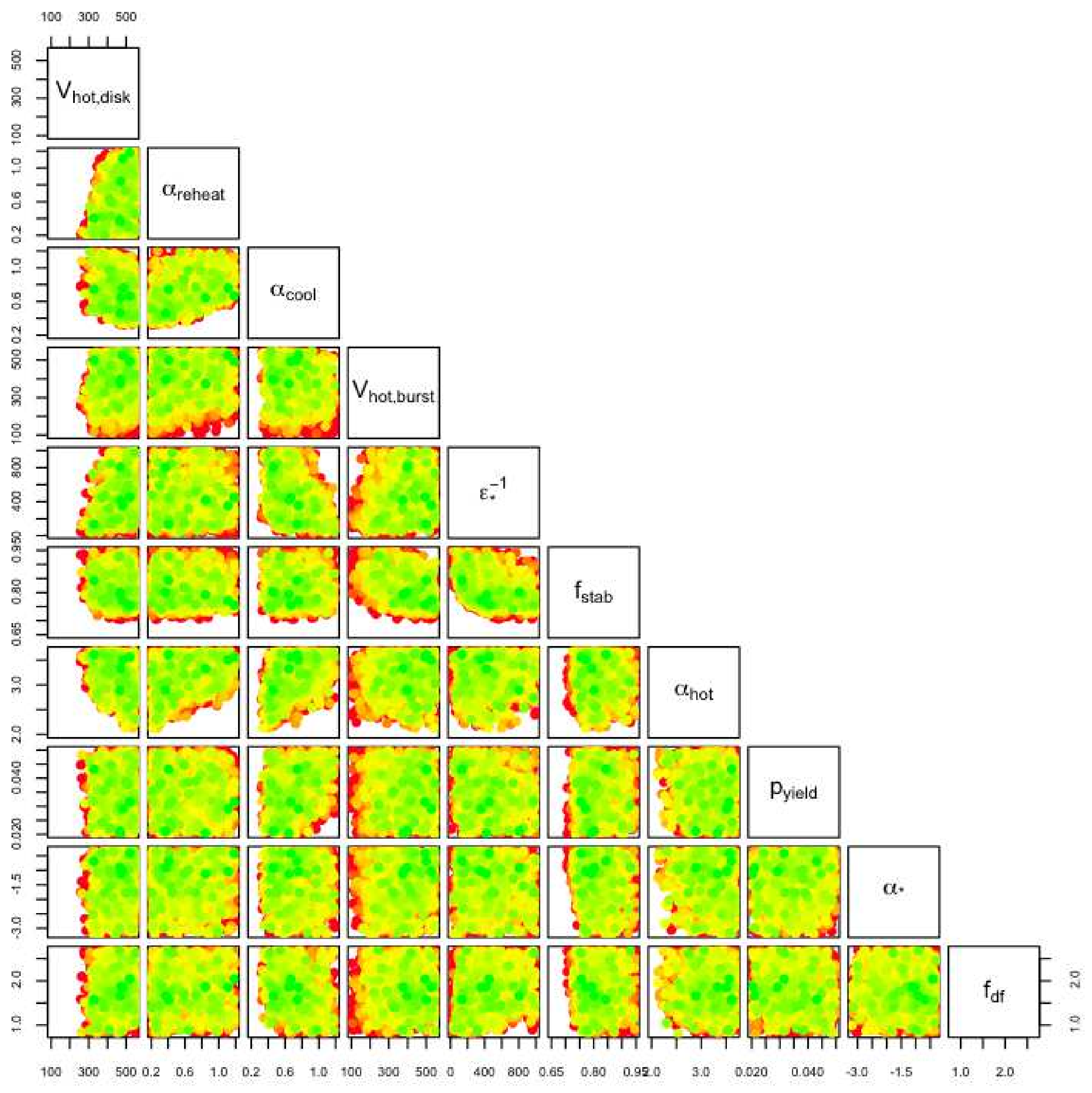
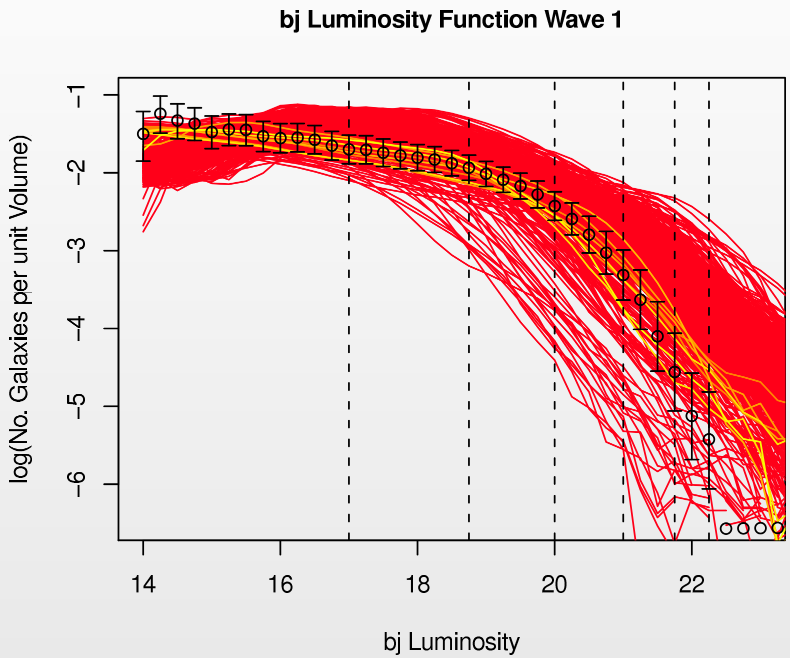


History Match: Wave 5 runs



bj Luminosity Output of Waves 1,2,3 and 5



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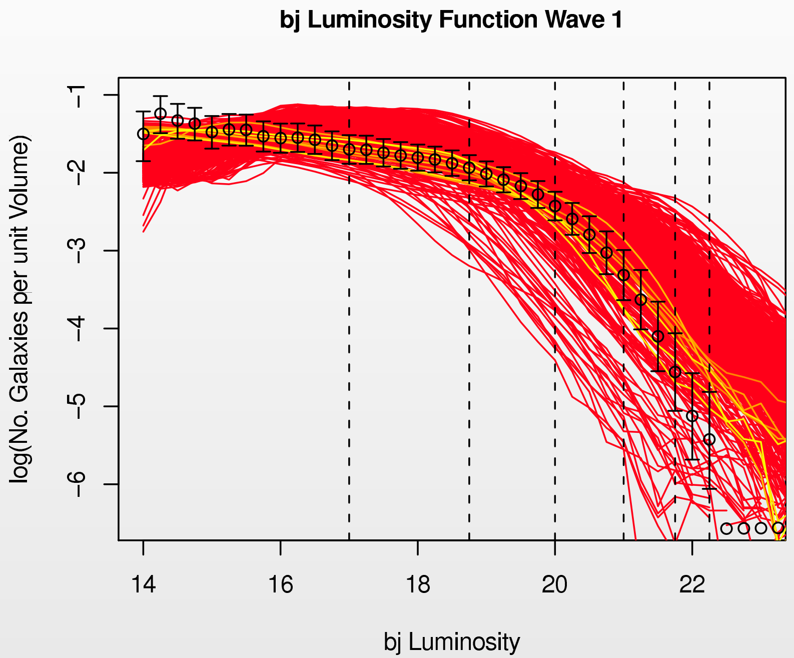

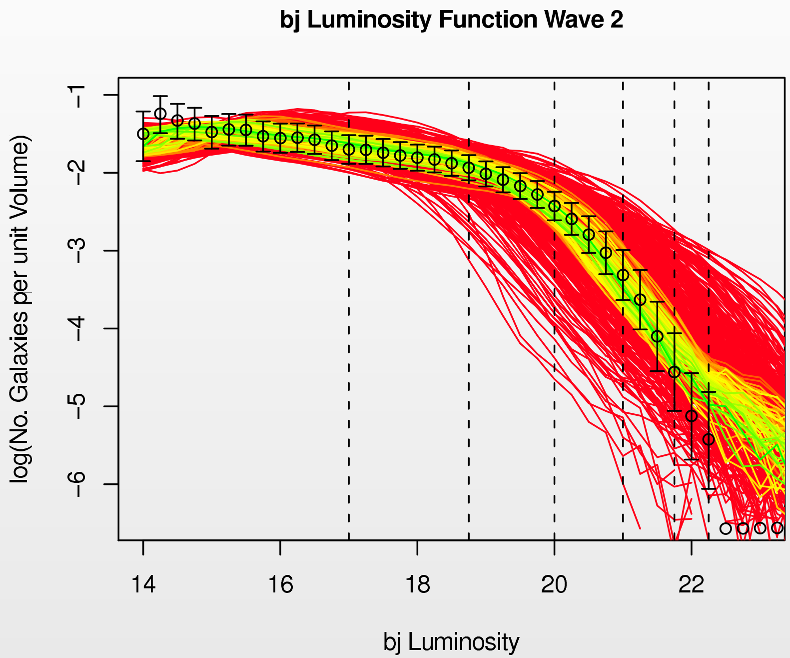

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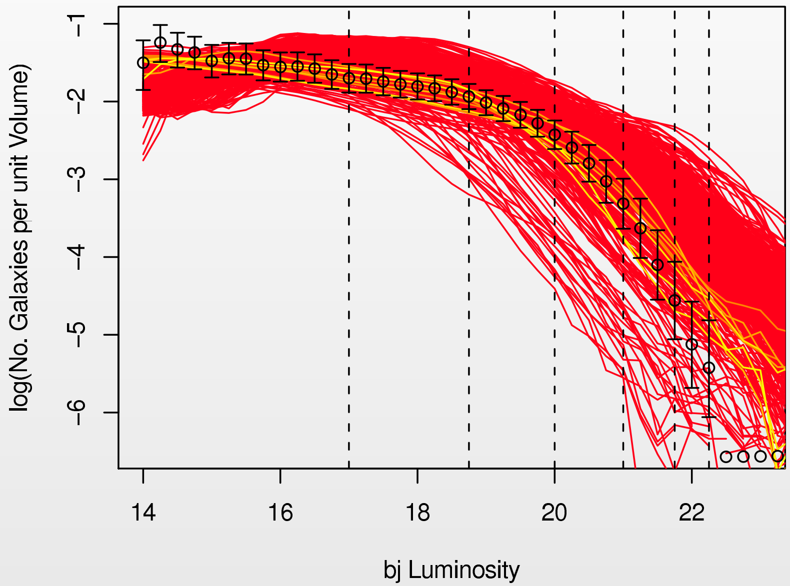
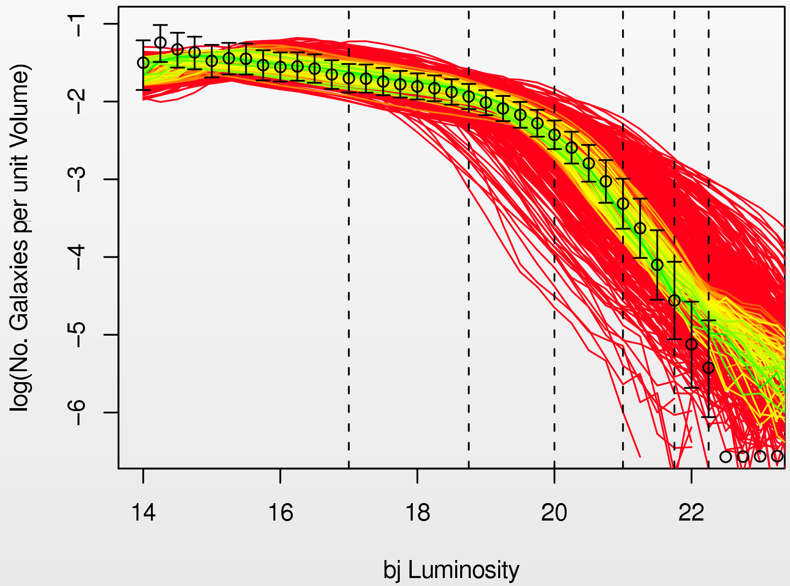


bj Luminosity Function Wave 2



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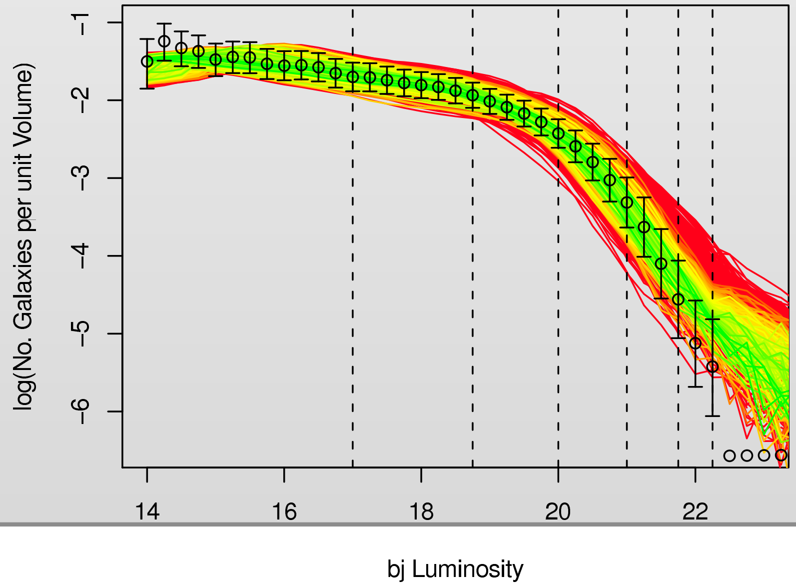

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Durham University

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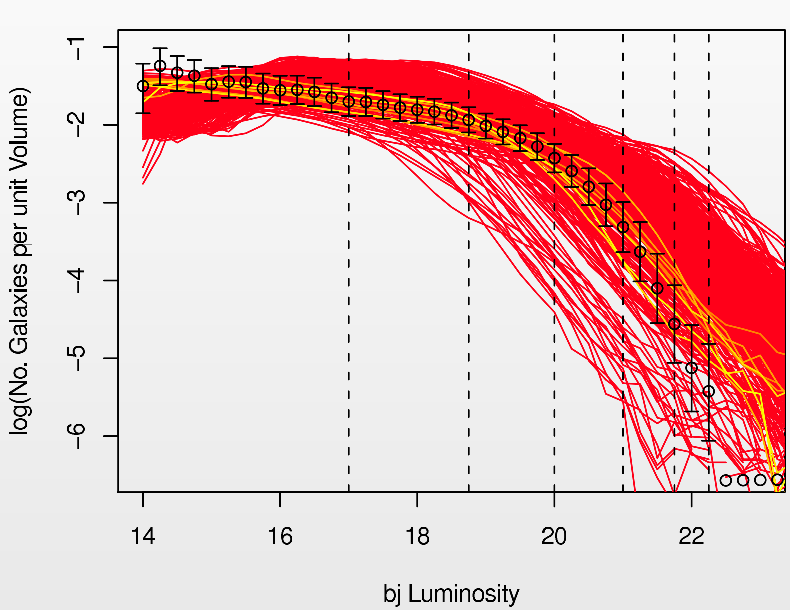

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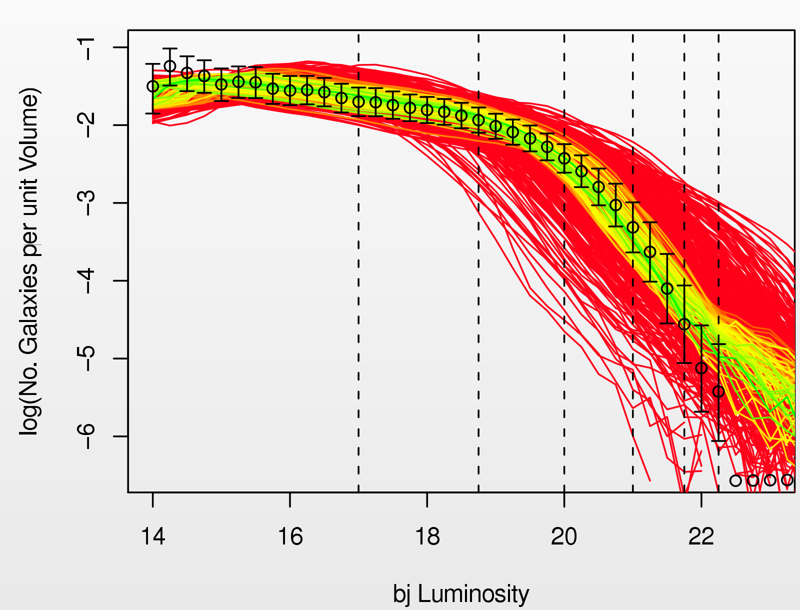

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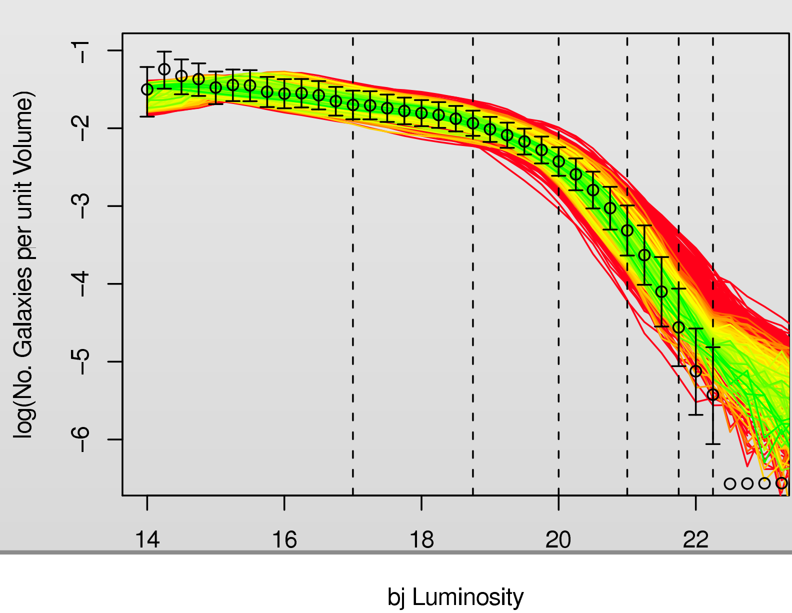

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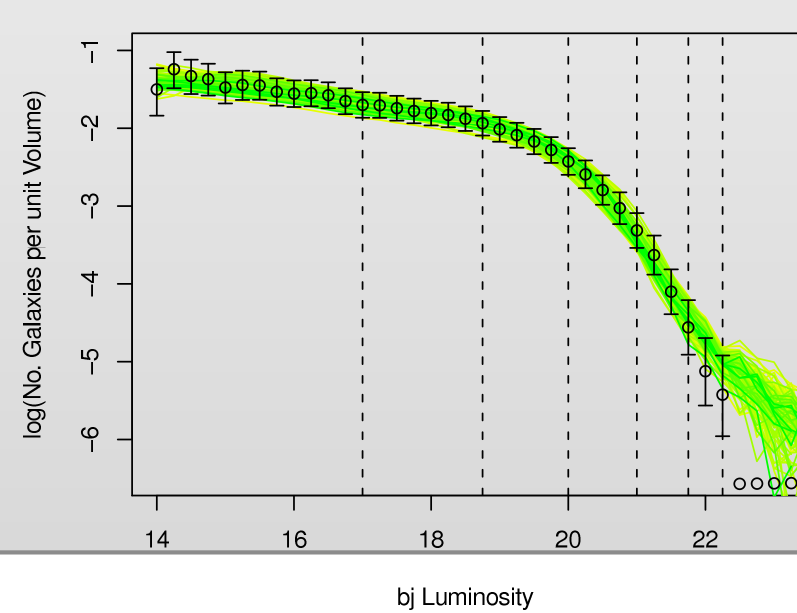
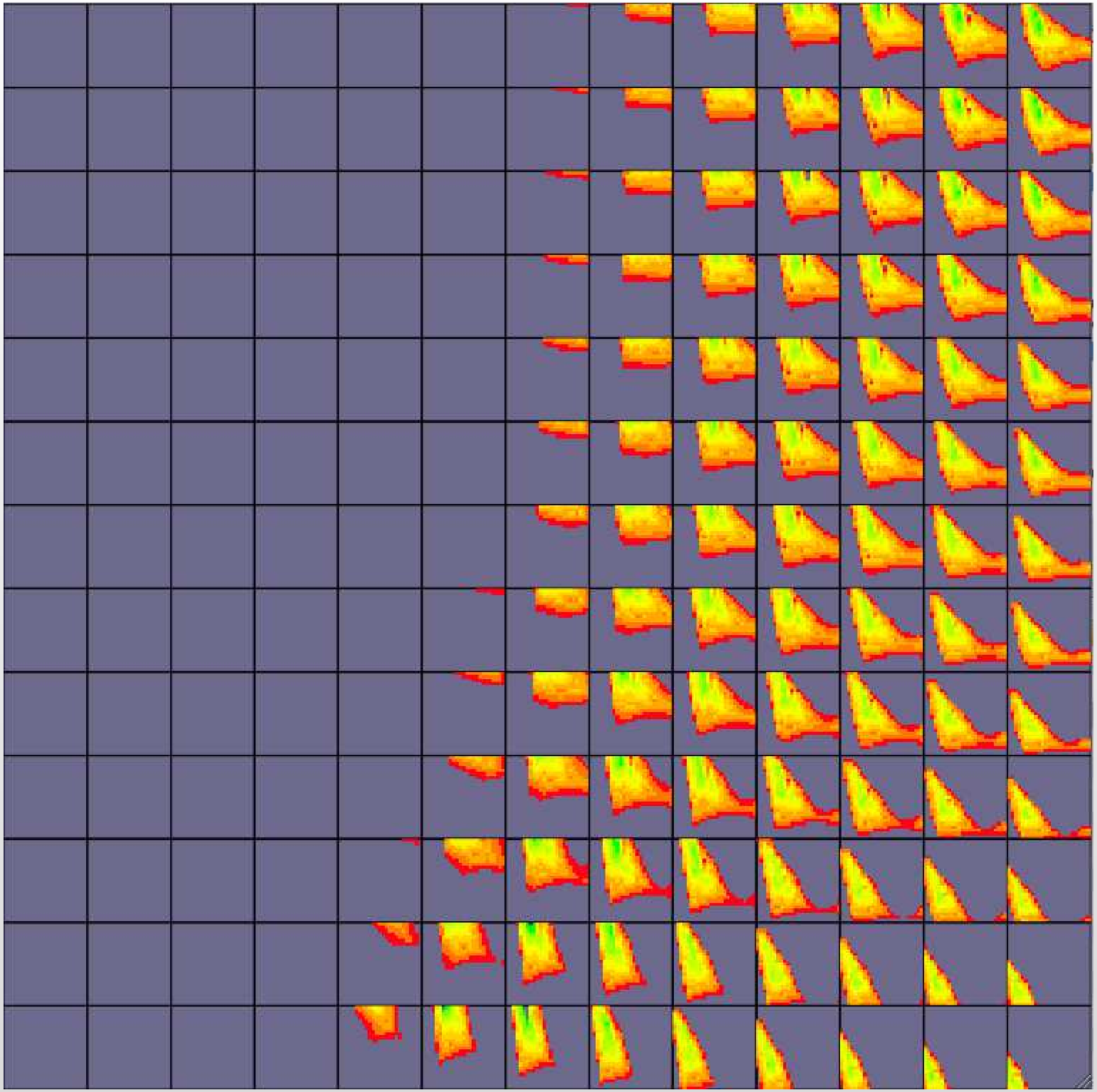


4-Dimensional Implausibility Plots: Anyone?



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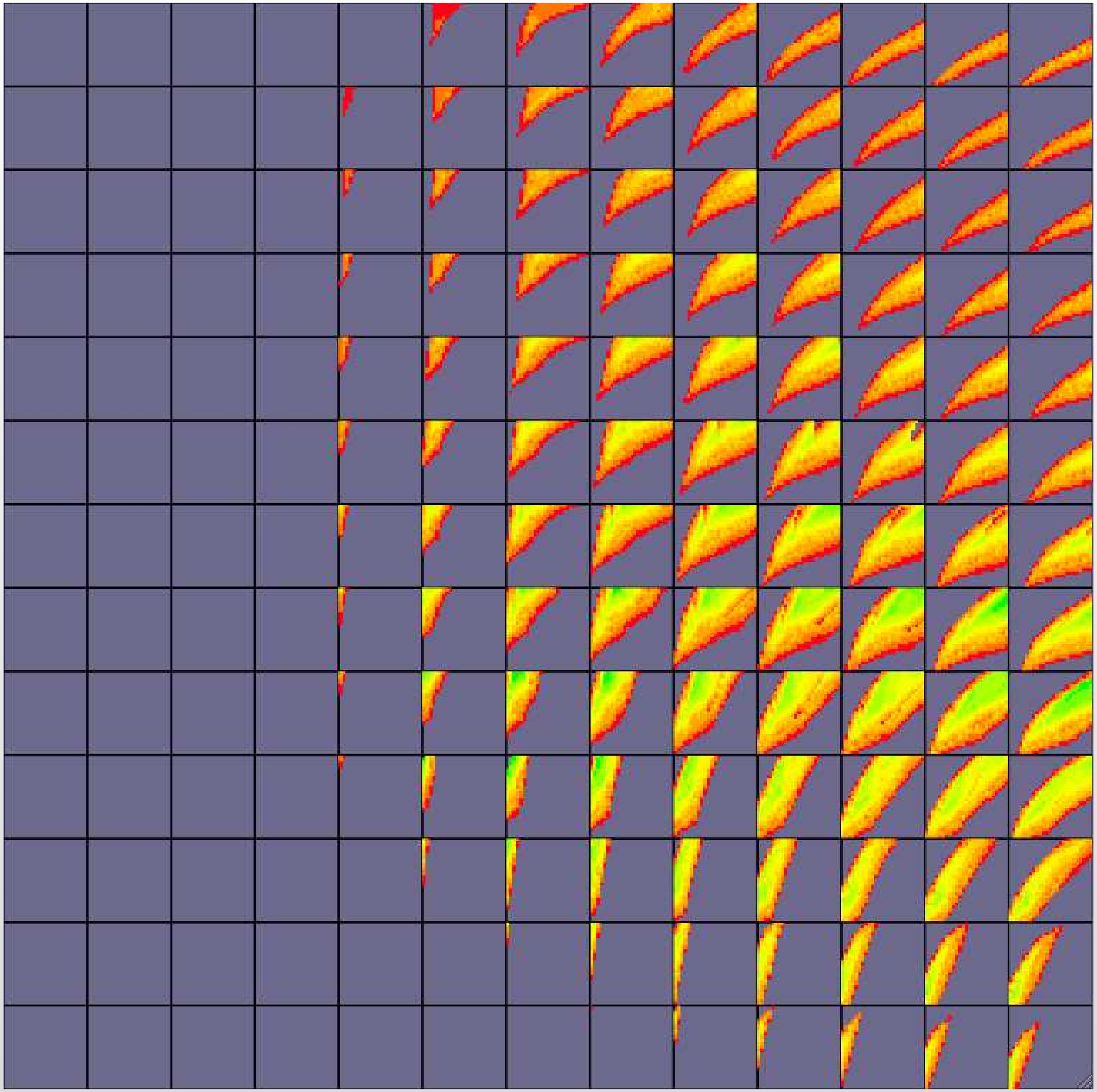

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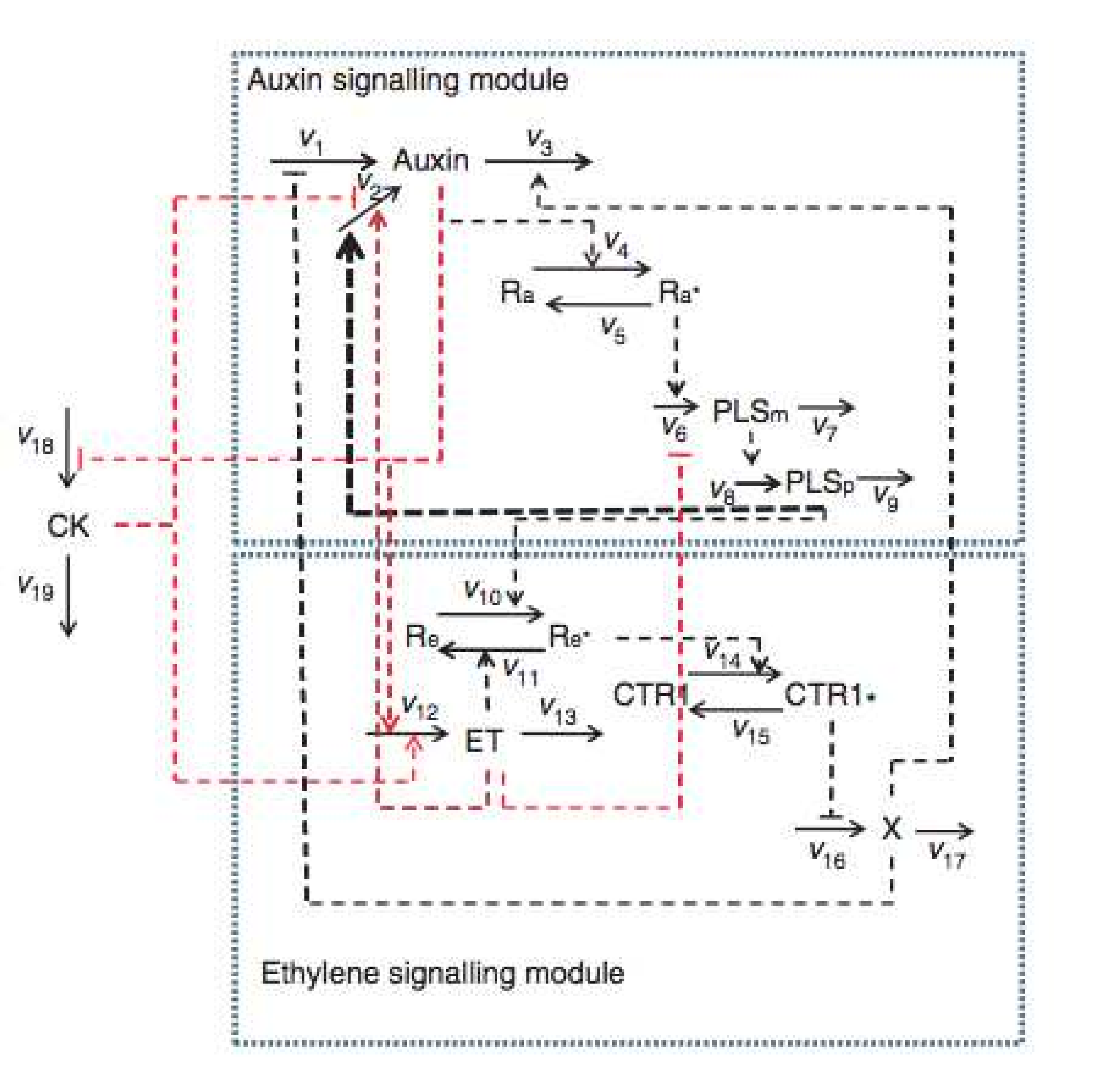
- Model has 12 outputs, only 4 of which can be measured.
- Model has 32 unknown input rate parameters which have ranges of 5 orders of magnitude,
- Here the input x is a vector of length 32, but the output $f(x)$ is more complex. Compare with the simple example where both x and f were 1 dimensional.

Slides describing model inputs and outputs.

Chemical Output	Initial concentration	Measurable
Auxin	0.1	Yes
X	0.1	
PLSp	0.1	Yes
Ra	0	
Ra_star	1	
CK	0.1	Yes
ET	0.1	Yes
PLSm	0.1	
Re	0	
Re_star	0.3	
CTR1	0	
CTR1_star	0.3	
IAA	0	
cytokinin	0	
ACC	0	

Reaction Network Model

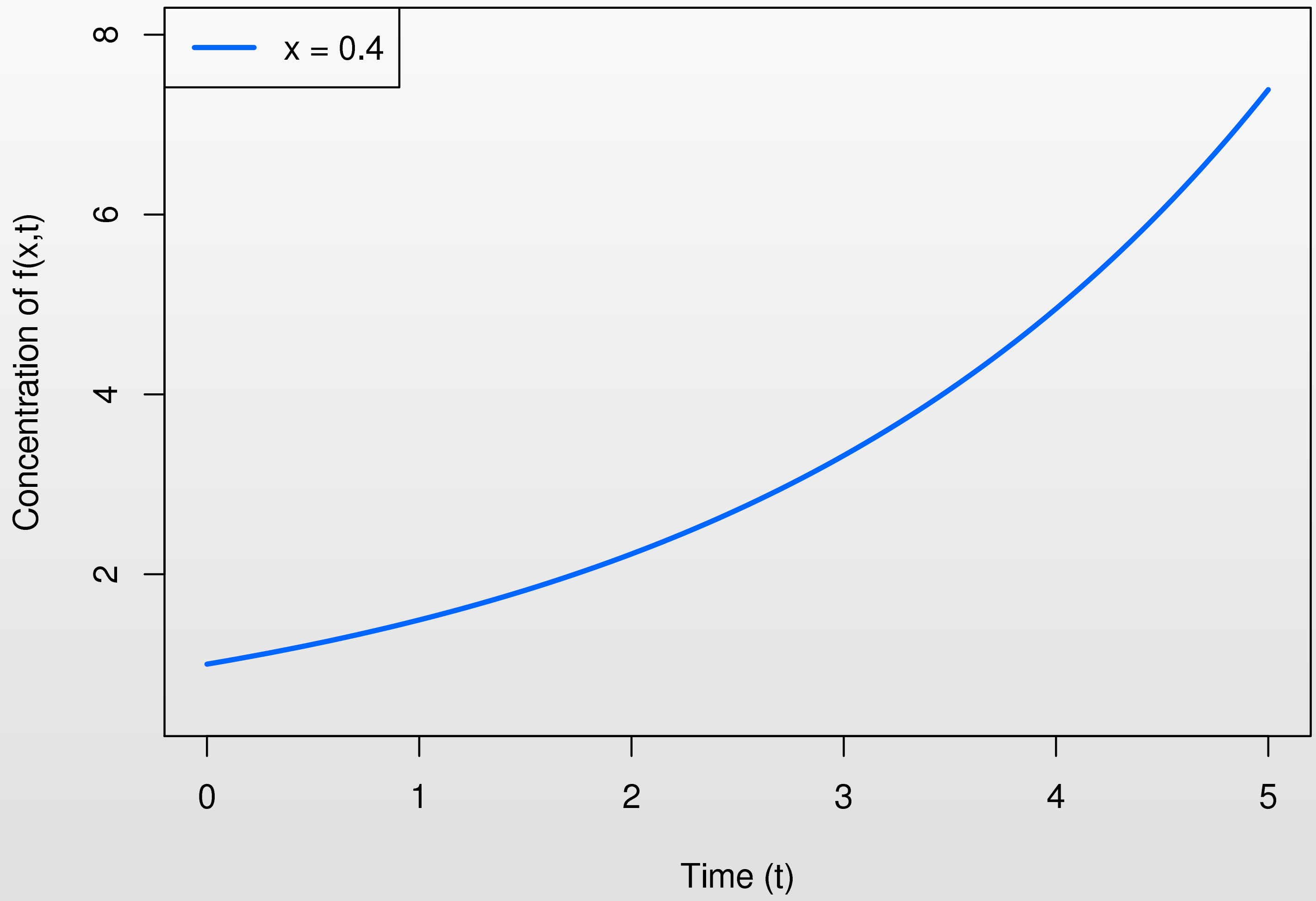


32 Reaction Rates: 32 Input parameters

Input	min	max	Input	min	max
k1	0.001	100	k1a	0.001	100
k2	0.0002	20	k2a	0.0028	280
k2b	0.001	100	k2c	1×10^{-5}	1
k3	0.002	200	k3a	0.00045	45
k4	0.001	100	k5	0.001	100
k6	0.3	0.3	k6a	0.0002	20
k7	0.001	100	k8	0.001	100
k9	0.001	100	k10	3×10^{-7}	0.03
k10a	0.0005	50	k11	0.005	500
k12	0.0001	10	k12a	0.0001	10
k13	0.001	100	k14	0.003	300
k15	8.5×10^{-5}	8.5	k16	0.0003	30
k16a	0.001	100	k17	0.0001	10
k18	0.0001	10	k18a	0.001	100
k19	0.001	100	k1vauxin	0.001	100
k1vCK	0.001	100	k1veth	0.001	100

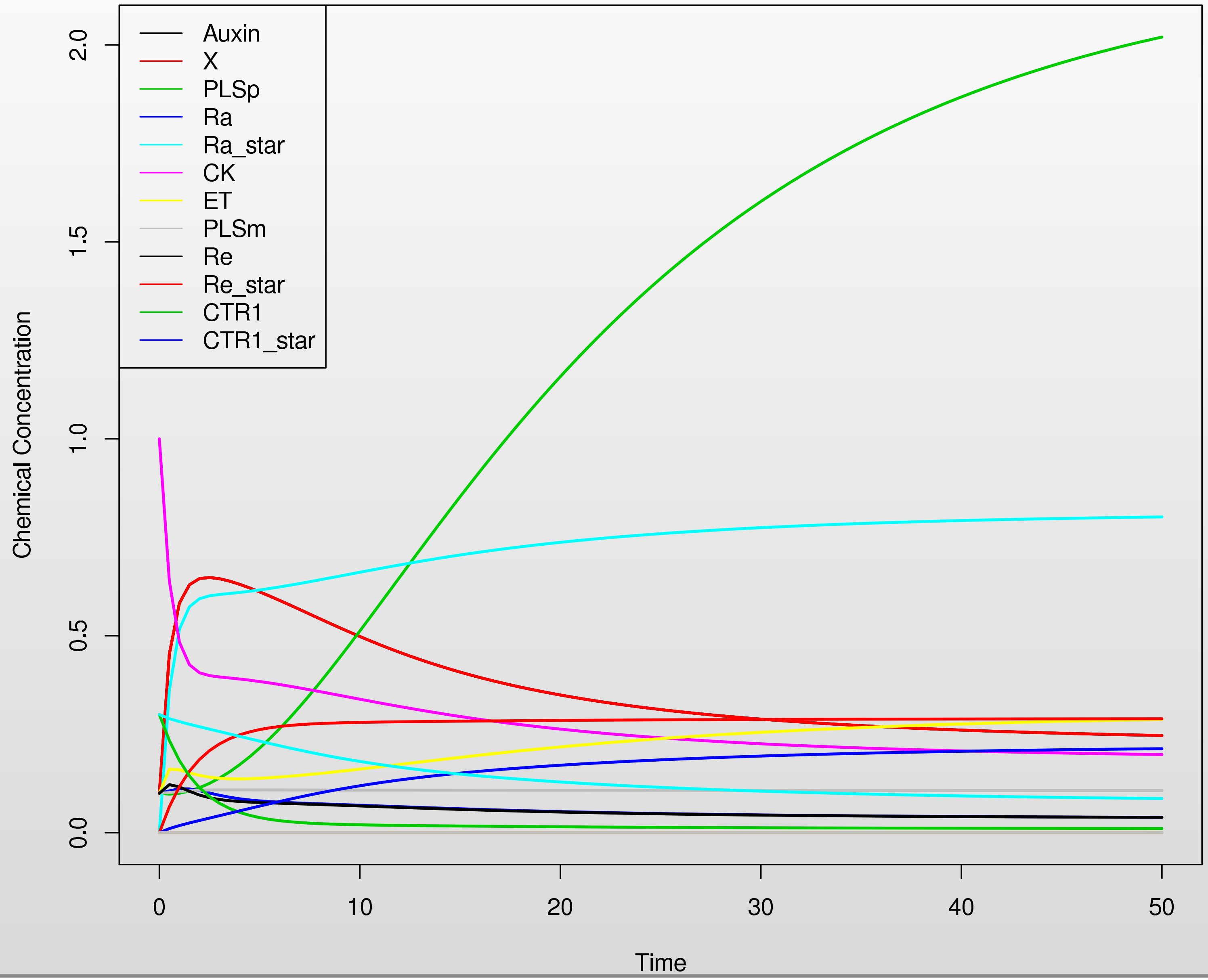
- So now the input $x =$ (k1, k1a, k2, k2a, . . . ,k19, k1vauxin, k1vCK, k1veth)

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.

Plots of outputs: Arabidopsis Model



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- The results are compared to the appropriate wild type and the resulting log ratio 'trends' combined with observed errors are compared to the model output. e.g.

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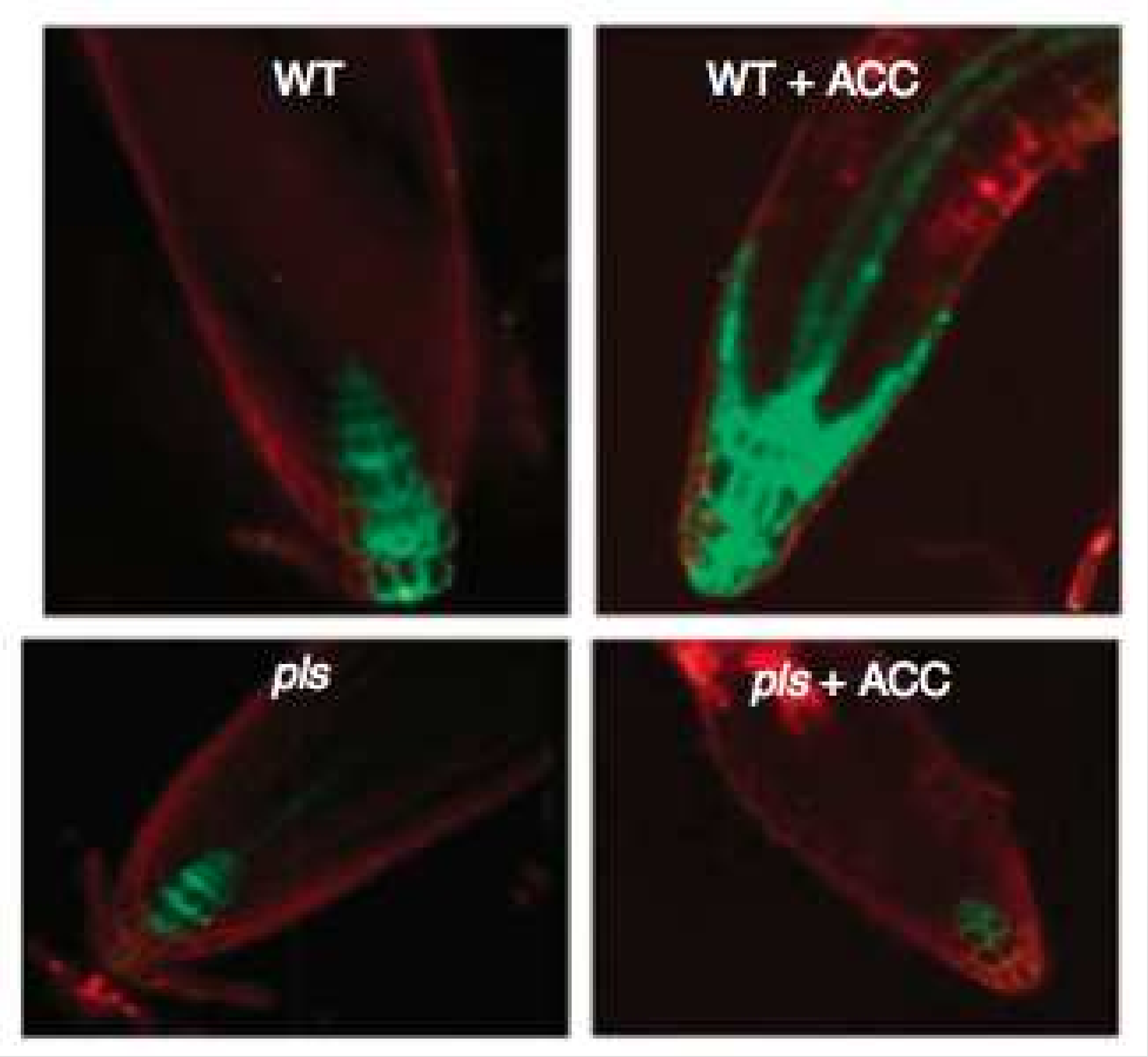
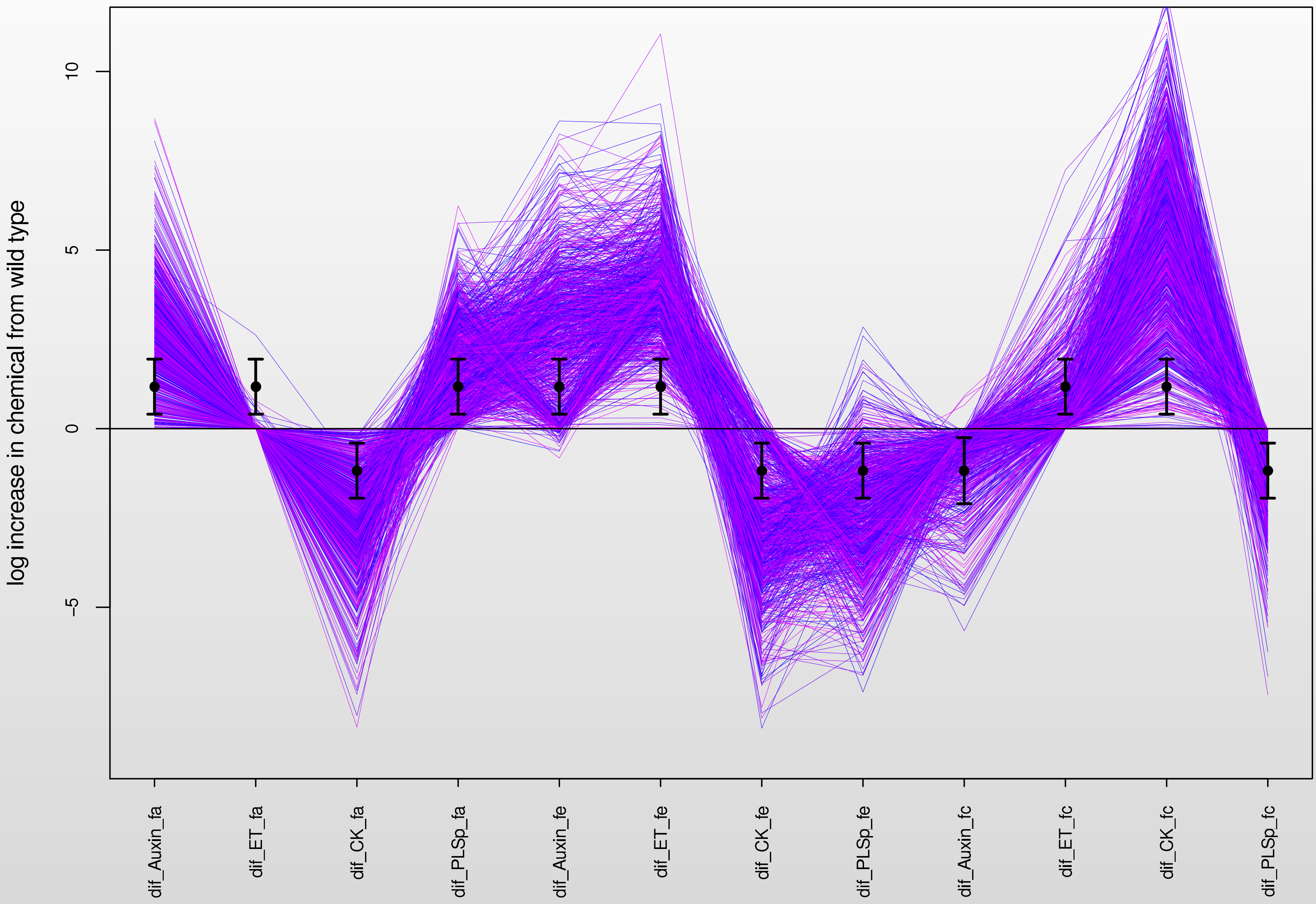
- Prior to this study, 16 of these experiments had been performed, so z is currently a vector of measurements of length 16 composed of log ratio trends.

Measurements of root hormone level.



Observed Trends plus 2000 runs of the model



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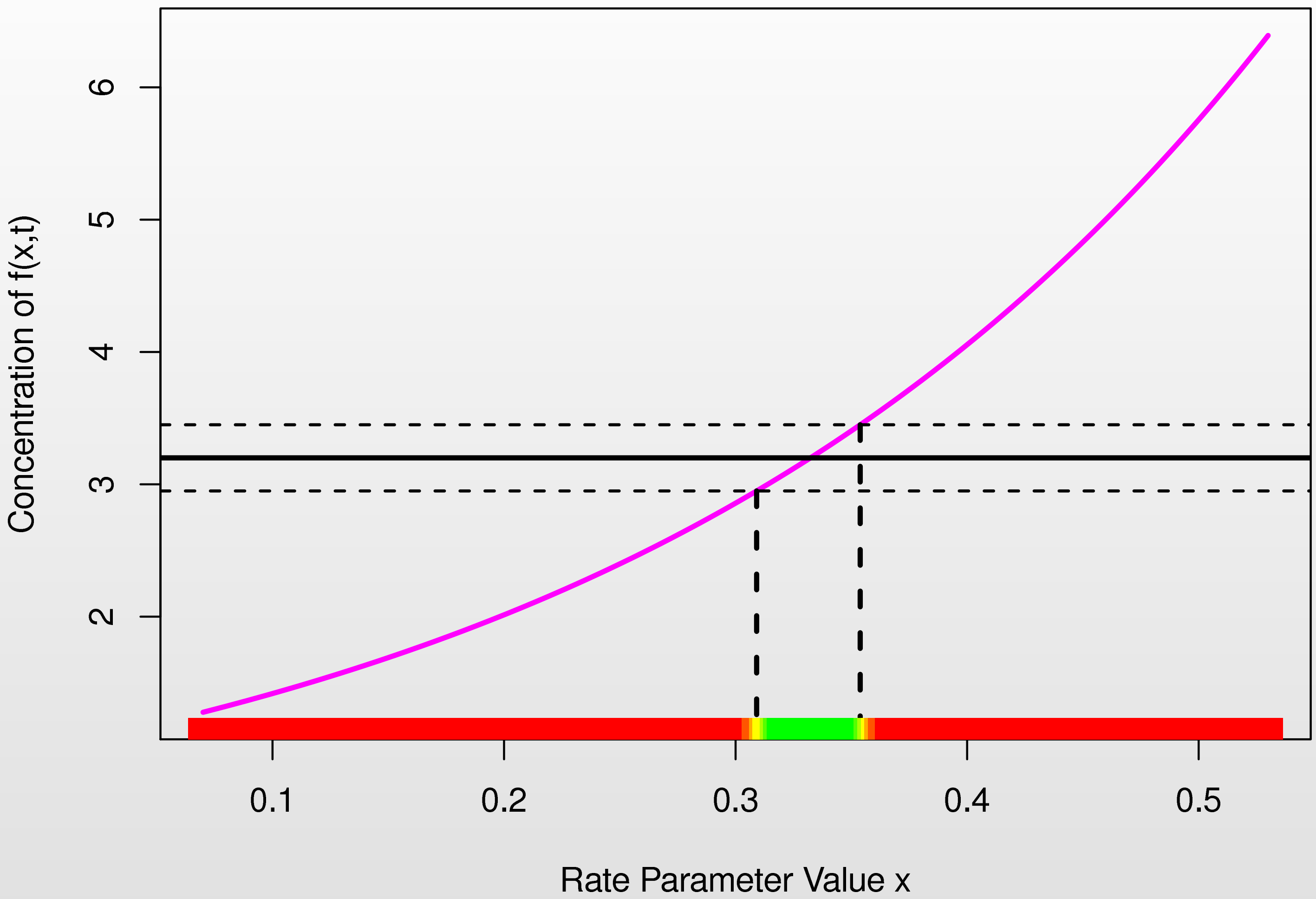
- To answer these we need to discuss observational errors, model discrepancy, emulation and iterative history matching using implausibility measures.

Observed errors and Model Discrepancy: 1D example



- 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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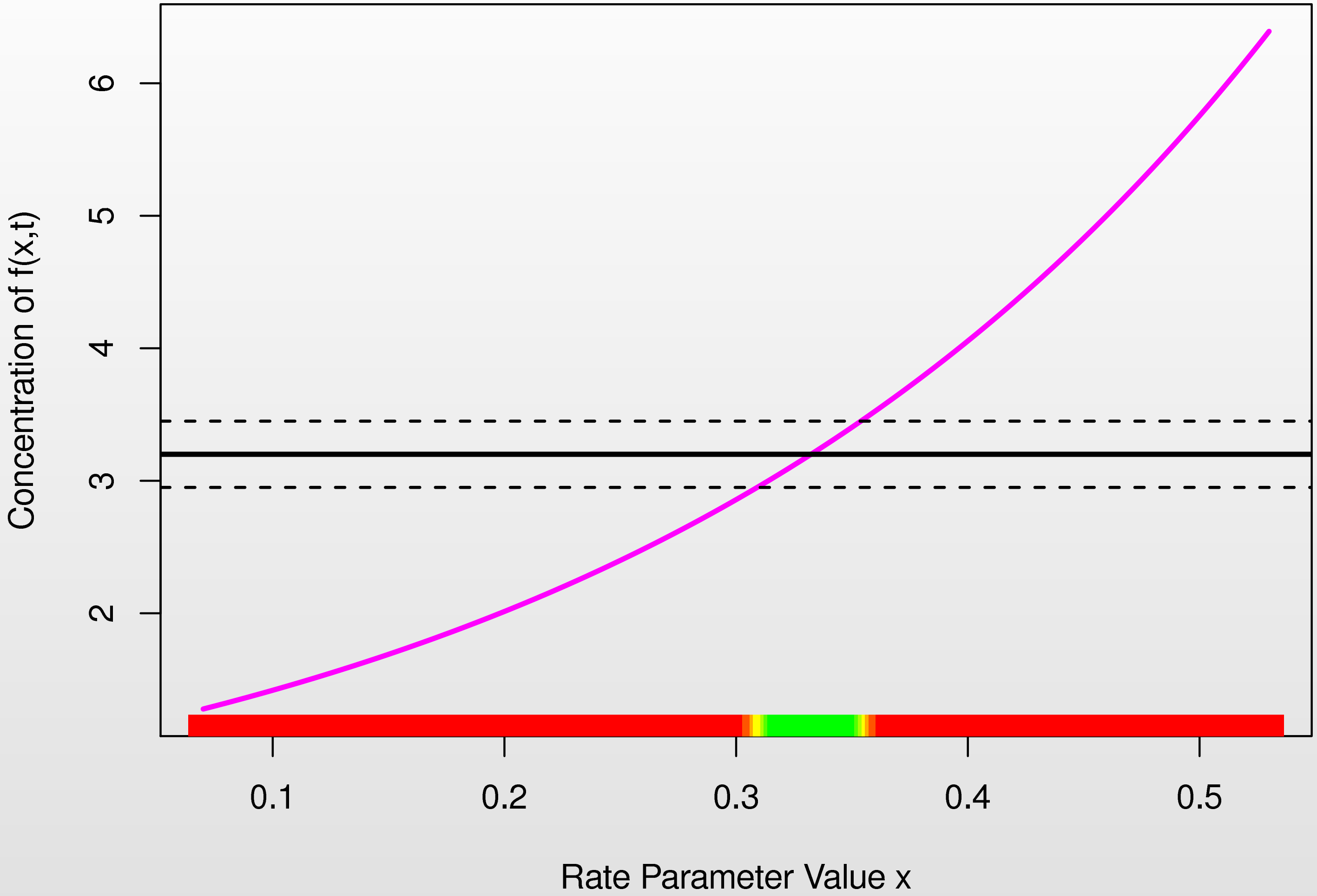

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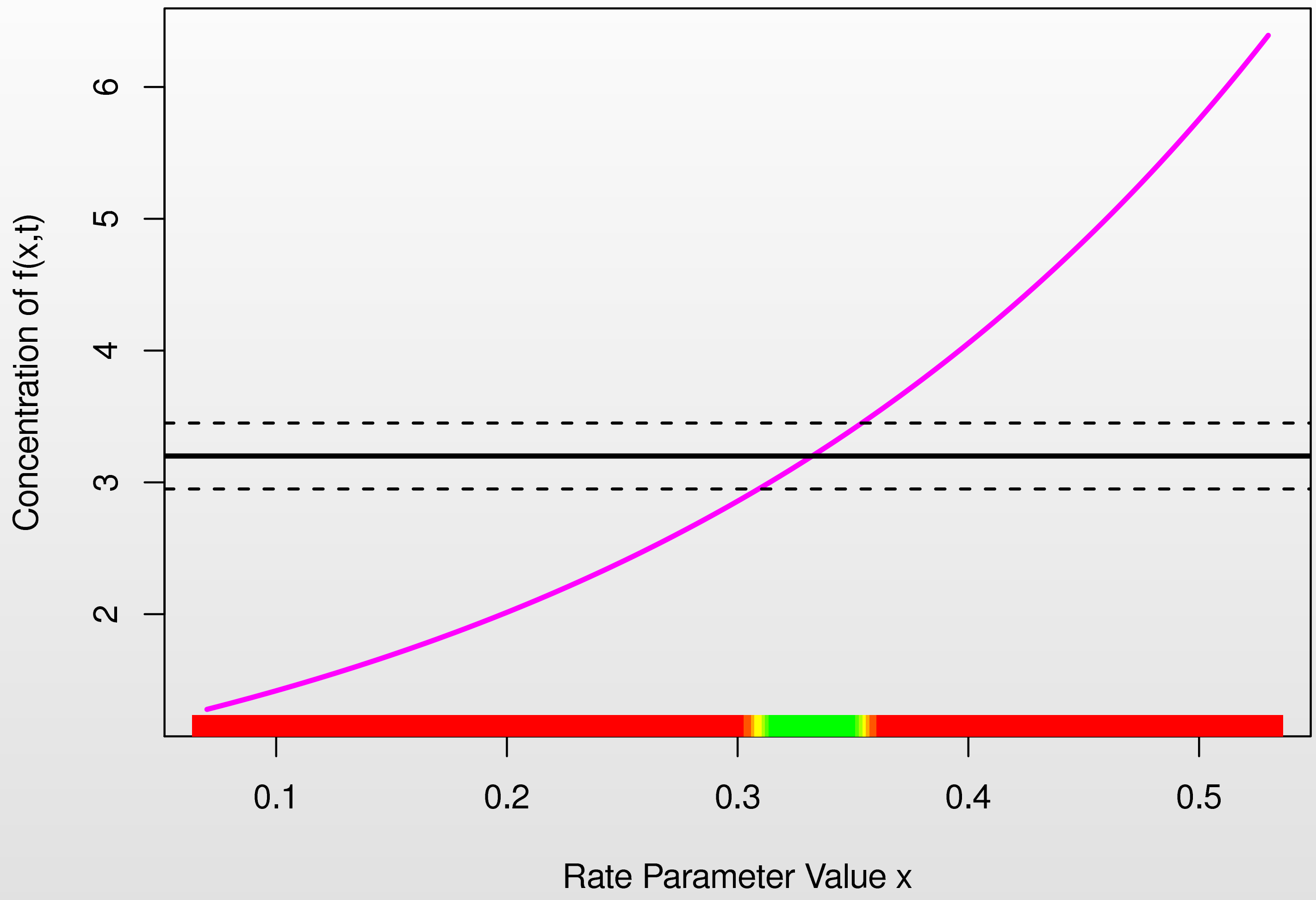

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- This uncertainty arises from many issues: is the form of model appropriate, is the model a simplified description of a more complex system etc?

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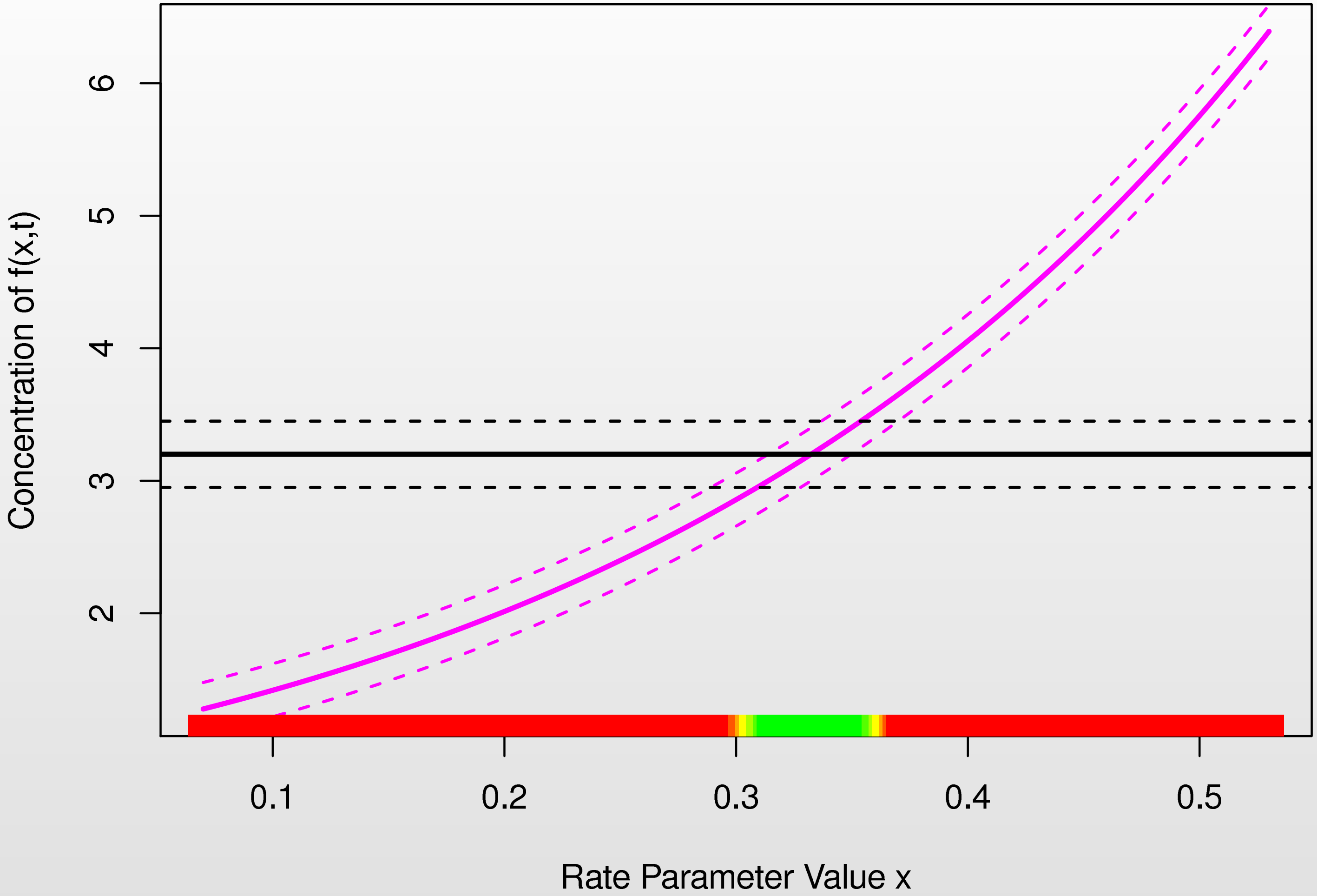

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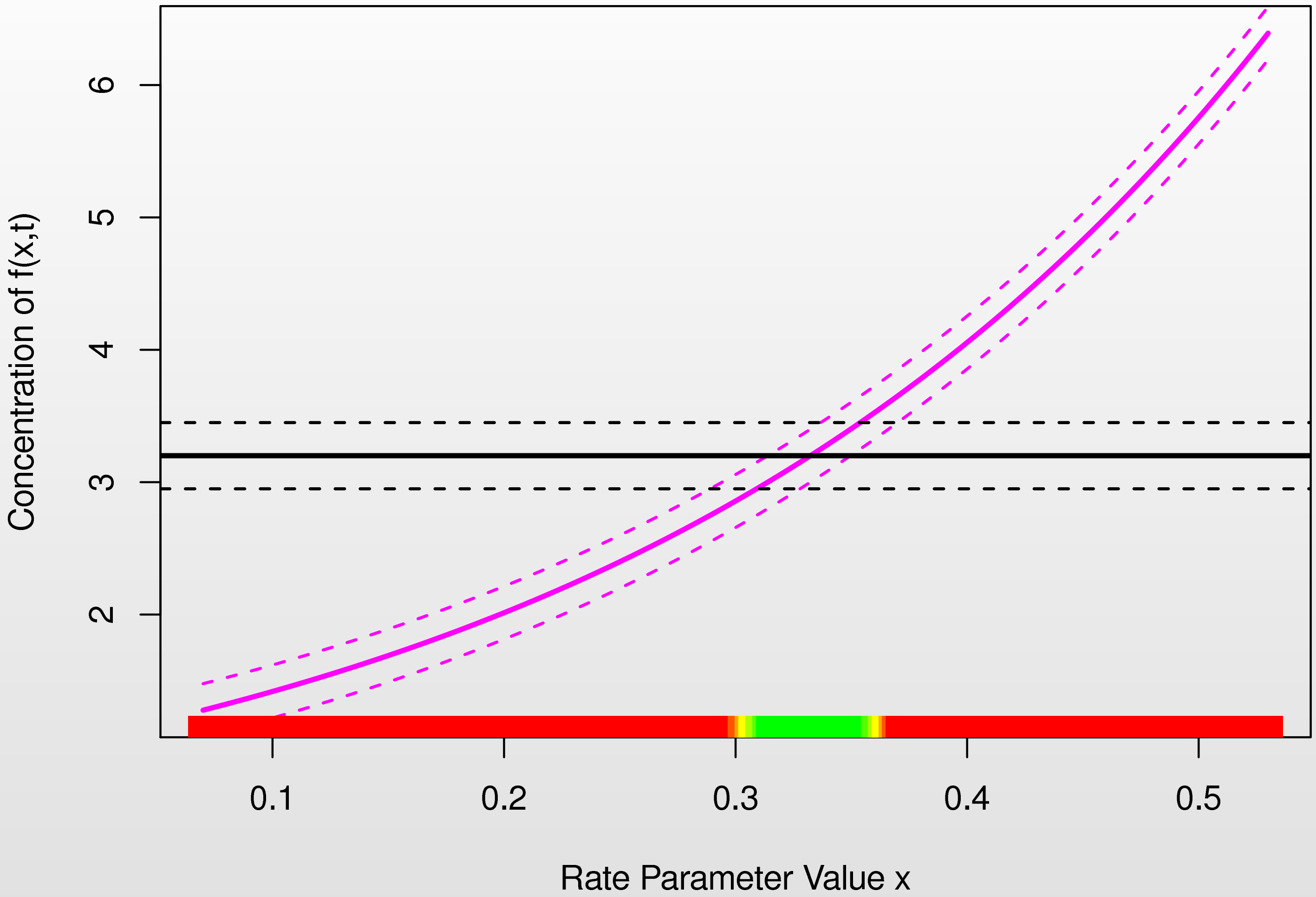

- Model discrepancy is represented as uncertainty around the model output $f(x)$ itself: here the purple dashed lines.
- This results in more uncertainty in x, and hence a larger range of x values.

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$$y = f(x^*) + d$$

where we define d to be the *model discrepancy* and assume that d is independent of f and x^*. We specify $\mathrm{E}[d]$ and $\mathrm{Var}[d]$.

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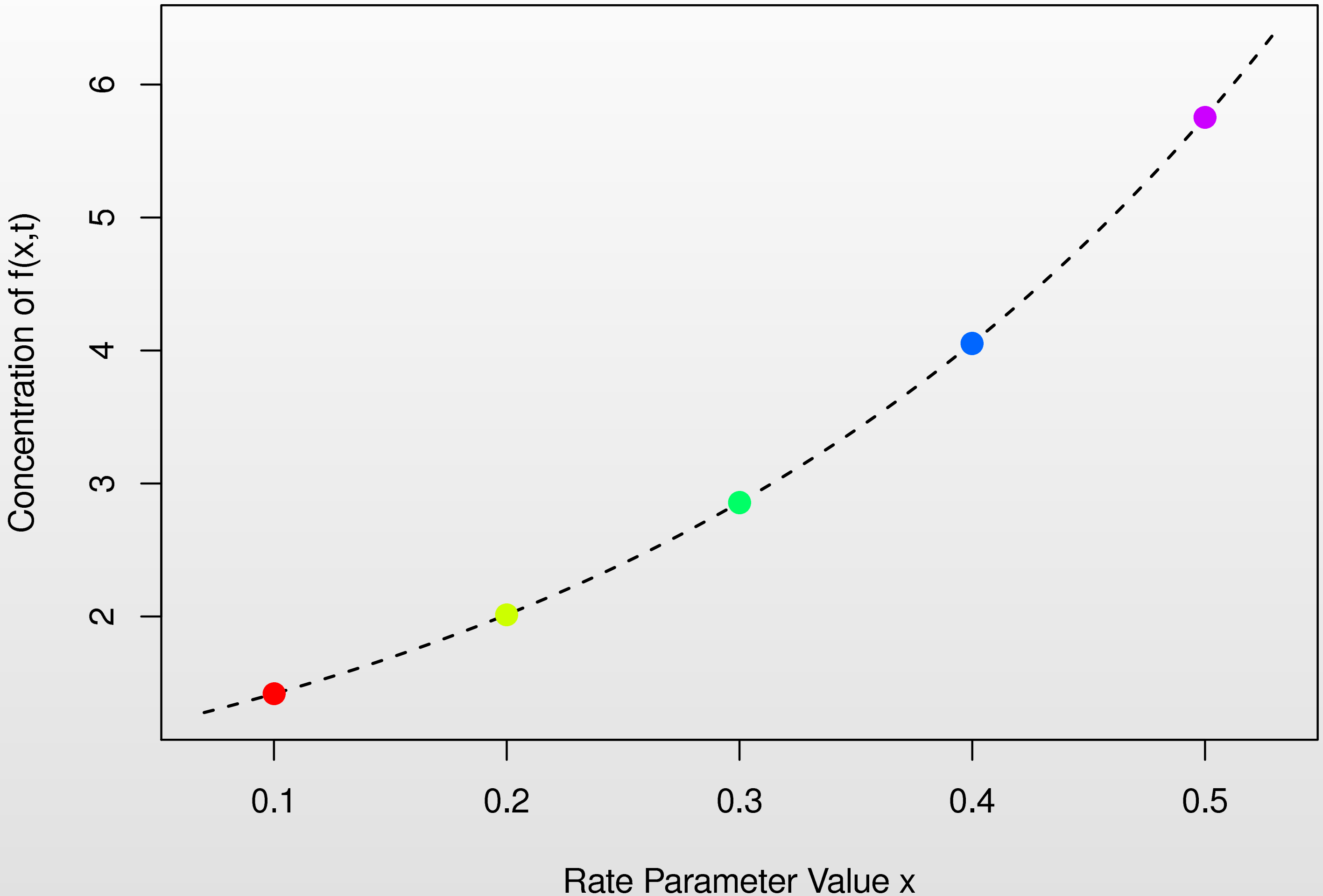
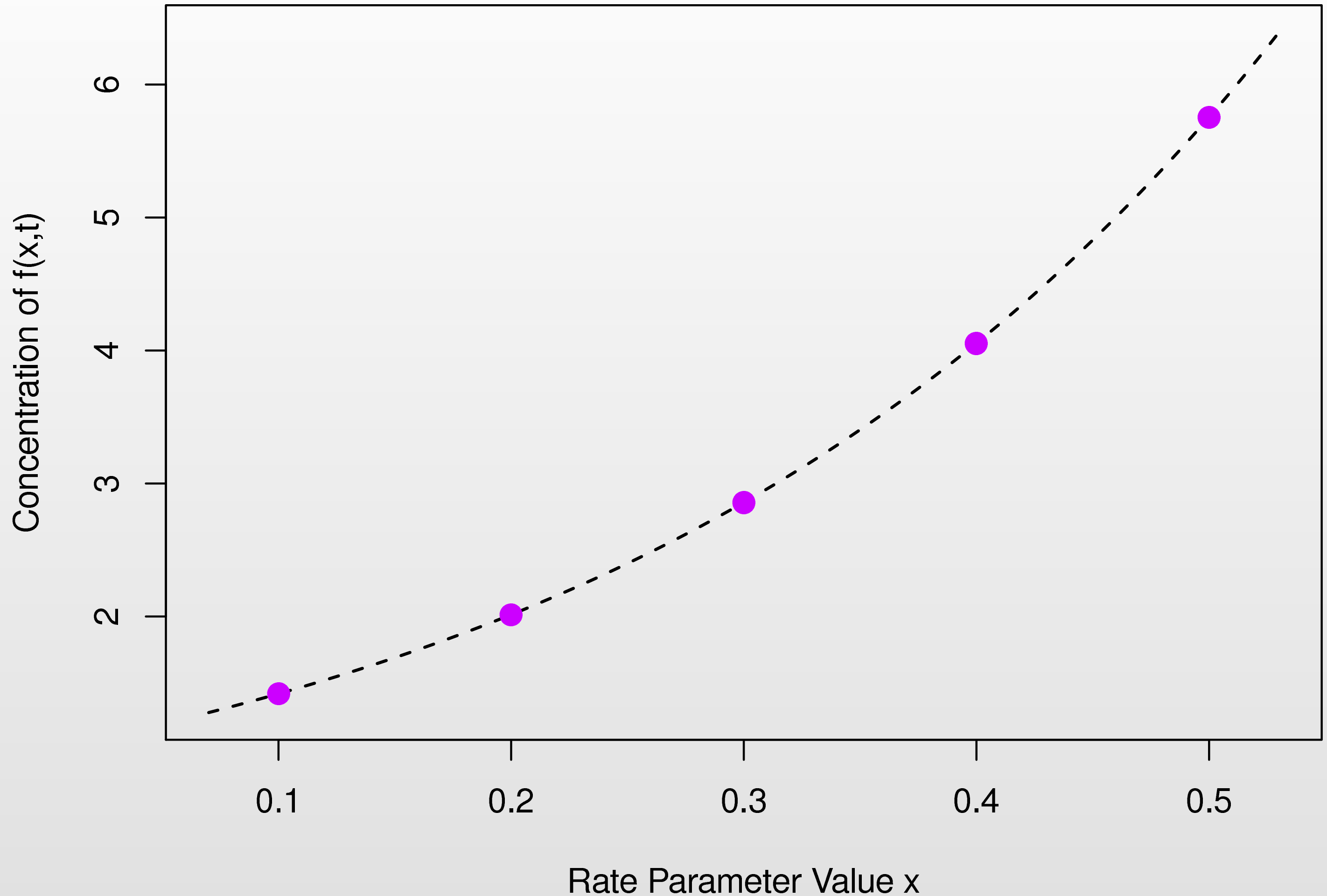
- We will use the Bayes Linear methodology, which only requires expectations, variances and covariances.

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.

Emulation: 1D example



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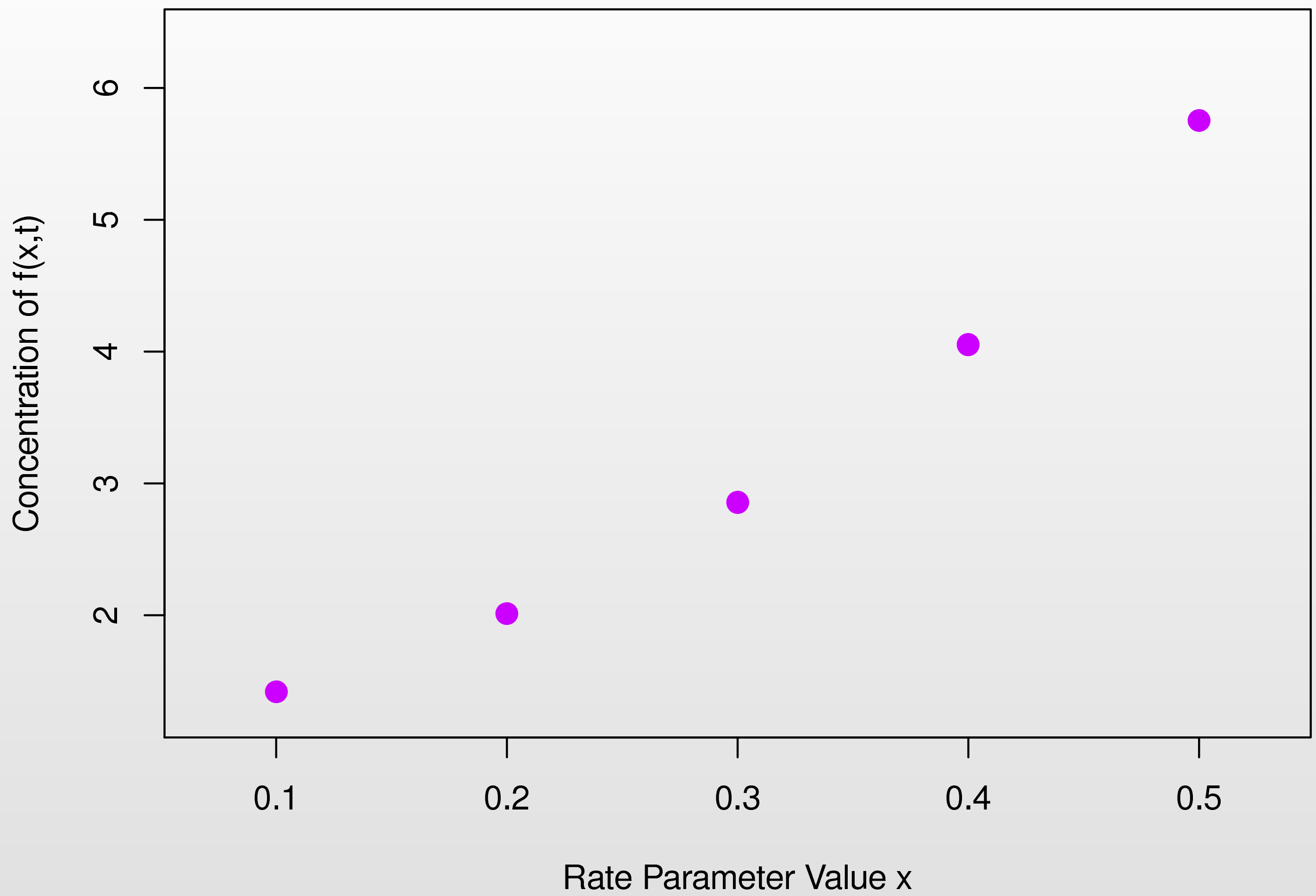
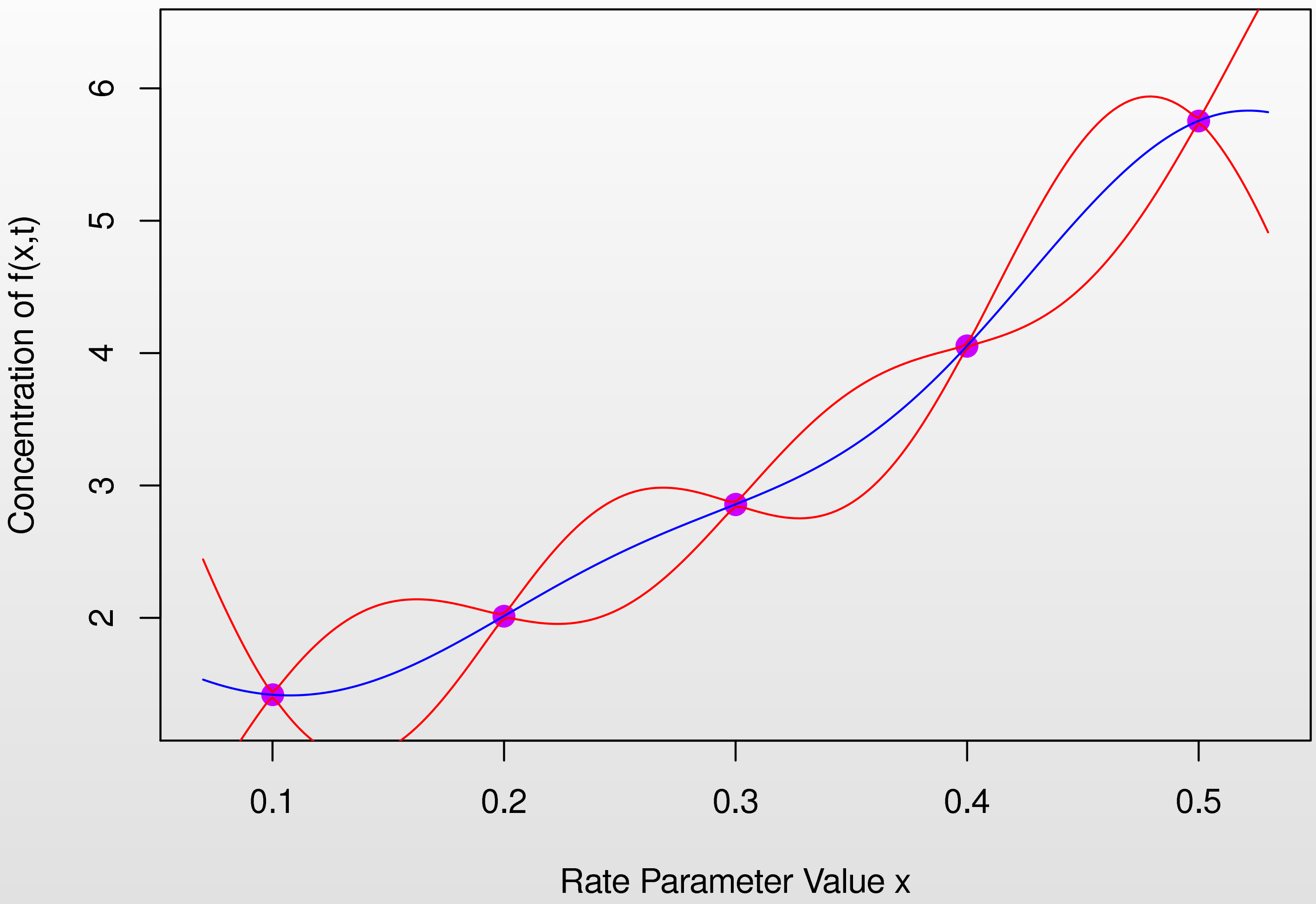


- Consider the graph of $f(x)$: in general we do not have the analytic solution of $f(x)$, here given by the dashed line.
- Instead we only have a finite number of runs of the model, in this case five.

Emulation: 1D example



- 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.

Arabidopsis: Emulation

- For each of the 16 outputs $f_i(x)$ 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 $u_i(x^A)$ have covariance structure given by:

$$\mathrm{Cov}(u_i(x_1^A), u_i(x_2^A)) \quad = \quad \sigma_i^2 \exp[-|x_1^A - x_2^A|^2/\theta_i^2]$$

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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 (details)

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

$$D_i = (f_i(x^{(1)}), f_i(x^{(2)}), \dots, f_i(x^{(n)}))^T$$

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- If we had provided prior distributions for each part of the emulator we could use Bayes Theorem to update our beliefs $\pi(f_i(x))$ about $f(x)$:

$$\pi(f_i(x)|D_i) = \frac{\pi(D_i|f_i(x))\pi(f_i(x))}{\pi(D_i)}$$

where $\pi(f_i(x))$ and $\pi(f_i(x)|D)$ are the prior and posterior pdfs for $f_i(x)$.

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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.

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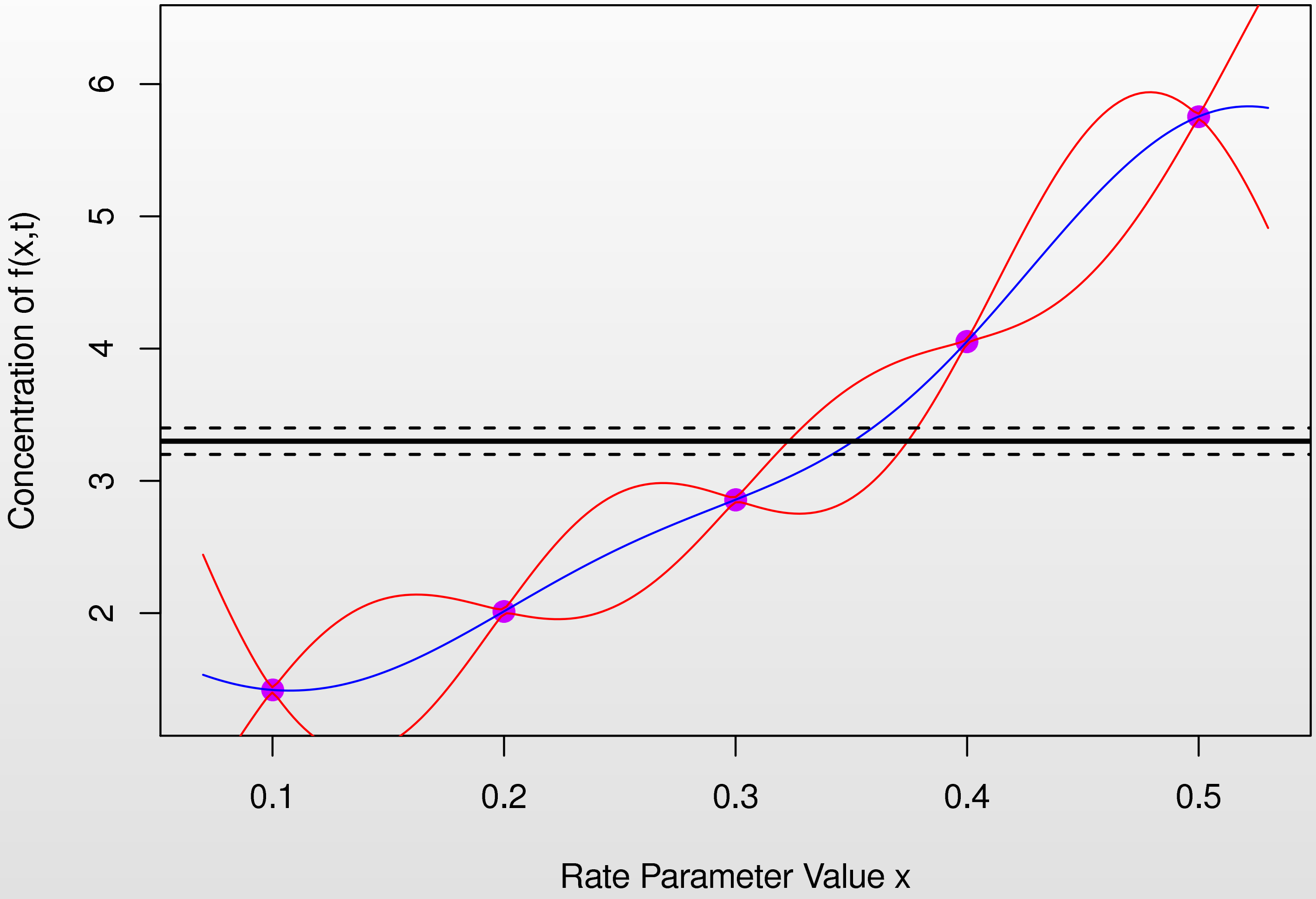
- There is a better way: if we are instead prepared to specify just the expectations, variances and covariances of the parts of the emulator, we can use Bayes Linear methodology.
- This is an alternative version of Bayesian statistics that is easier to specify and far easier to calculate with.
- Instead of Bayes Theorem we use the Bayes linear update:

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

where $\mathrm{E}_{D_i}(f_i(x))$ and $\mathrm{Var}_{D_i}(f_i(x))$ are the Bayes Linear adjusted expectation and variance for $f_i(x)$ at new input point x, and are all that are needed for the subsequent implausibility measures and history match.

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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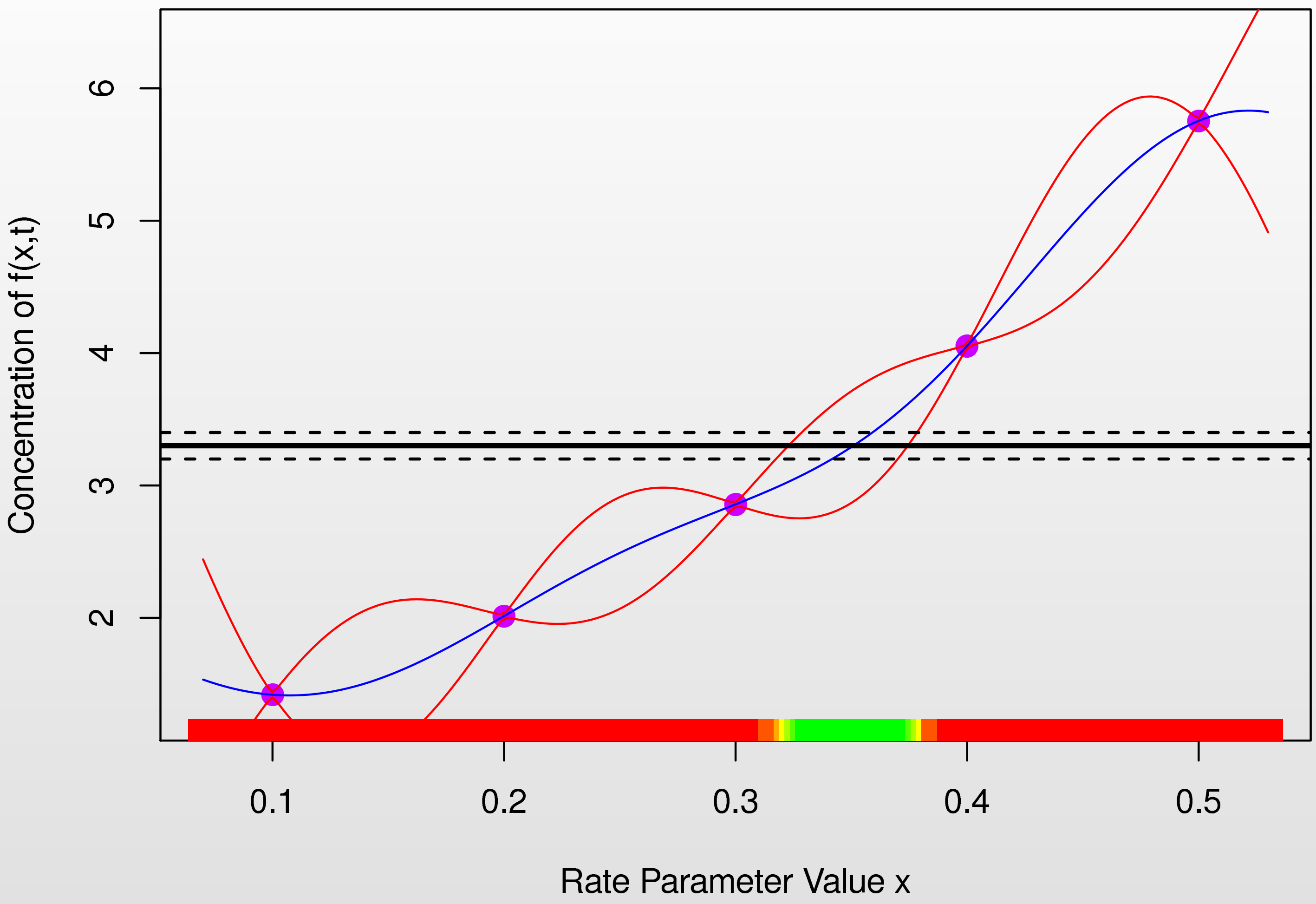

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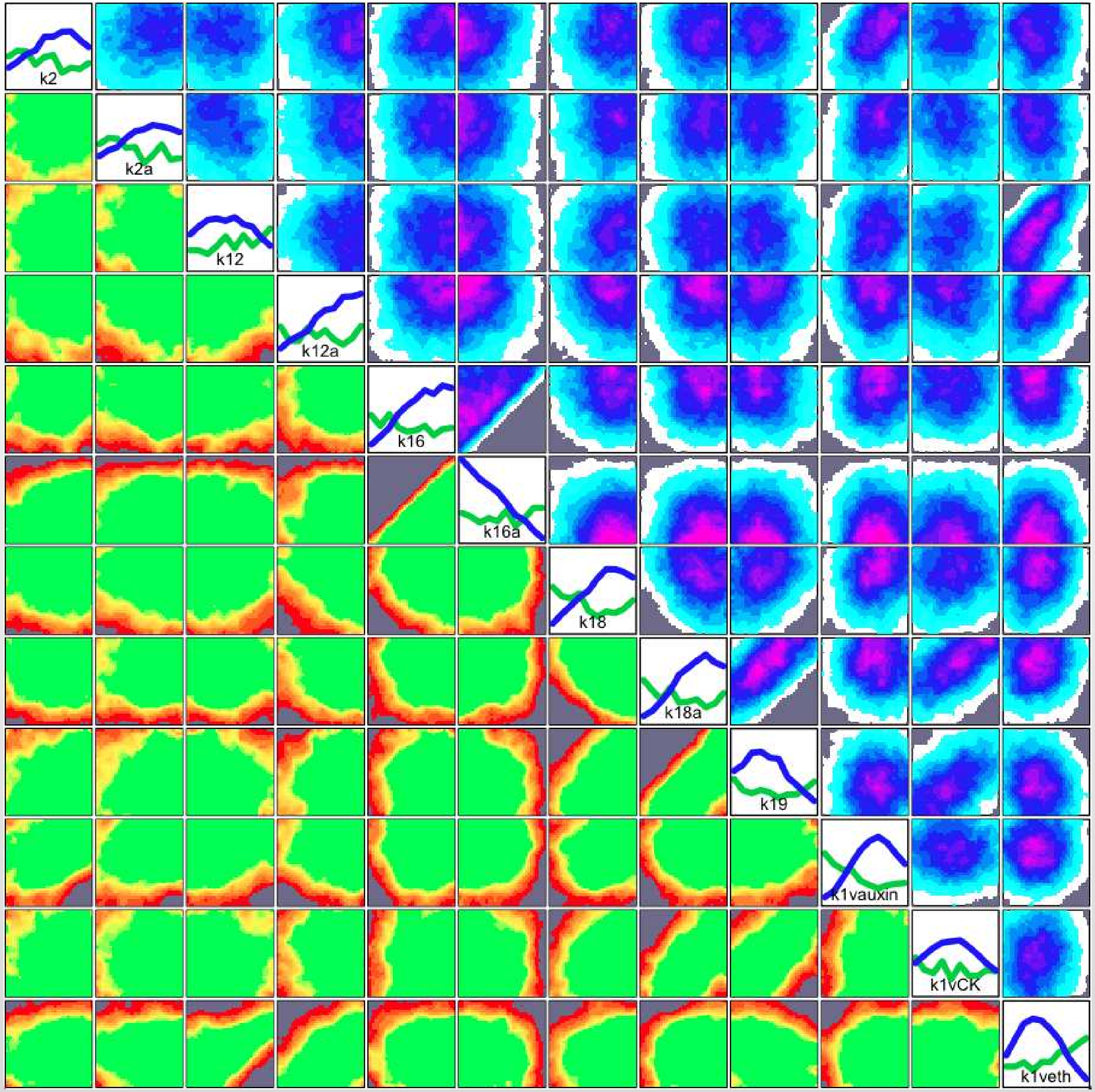

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We can now calculate the **Implausibility** $I_{(i)}(x)$ at any input parameter point x for each of the $i = 1, .., 16$ outputs. This is given by:

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

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- We can then impose a cutoff $I_{(i)}(x) < c_M = 3$ to discard regions of input parameter space that we now deem to be implausible (Pukelsheim).

Multivariate Implausibility Measure (details)

- If we have constructed a multivariate model discrepancy, we can define a multivariate Implausibility measure, using only the outputs in Q_i:

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

  which becomes:

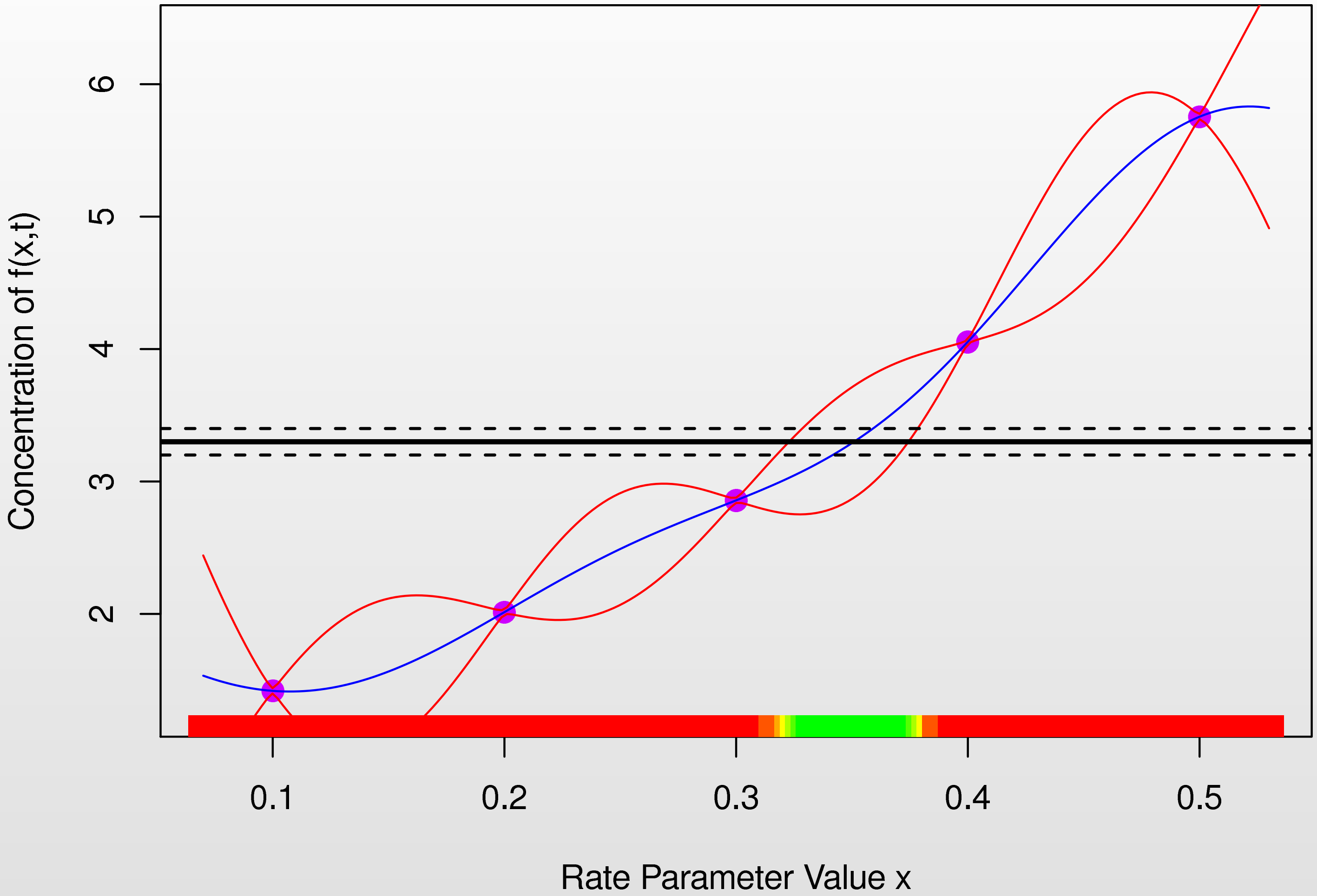
$$I^2(x) = (\mathrm{E}_D[f(x)] - z)^T (\mathrm{Var}_D[f(x)] + \mathrm{Var}[d] + \mathrm{Var}[e])^{-1} (\mathrm{E}_D[f(x)] - z)$$

- where $\mathrm{Var}_D[f(x)]$, $\mathrm{Var}[d]$ and $\mathrm{Var}[e]$ are now the multivariate emulator variance, multivariate model discrepancy and multivariate observational errors respectively (all matrices).

- We now have two implausibility measures $I_{(i)}(x)$ 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



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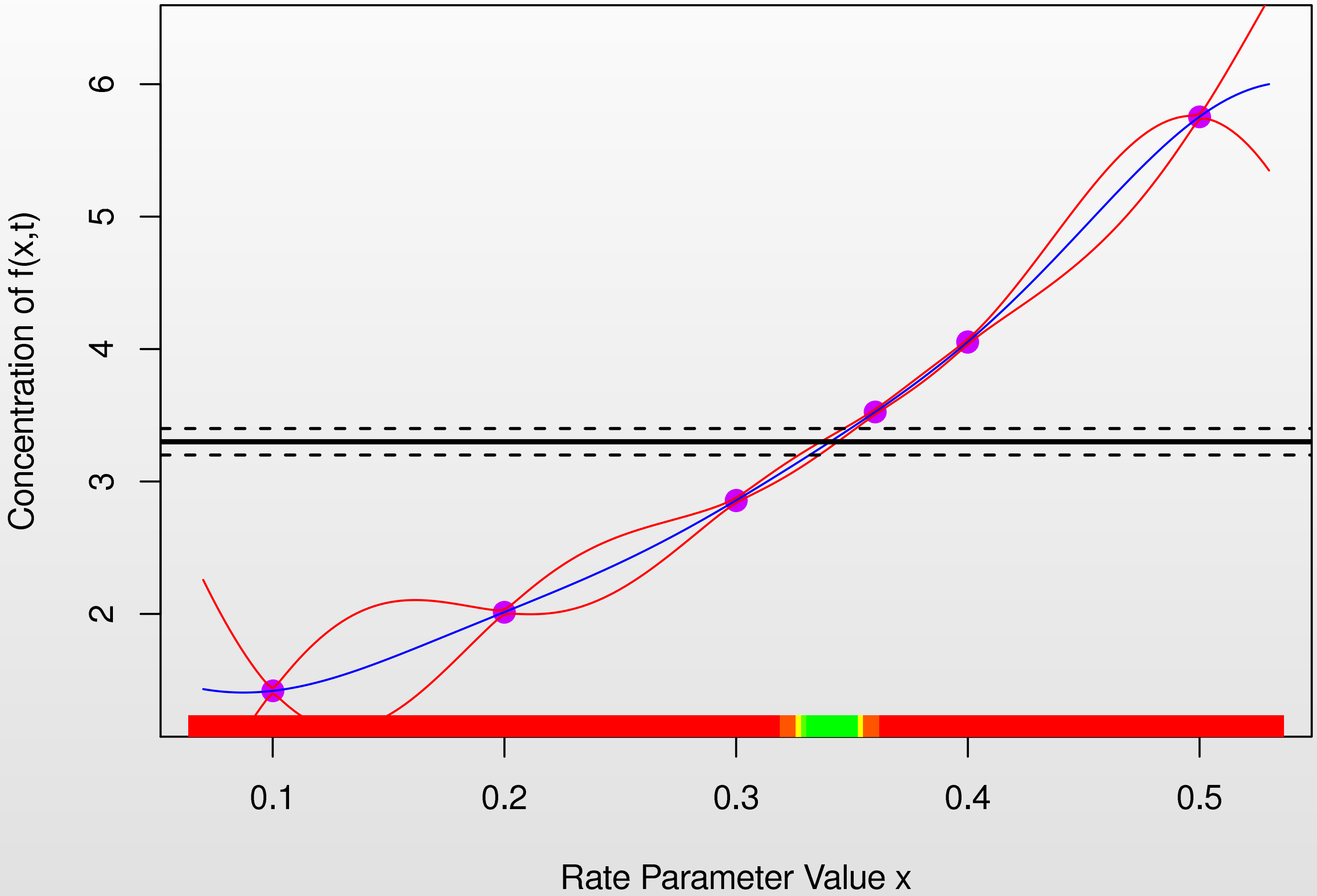

- We perform a 2nd iteration or wave of runs to improve emulator accuracy.

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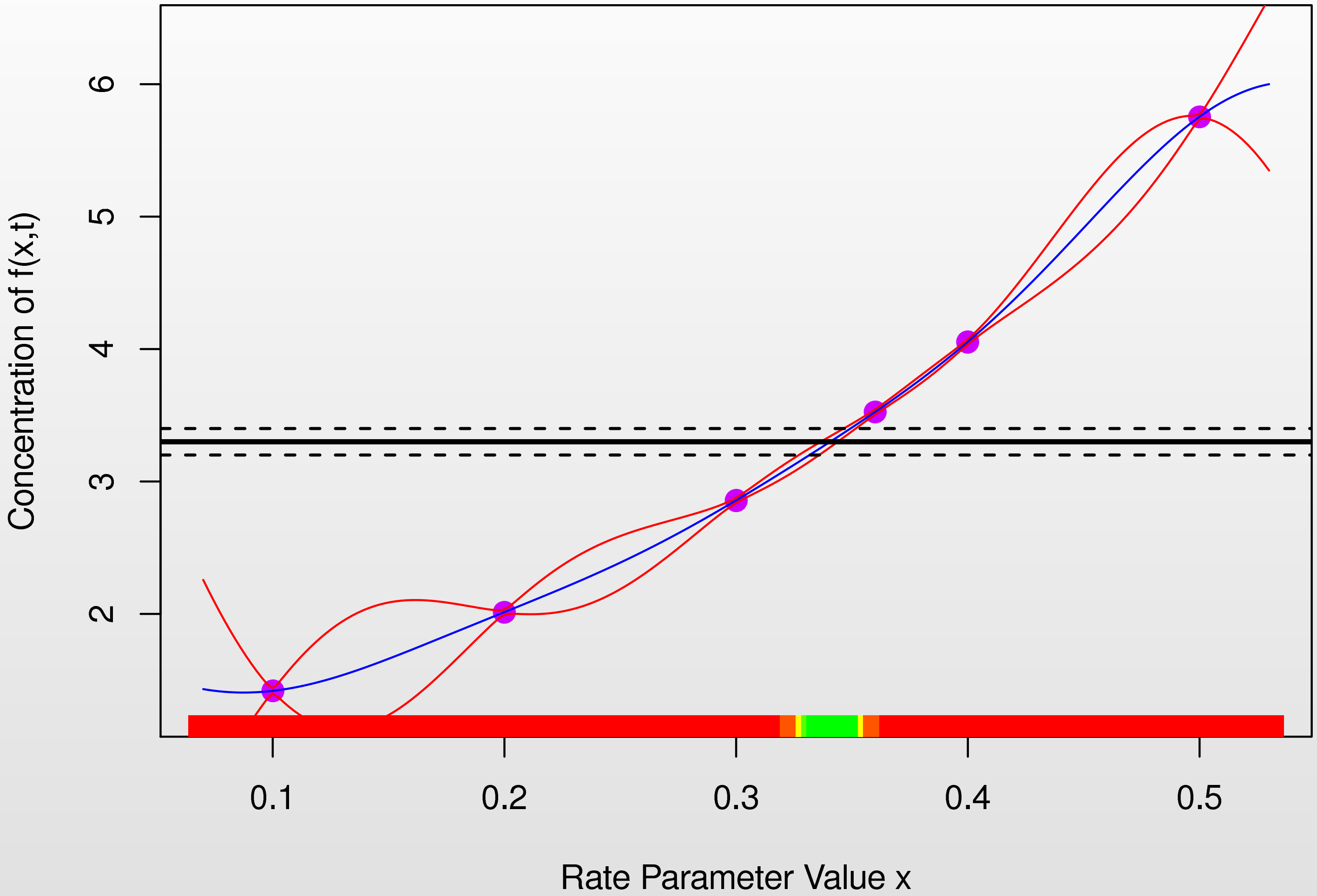

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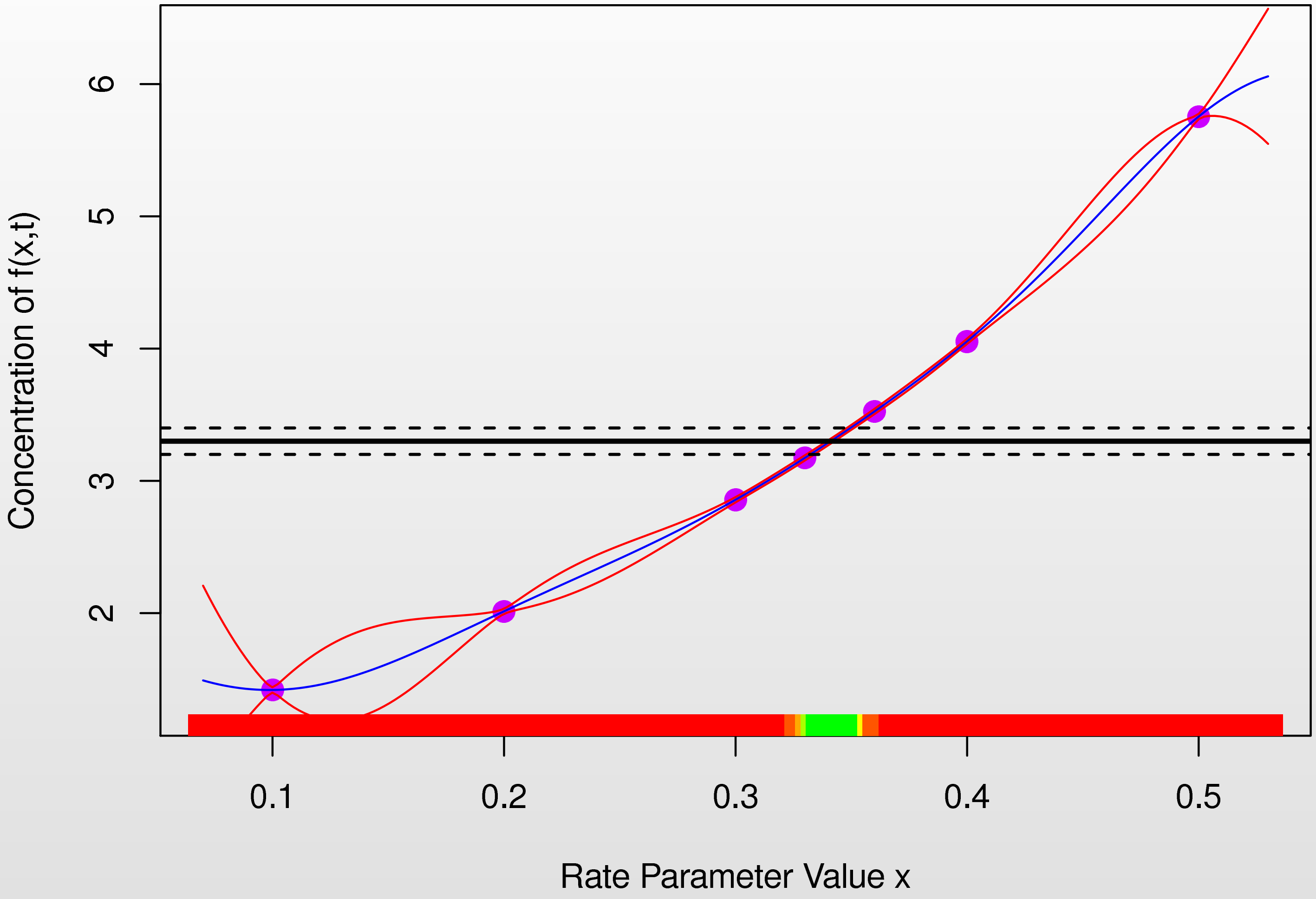
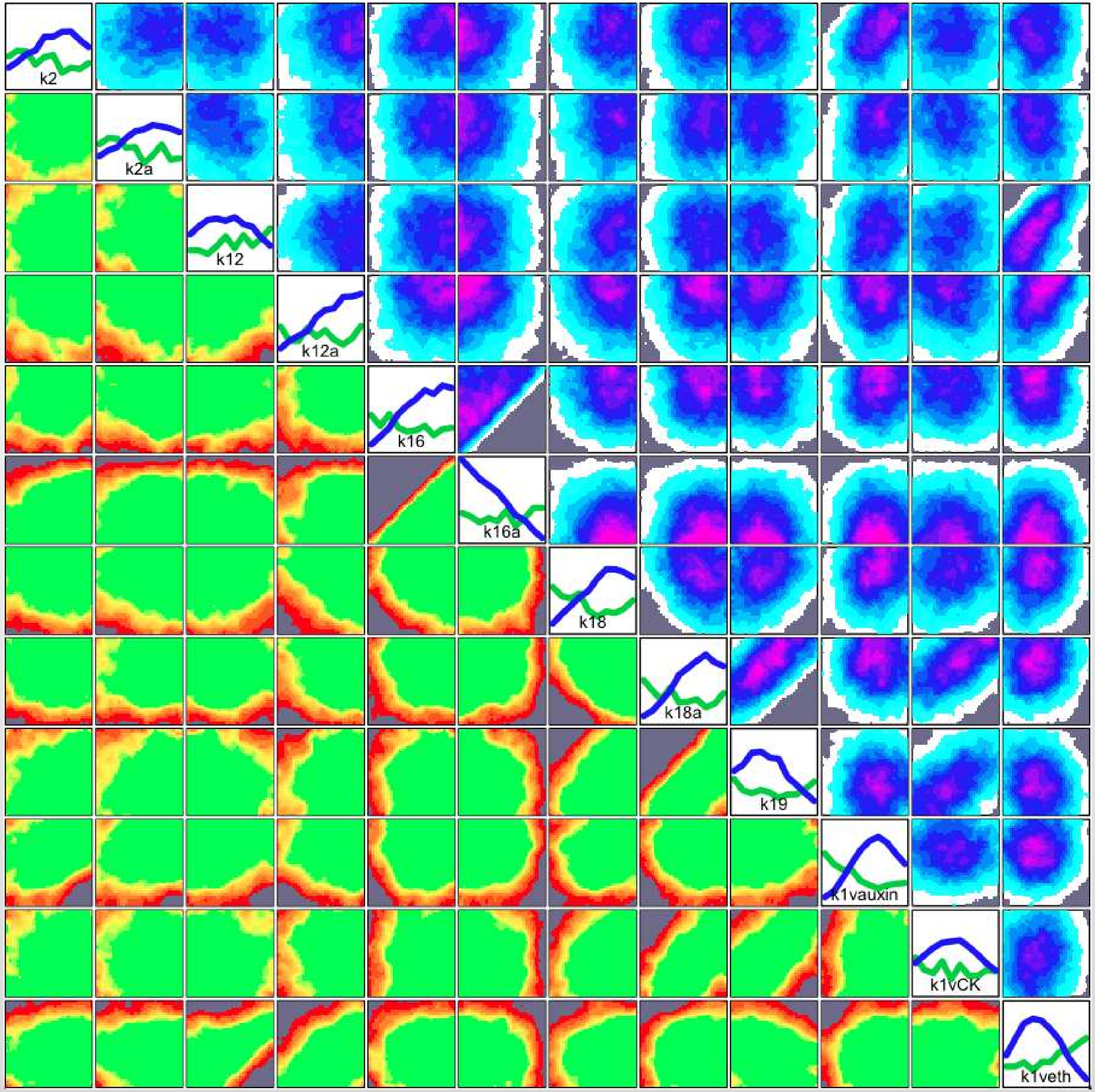
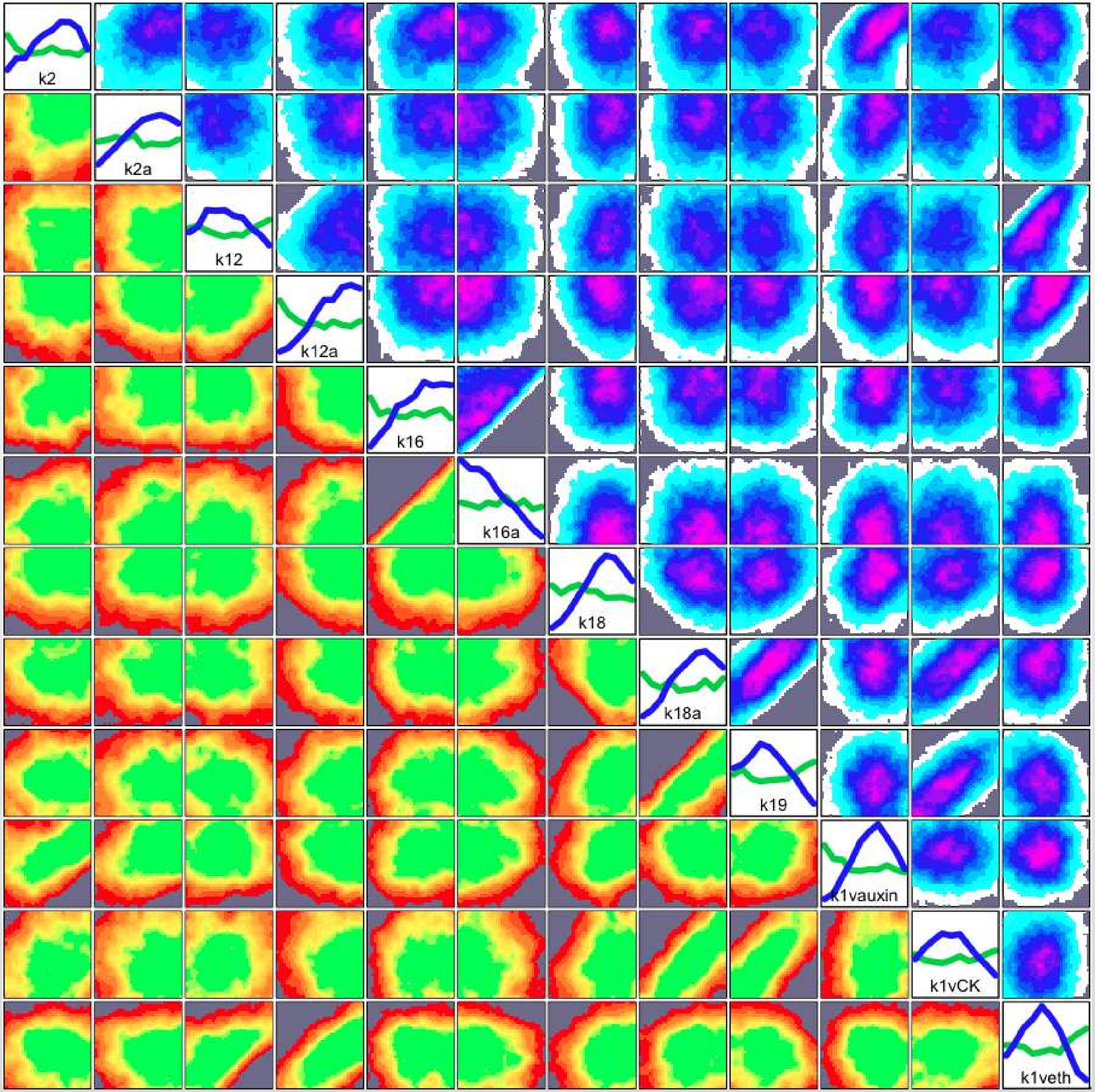


- We perform a 2nd iteration or wave of runs to improve emulator accuracy.
- The runs are located only at non-implausible (green/yellow) points.
- Now the emulator is more accurate than the observations, and we can identify the set of all x values of interest.

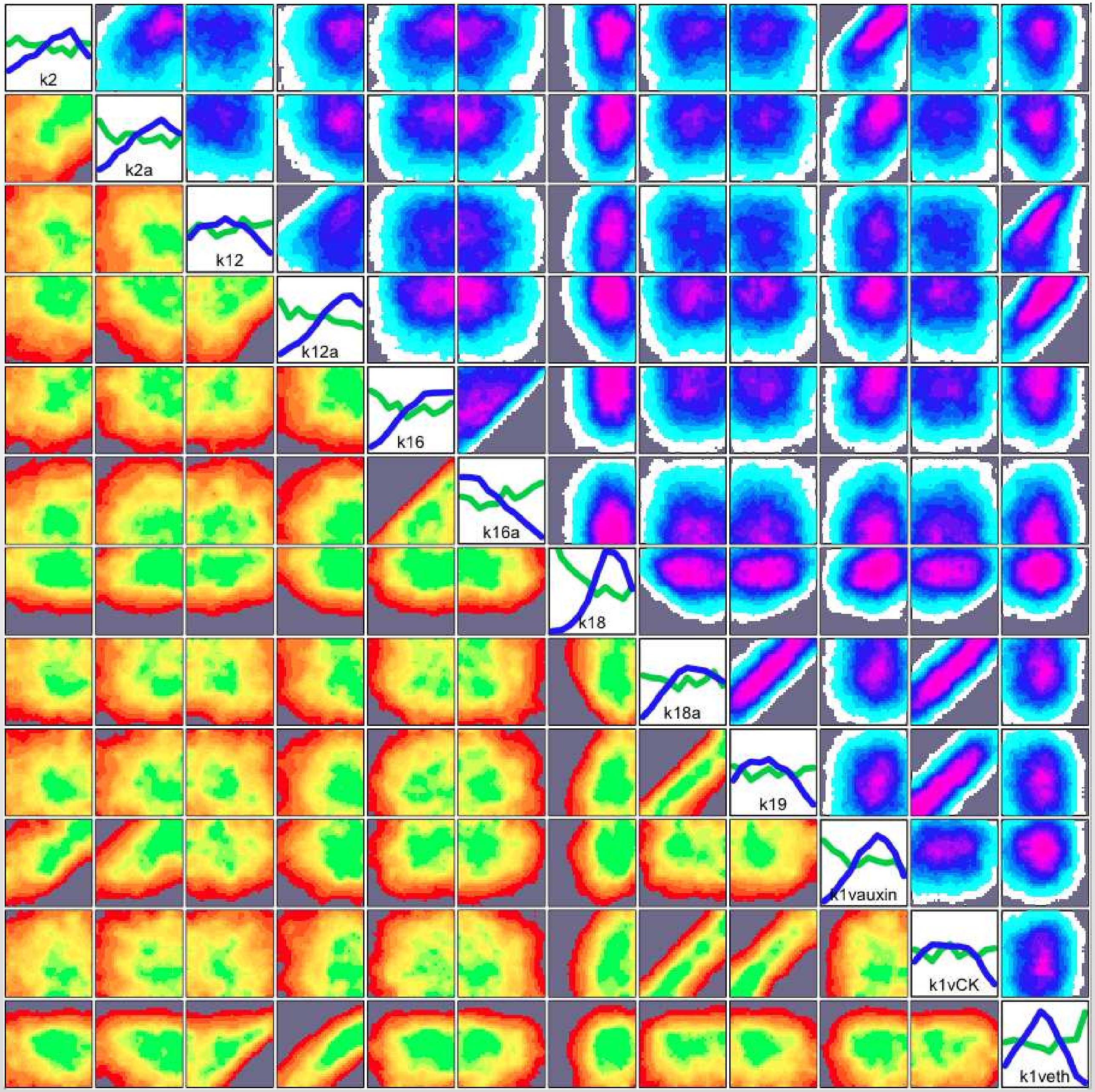
Iterative Input Space Reduction: Arabidopsis Model Wave 1



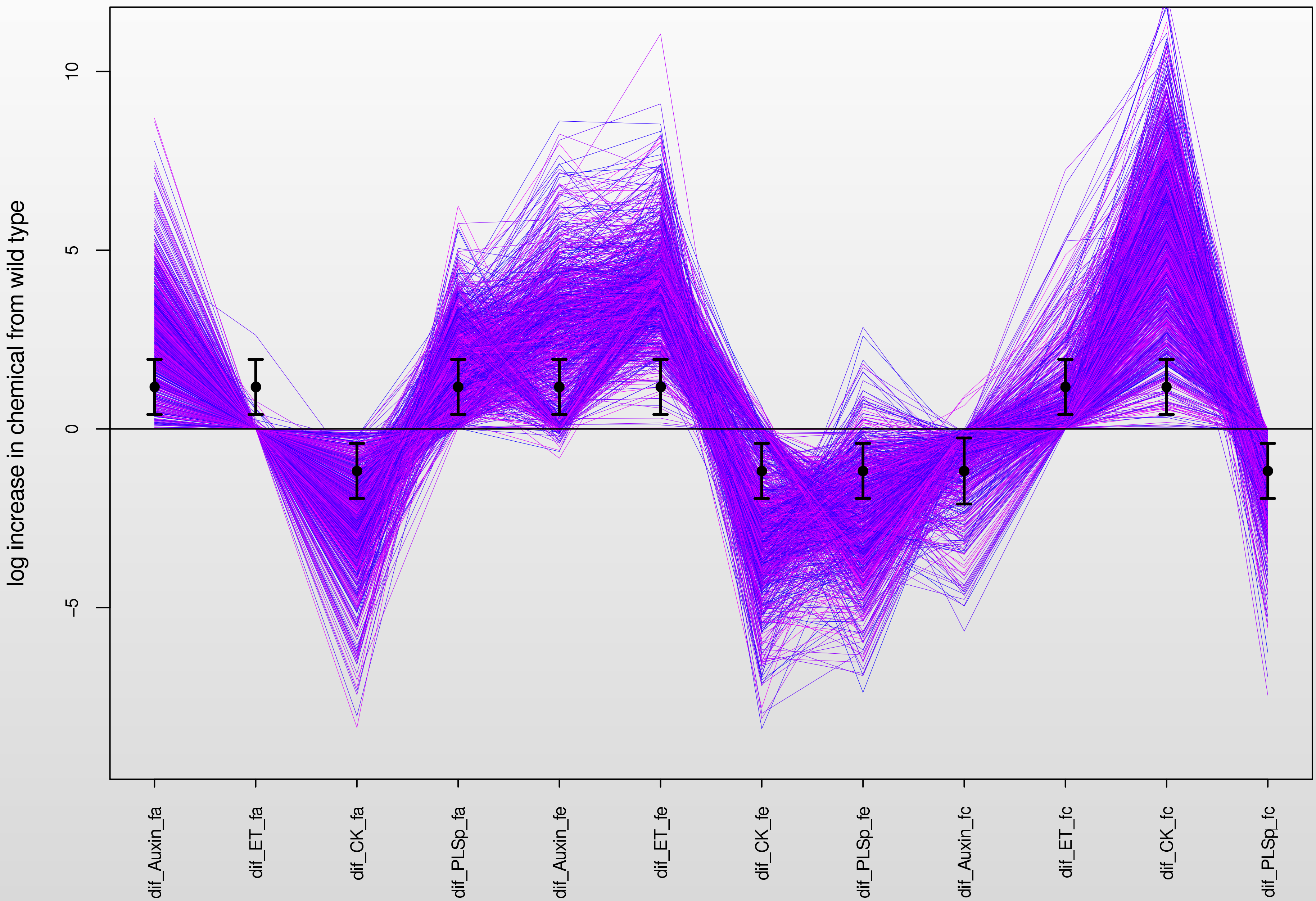
Iterative Input Space Reduction: Arabidopsis Model Wave 2



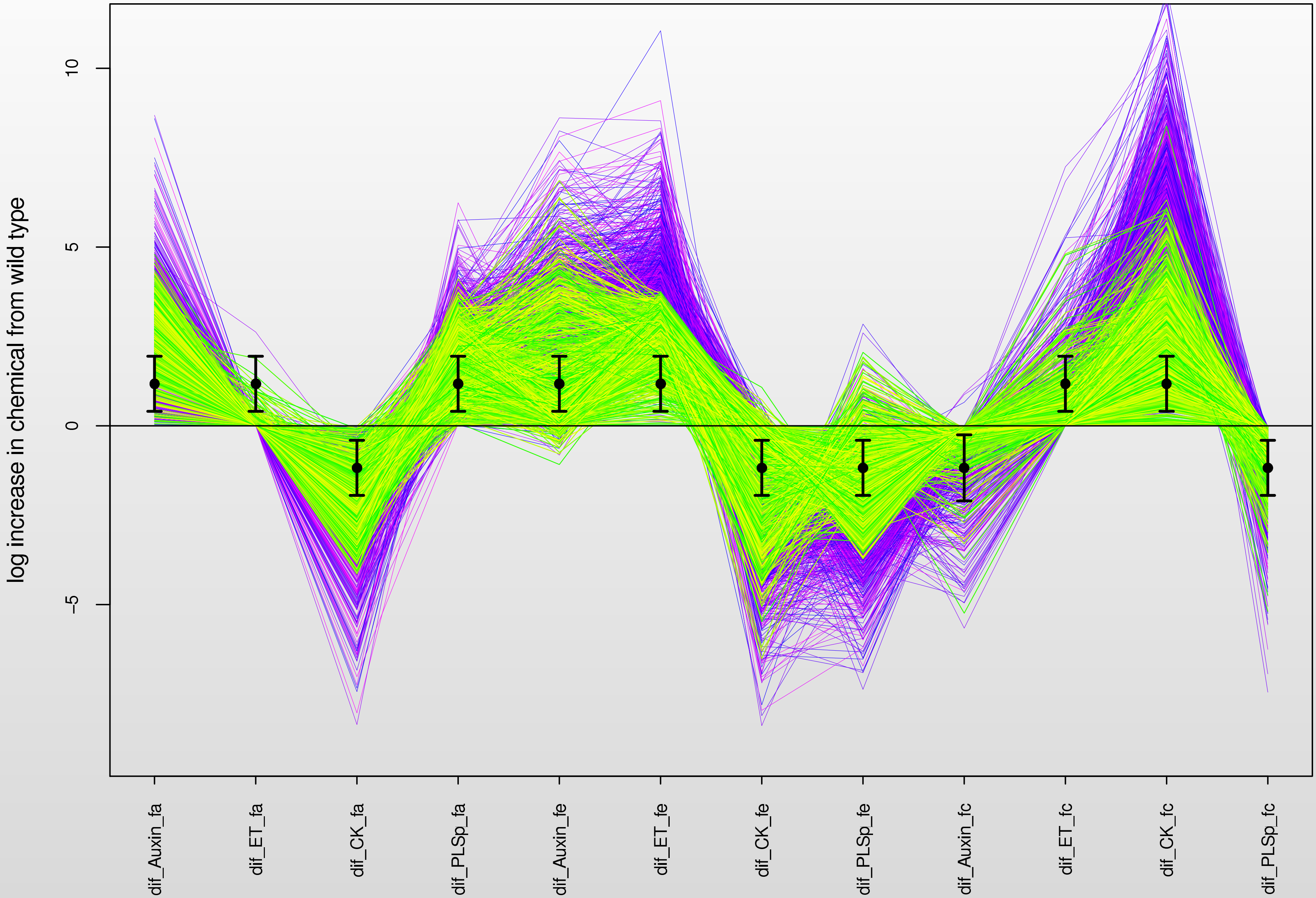
Iterative Input Space Reduction: Arabidopsis Model Wave 3



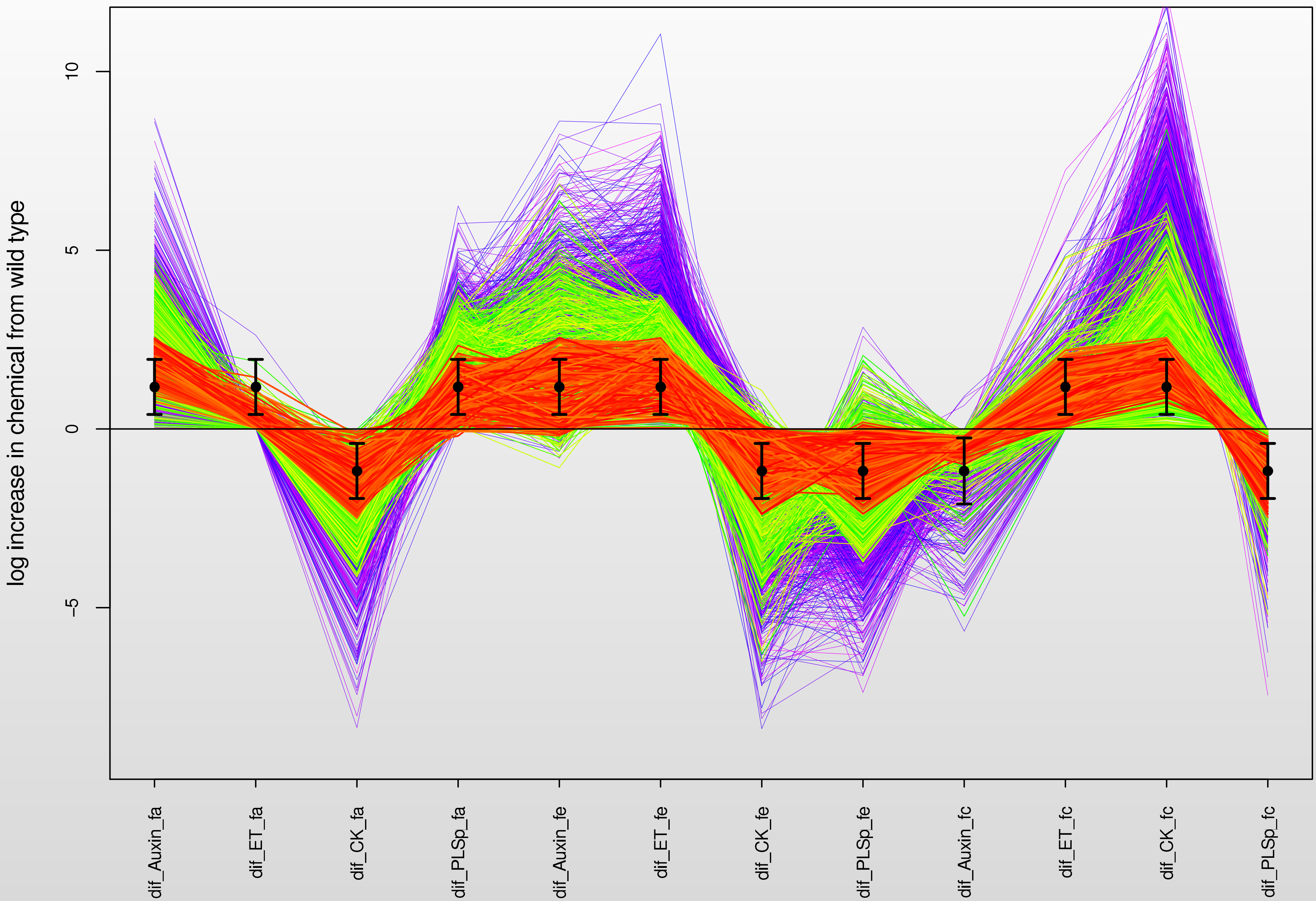
Iterative Strategy for Arabidopsis Model: Wave 1



Iterative Strategy for Arabidopsis Model: Waves 1 and 2



Iterative Strategy for Arabidopsis Model: Wave 1, 2 and 3



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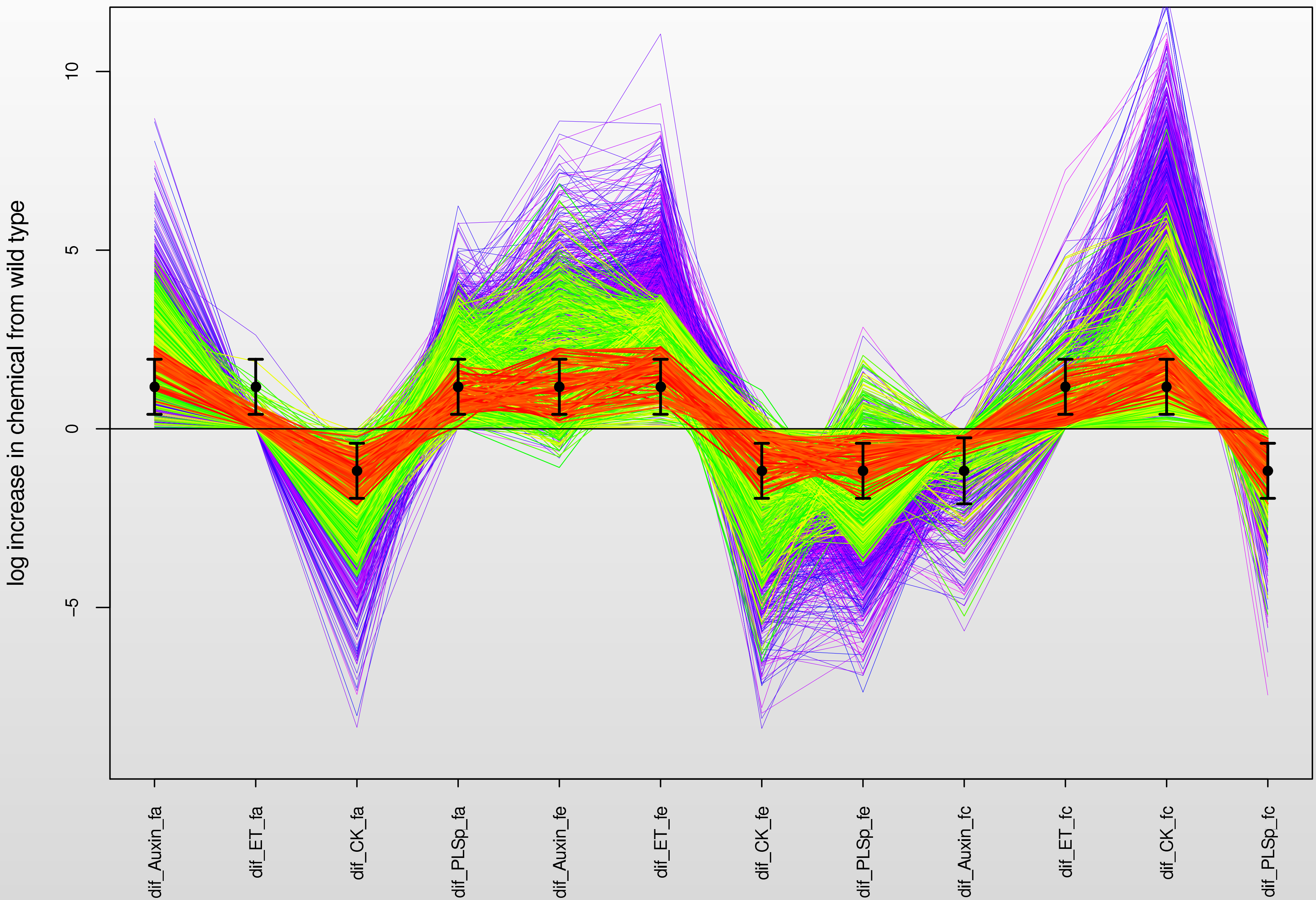


Iterative History Matching for Reducing Input Space. (details)

We use an iterative strategy to reduce the input parameter space. Denoting the current non-implausible volume by $\mathcal{X}_j$, at each stage or wave we:

1. Design and perform a set of runs over the non-implausible input region $\mathcal{X}_j$
2. Identify the set Q_{j+1} of informative outputs that we can emulate easily
3. Construct new emulators for $f_i(x)$, where $i \in Q_{j+1}$ defined only over $\mathcal{X}_j$
4. Evaluate the new implausibility functions $I_i(x), i \in Q_{j+1}$ only over $\mathcal{X}_j$
5. Define a new (reduced) non-implausible region $\mathcal{X}_{j+1}$, by $I_M(x) < c_M$, which should satisfy $\mathcal{X} \subset \mathcal{X}_{j+1} \subset \mathcal{X}_j$
6. Unless (a) the emulator variances are now small in comparison to the other sources of uncertainty (model discrepancy and observation errors) or (b) computational resources are exhausted or (c) all the input space is deemed implausible, return to step 1
7. If 6(a) true, generate a large number of acceptable runs from the final non-implausible volume $\mathcal{X}$

Why Does Iterative Refocussing Work? (details)

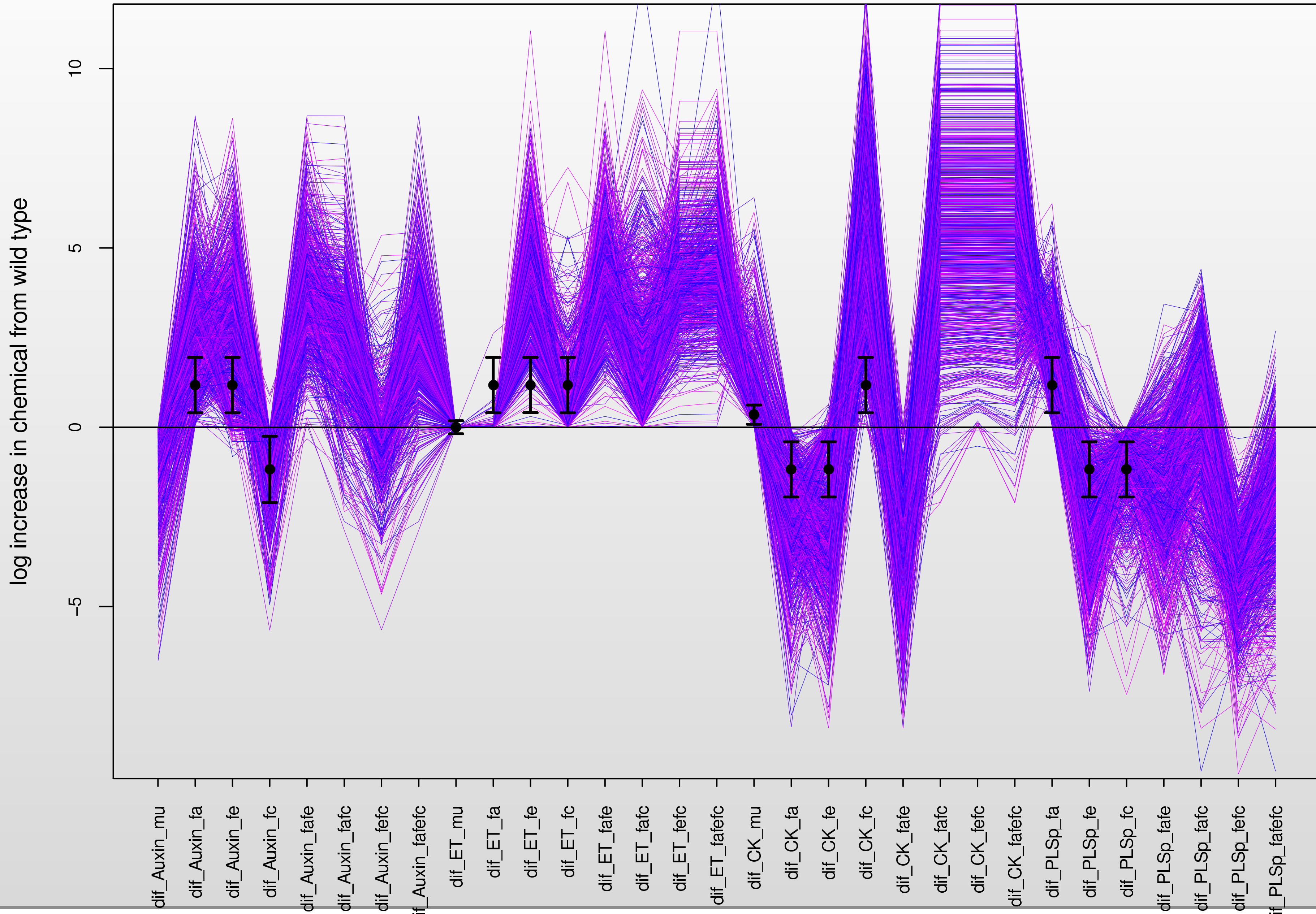
Why do we reduce space in waves? Why not attempt to do it all at once? Because this requires an accurate emulator valid over whole input space.

- In contrast, the iterative approach is far more efficient.
- At each wave the emulators are found to be significantly more accurate (in that $\mathrm{Var}[f(x)]$ becomes smaller). This is expected as:

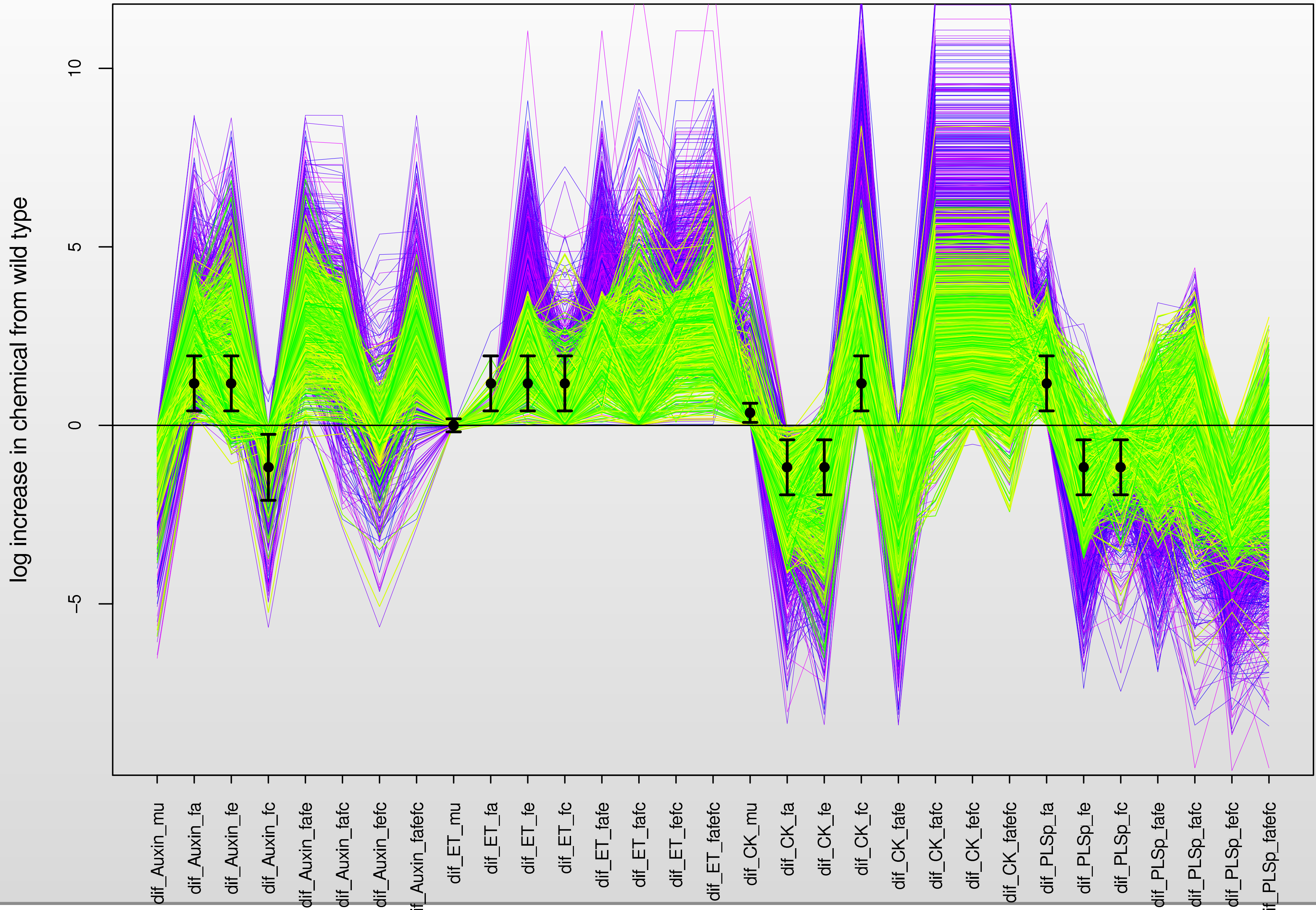
  1. We have ‘zoomed in’ on a smaller part of the function, it will be smoother and most likely easier to fit with low order polynomials.
  2. We have a much higher density of runs in the new volume, and hence the Gaussian process part of the emulator will do more work.
  3. We can identify more active variables, leading to more detailed polynomial and Gaussian process parts of the emulator, as previously dominant variables are now somewhat suppressed.
  4. We can hence add more outputs to the set of informative and easy to emulate outputs Q_k.

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

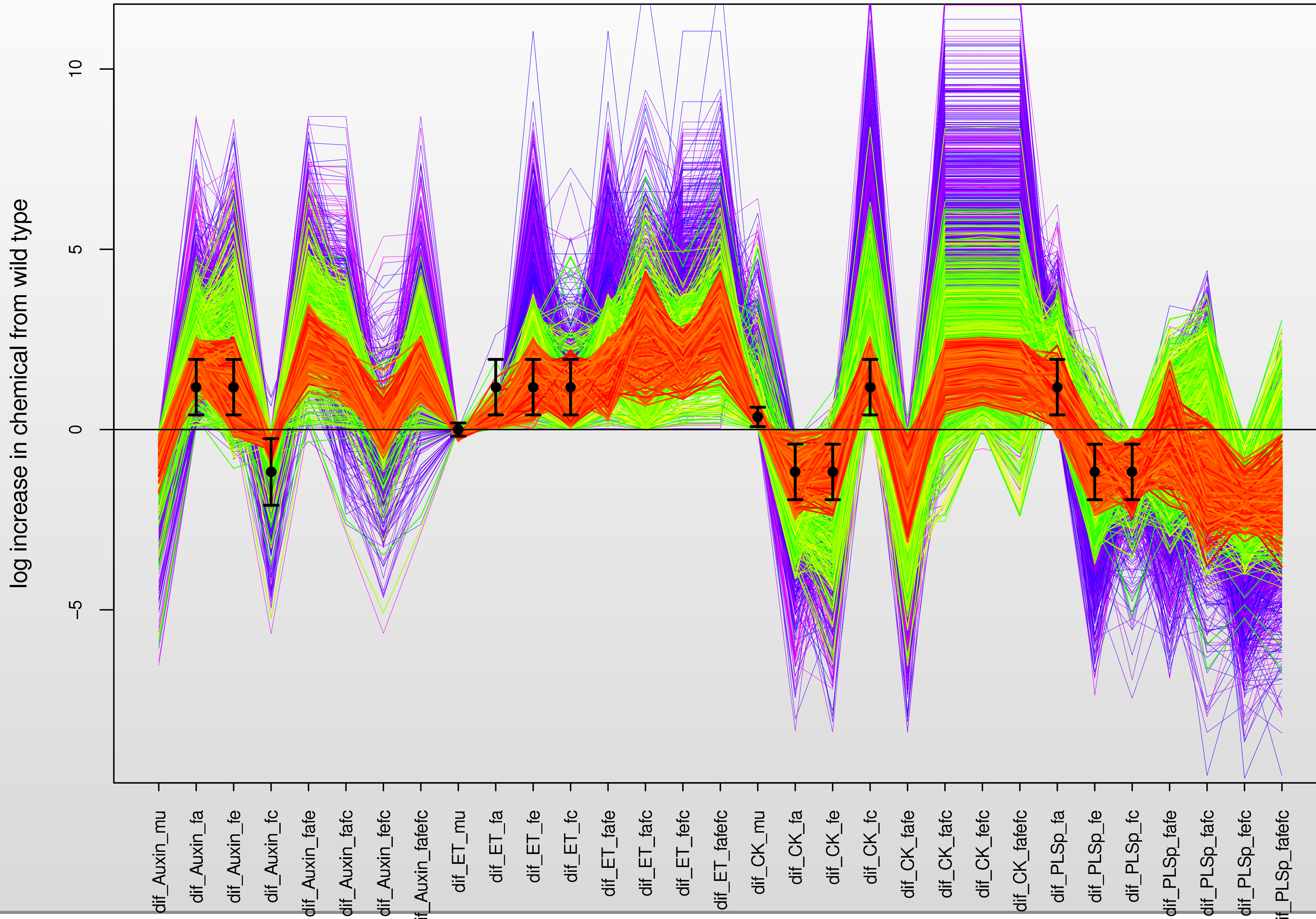
Iterative Strategy for Arabidopsis Model: Wave 1



Iterative Strategy for Arabidopsis Model: Waves 1 and 2



Iterative Strategy for Arabidopsis Model: Waves 1, 2 and 3



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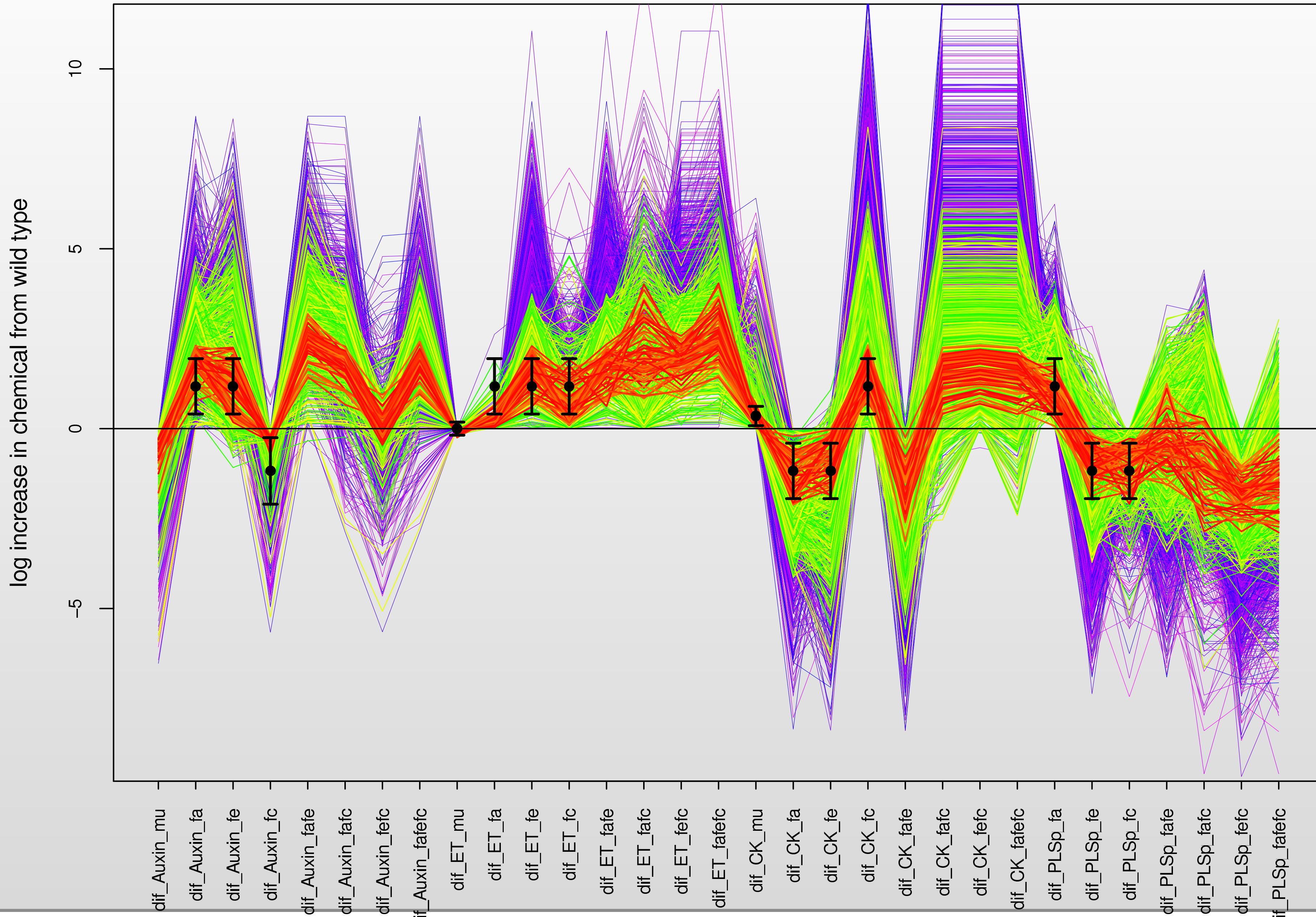

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- We will select 4 experiments from 80 based on an expected space reduction criteria, using implausibility measures.

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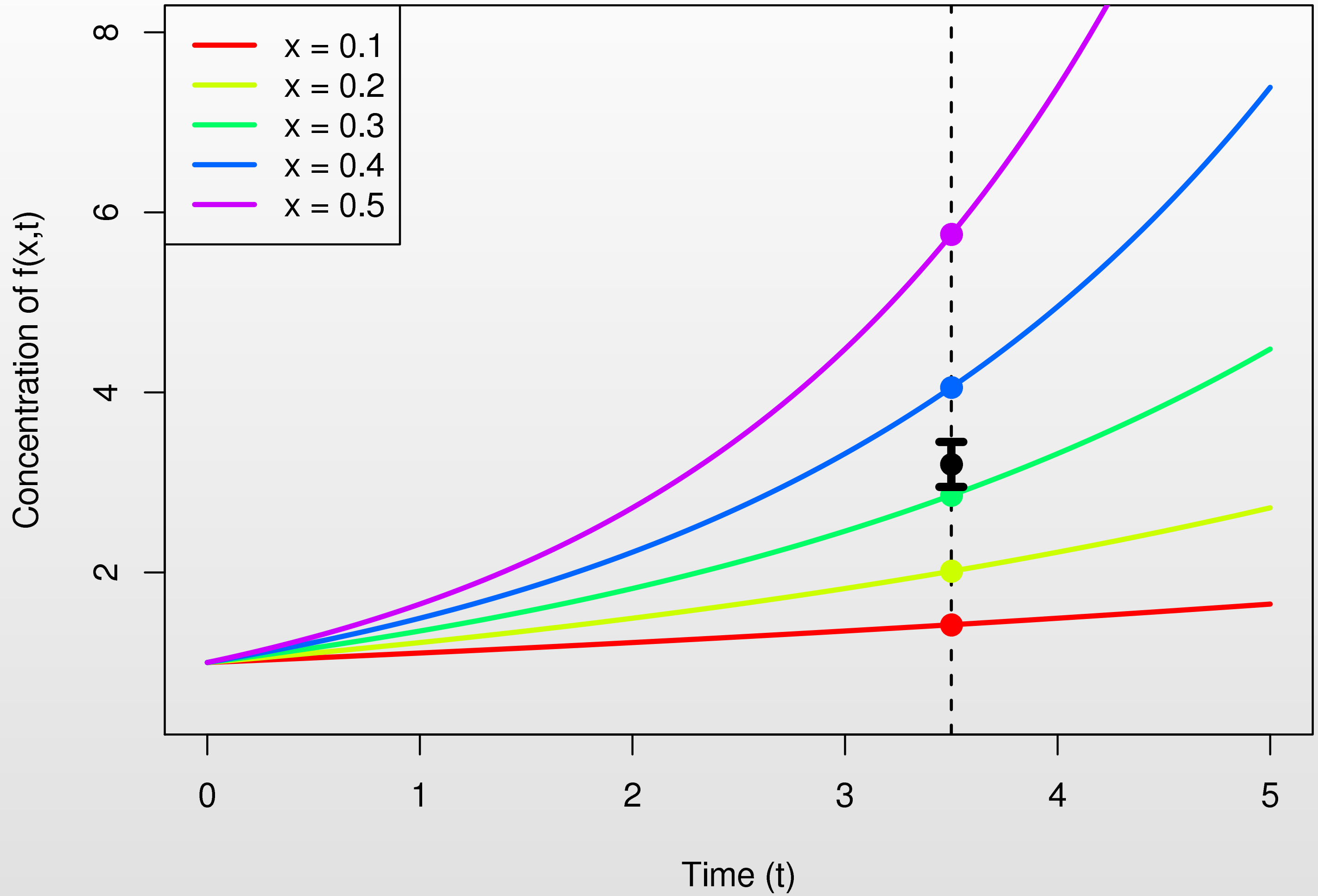
- We hence expect to learn most efficiently about the rate parameters x from this design of 4 experiments.

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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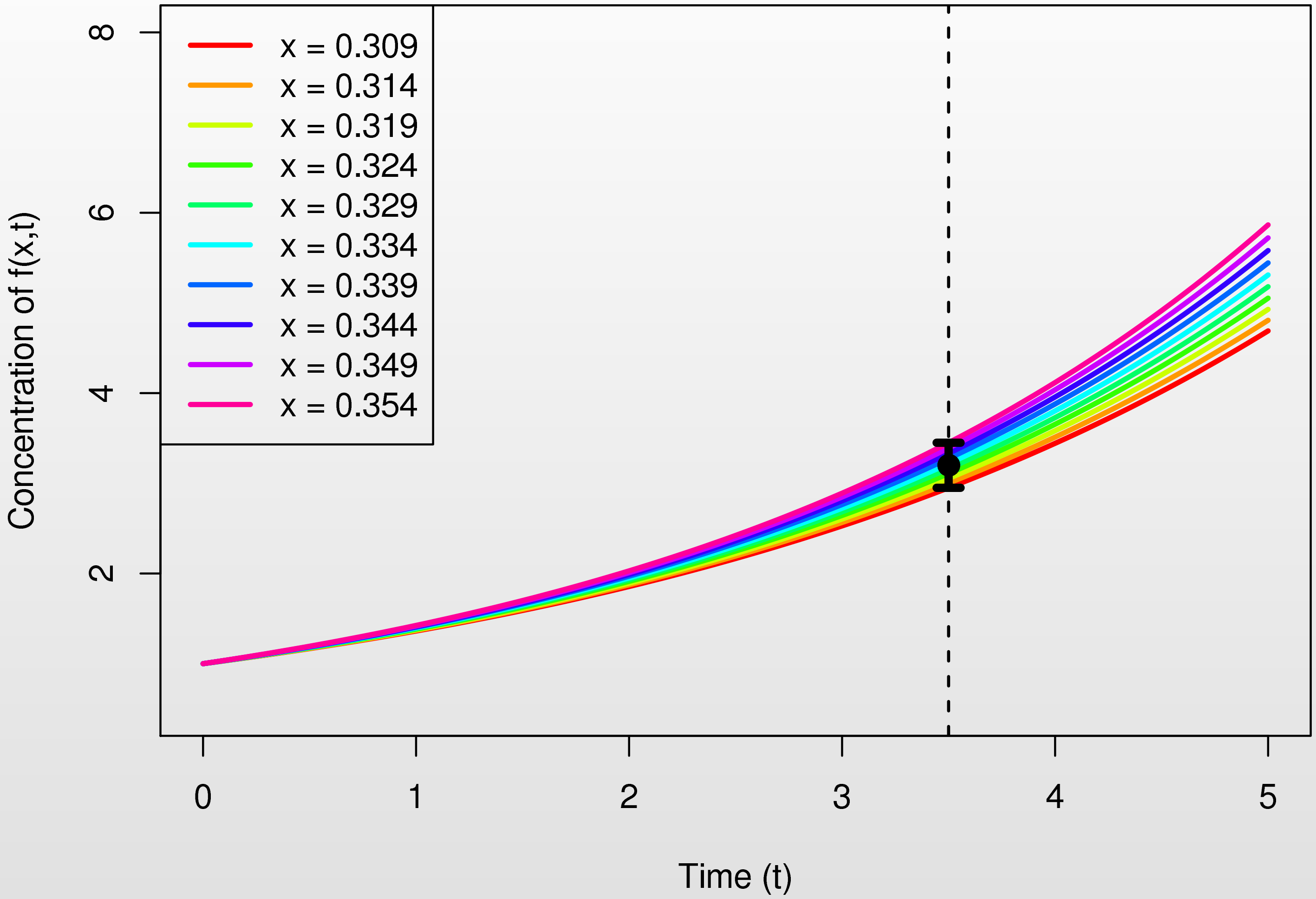

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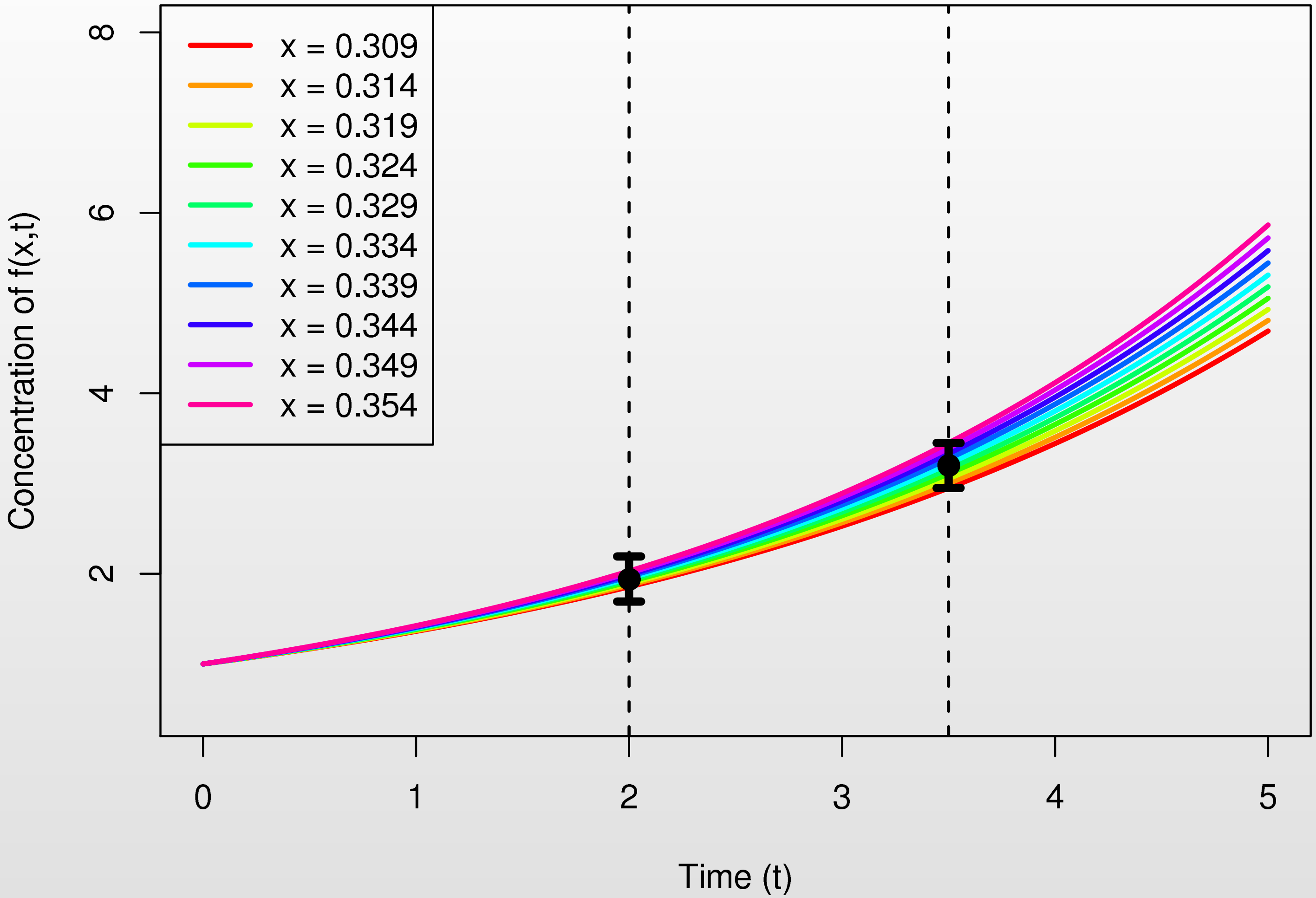

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- We can check the predictions made by these runs for $Y(t = 2)$.

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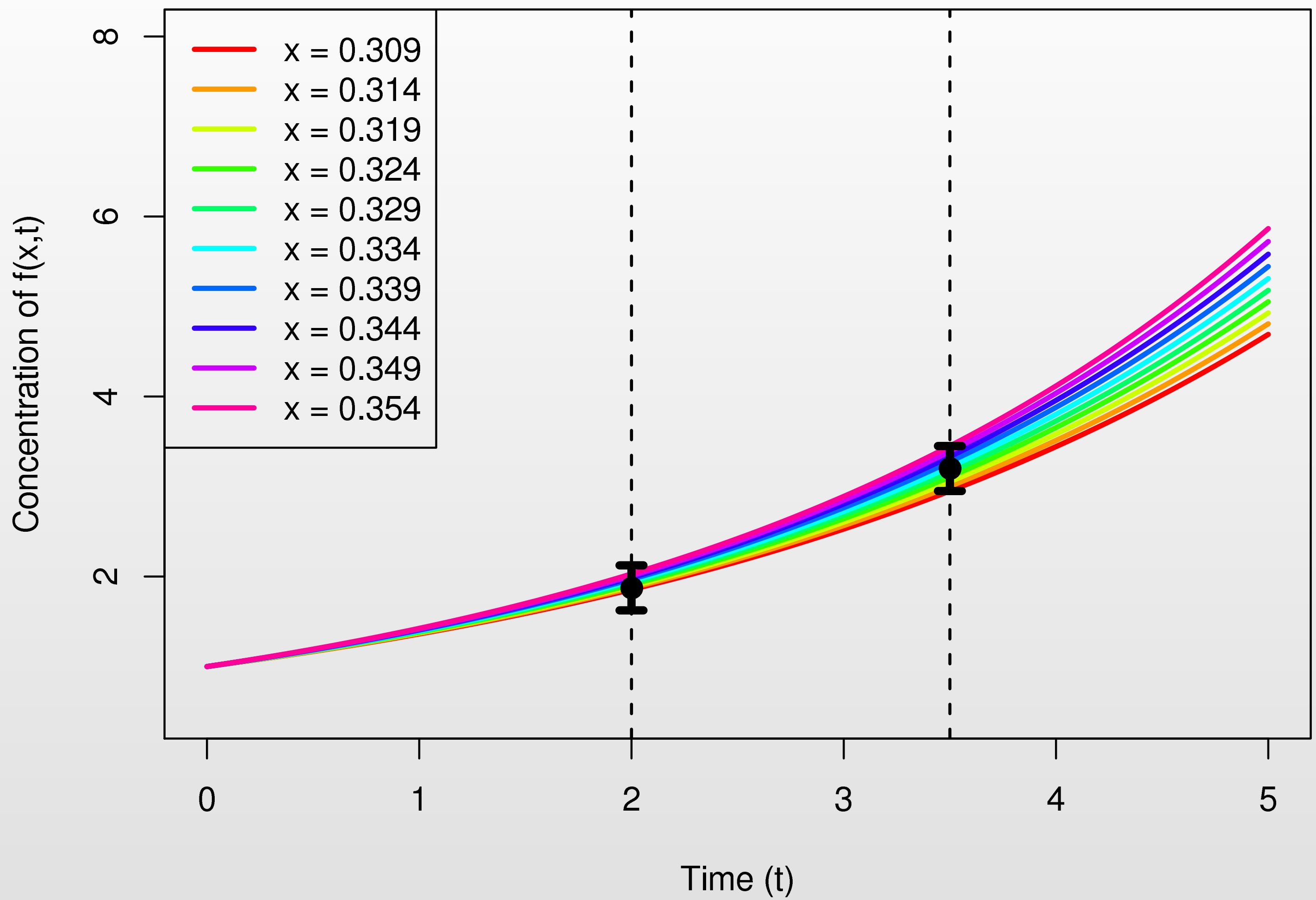

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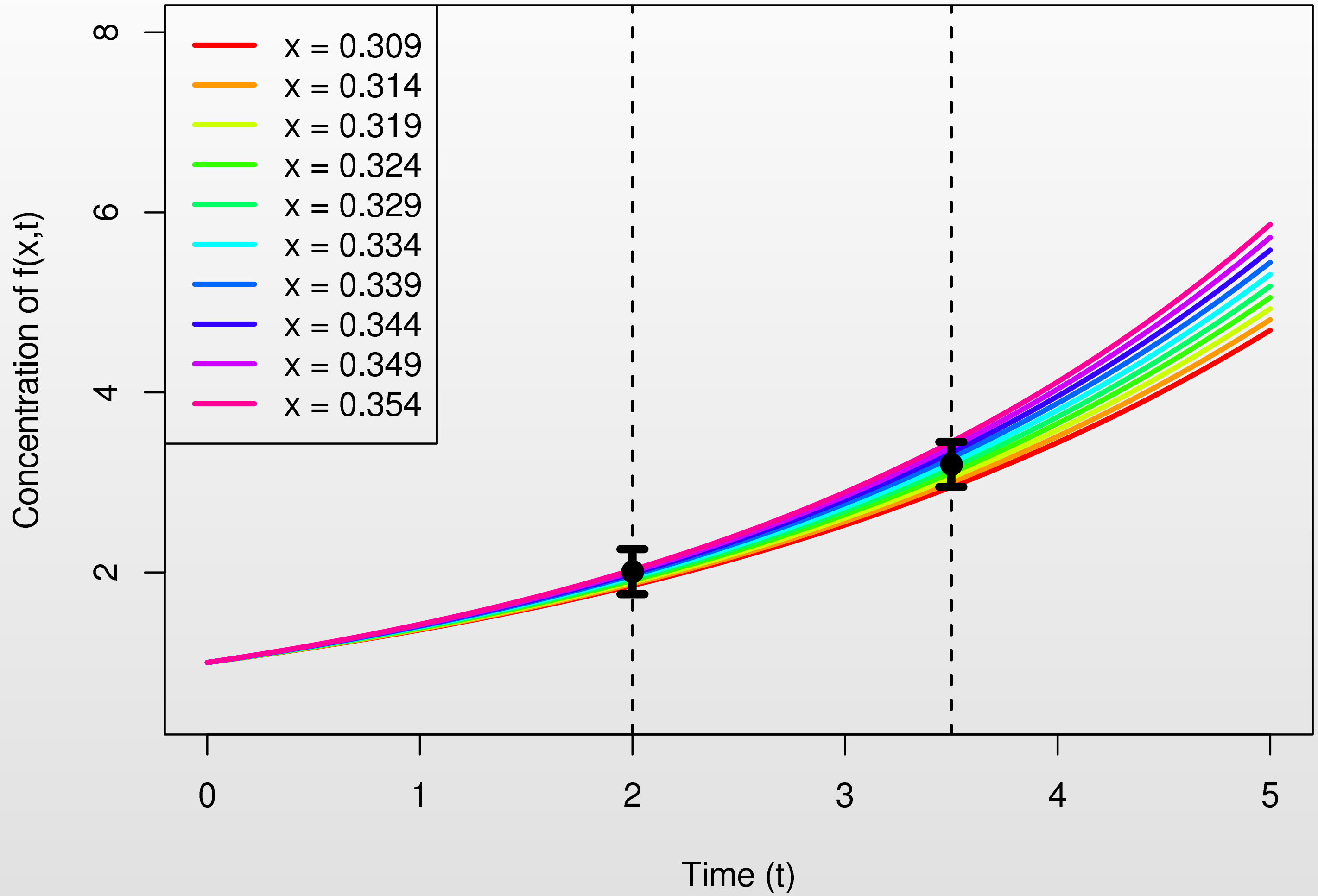
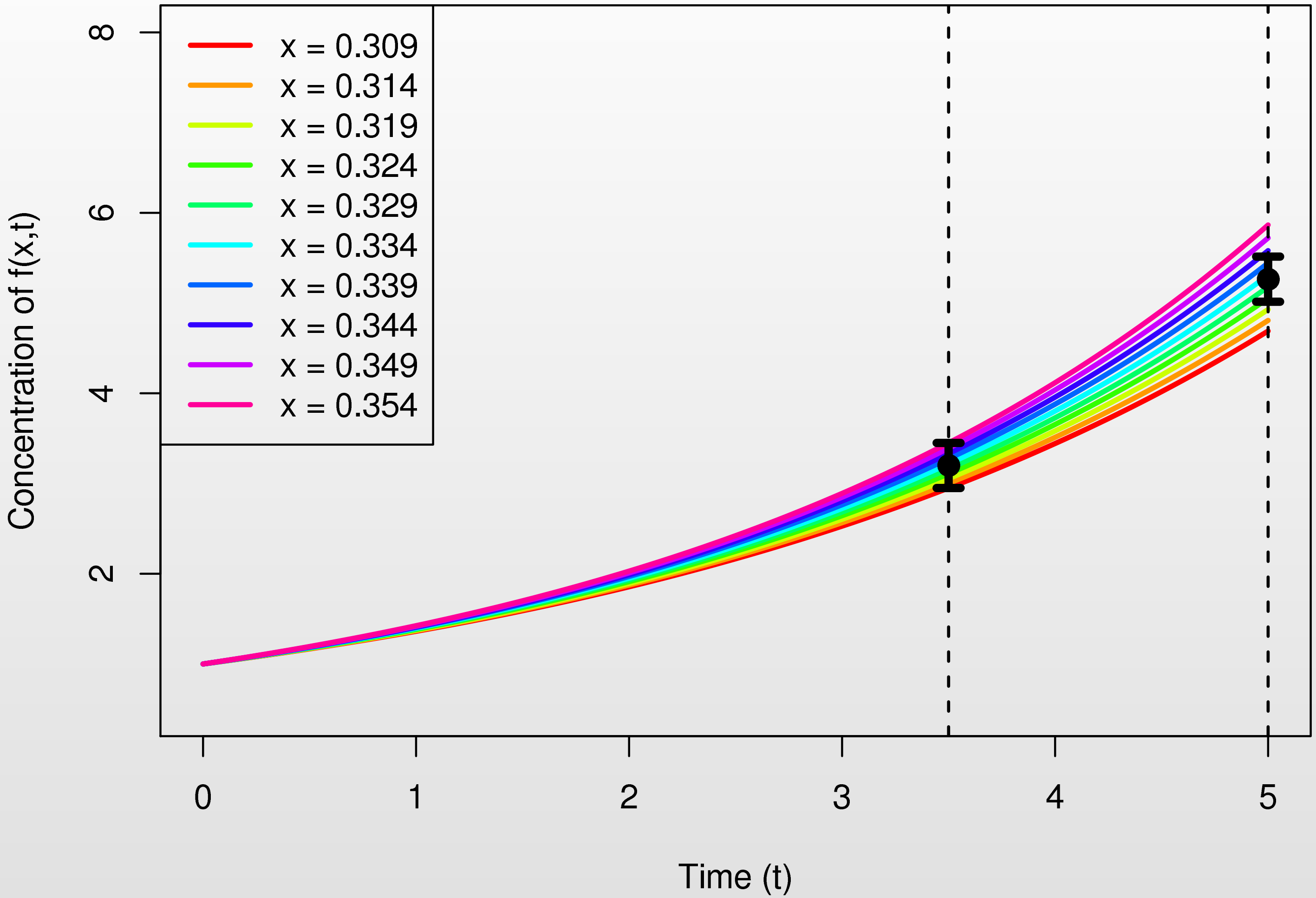


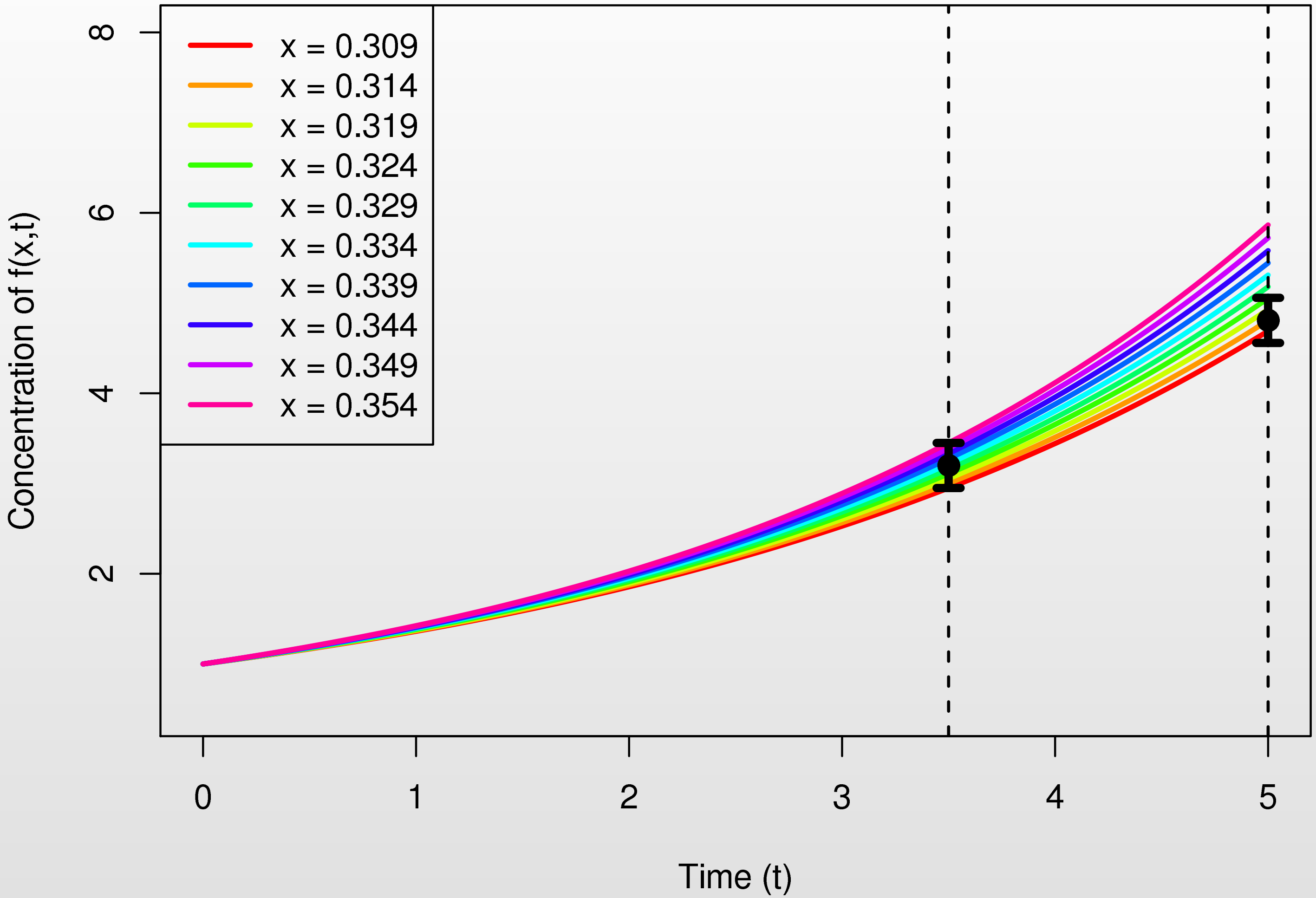
- The predictions imply that any measurement of $Y(t=2)$ is highly unlikely to be informative for x.
- This is due to the measurement errors swamping the signal from the model output $Y(t=2)$.

Designing new experiment: 1D example



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

Designing new experiment: 1D example



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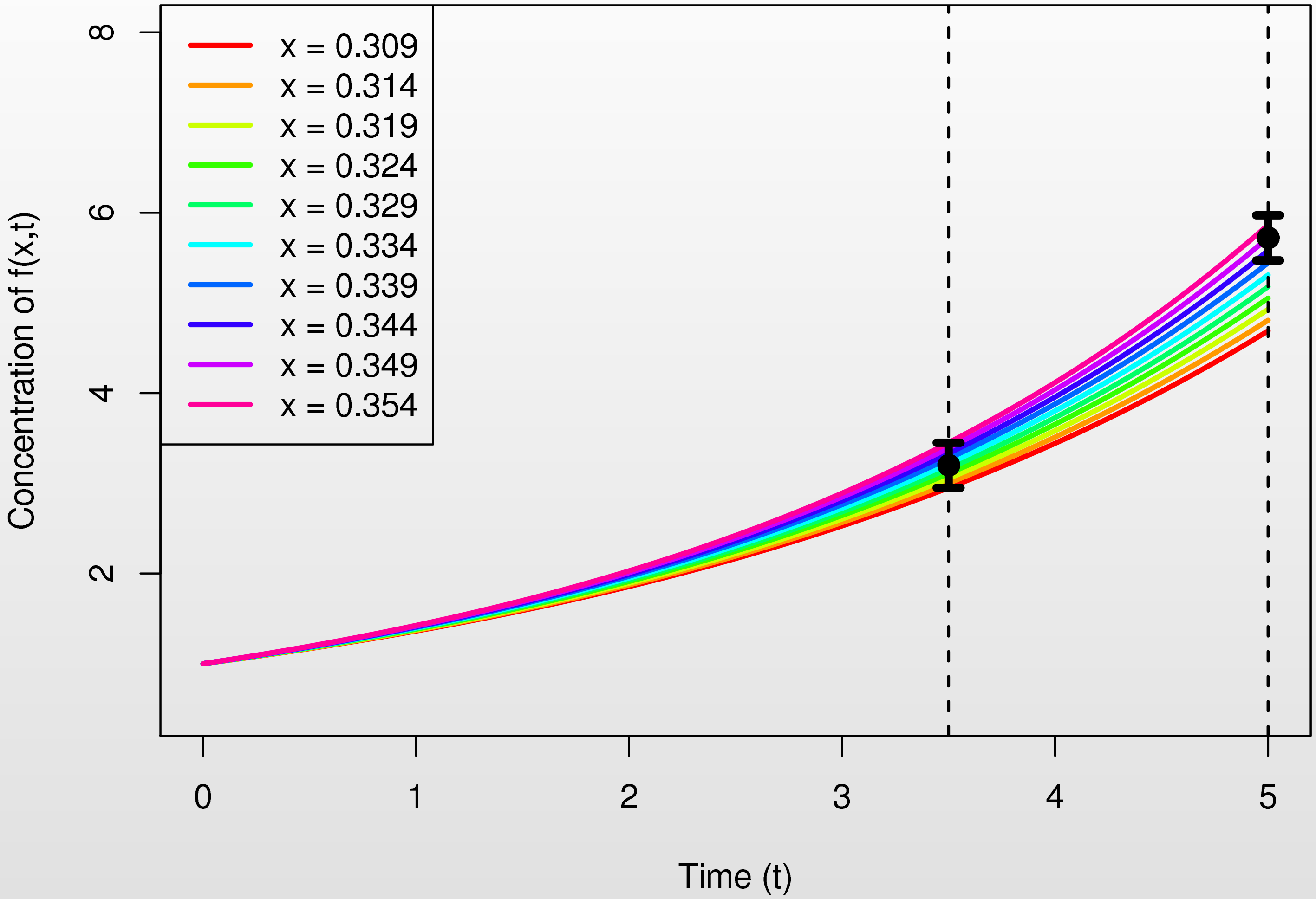
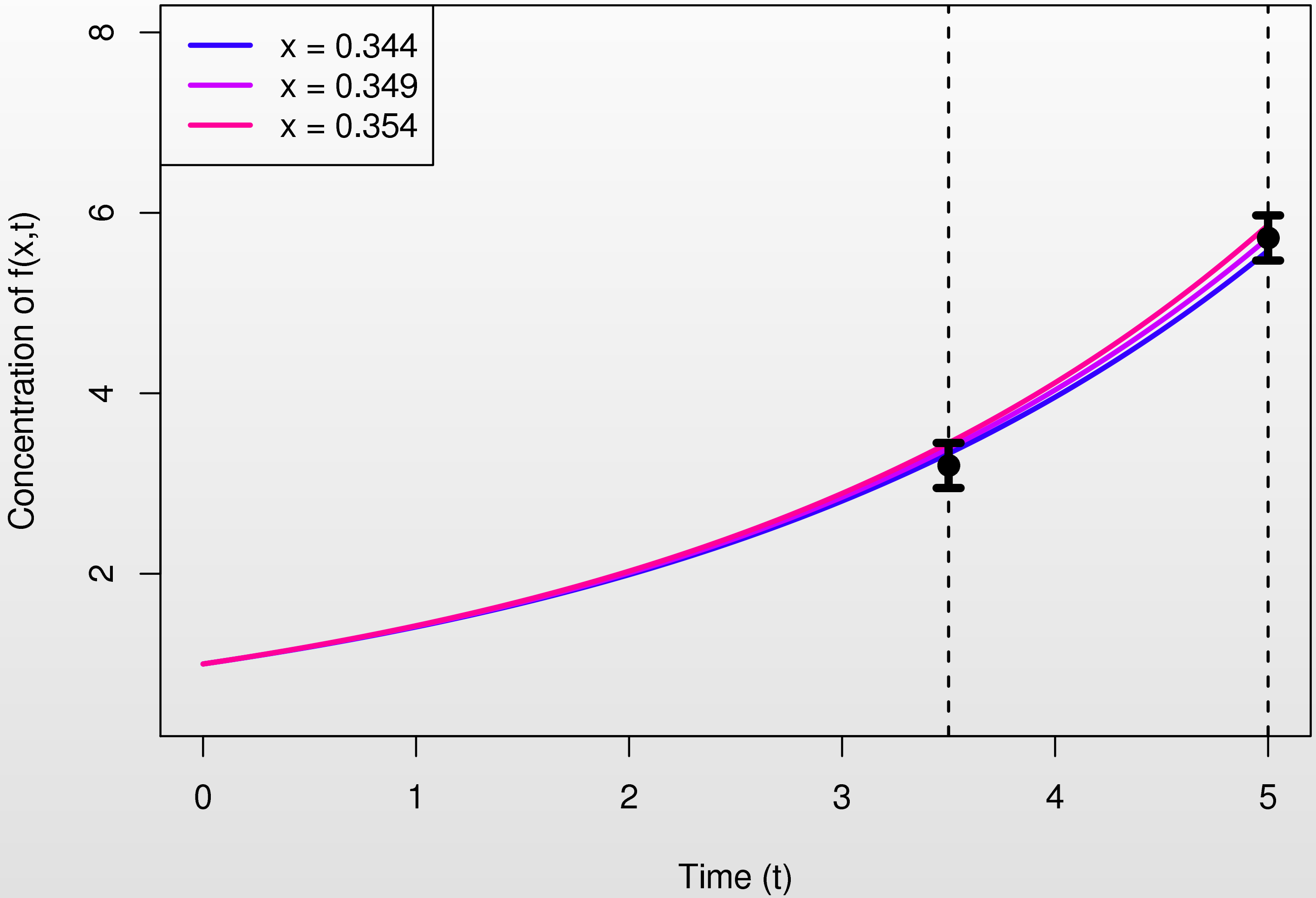
Designing new experiment: 1D example



- 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



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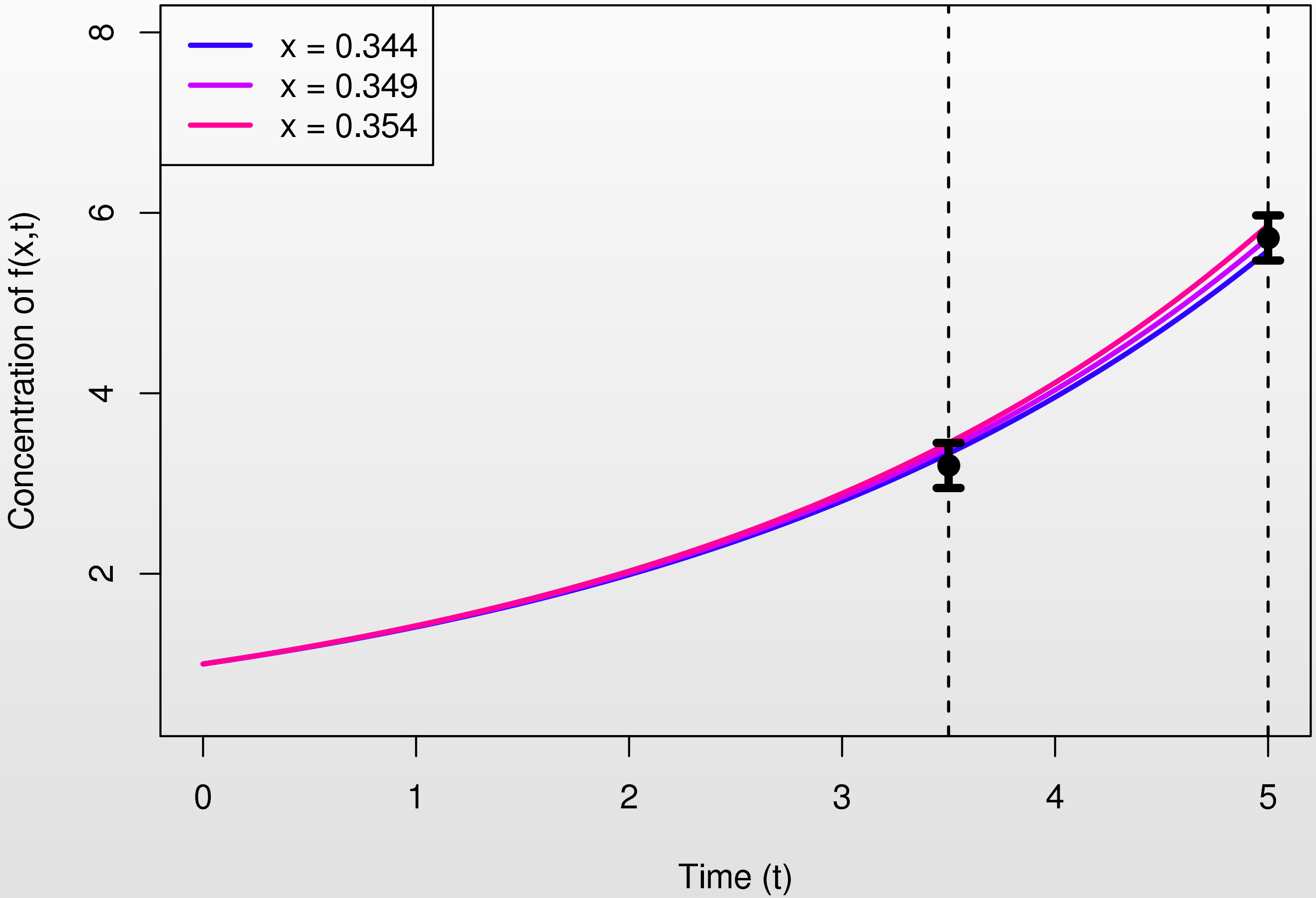

- For one possible measurement, see that non-implausible values of x would lie between 0.344 and 0.354, ruling out 70% of the possible values of x.
- This high expected space reduction in x implies that Experiment B, measuring $f(x,t)$ at $t = 5$, is clearly the best choice.

Space Cut Out Criteria

- Consider the implausibility measure for a future measurement z_i :

$$I_{(i)}^2(x) = \frac{|\mathrm{E}[f_i(x)] - z_i|^2}{(\mathrm{Var}[f_i(x)] + \mathrm{Var}[d_i] + \mathrm{Var}[e_i])}$$

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- Given z_i, define the indicator function $\mathrm{I}_i(x, z_i)$ s.t.

$$\mathrm{I}_i(x, z_i) \;=\; \begin{cases} 1 & \text{if} \quad I_{(i)}(x) > c_M, \quad x \text{ cut out} \\ 0 & \text{if} \quad I_{(i)}(x) < c_M, \quad x \text{ not cut out} \end{cases} \qquad (1)$$

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- For given z_i, the fraction of space cutout S_i due to output i is:

$$S_i(z_i) \;=\; \frac{1}{V_{\mathcal{X}}} \int_{x \in \mathcal{X}} \mathrm{I}_i(x, z_i) dx$$

Space Cut Out Criteria

- Given the best input x^*, and distributional assumptions for z_i we have that:

$$z_i | x^* \quad \sim \quad N(\mu_i(x^*), \sigma_i^2(x^*) + \mathrm{Var}[d_i] + \mathrm{Var}[e_i])$$

with $\mu_i(x^*) = \mathrm{E}_{D_i}[f_i(x{=}x^*)]$ and $\sigma_i(x^*) = \mathrm{Var}_{D_i}[f_i(x{=}x^*)]$.

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- We choose output i to maximise $\mathrm{E}[S_i]$.
- In fact we want to choose 4 outputs i, j, k, l such that the analogous expected space cut out $\mathrm{E}[S_{i,j,k,l}]$ is maximised.

Approximate Space Cut Out Criteria

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- where we approximate the z_i integral by simulating n_{sim} draws of z_i from $\pi(z_i|x_k^*)$ for each x_k^*. Can do analytically in some cases.

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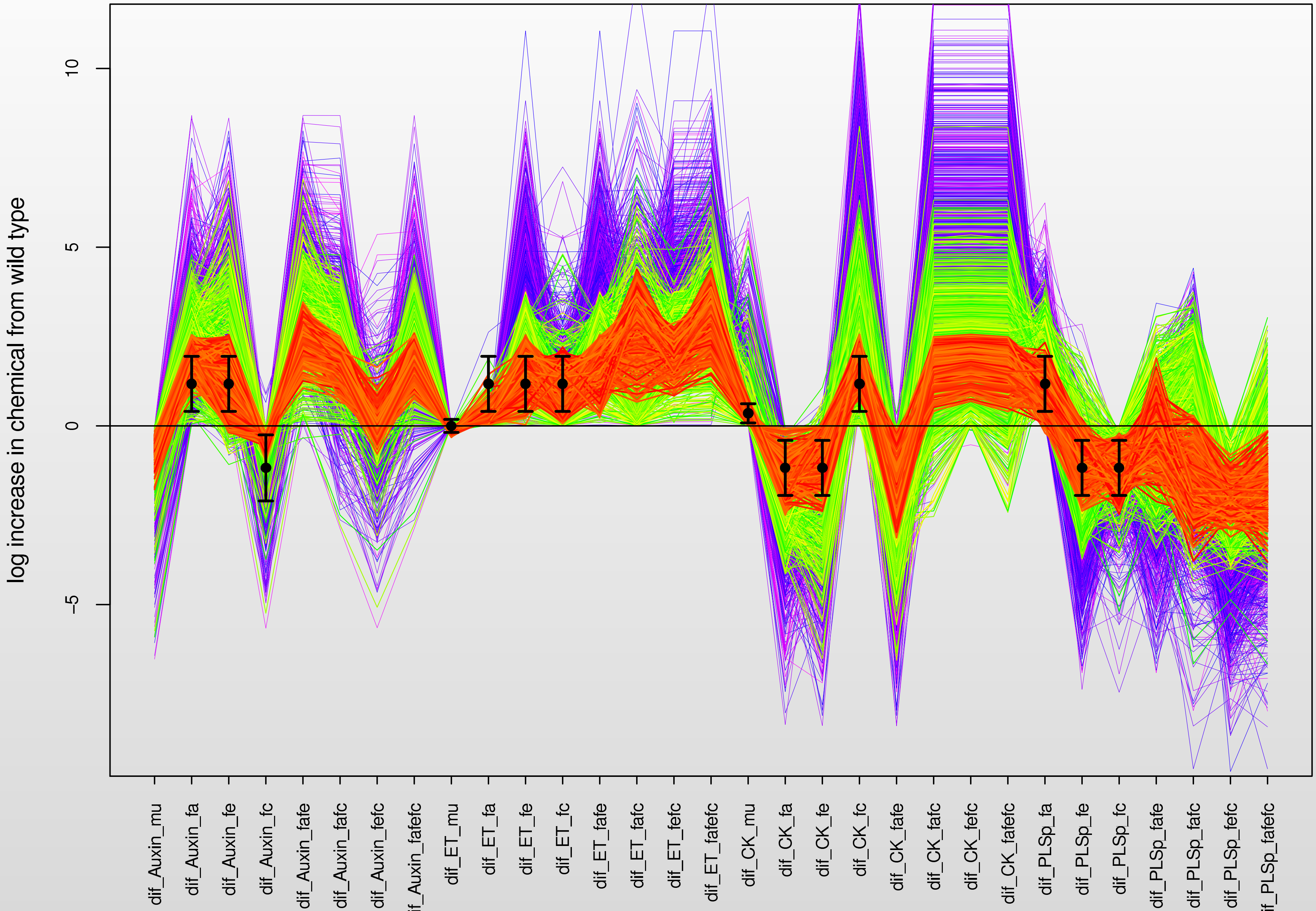
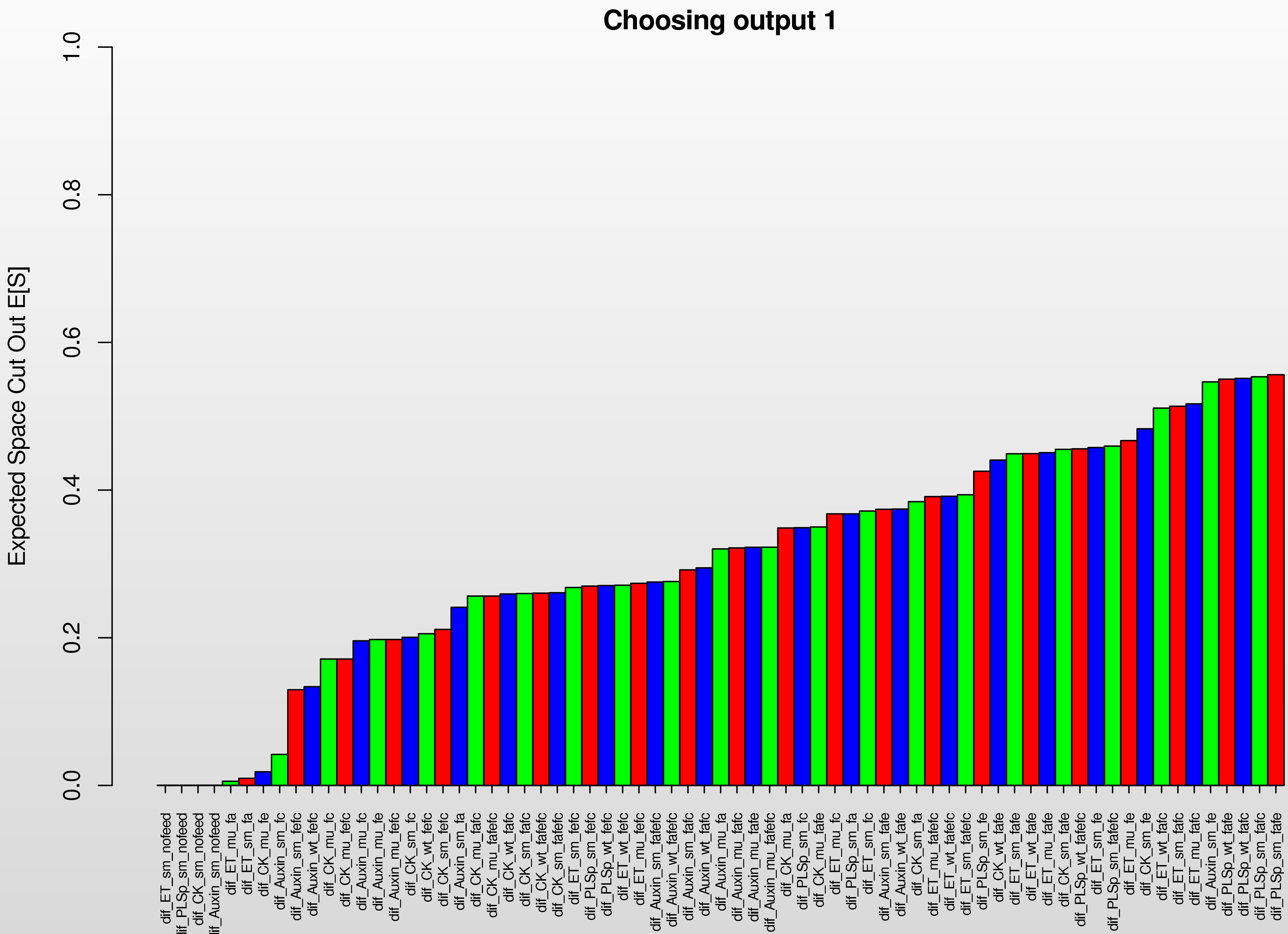
- Again, we are interested in the analogous multivariate quantity $\mathrm{E}[S_{i,j,k,l}]$

History Matching Plots Plus New Outputs



Space Cut Out Criteria for New Outputs



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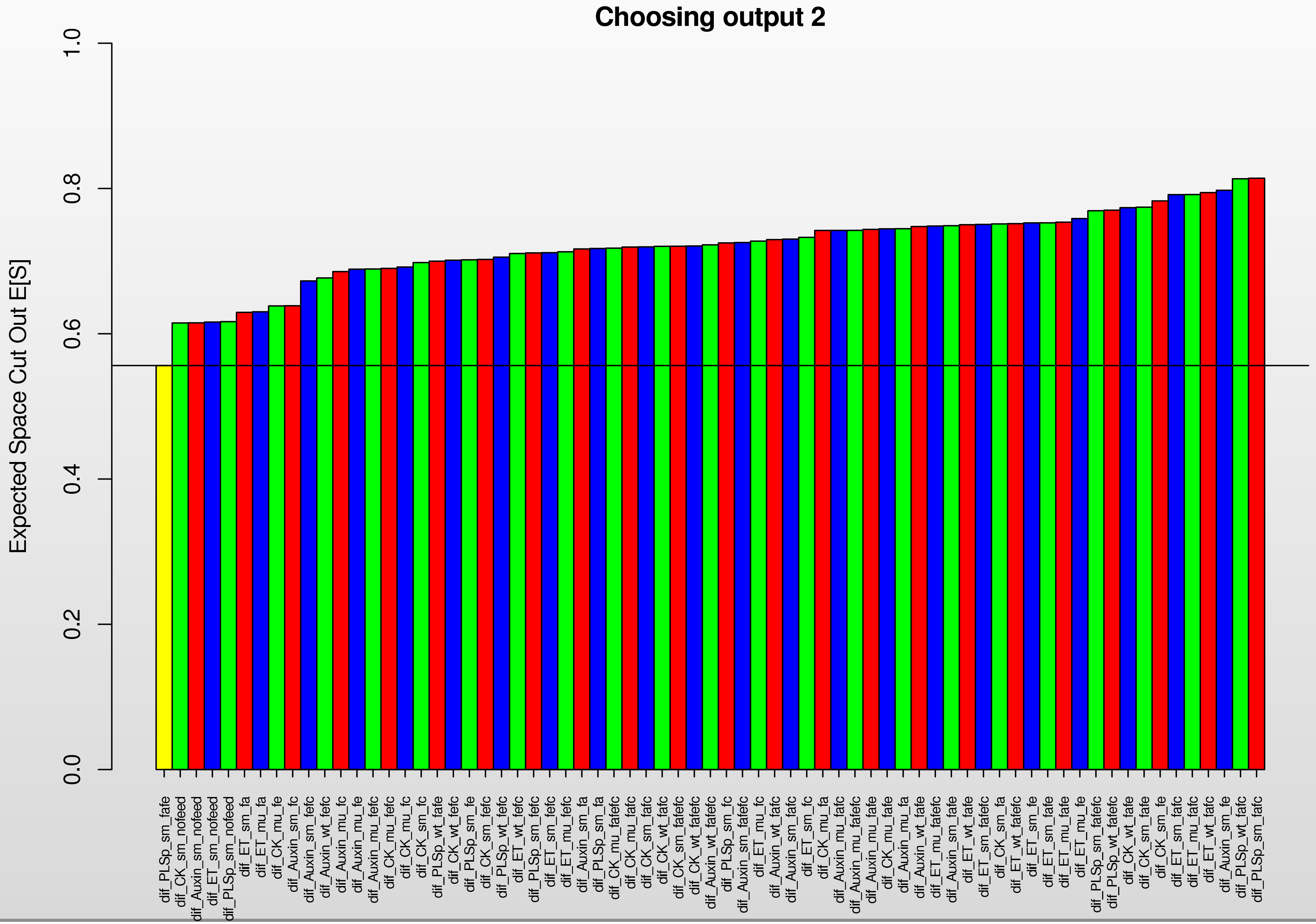

Space Cut Out Criteria for New Outputs

Durham University

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Predictions for New Outputs

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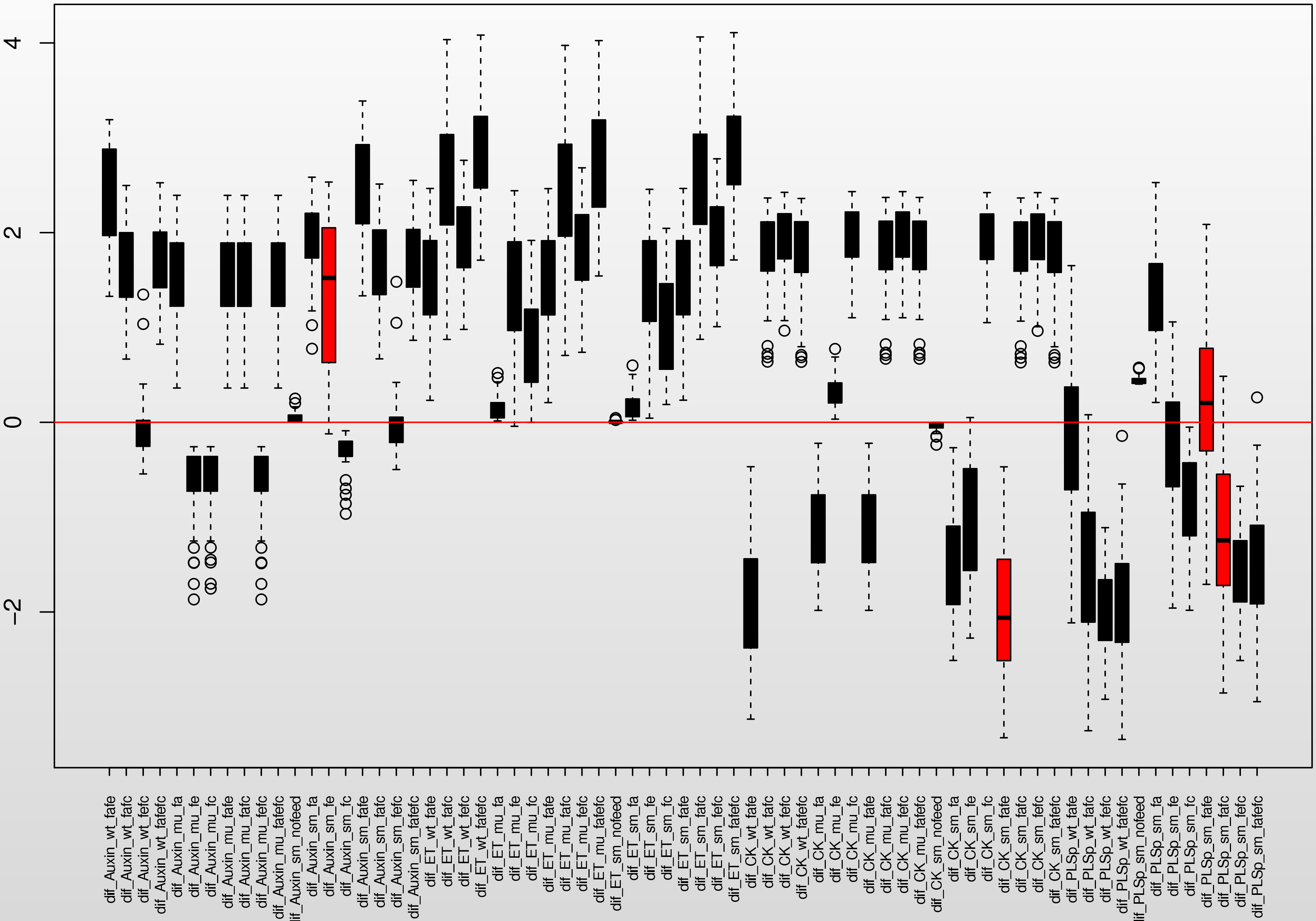

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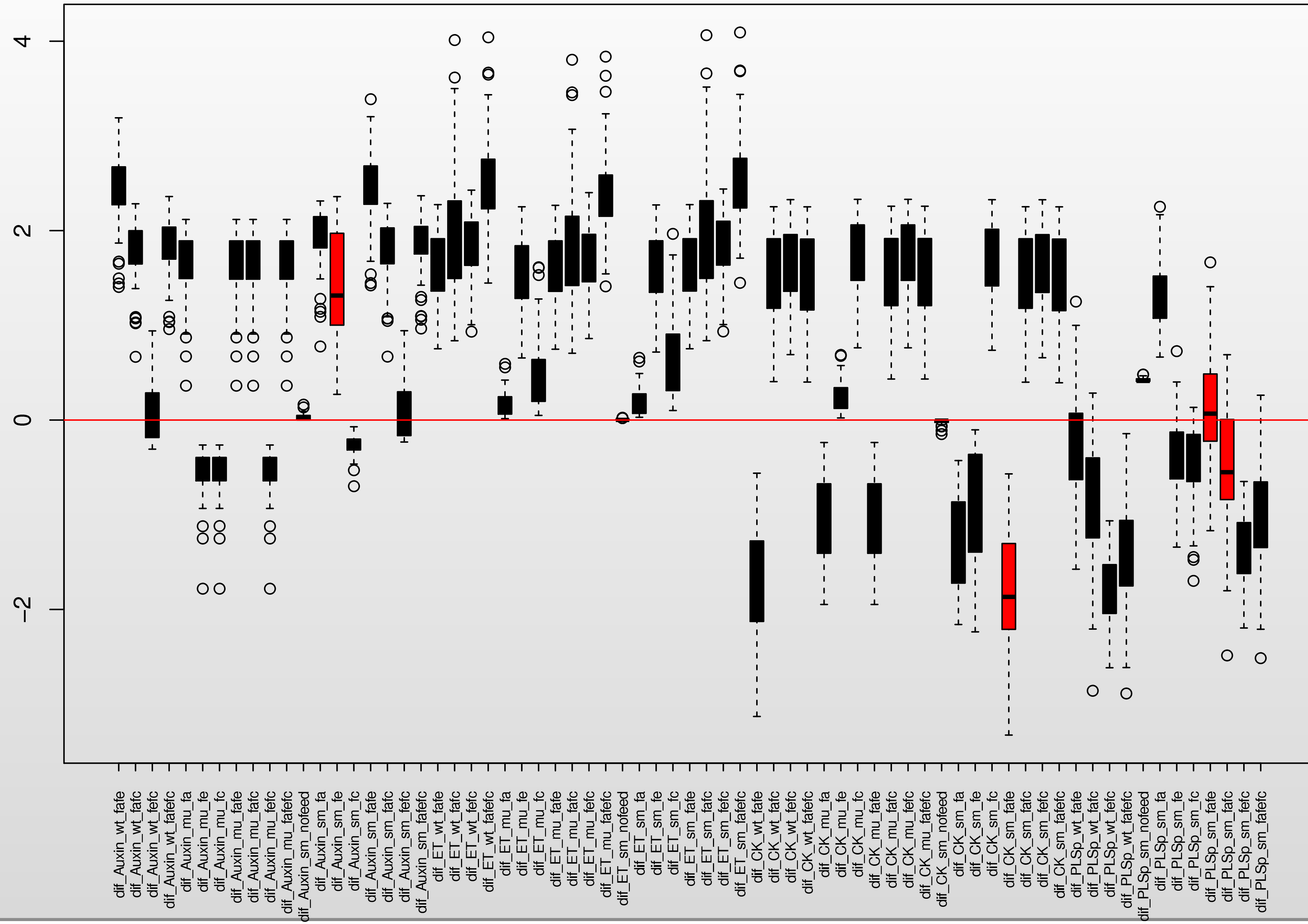

Experimental Design Results: 4 new experiments chosen

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plant	chemical measured	feeding regime	expected space cut
PSLox	PLSp	auxin $+$ ethylene	56%
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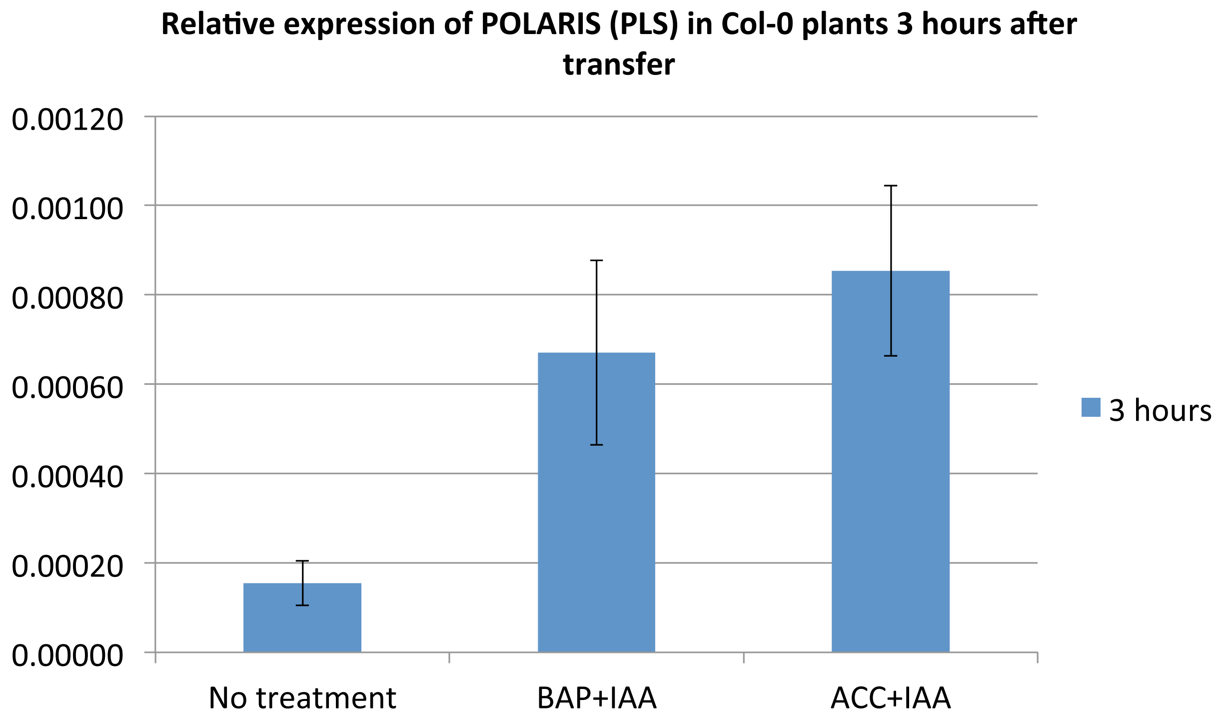
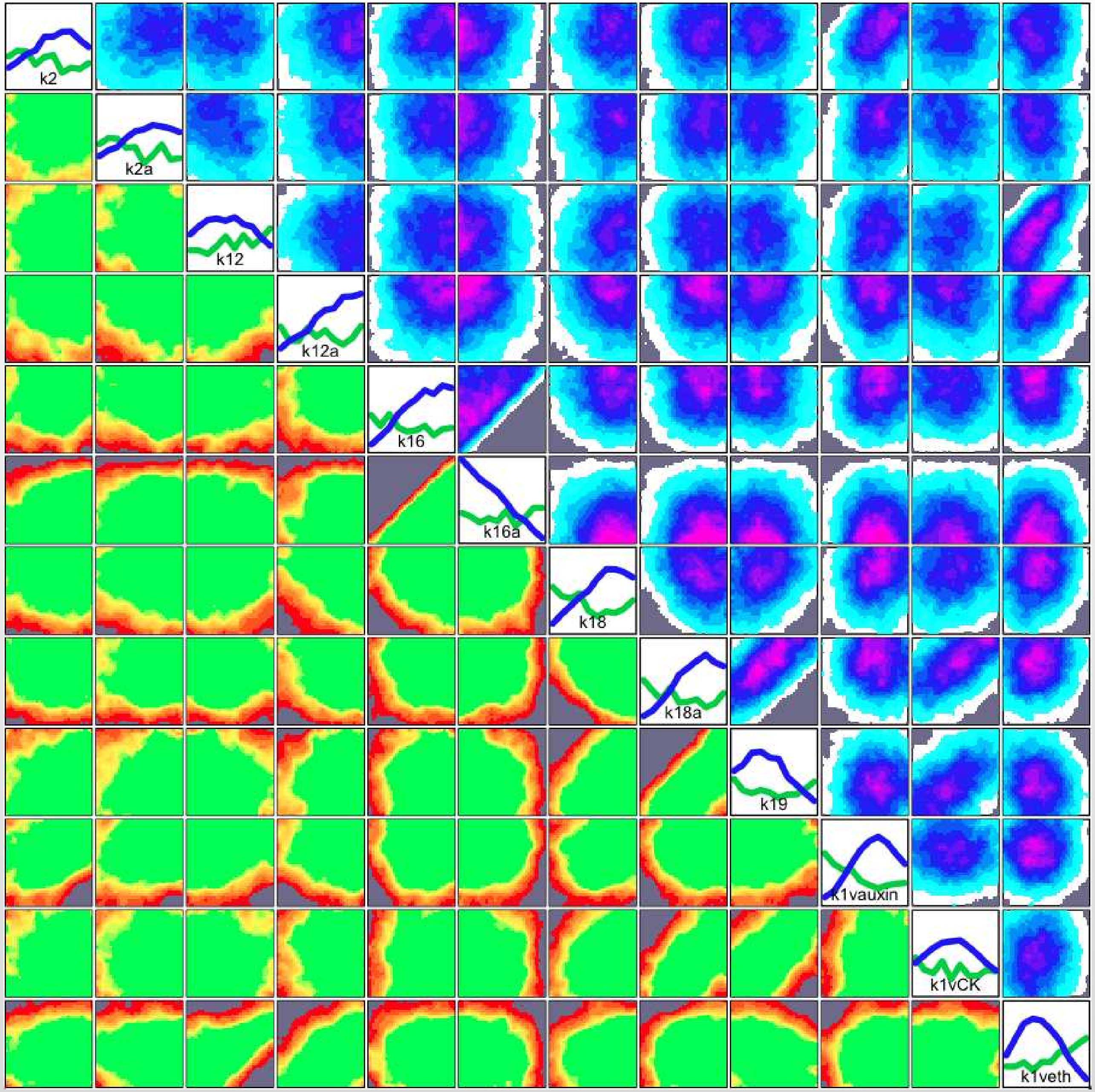
- First two experiments completed (after some problems), the other two delayed.

Results for First Two New Experiments

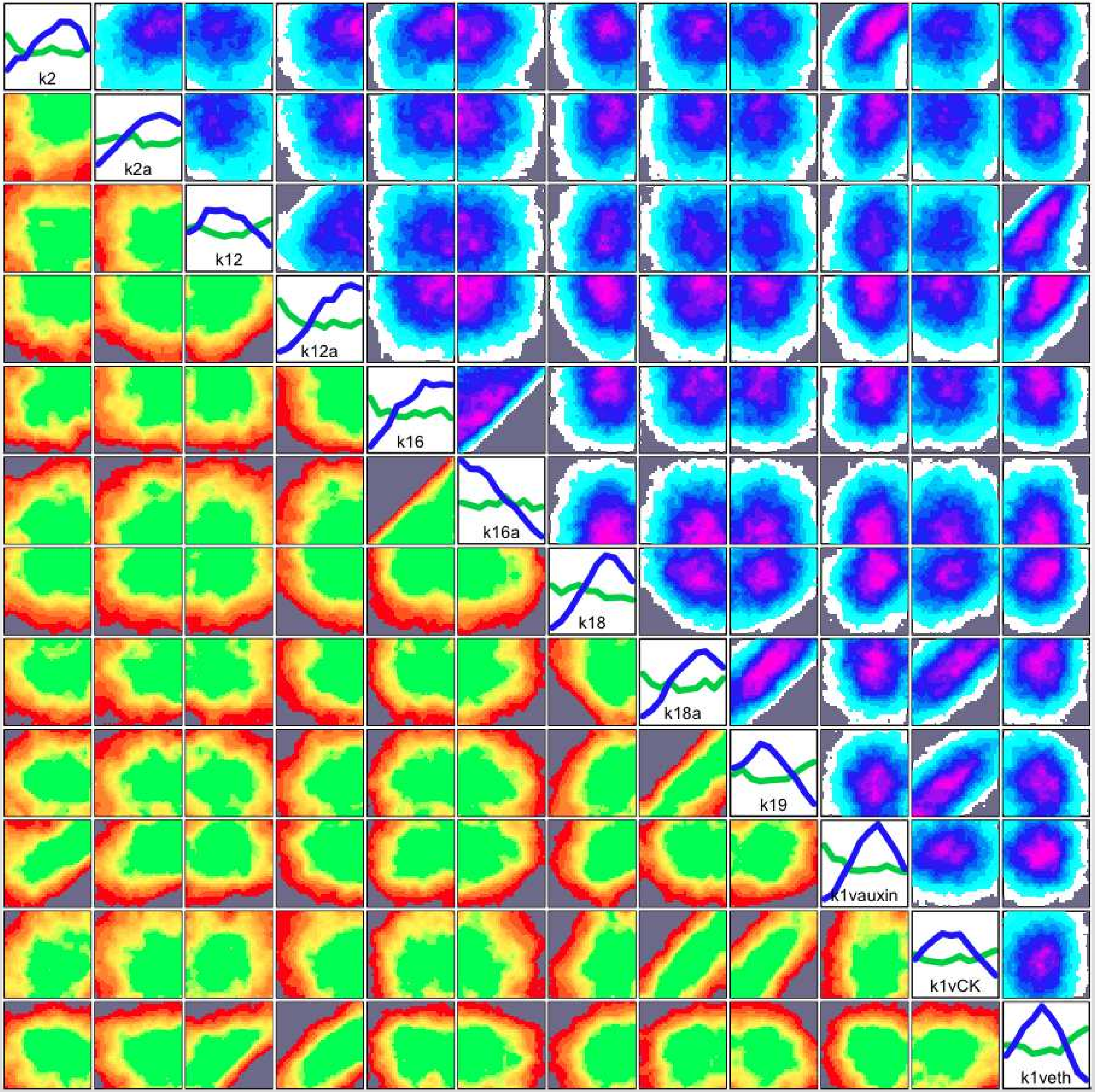


Seven day old Columbia wildtype plants were transferred to media containing either cytokinin and auxin (BAP + IAA), an ethylene precursor and auxin (ACC + IAA) or no hormone treatment. After three hours, the relative abundance (expression) of the POLARIS mRNA was measured with qPCR. Three separate biological replicates were used and error bars represent the standard error of the mean.

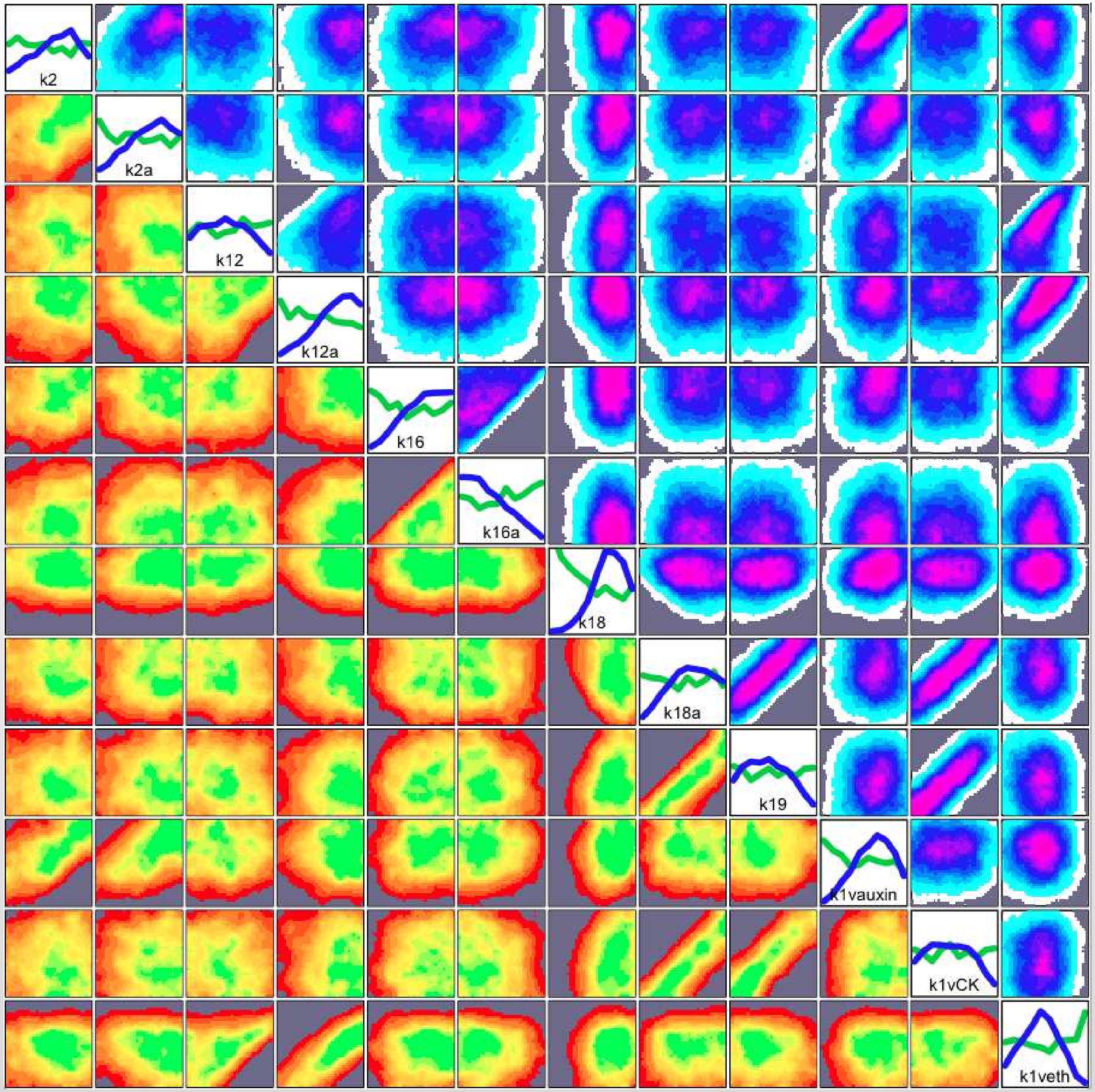
Iterative Input Space Reduction: Arabidopsis Model Wave 1



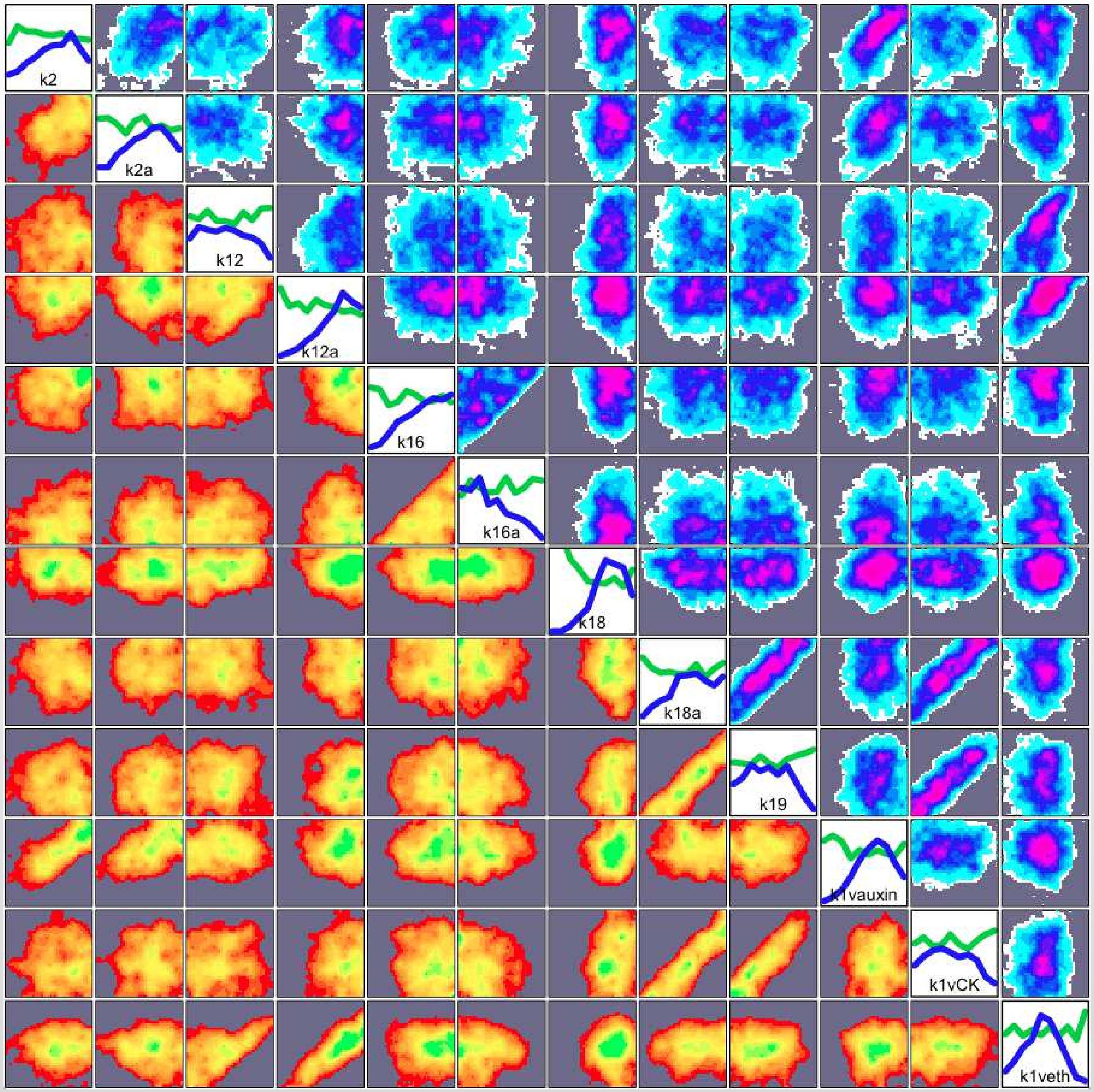
Iterative Input Space Reduction: Arabidopsis Model Wave 2



Iterative Input Space Reduction: Arabidopsis Model Wave 3



Arabidopsis Model with 2 New Results



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- We have chosen experiments to learn about all input or rate parameters using the expected space reduction criteria: we could have chosen to learn about specific rate parameters of interest.
- We can also design experiments to challenge the model, i.e. to validate it if necessary.

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- 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.
- Only once we have incorporated all major sources of uncertainty we can then make predictions for future experiments, and then design expensive experiments.

References

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