

# Using Gnuplot for Model Fitting

Biochemistry Boot Camp 2017  
Session #4  
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## *Think and Discuss*

What is a scientific model?

## Properties of Models

- Explain an observable quantity (e.g. measured heat, growth rate, etc.)
- Express quantity in terms of understandable parameters and fundamental constants (equilibrium constant, rate constants, etc.)
- Should be predictive (so we can test the model)

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## Examples: Biochemical Models

- Single site binding:  $P + L \rightleftharpoons PL$

$$\bar{v} = \frac{[PL]}{P_0} = \frac{(P_0 + L_0 + K) - \sqrt{(P_0 + L_0 + K)^2 - 4P_0L_0}}{2P_0}$$

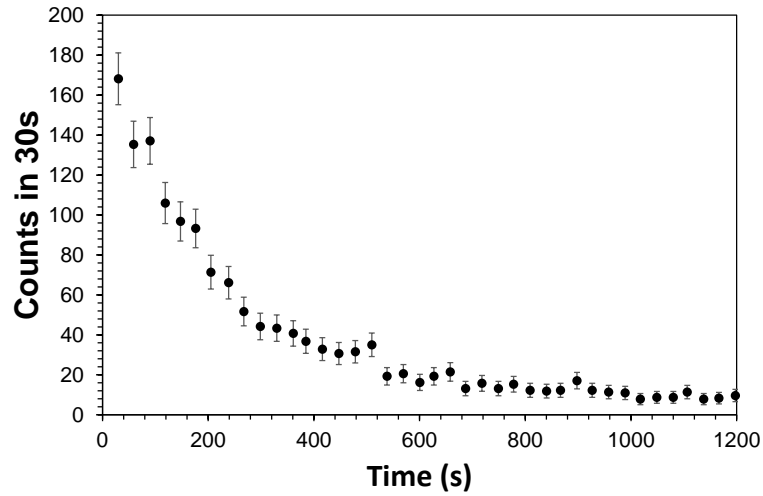
- Folding vs. Temperature:  $N \rightleftharpoons U$

$$f = \frac{1}{1 + K} = \frac{1}{1 + e^{-(\Delta H^0 - T\Delta S^0)/RT}}$$

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## Example Radioactive Decay

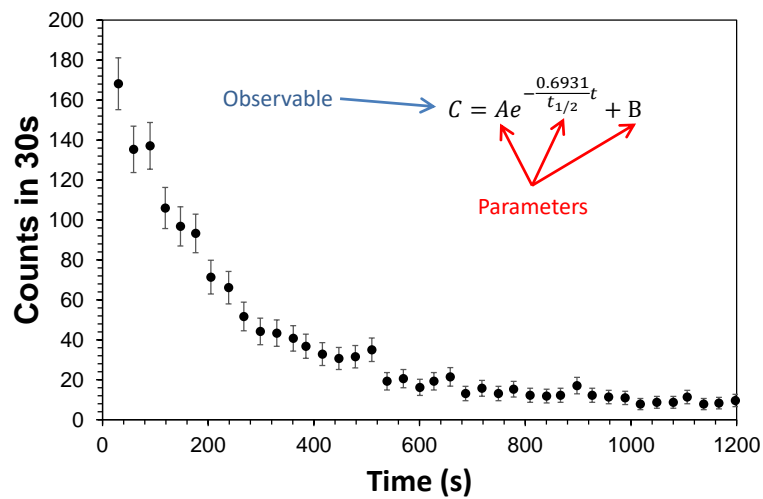
### Radioactive Decay of $^{137m}\text{Ba}$



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## Example Radioactive Decay

### Radioactive Decay of $^{137m}\text{Ba}$



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## How to Find Parameters?

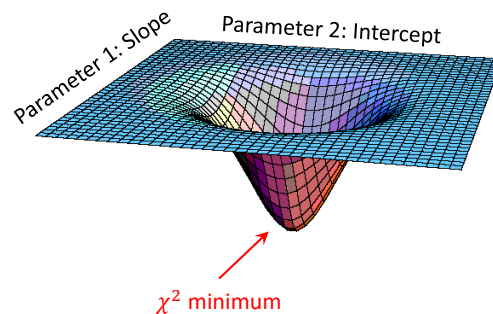
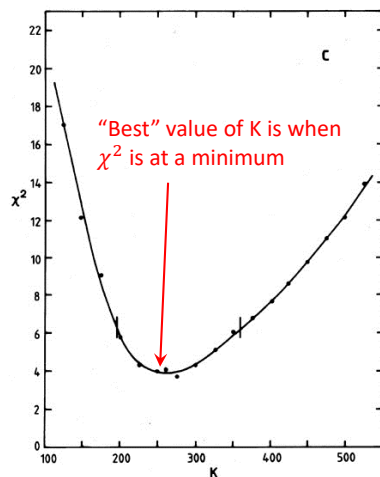
- Minimize the difference between the observed and model-calculated values:

$$\chi_n^2 = \frac{1}{N_d} \sum_i \left\{ \frac{1}{\sigma_i^2} [y_i - f(x_i)]^2 \right\}$$

- Definitions:
  - $y_i$  = observed data point  $i$
  - $f(x_i)$  = model calculated point  $x_i$  (will change when parameters are changed)
  - $\sigma_i$  = uncertainty for point  $i$
  - $N_d$  = # of observations - # of parameters

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## Minimizing Chi-Square



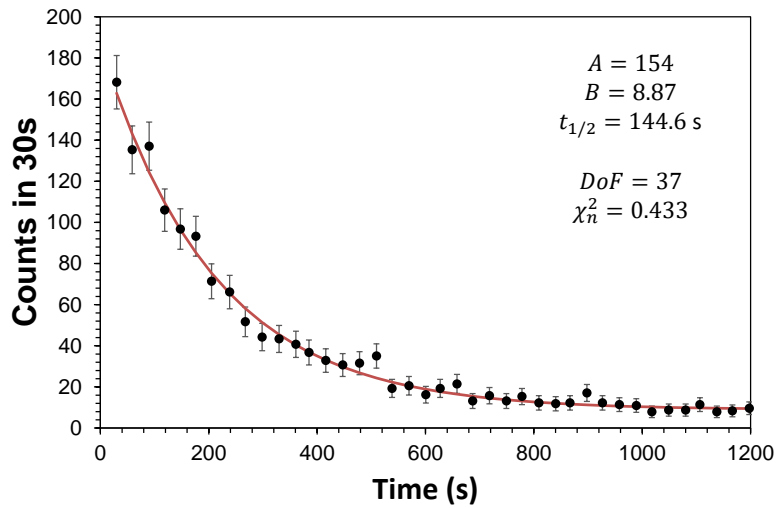
- Minimizing  $\chi^2$  works for multiple parameters, too
- Finding the global minimum can be hard

[https://ned.ipac.caltech.edu/level5/Wal2/Wal3\\_4.html](https://ned.ipac.caltech.edu/level5/Wal2/Wal3_4.html)

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## Example Radioactive Decay

### Radioactive Decay of $^{137\text{m}}\text{Ba}$

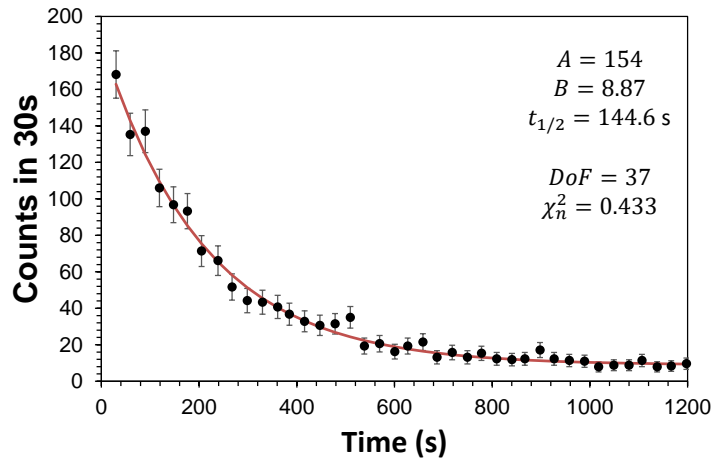


### *Think and Discuss*

The accepted half-life for  $^{137\text{m}}\text{Ba}$  is 153 s. Is our value of 144.6 good?

How to Assess a Fit:  
#1: Does the fit look good?

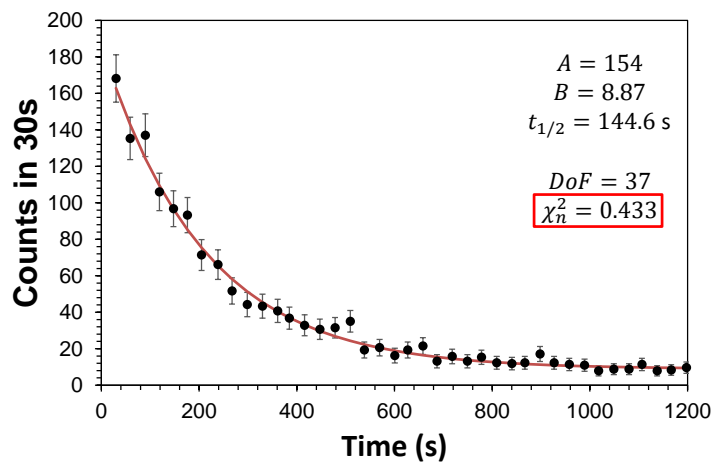
Radioactive Decay of  $^{137m}\text{Ba}$



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How to Assess a Fit:  
#2: Is Normalized Chi-Square ( $\chi_n^2 \leq 1.0$ )?

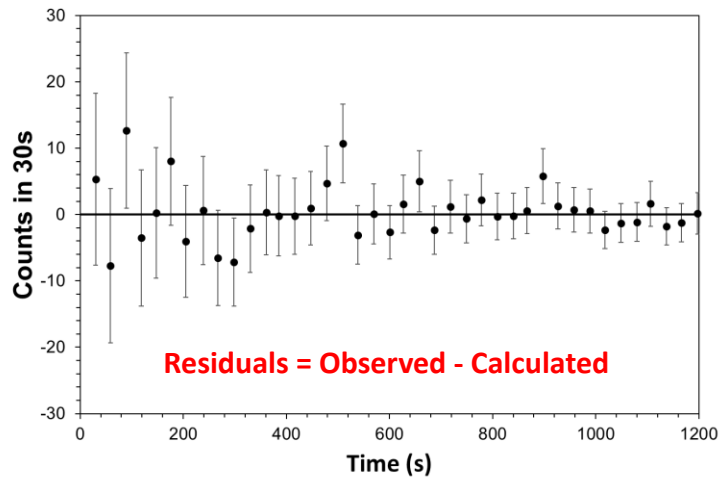
Radioactive Decay of  $^{137m}\text{Ba}$



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## How to Assess a Fit: #3: Check the Residuals Plot

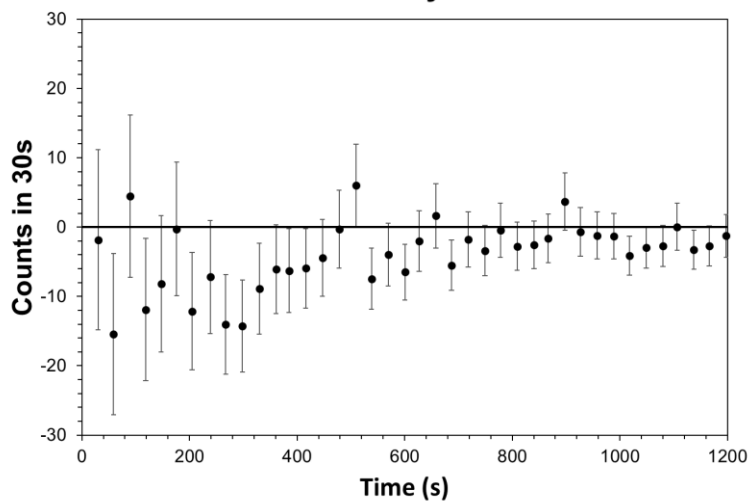
### Radioactive Decay of $^{137m}\text{Ba}$



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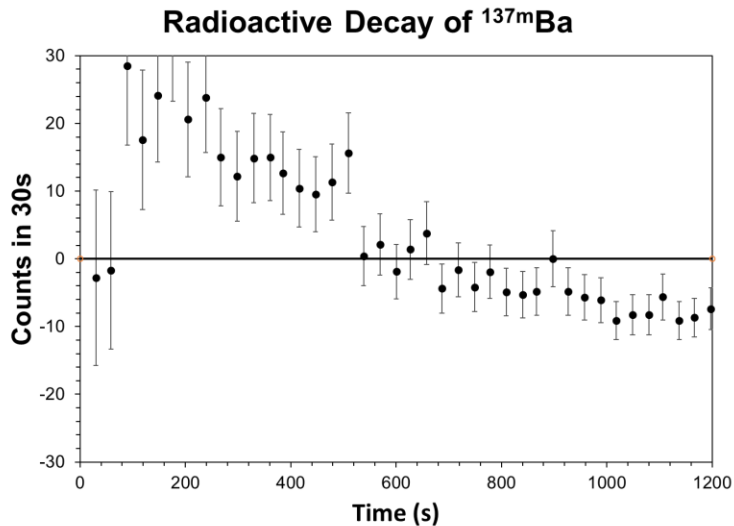
## Bad Fit Example: Model Over-Predicts Data

### Radioactive Decay of $^{137m}\text{Ba}$



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## Bad Fit Example: Systematic Trends in Residuals

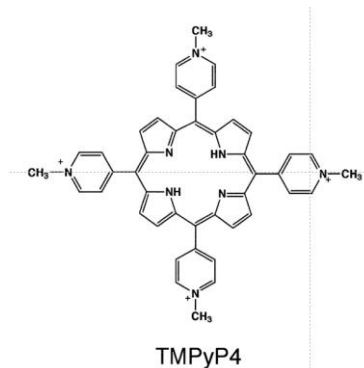
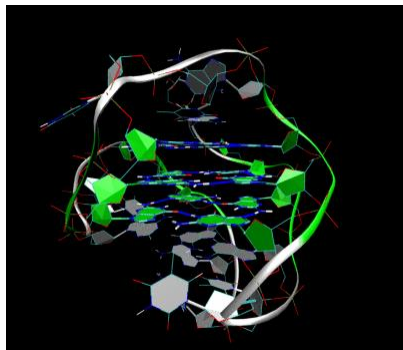


## Biochemical Model Building

- **Step 1:** Come up with a hypothesis about how a system works
  - How many binding sites?
  - Is there cooperativity?
- **Step 2:** Translate the qualitative hypotheses into an observable mathematical form with *parameters*
  - Example parameters:  $K$ ,  $\tau$ ,  $N$
  - Parameters may not be known
- **Step 3:** Design an experiment that that can produce observables from step 2; perform the experiment
  - *Optimize* the parameters to make the fit look as good as possible
- **Step 4:** Assess the fit – Is the agreement convincing?



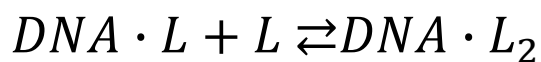
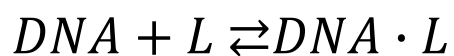
## Practical Example: DNA Binding



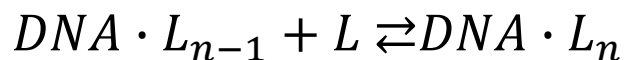
- What is association constant?
- How many binding sites?

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## Practical Example: DNA Binding



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- Assumption in our model: All equilibrium constants are identical (equivalent binding)

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## Practical Example: DNA Binding

- Experimentally, it is possible to measure the degree of binding ( $\bar{\nu}$ ) as a function of free drug concentration ( $L$ ):

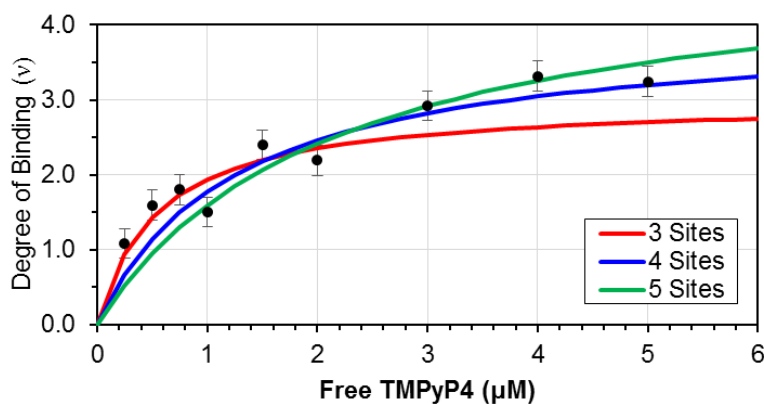
$$\bar{\nu} = \frac{nK_{eq}L}{1 + K_{eq}L}$$

- We observe  $\bar{\nu}$  and  $L$ ;  $K_{eq}$  and  $n$  are the parameters.

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## Practical Example: DNA Binding

### Binding of TMPyP4 to Quadruplex DNA



- Download this data as `binding.txt` from the website.

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## The Power of Gnuplot

- Minimizing chi-square can be very tricky; Excel isn't always up to the task
- What about estimating uncertainties of the parameters?
- Gnuplot is a tool that can handle some of these challenges (see tutorial)

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## Summary

- Biochemical models allow us to quantify and predict the behavior of biological systems
- Fitting parameters allow us to optimize agreement between model and observations
- Programs like Gnuplot enable generalized model fitting with statistical analysis