Data-driven parameter inference for gene circuit modeling

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Introduction

- **Our goal:** Accurate **model-driven** designs for synthetic biology.

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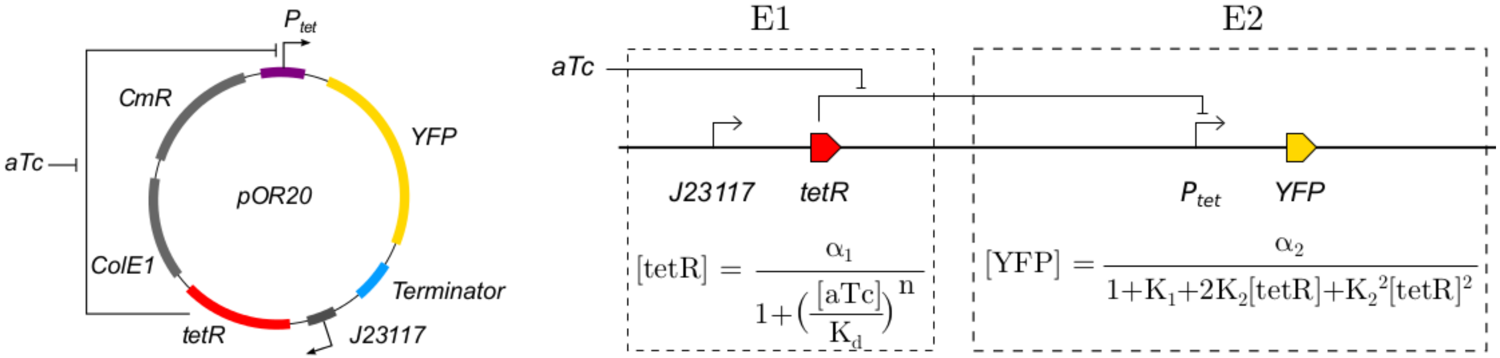
- **Our goal:** Accurate **model-driven** designs for synthetic biology.
- **Challenge**
  - Lack of **accurate** parameter values
    - Measuring **directly** from experiment is **difficult**
    - Estimating **indirectly** from experimental data is **inaccurate**

Example: Inference



(***Tamsir et al, Nature, 2011***)

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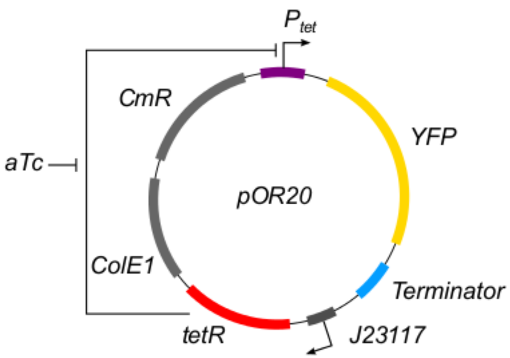

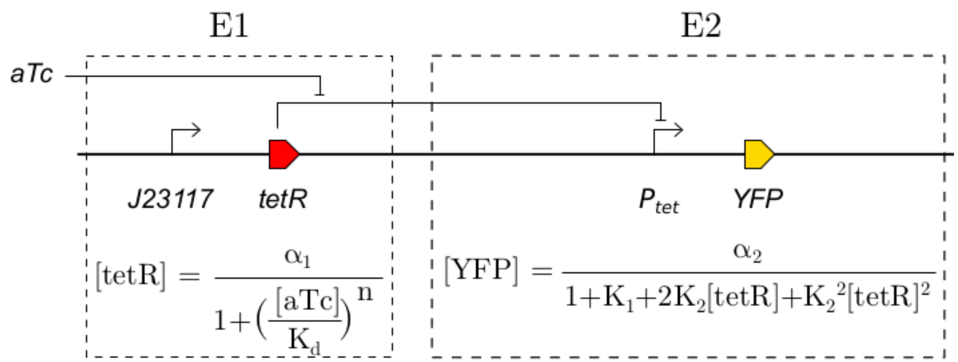

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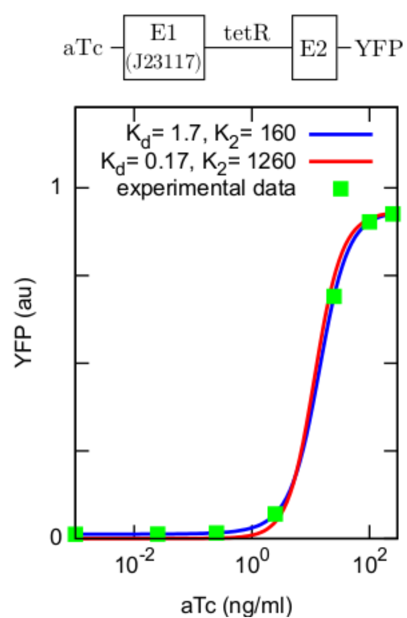

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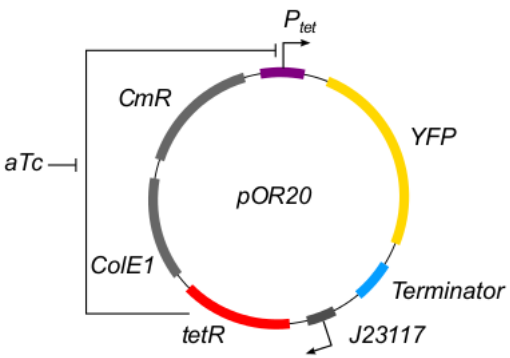

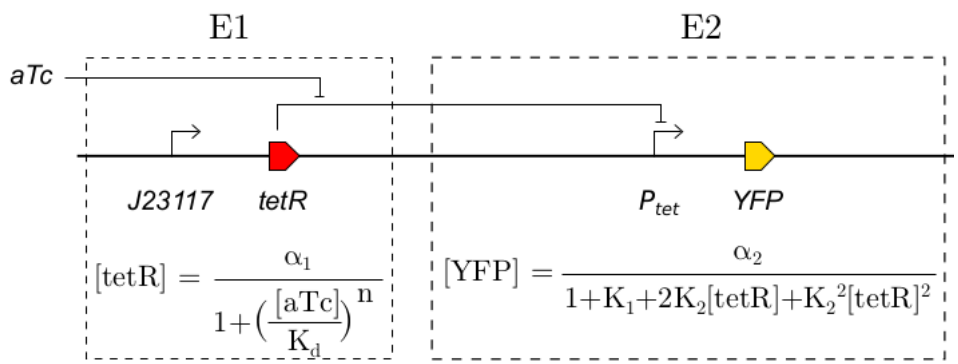

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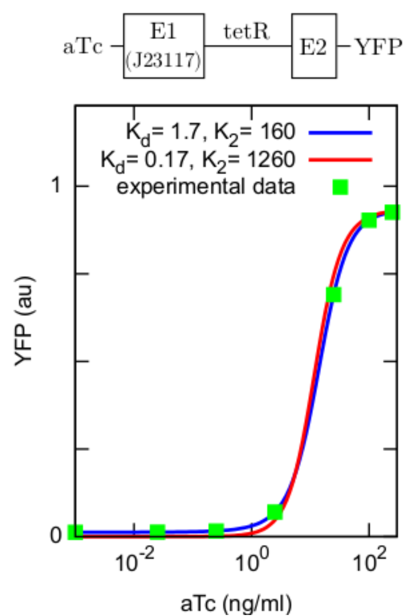

Multiple solutions
(K_d = 1.7, K_2 = 160)
vs (K_d = 0.17, K_2 = 1260)

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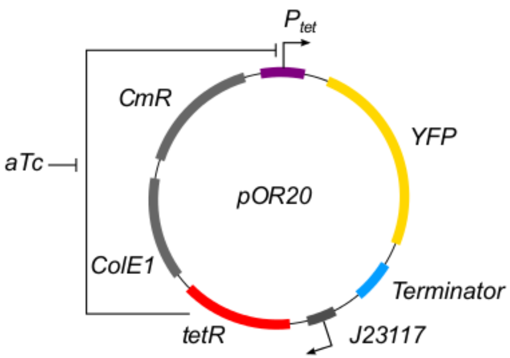

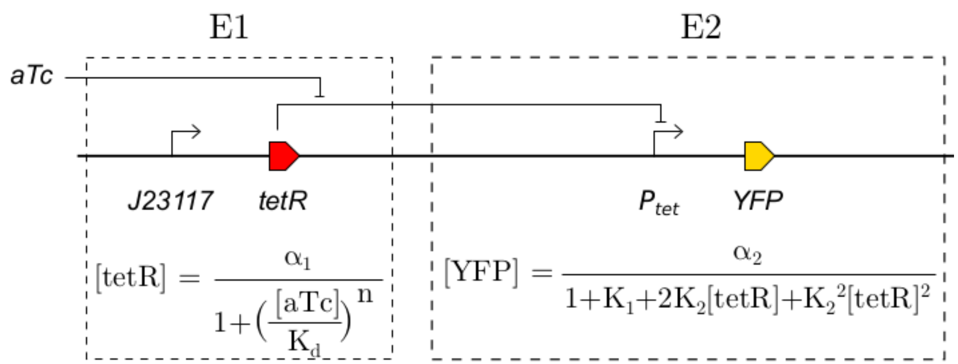

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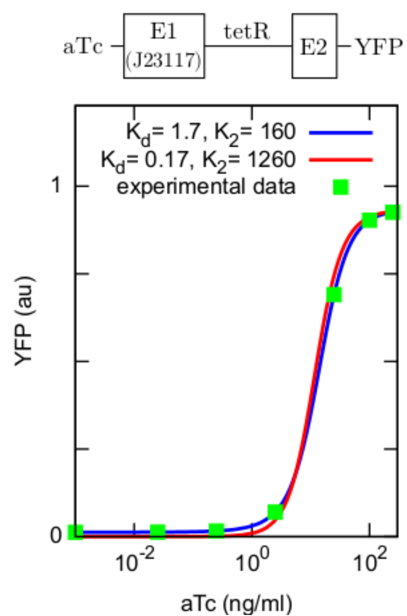

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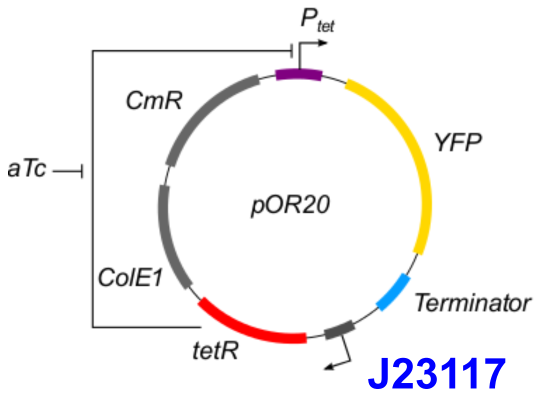
Parameters K_d, K_2 are uncertain!

Example: Design with uncertain parameters



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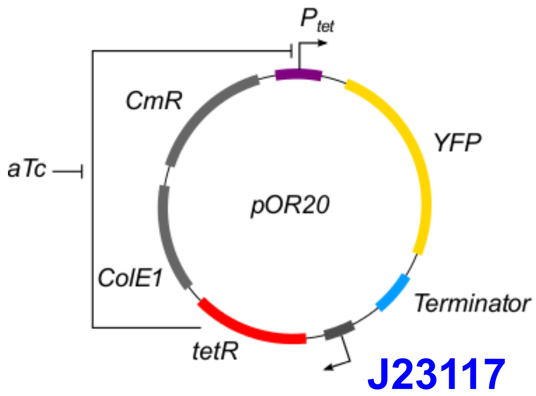

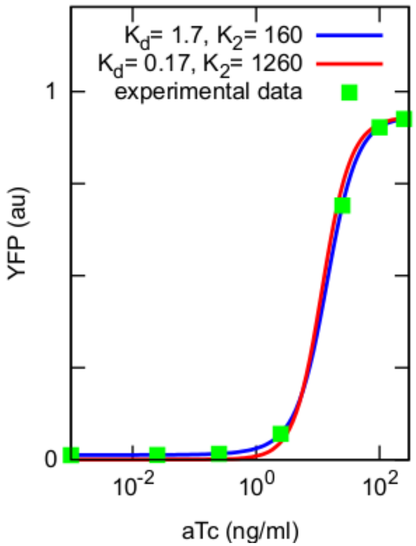

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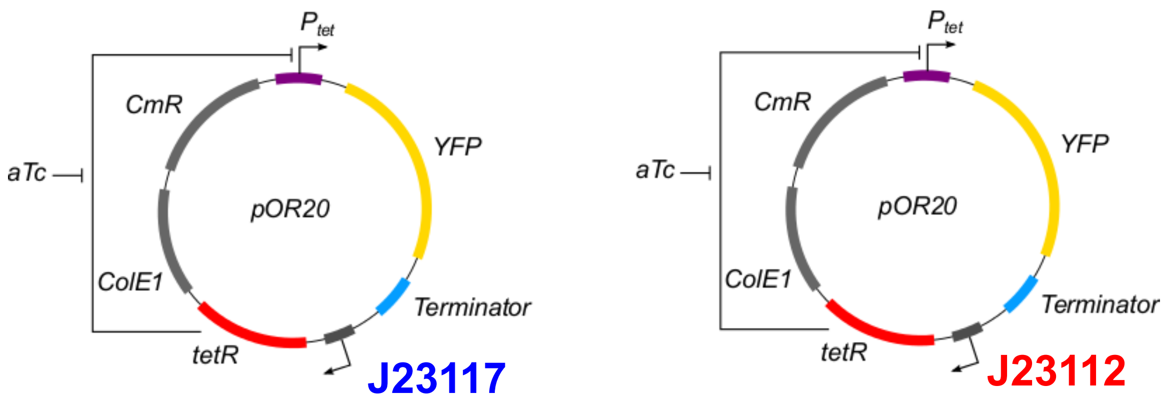

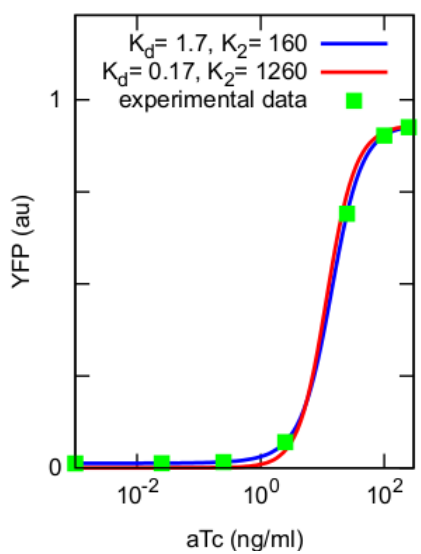

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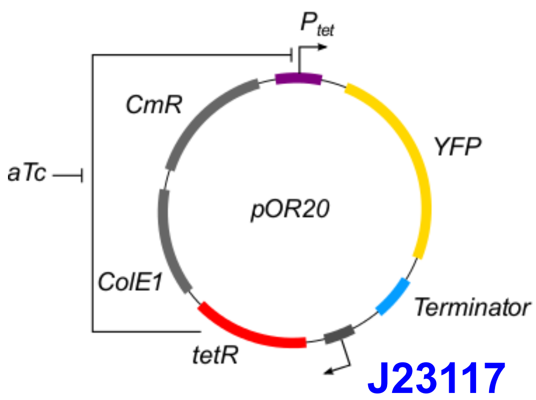

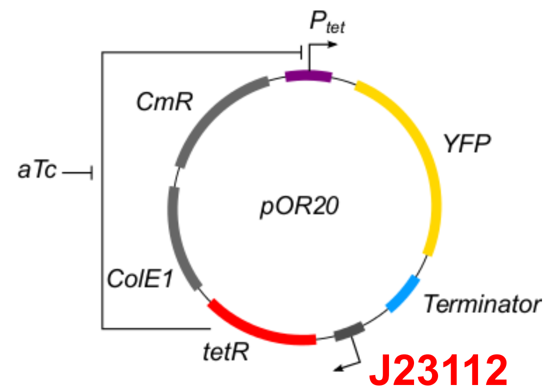

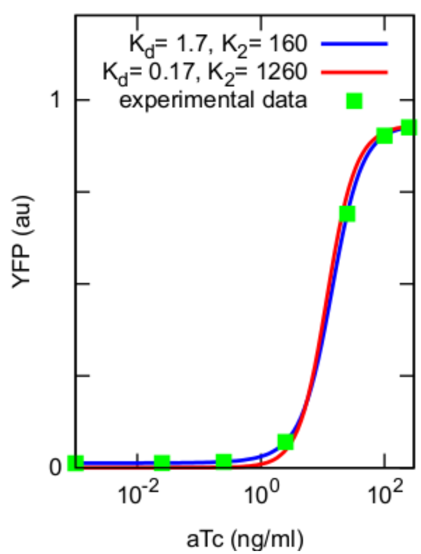

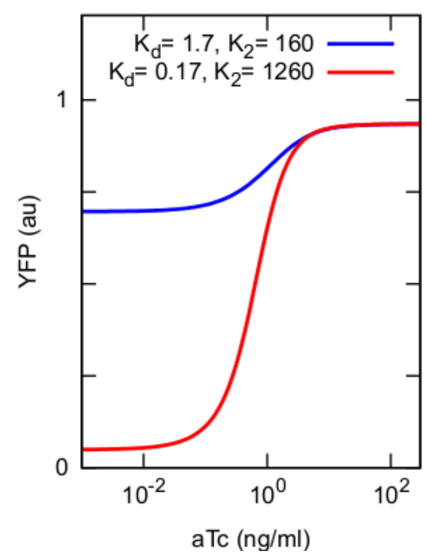

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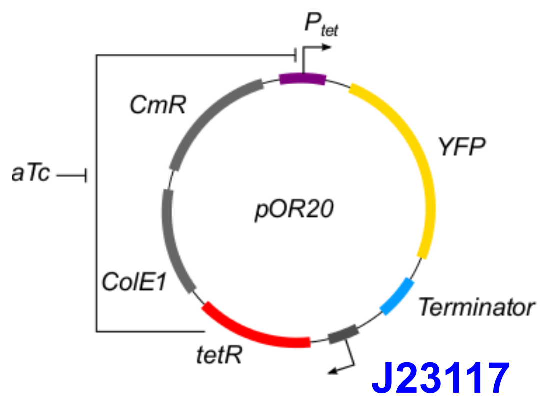

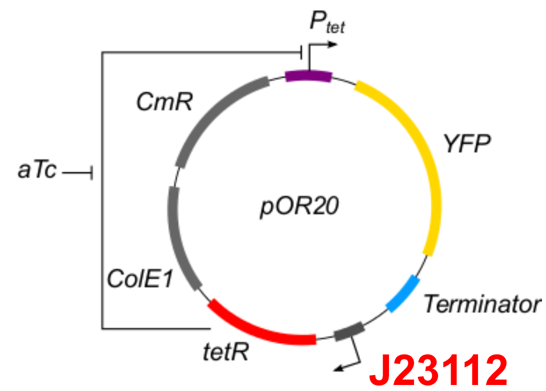

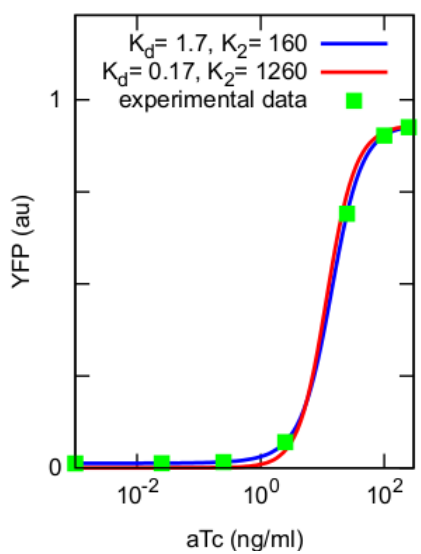

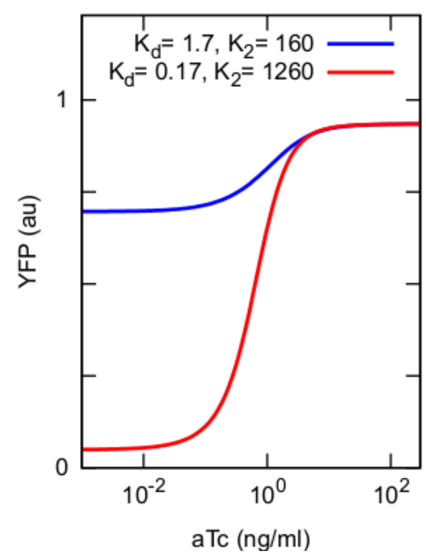

Circuit behavior prediction is unreliable!

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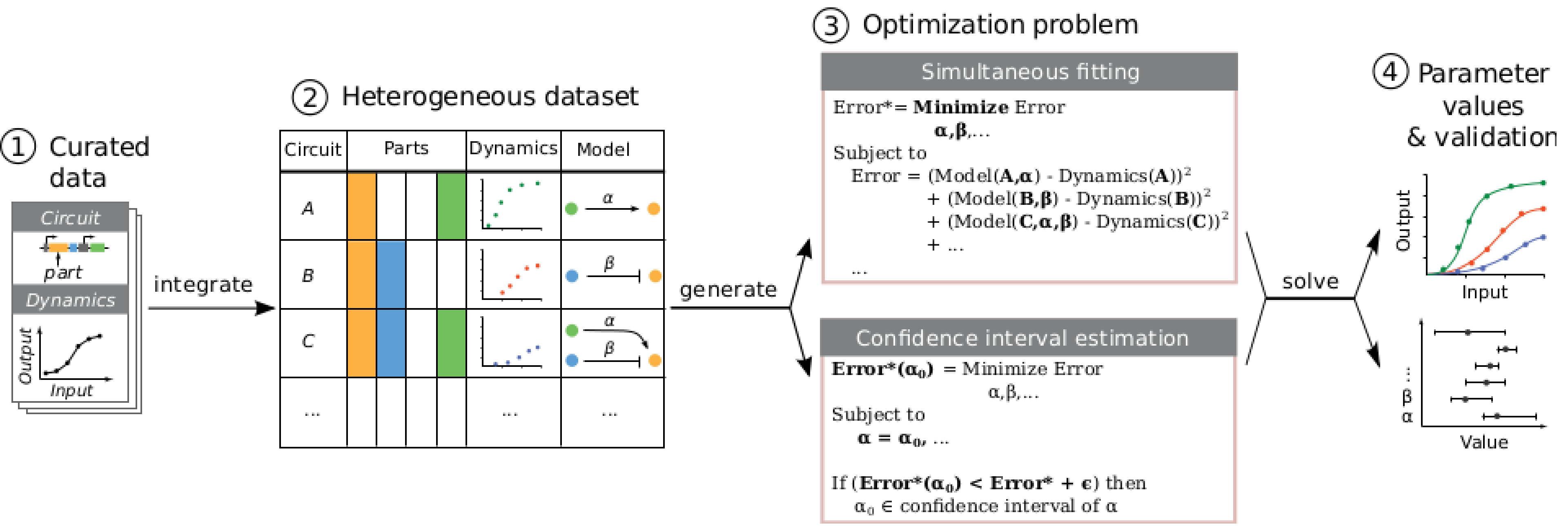
    - **Prohibitively costly**
  - Data-driven alternative: Integrate data from overlapping circuits and infer parameters
    - **Simple**

Approach



1 Curated data
Circuit
part
Dynamics
Output
Input
integrate
2 Heterogeneous dataset
Circuit
Parts
Dynamics
Model
A
B
C
α
β
...
generate
3 Optimization problem
Simultaneous fitting
Error* = Minimize Error
α,β,...
Subject to
Error = (Model(A,α) - Dynamics(A))²
+ (Model(B,β) - Dynamics(B))²
+ (Model(C,α,β) - Dynamics(C))²
+ ...
...
Confidence interval estimation
Error*(α₀) = Minimize Error
α,β,...
Subject to
α = α₀, ...
If (Error*(α₀) < Error* + ε) then
α₀ ∈ confidence interval of α
solve
4 Parameter values & validation
Output
Input
α
β
Value

Curated data

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- From 138 publications containing gene circuits of *E. coli*

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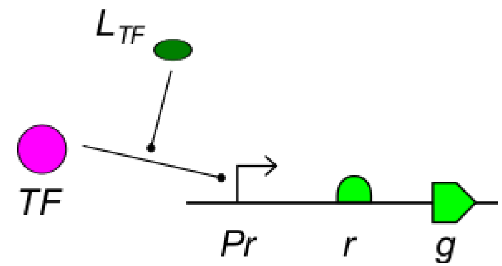
  - Only 13 publications with 34 datasets

Circuit model

Translation $\mu_g = N_g \alpha_r \nu_g^{(1)}$



Transcription

$$\nu_g^{(1)} = \begin{cases} \beta_{Pr} + \dfrac{\alpha_{Pr} - \beta_{Pr}}{1 + \left(\frac{K_{Pr}}{\mu'_{TF}}\right)^{n_{Pr}}} & TF \text{ is an activator} \\ \beta_{Pr} + \dfrac{\alpha_{Pr} - \beta_{Pr}}{1 + \left(\frac{\mu'_{TF}}{K_{Pr}}\right)^{n_{Pr}}} & TF \text{ is a repressor} \end{cases}$$

Ligand binding

$$\mu'_{TF} = \begin{cases} \mu_{TF} & TF \text{ is non-inducible} \\ \dfrac{\mu_{TF}}{1 + (\frac{[L_{TF}]}{K_{L_{TF}}})^{n_{L_{TF}}}} & TF \text{ binds with } L_{TF} \text{ and } TF \text{ binds to } Pr \\ \dfrac{\mu_{TF}}{1 + (\frac{K_{L_{TF}}}{[L_{TF}]})^{n_{L_{TF}}}} & TF \text{ binds with } L_{TF} \text{ and } L_{TF} - TF \text{ binds to } Pr \end{cases}$$

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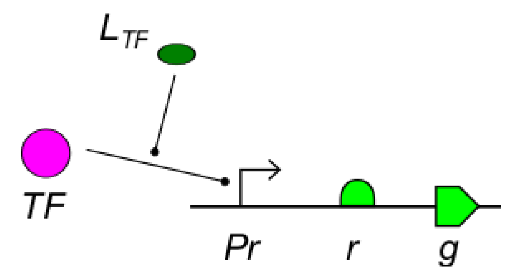

Consistent minimal model over all circuits

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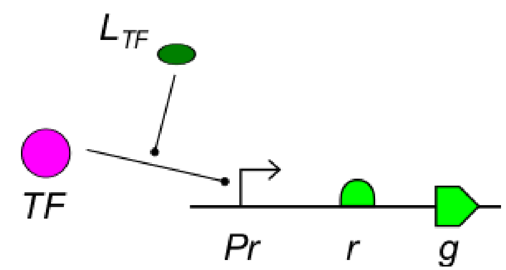

Consistent minimal model over all circuits

Parameter	Description	Unit
α_r	RBS strength	Relative RBS unit (RRU), normalized by BBa_B0032
$\nu_g^{(1)}$	Expression level of one copy of g	Relative promoter unit (RPU), normalized by BBa_J23101
α_{Pr}, β_{Pr}	Promoter strength & basal level	RPU
μ_g, μ_{TF}	Protein expression level of g, TF	RRU×RPU
K_{Pr}	Binding affinity	RRU×RPU
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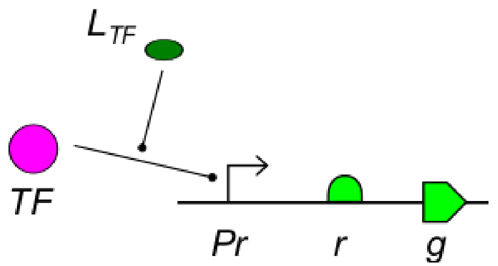

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Relative unit

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Fitting a single model

- Log-likelihood

$$LL(D|\theta) = -\frac{1}{2}\sum_{i=1}^{n}\left(\frac{M(x_i,\theta) - y_i}{\sigma_i}\right)^2 + const$$

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Fitting a single model

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Exp. data

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Exp. data parameter set # data point

model

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Fitting a single model

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Exp. data **parameter set** **# data point**

model **Exp. input**

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Exp. output standard error

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Exp. output standard error

- Maximum log-likelihood

$$\theta^* = \underset{\theta}{argmax}\ LL(D|\theta)$$

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Confidence interval

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- Measuring the uncertainty of a parameter

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$$CI_\alpha(\theta_i) = \left\{ x \mid \max_{\theta|\theta_i=x} LL(D|\theta) \leq \max_\theta LL(D|\theta) - \Delta(\alpha) \right\}$$

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One parameter

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One parameter

Threshold

Fitting multiple models

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  - Fit each model independently

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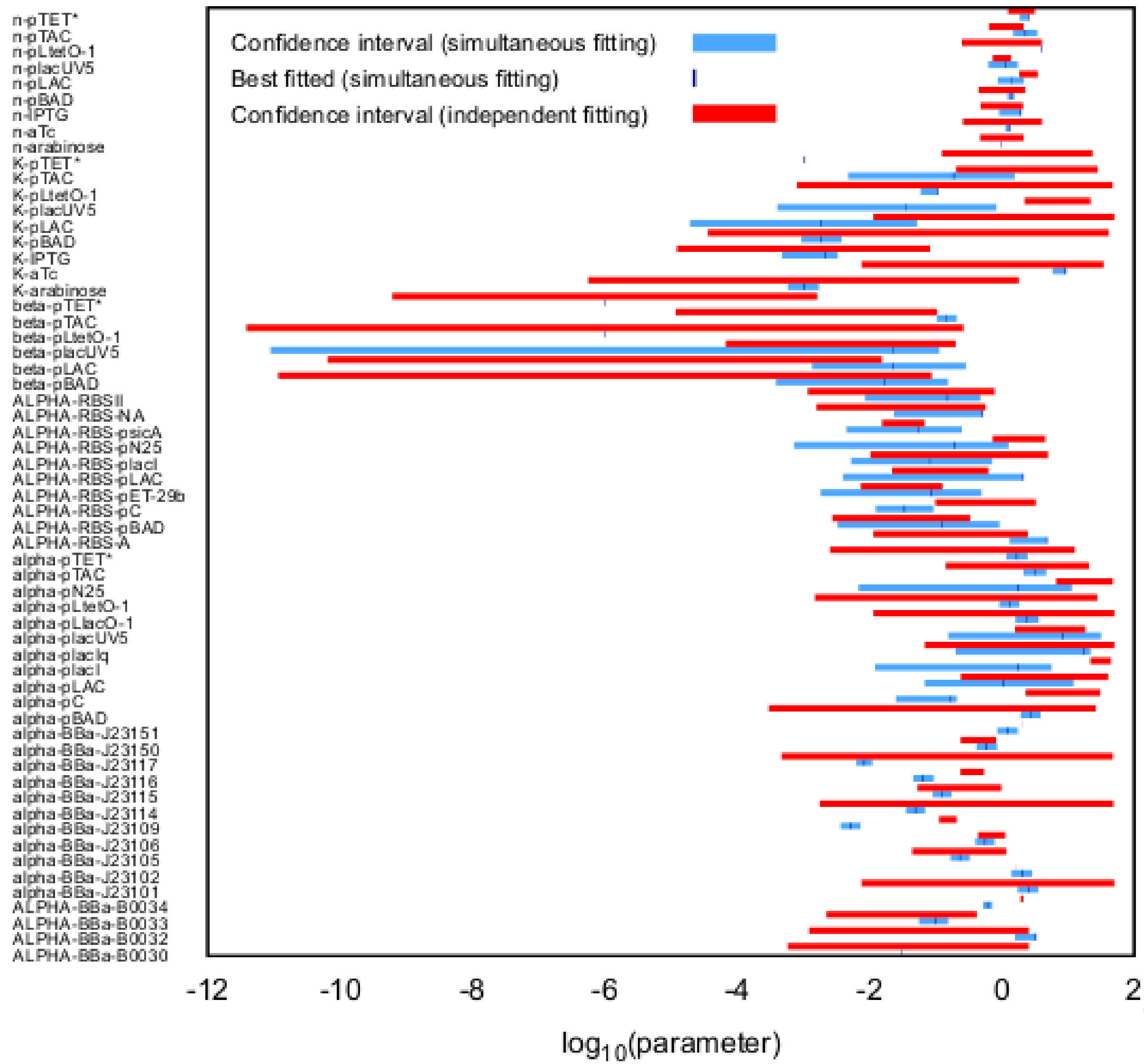
- Independent fitting
  - Fit each model independently
- Simultaneous fitting
  - Fit all models at the same time
- Sequential fitting
  - Fit each model, one by one
  - The results from the former fittings are used in the latter fittings

Simultaneous fitting vs independent fitting



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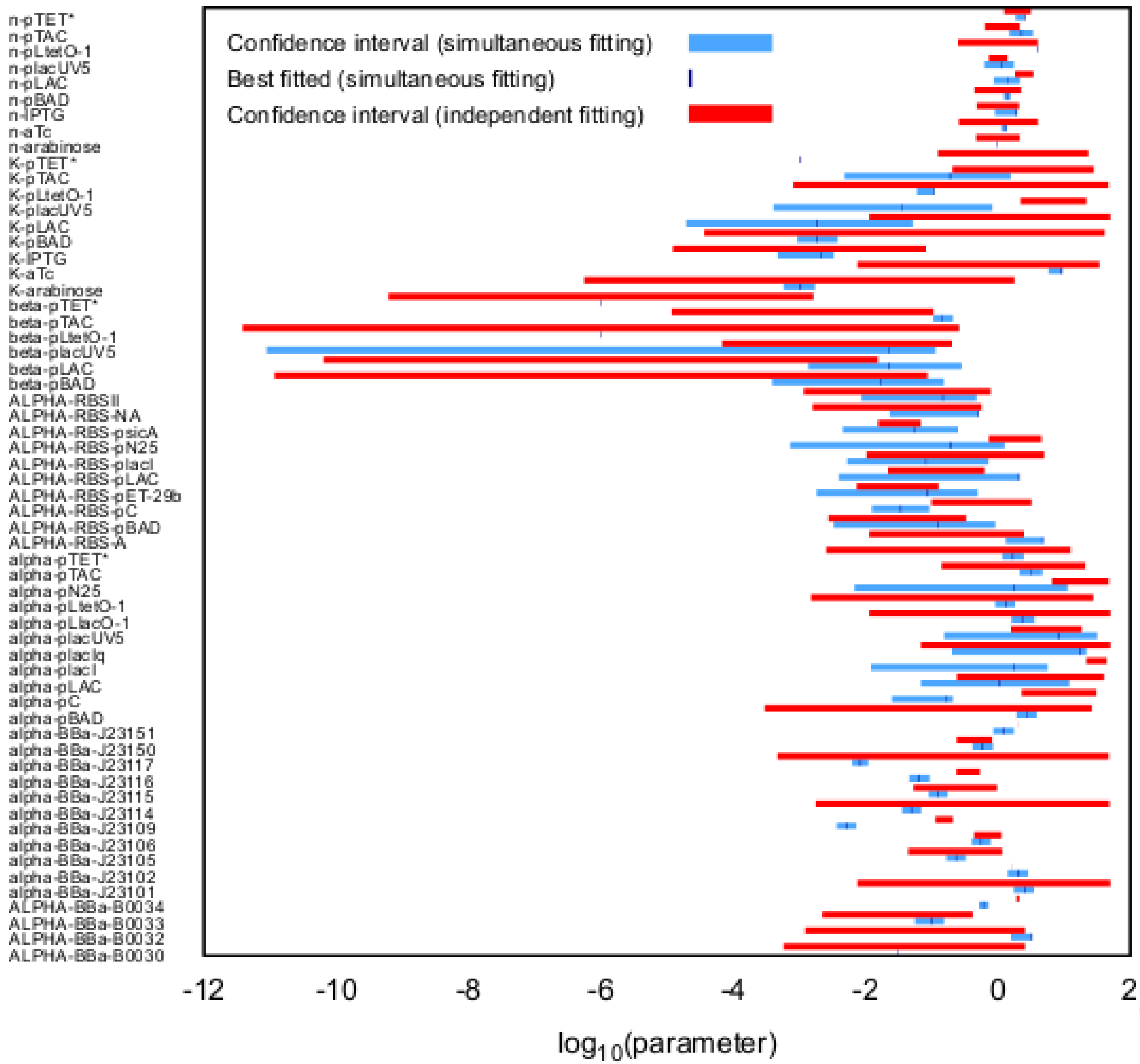
Simultaneous fitting vs independent fitting

Confidence interval length (log-scale) reduces 19% in average



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Simultaneous fitting vs sequential fitting

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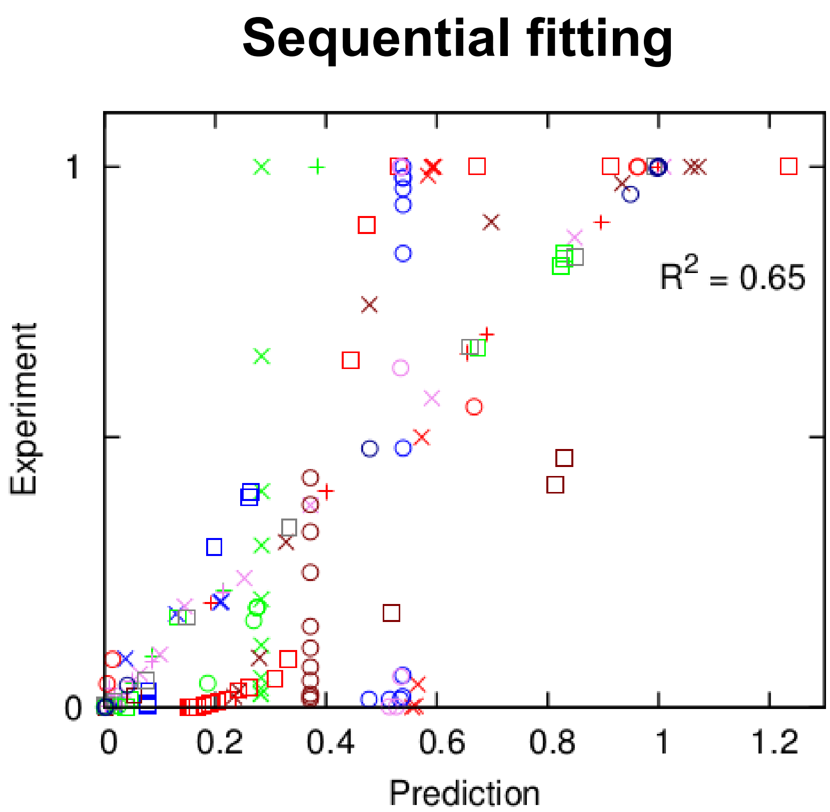

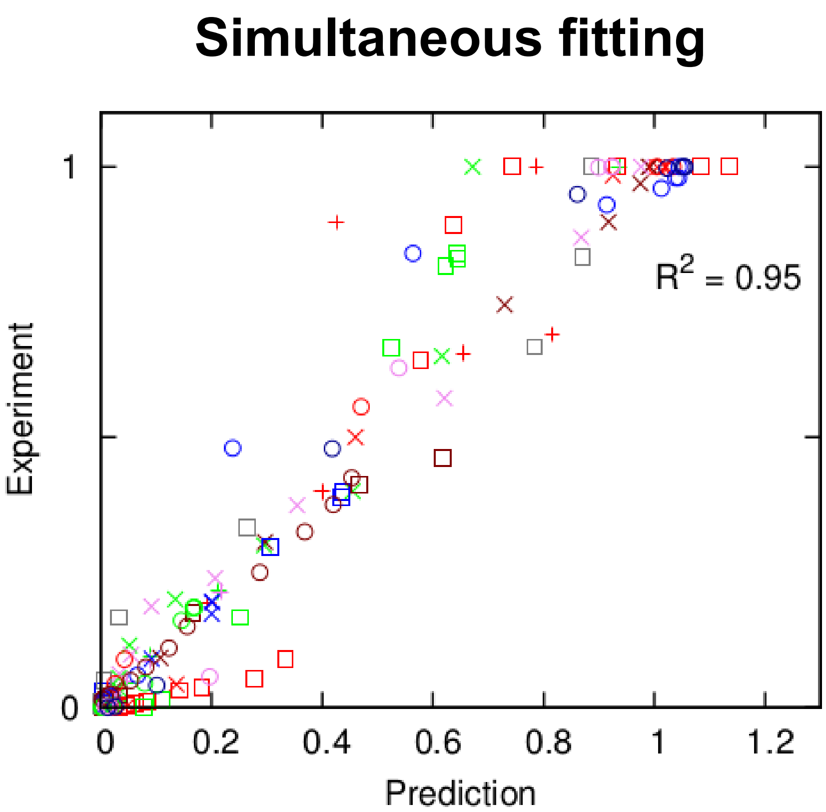

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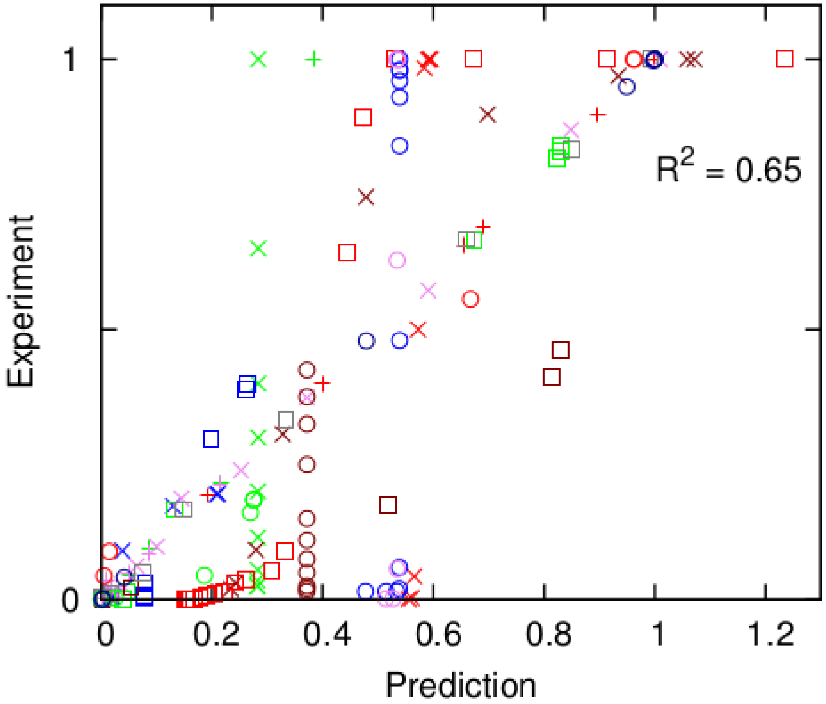
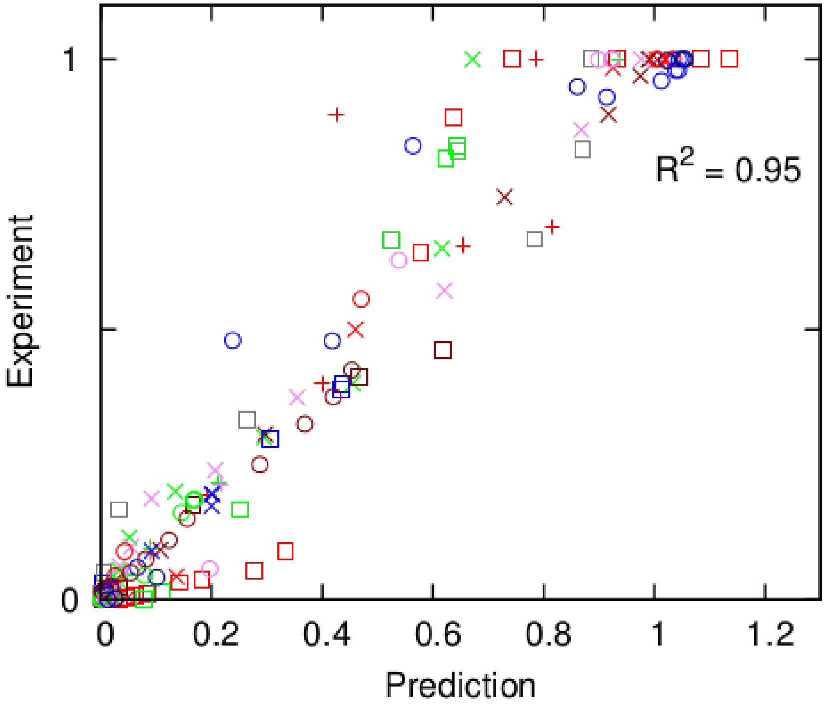
Simultaneous fitting vs sequential fitting

Sequential fitting



Simultaneous fitting



Error reduction: R^2 = 0.95 vs R^2 = 0.65

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Results

- Data integration & simultaneous fitting

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  - CI reduction: 19%

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  - CI reduction: 19%
  - Error reduction: $R^2 = 0.95$ vs $R^2 = 0.65$
  - Running time: 5x increase

Currently working on

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- Model extensions

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  - RNA-RNA interactions

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  - Protein-protein interactions

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- Experimental validation

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BLUE WATERS PROJECT

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