Development of High Integrity Diagnostics
Results Calculation Algorithms
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\[ f(x, \bar{p}) = p_1 \cdot \left(1 + p_2 \cdot x + \frac{p_3}{\left(1 + e^{-p_4(x-p_5)}\right) \cdot \left(1 + e^{-p_6(x-p_7)}\right)}\right) \]
Laboratory Diagnostics and Stakeholder Measurement Data and Calculation Algorithm Data Zoos Application Examples Conclusions
Diagnostics are about gathering medical data …to be transformed into actionable information.
High Integrity Diagnostics Results Calculation

Stakeholders Expectations

- **Business Development** expects superiority to competition
- **Assay/reagent developer** expects solution for problematic data
- **Finance** expects minimal development effort
- **Software implementation** expects simple formula and no future changes
- **Project management** expects finalization long before clinical trials
- **Regulatory bodies** expect design documentation and verification
- **Insurance/payer** expects a precise result at minimal cost
- **Patient** expects correct treatment based on accurate result
Laboratory Diagnostics and Stakeholder

Measurement Data and Calculation Algorithm

Data Zoos

Application Examples

Conclusions
High Integrity Diagnostics Results Calculation

Biochemical Influence Factors on PCR Reaction
High Integrity Diagnostics Results Calculation

Influence Factors on PCR Fluorescence Signals

Fluorescence Signal

Outlier

Color Crosstalk

Signal Imprecision

Signal Scale

Cycles
High Integrity Diagnostics Results Calculation
Implementation Expectations and Solutions

- Explainable to Biologists (challenge for an engineer)
  
  Data ➔ Shape ➔ Features ➔ Results

- Clearly defined for software engineers (challenge for a mathematician)
  
  Nonlinear regression model algorithm

- Minimal adaption effort to minimize validation scope and effort
  
  Calculation algorithm parametrization
High Integrity Diagnostics Results Calculation

Model Building

How does a kinetic PCR signal look like?

Answer of a physicist: Make a model

- Fits well to the data
- Comprehensive (describes key effects)
- Correct asymptotic behavior (global)
- As simple as possible (but no more)

\[
f(x, \vec{p}) = p_1 \cdot \frac{p_3}{1 + p_2 \cdot x + \left(1 + e^{-p_4 \cdot (x-p_5)}\right) \cdot \left(1 + e^{-p_6 \cdot (x-p_7)}\right)}
\]
High Integrity Diagnostics Results Calculation

Mathematical Kinetic PCR Model Function

\[ 1 + \frac{P_3}{(1 + e^{-P_4(x - P_5)}) (1 + e^{-P_6(x - P_7)})} \]

Animation created with MATHEMATICA
High Integrity Diagnostics Results Calculation
Development Approaches

• Lack of data. Possible approaches to foresee exceptional cases:
  – Use normal data, assume normal distribution of exceptions ($6\sigma$)
  – Generate a lot of real data (microelectronics, car industry deliverers)
  – ➔ Collect exceptions from similar applications, extrapolate from experience

• Scope unsettled. Approaches to deal with changes:
  – Start only when the discussion is finished (wait and see)
  – Imagine fully flexible solution (agile)
  – ➔ Develop with assumptions, expect and foresee them to change
High Integrity Diagnostics Results Calculation

Data Zoos: Data and Annotations
Kinetic Algorithm Seminar

Data Zoo: Special Data and Result Expectations

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**negative**

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**positive**

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**positive**

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**invalid**
High Integrity Diagnostics Results Calculation
Qualitative Expert System: «positive/negative»

- Asymptotic growth is high enough
- Nonlinear curve shape
- Maximal Slope is high enough
- End signal is high enough

All criteria fulfilled?

Positive Curve Call
High Integrity Diagnostics Results Calculation

Algorithm Parameter Development Example

RFI versus F value of Kinetic Algorithms: Light Cycler 96

- Positive
- Negative
- Equivocal

F Value for comparison of Kinetic PCR Model and Linear Function
High Integrity Diagnostics Results Calculation

Zika-Virus Blood Screening Story

• Existing platform (consumables, instrument and software)

• Development blood screening assay at two sites: Switzerland and California

• Versatile algorithm (parameterizeable without software code change)

• Initial settings (limits): educated guess, enabled fast start

• 5000 artificial and real samples with prototype reagent ➔ data zoo

• Settings adjustment based on data zoo annotations and experience ➔ Fastest development of blood screening application

➔ During April 3–June 11, 2016, a total of 68 (0.5%) presumptive viremic donors were identified from 12,777 donations tested in Puerto Rico

http://www.cdc.gov/mmwr/volumes/65/wr/mm6524e2.htm
Laboratory Diagnostics and Stakeholder

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Conclusions

• Health industry: Cost pressure, excellent performance expectations, regulatory hurdles to changes (improvements)

• Approach different stakeholders and interact in their thinking world (explainable concept are key)

• Collect and store experience (data and expectations)

• Expertise allows «extrapolation» to borderline and exception cases.

• In order to stay competitive adaptable solutions are necessary.

«A good developer develops in a way that allows extensions and adjustments of the design!»
Doing now what patients need next
Rolf Knobel is a trained physicist from ETH Zürich. He is working for Roche Diagnostics for 27 years. He has built up and led the molecular diagnostics system integration department. He has been instrument architect in several systems development projects. He is working as algorithms developer and application specialist for result calculation. At the moment he is process manager for systems architecture in the lead systems engineer department. He holds a double digit number of patents in the area of automation, processing and calculation. Rolf Knobel is married and has one daughter and two sons. He is a correspondence chess Grandmaster.