Modeling of Vaccinations & Infectious Diseases

Calibration I – Optimization

1st GENID Summer School on Infectious Disease Modeling

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Use of infectious disease models

- The spread of infectious diseases is usually very dynamic ⇒ Population effects of intervention are hard to capture with studies
- Modeling is an established tool for assessing the effectiveness of intervention (even for questions around reimbursement)
- Different understanding of *modeling*:
  - (Mechanistic) simulations vs. (statistic) models
  - Prognosis- vs. scenario models
- Infectious disease models are often a statistical models with structural (mechanistic) components to answer counter-factual (what-if) questions

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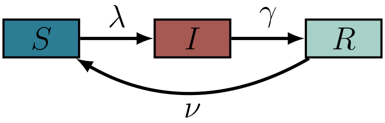
Mechanistic Model



- Model structure is given by a-priori knowledge about the system
- Goal: Estimating the effect of changes of input parameter values on the model outcome / overall system

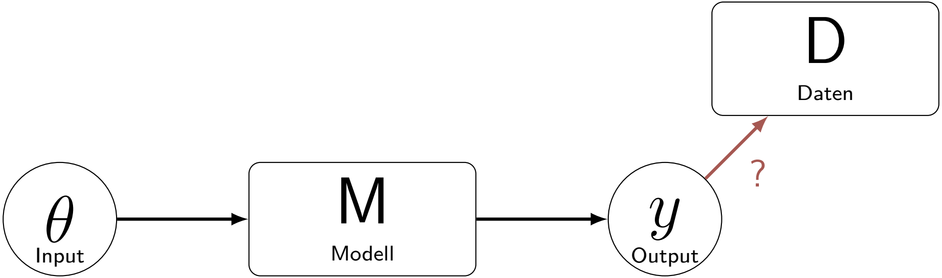
Statistical Model

$$y = \alpha + \beta X$$

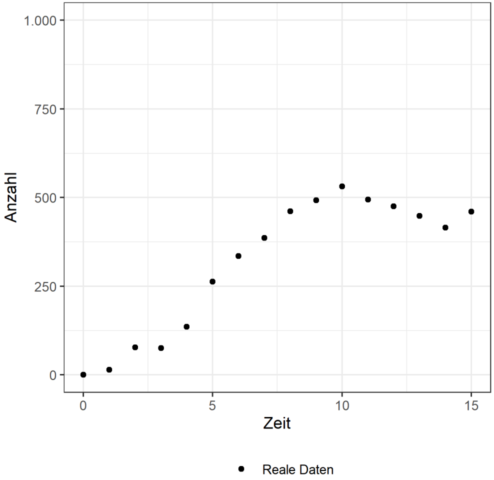
- Flexible and/or agnostic "model structure"
- Goal: Find associations between variables in data

- Due to incomplete evidence, purely mechanistic models (simulations) will not reproduce the observed dynamic of the transmission in the population
- The combination of mechanistic and statistic model allows,
  - finding missing parameter values
  - interpolation of missing data points (or prediction of future data points)
  - To test hypothesis about associations between input parameters of the model
  - extrapolate counter-factual (what-if) scenarios

How can we make a model reproduce observed data using calibration / model fitting?



Procedure of model calibration



1. Define a **calibration target** (i.e., what data should the model reproduce)
2. Define **"free" parameters** and perform an initial model run (using *best guess* values from the literature)
3. Compare real, observed data with the model output via a **Goodness-of-Fit** (GoF) function
4. **Change** the values of the "free" parameters $\Rightarrow$ go to step 2

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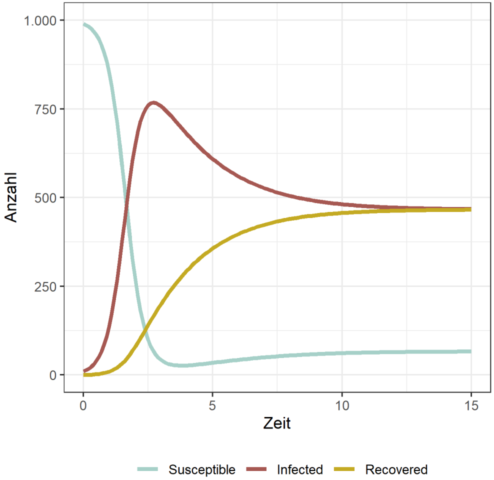

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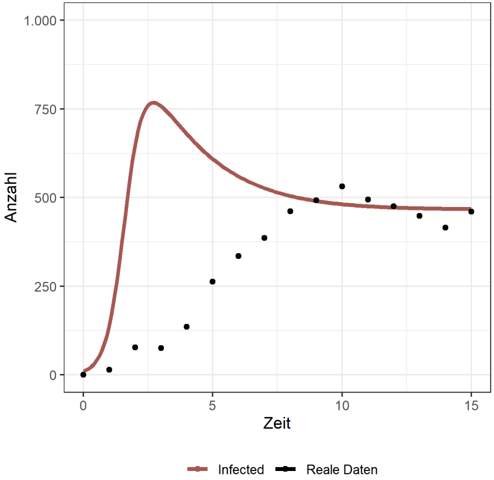

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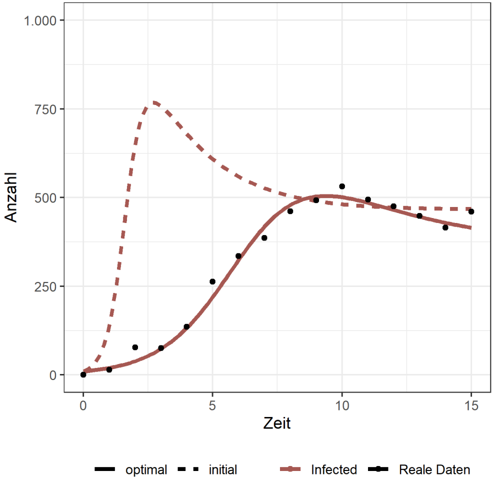

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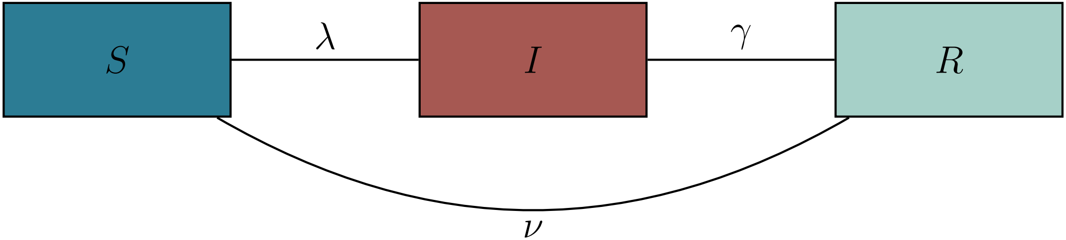
- Usually, infectious disease models are fitted to **prevalence** or **incidence** of a certain disease outcome
- Outcomes usually consist of
  - Infections
  - Symptomatic infections
  - Cases using the health care system (e.g. outpatient visit, hospitalizations)
  - Deaths
- **Prevalence** corresponds to the number of persons in a *State* at time t
- **Incidence** corresponds to the *Flow* into a state over time period $t_0 - -t_1$



S
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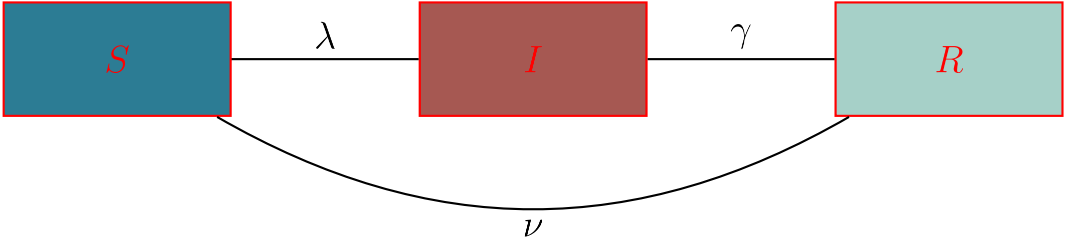
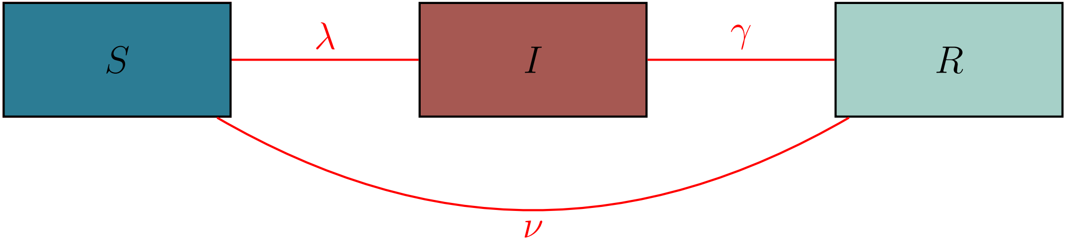
1. Kalibrierungsziele

Procedure of model calibration

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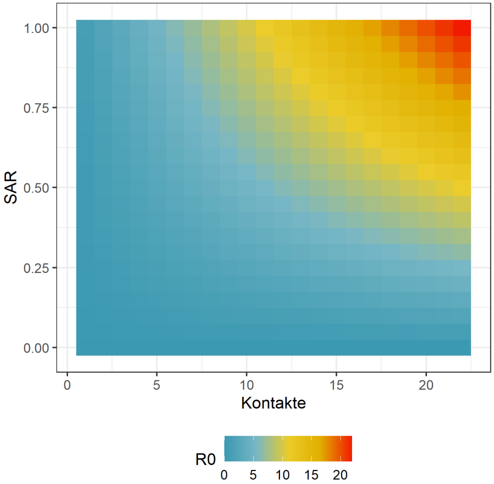
- Basically, one can set as many parameters as free parameters as you like (even all of them) (*states* as well as *flows*)
- Infectious disease model usually calibrate the *secondary attack rate* (SAR) or the reproduction number R_0 directly, as these are often unknown and have a great impact on the transmission dynamics
- When choosing free parameters, the problem of **identifiability** may arise



- No unique solutions can be found, if parameters are strongly correlated or if one free parameter can be represented as a linear-combination of other free parameters
- For example, a certain value of R_0 can either be achieved by a high number of contacts and a lower SAR or via a low number of contacts and a high SAR

- How can you measure the goodness-of-fit of a model (i.e., how well the model output corresponds to observations)?
  - **Squared Error:** $Q(\theta) = \sum_{i=1}^{n}(f(x_i, \theta) - x_i)^2$
  - **Chi-Squared:** $\chi(\theta) = \sum_{i=1}^{n}(\frac{f(x_i,\theta)-x_i}{\sigma_i})^2$
  - **likelihood:** $\mathcal{L}(\theta|x) = P_\theta(X = x)$ (discrete variable) bzw. $\mathcal{L}(\theta|x) = f_\theta(x)$ (continuous variable)
- Squared Error (also *Mean Squared Error*; MSE or *Root Mean Squared Error*; RMSE) should be minimized
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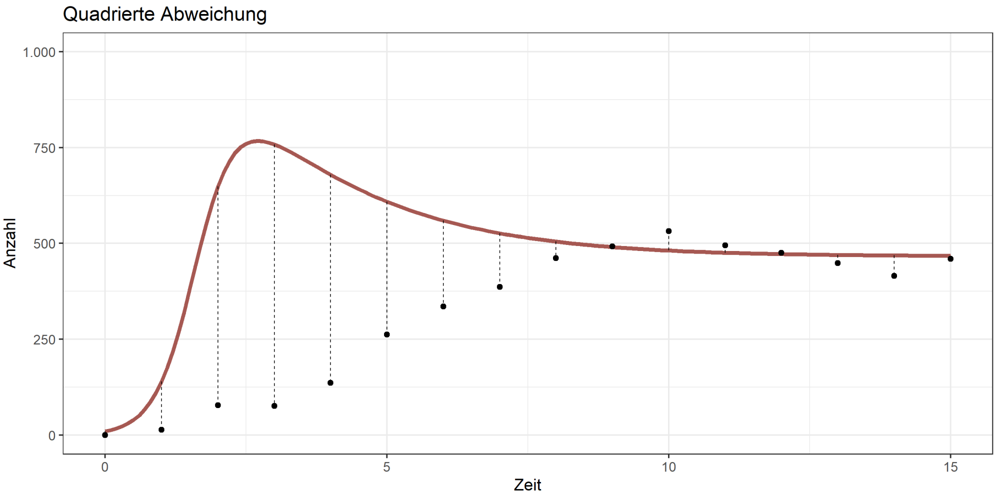

Quadrierte Abweichung
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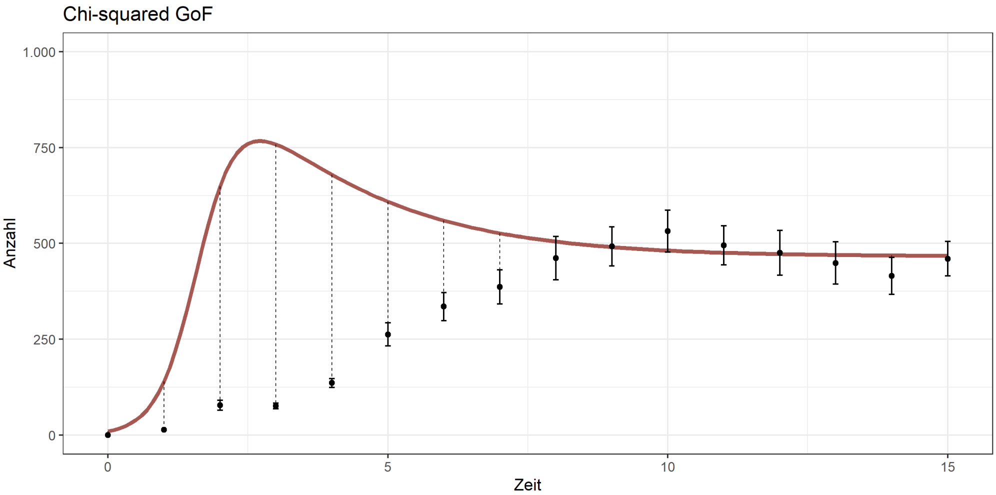

Chi-squared GoF
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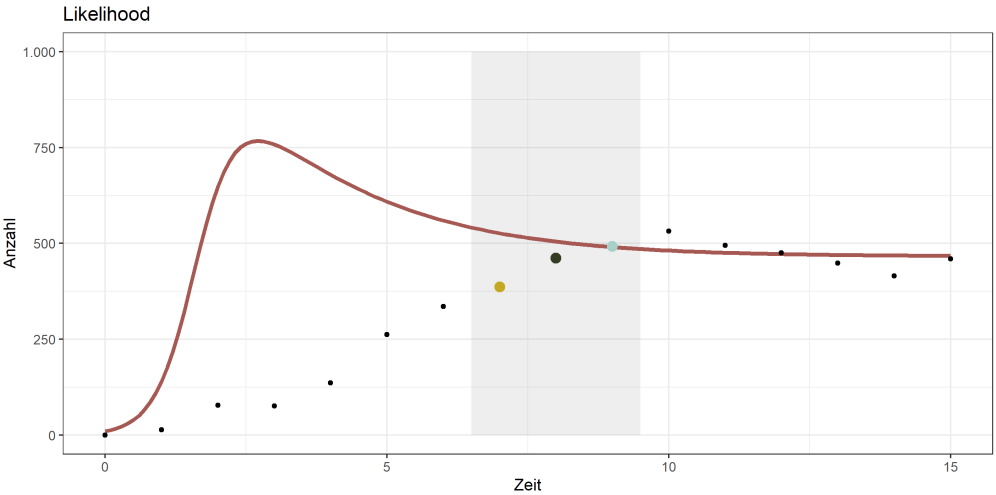

Likelihood
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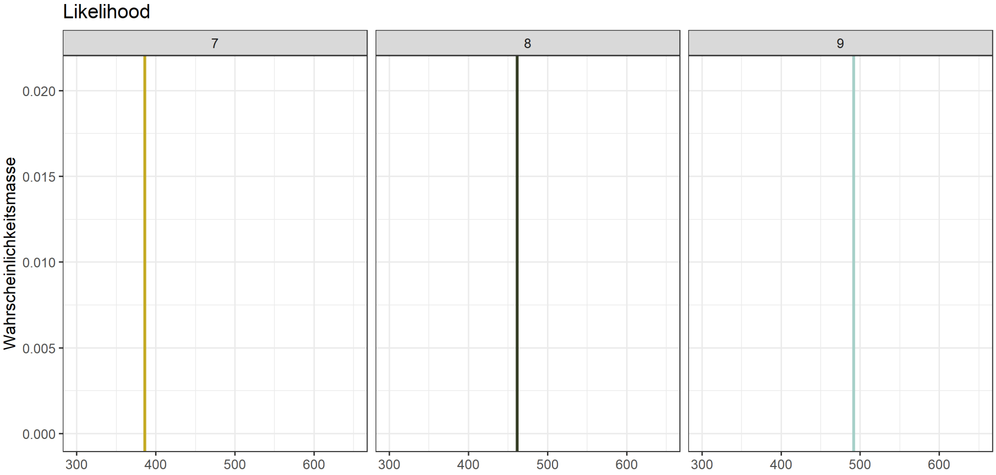

Likelihood
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Wahrscheinlichkeitsmasse
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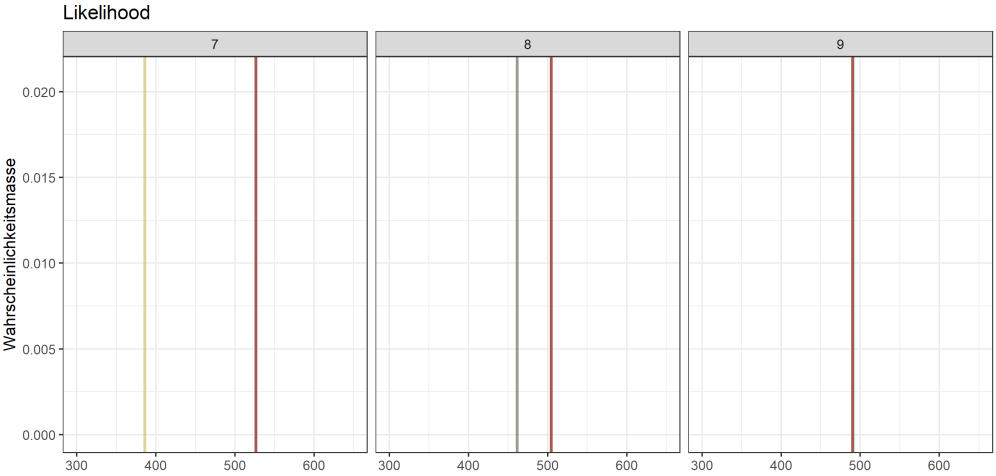

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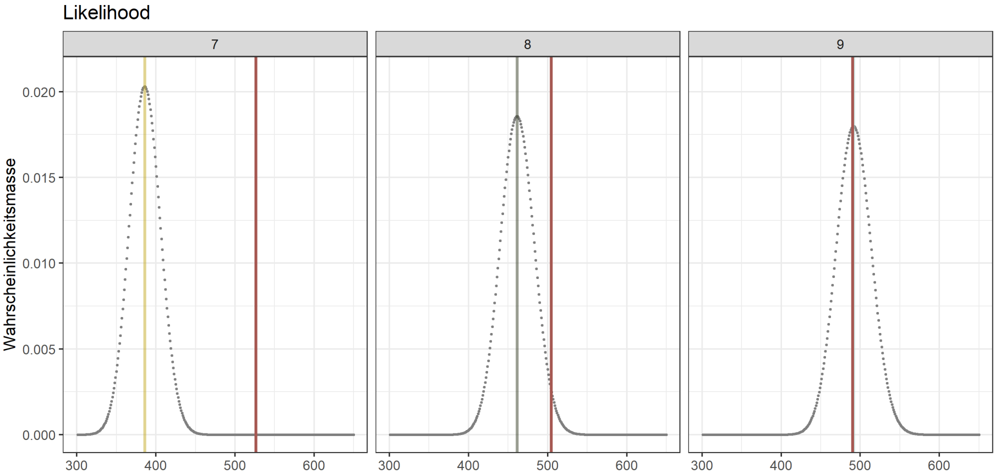
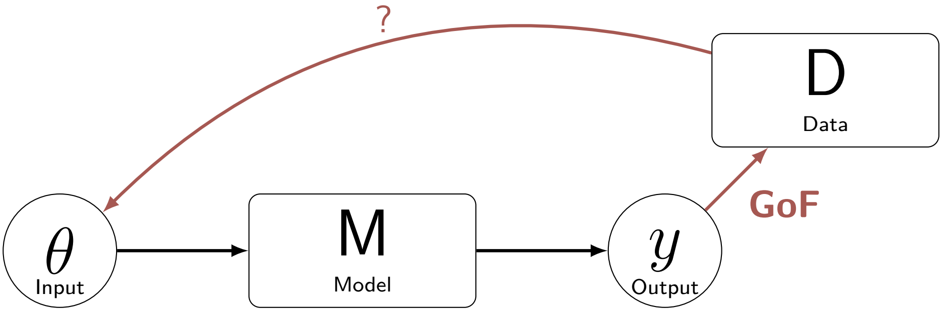
3. Goodness-of-Fit
Procedure of model calibration

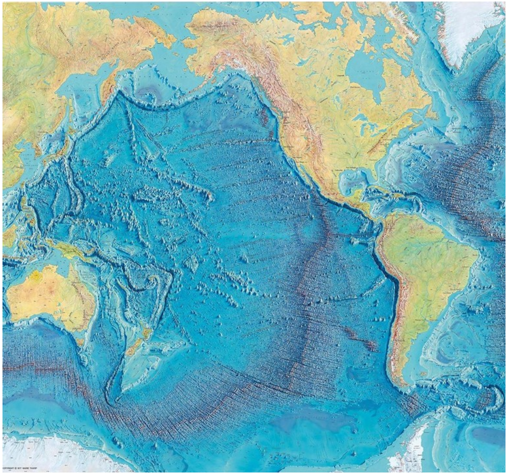


- *log-likelihood* is the most common GoF-measure
- The calibration process will be slow or difficult, if the initial values of the free parameters are far away from the optimal values
- The calibration target usually dictates the choice of the probability distribution
  - Poisson- or negative Binomial-distribution for count data
  - Gamma-distribution for variables with support $x \in \mathbb{R}^+$
  - Beta- or Binomial-distribution for $x \in [0, 1]$
- Combinations of calibration targes or rather their GoFs can be combined

Goal of the **adaption** step is finding a value for θ leading to the optimal GoF

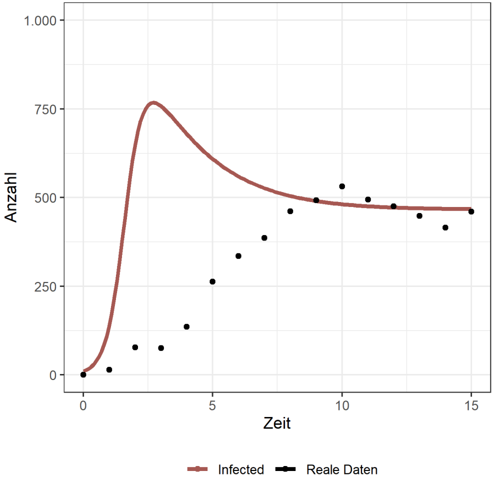


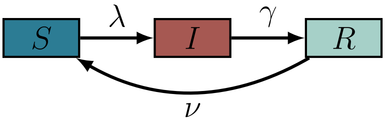
How do we find the deepest point of the ocean?



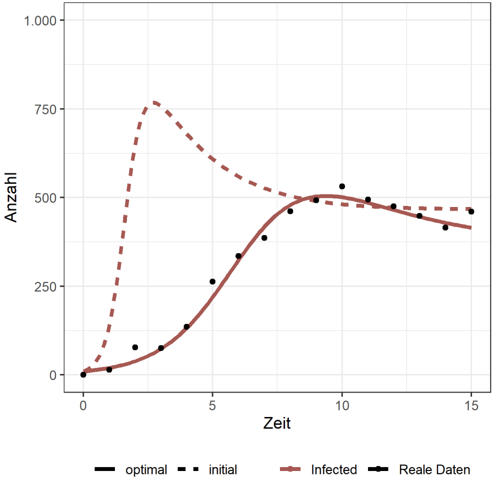
- How do we find latitude and longitude of the deepest point of the ocean?
- We do not know the map of the ocean
- With each dive, we can only explore one geographic position on the ocean floor
- Dives are very expensive, so
  - we want to find the deepest point as fast as possible or with the least amount of dives
  - there is a maximum number of dives that can be performed
- Our echosounder can only measure the depth in meters (not cm or mm)

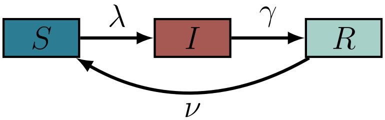
Example	**Models**
Depth	GoF
Latitude & Longitude	free parameters θ
Dive	Model run
Costs of dive	*run-time* of the model
precision of echosounder	acceptance criteria





- $\gamma = \dfrac{1}{5}$ and $\nu = \dfrac{1}{5}$
- Starting population $S = 990$, $I = 10$ and $R = 0$
- Free parameter λ
- How to we arrive at the true (optimal) $\lambda = 0.9$ starting from $\lambda = 3$?





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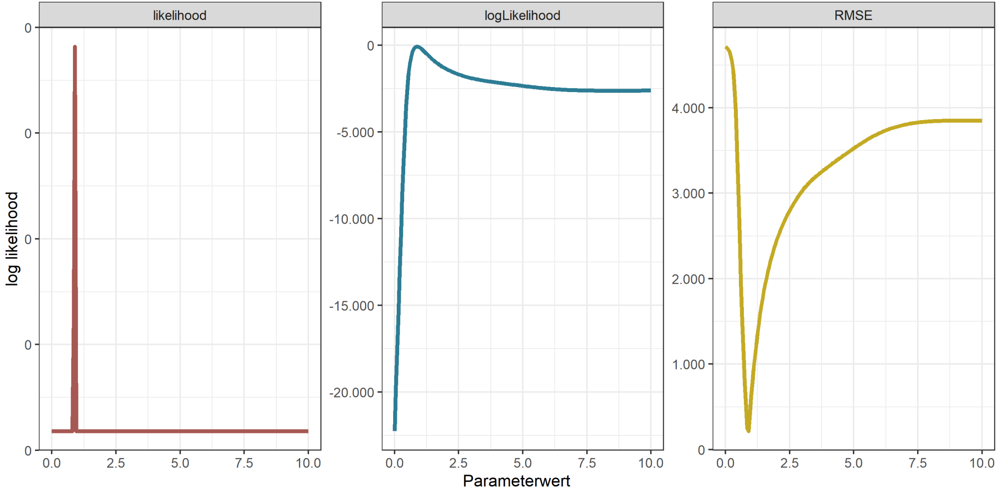
likelihood
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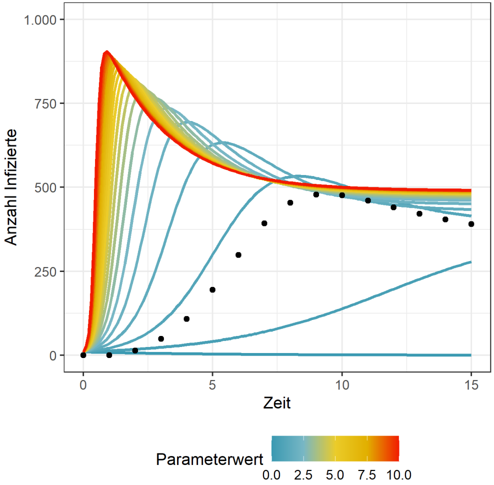
Overview algorithms

Adaption step

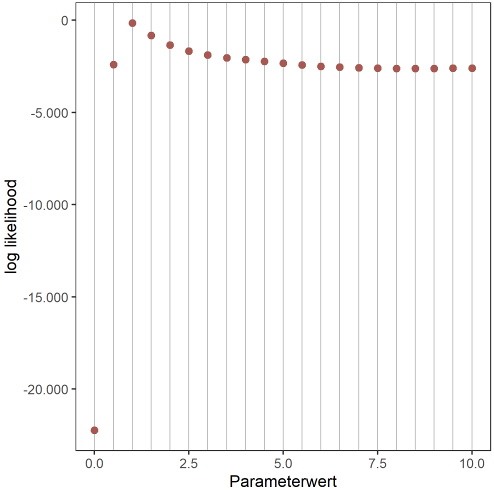
- There are many methods and algorithms available for adaption step
- Even for the same algorithm, countless implementations with slight variations can be found
- The following slides try to show the basic ideas of three different classes of **optimization** algorithms

The *grid search* method **systematically** tries different values for λ

1. Define limits for the values of each free parameter (e.g., $p_1 \in [0, 100]$ and $p_2 \in [0, 1]$)
2. Define an interval for each of the value ranges defined in step 1 (e.g., 10 for p_1 and 0.1 for p_2)
3. Evaluate / run the model for all combinations of the previously defined values (e.g. $\{(0; 0), (0; 0.1), \ldots, (10; 0), (10; 0.1), \ldots, (100; 1)\}$)



- Variation of parameter λ between 0 and 10 using a step of 0.5
- Calculate the GoF-measure for each model run
- Choos the model with the best (optimal) GoF-measure



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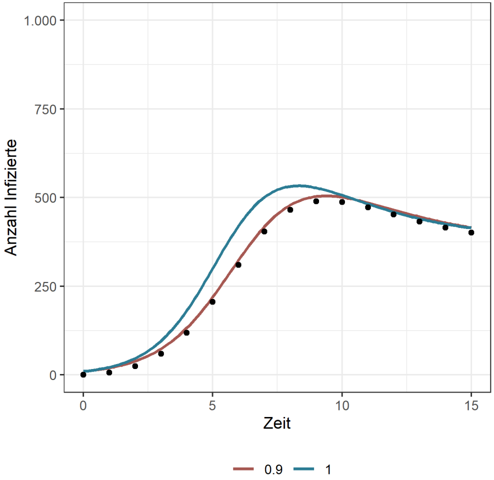

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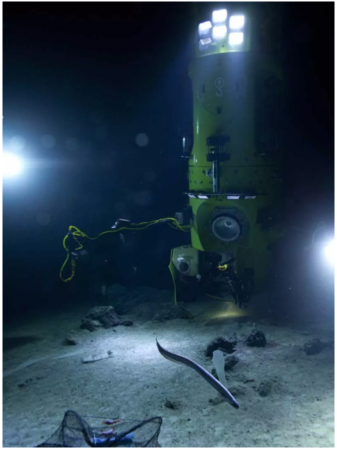
Pros

- Easy to implement
- Parallelization easily possible
- Highly reproducible

Cons

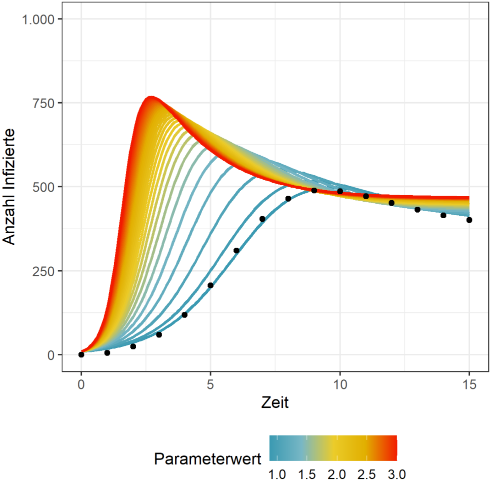
- Unclear, if the best value is within the defined value range
- Unclear, if better value might be between intervals
- *curse of dimensionality*: Using interval with 100 values and 5 Parameters
  $\Rightarrow 100^5 = 10,000,000,000$ model runs (*run-time* of 0.1 seconds leads to 31.8 years of computation time)



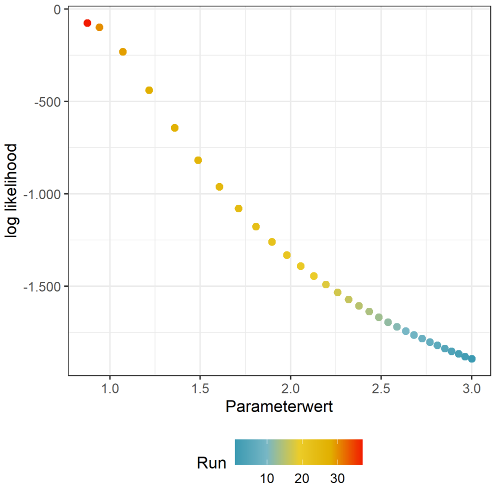
- We measure the depth with each dive
- With a little more effort (costs) we can retrieve more information on the ocean floor:
  - How strongly and in which direction does the floor descent? (1. derivaite)
  - Is it getting more steaper or more shallower? (2. derivative)
- Gradient-based algorithms use this additional information, but come with additional costs

Gradient Descent algorithm

1. We first measure at an (random) initial point (x_0) of the free parameters and calculate the GoF ($F(x)$)
2. Calculate the 1. derivative at intial point $x_0 \Rightarrow$ Calculate direction of steepest descent (Jacobian $\nabla F(x)$)
3. We follow the direction of the steepest descent for a distance γ to point x_1
4. Repeating steps 2 and 3 ($x_{n+1} = x_n - \gamma_n \nabla F(x_n)$) ideally leads to the optimal values x^* of the free parameters
5. The search stops, as soon as we hit a maximum number of model runs, or as soon as the GoF of x_{n+1} does not improve by a certain increment compared to the GoF of x_n



- Begin gradient descent at initial parameter value 3
- Step size γ is set to $1/20,000$
- Maximum of 100 iterations
- The algorithm converges regularly after 37 Iterationen, i.e., it found the optimal value



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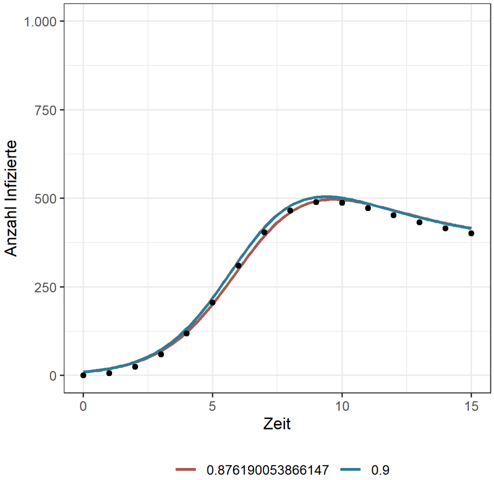

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Pros

- Very efficient, i.e., finds the optimal value with few model runs
- Very fast, if the 1. derivative of $F(x)$ (Jacobian) is known or can be analytically derived

Cons

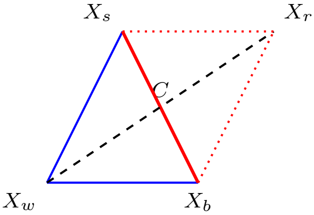
- GoF-function needs to be differenciable (problematic for non-continuous GoF-functions)
- Approximation of the Jacobian needs additional model runs
- Might get stuck in local minima
- Step size of $gamma$ too large $\rightarrow$ Zick-Zack-ing over the optimal values
- Step size of $gamma$ too small $\rightarrow$ algorithm becomes in-efficient

- Most algorithm are searching for parameter values in $\mathbb{R}$
- This might lead to unwanted effects, e.g., if SAR becomes negative $\Rightarrow$ persons vanish from the model population
- Transforming parameters can solve this problem:
  - $\mathbb{R} \to \mathbb{R}^+$: e^x (log-link)
  - $\mathbb{R} \to (0, 1)$: $\frac{e^x}{1+e^x}$ (logit-link)

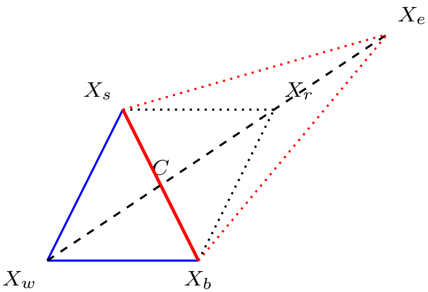
- Extensions of the *gradient descent* algorithm are mostly about determining the step size γ, ideally making large steps with small descent and small steps for great descent
- E.g., Newton-method of BFGS are using the Hessian **H** (2. derivative) instead of the Jacobian **J** (1. derivative)
- This increases the requirenments on the GoF-function (at leat 2 times differenciable, ideally with onyl one minimum)
- If it is possible to approximate **H**, the negative inverse $-\mathbf{H}^{-1}$ can be used to approximate the covariance matrix of the free parameters. I.e, this makes it possible to calculate the variance or confidence intervals of the estimates.

Nelder-Mead algorithm

1. for n free parameters calculate the GoF for a simplex of $n + 1$ points $x_1, \ldots, x_{n+1}$
2. Sort the points by their GoF-function $f(x)$
3. Calculate the centroids C between all points, besides the point with the worst GoF (x_w)
4. Perform one of **4** possible calculations steps or transformations
5. Stop the search after maximum of iterations, reaching a specific size of the simples or no relevant improvement of the GoF



1. **Reflection**: Calculate $x_r = C + \alpha(C - x_w)$, if $f(x_w) < f(x_r) \leq f(x_b)$ replace x_w by x_r
2. **Expansion**: If $f(x_r) > f(x_b)$, calculate additional point $x_e = C + \gamma(x_r - C)$. Replace x_w by x_r or x_e, whichone is better
3. **Contraction**: If $f(x_r) < f(x_s)$, calculate $x_c = C + \beta(x_w - C)$. If $f(x_c) > f(x_w)$, replace x_w by x_c
4. **Shrink Contraction**: If none of the above, reject all points besides x_b and calculate new coordinates for all other points via $x_j = x_b + \delta(x_j - x_b)$



1. **Reflection**: Calculate $x_r = C + \alpha(C - x_w)$, if $f(x_w) < f(x_r) \leq f(x_b)$ replace x_w by x_r
2. **Expansion**: If $f(x_r) > f(x_b)$, calculate additional point $x_e = C + \gamma(x_r - C)$. Replace x_w by x_r or x_e, whichone is better
3. **Contraction**: If $f(x_r) < f(x_s)$, calculate $x_c = C + \beta(x_w - C)$. If $f(x_c) > f(x_w)$, replace x_w by x_c
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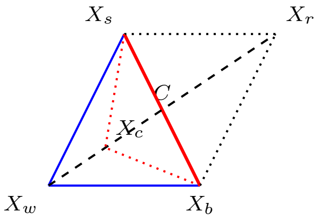

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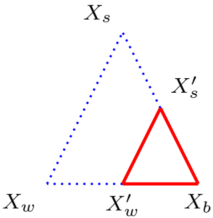

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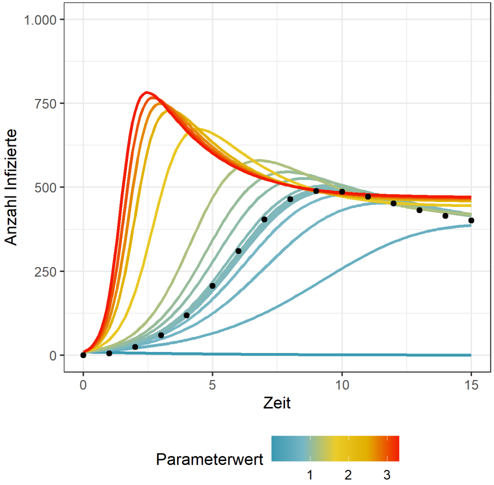
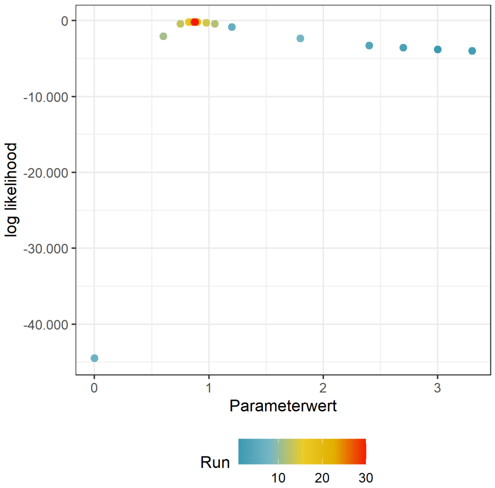


- Start Nelder-Mead for inital parameter value 3
- Using the following values for the control parameters of the algorihtm:
  - *Reflection* α: 1
  - *Expansion* γ: 2
  - *Contraction* β: 0.5
  - *Shrink Contraction* δ: 0.5
- Maximum of 100 iterations possible
- Algorithm converges successfully after 30 iterations, i.e., finding the optimal value



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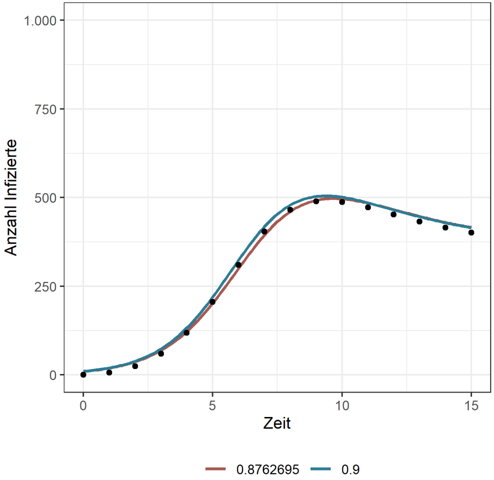

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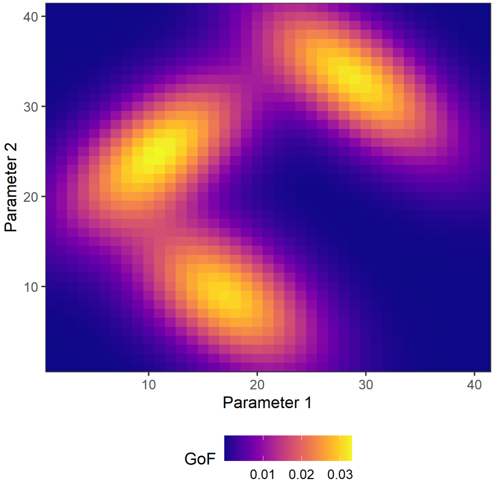
Pros

- Can find the optimal parameter values with few model runs
- It is not necessary to calculate or approximate $\mathbb{J}$ or $\mathbb{H}$ and less problematic for non-continuous GoF functions

Cons

- Selecting the initial simplex may lead to local search resultung in local minimum
- Unlucky choice of control parameters α, β, γ and δ may lead to long run times
- Not suitable for many free parameters $(N > 20)$
- Several model evaluations (model runs) per iteration of the algorithm
- Results for very shallow GoF functions might depend on the acceptance criterium



- Gradient-based algorithms are very efficient, but prone to find local minima and are problematic for "unsmooth" GoF-functions
- **J** and **H** are usually not known or cannot be derived analytically for (complex) differential equation models (or agent-based models) and need to be approximated (costs!)
- Acceptance criteria for IDM usually need to be set more forgiving than for other problems

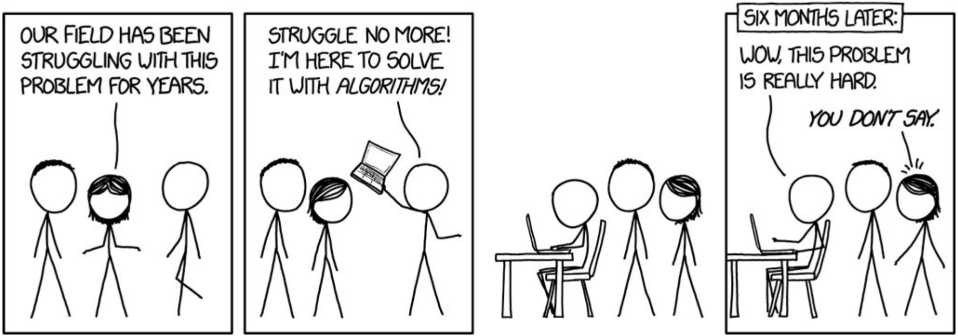
- In contrast to regression models, optimization algorithms for infectious diseae models rather take hours or days than seconds
- Keeping the cost of each model run low is absolutely essential. I.e., having fast code and remove unnecessary parts.
- A run-time of 1 second translates to 28 hours for 100.000 iterations
- Only few (mostly inefficient) algorithms *grid-search* can be parallelized, as step $n+1$ depends on the result of step n

- Keep the number of free parameters to a minimum to avoid *overfitting* (especially for scenario models)
- Start with few parameters and try to identify from the results where additional parameters might yield gains in the GoF, e.g., age-specific rates
- It maybe useful to use "meta"-parameters, for example for age- or time-dependencies
- Instead of having one free parameter per age group or time step, work with linear equations (e.g., $\beta_0 + \beta_1 * AGE$) or *splines*
- But watch for artefacts in your extrapolations!

Fazit

- Calibration is the second most time-intensive part of modeling (after searching for data input)
- All algorithms require certain assumptions, to be effienct at ”clever guessing” the right parameter values
- Violating these assumptions might lead to false results or inefficient calibration
- The choice of the free parameters, the calibration targets and the choice and setup of the opimization algorithm should be in line

Thank you very much for your attention!



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