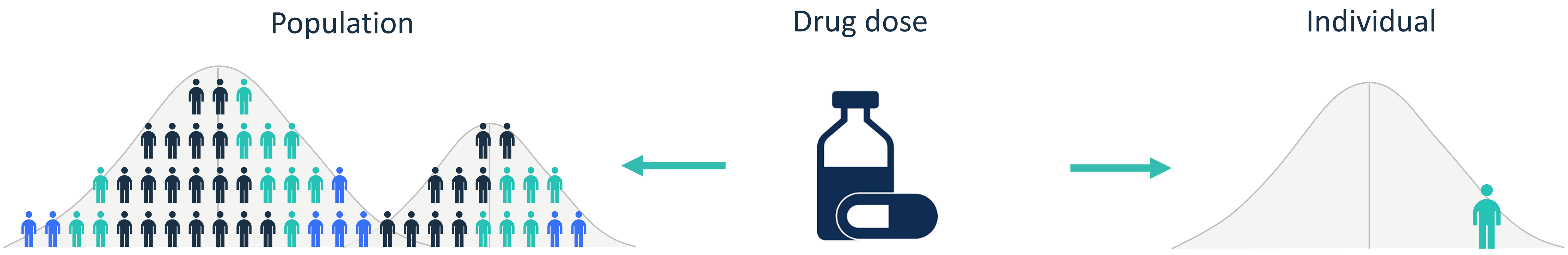
Building a Medical Device with R

Ron Keizer
Chief Scientific Officer

InsightRX

What do we build?



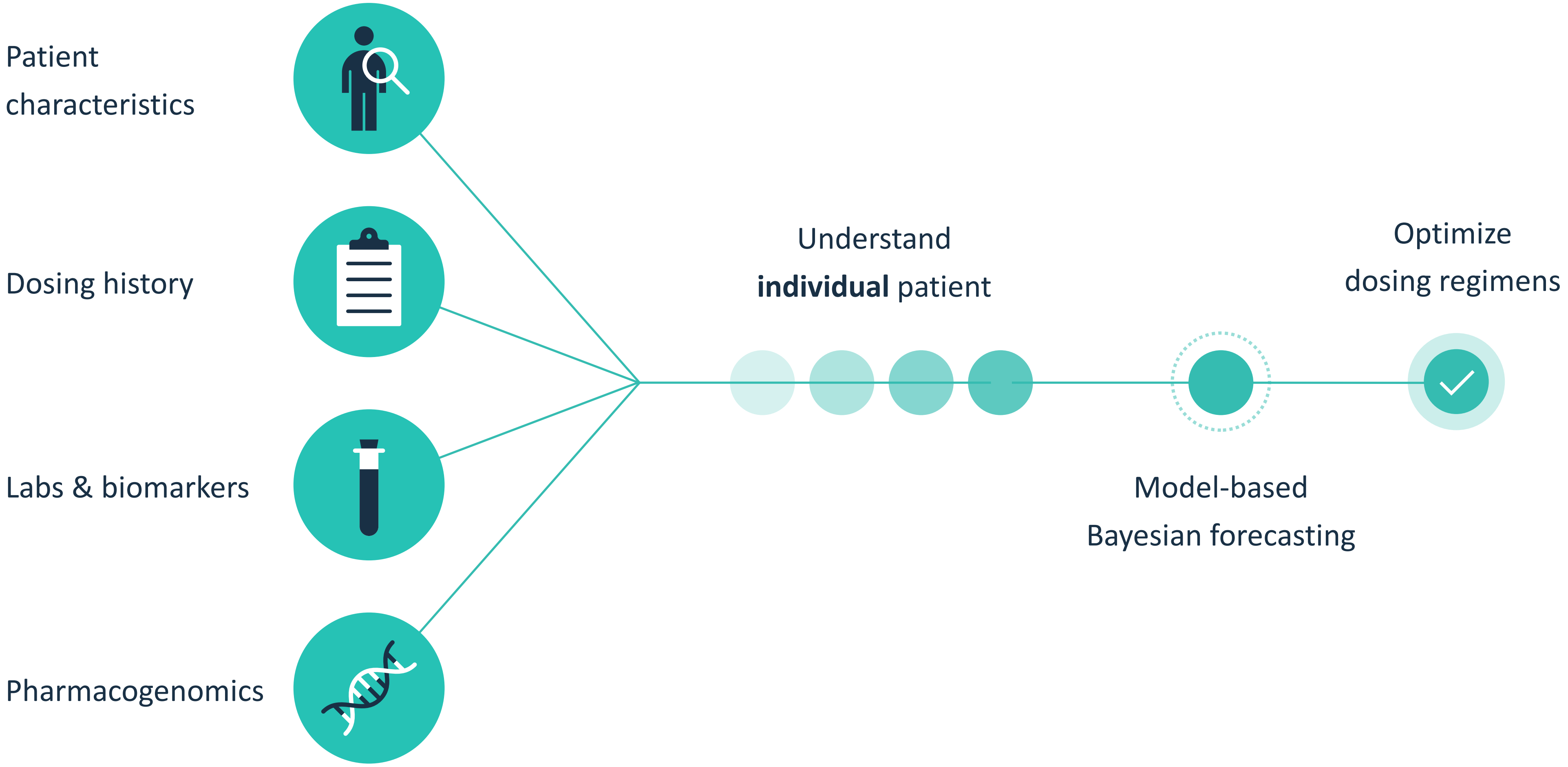
Population

Drug dose

Individual

Drugs
Antibiotics
Chemotherapy
Transplantation

Populations
Neonates / children
Elderly
Critically ill



Patient characteristics

Dosing history

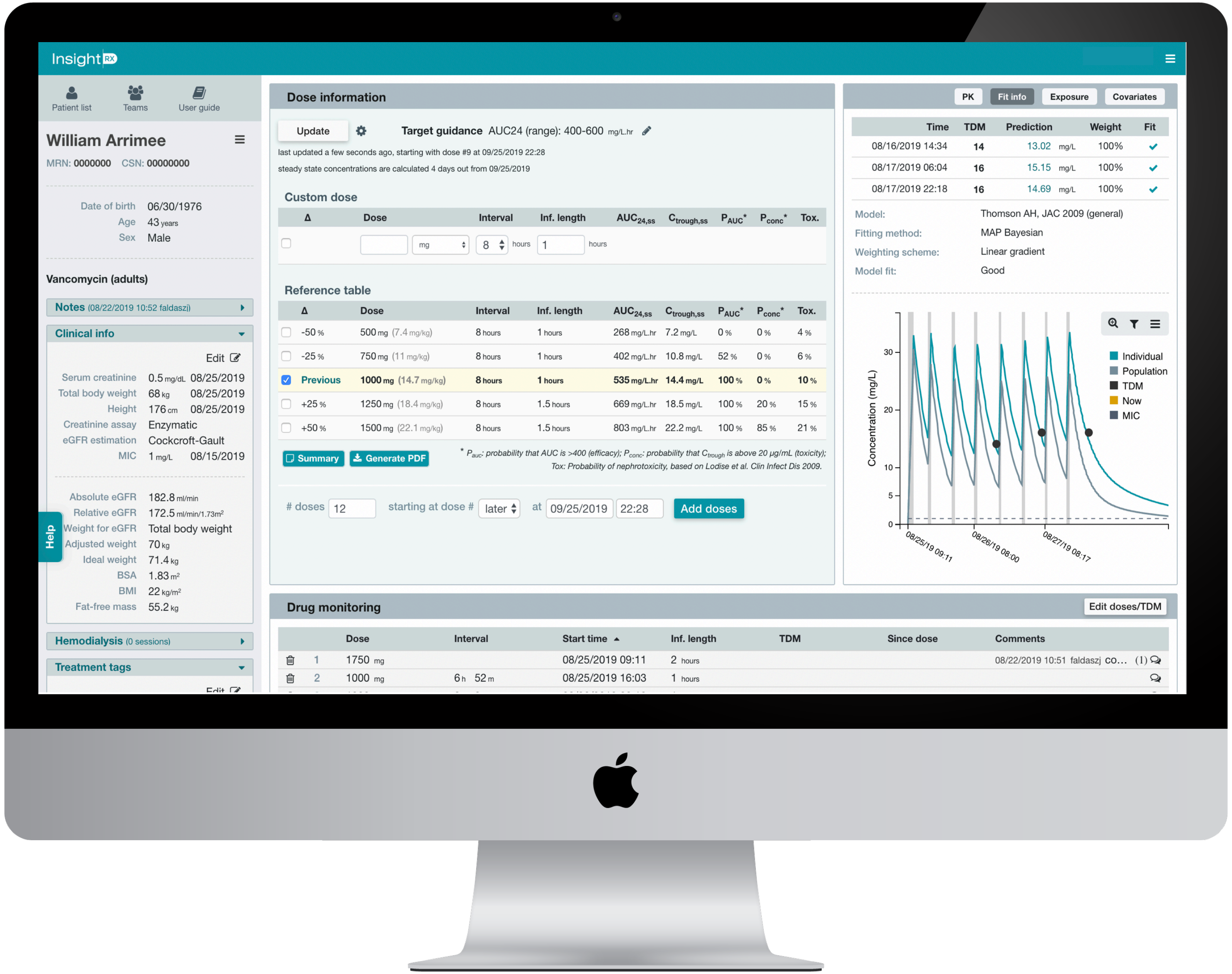
Labs & biomarkers

Pharmacogenomics

Understand **individual** patient

Model-based Bayesian forecasting

Optimize dosing regimens



Insight RX

Patient list | Teams | User guide

William Arrimee

MRN: 0000000 CSN: 00000000

Date of birth	06/30/1976
Age	43 years
Sex	Male

Vancomycin (adults)

Notes (08/22/2019 10:52 faldaszj)

Clinical info

Edit

Serum creatinine	0.5 mg/dL	08/25/2019
Total body weight	68 kg	08/25/2019
Height	176 cm	08/25/2019
Creatinine assay	Enzymatic	
eGFR estimation	Cockcroft-Gault	
MIC	1 mg/L	08/15/2019

Absolute eGFR	182.8 ml/min
Relative eGFR	172.5 ml/min/1.73m²
Weight for eGFR	Total body weight
Adjusted weight	70 kg
Ideal weight	71.4 kg
BSA	1.83 m²
BMI	22 kg/m²
Fat-free mass	55.2 kg

Hemodialysis (0 sessions)

Treatment tags

Edit

Help

Dose information

Update

Target guidance AUC24 (range): 400-600 mg/L.hr

last updated a few seconds ago, starting with dose #9 at 09/25/2019 22:28

steady state concentrations are calculated 4 days out from 09/25/2019

Custom dose

	Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*	Tox.
□		mg	8 hours	1 hours					

Reference table

	Δ	Dose	Interval	Inf. length	$AUC_{24,ss}$	$C_{trough,ss}$	P_{AUC}*	P_{conc}*	Tox.
□	-50 %	500 mg (7.4 mg/kg)	8 hours	1 hours	268 mg/L.hr	7.2 mg/L	0 %	0 %	4 %
□	-25 %	750 mg (11 mg/kg)	8 hours	1 hours	402 mg/L.hr	10.8 mg/L	52 %	0 %	6 %
☑	Previous	1000 mg (14.7 mg/kg)	8 hours	1 hours	535 mg/L.hr	14.4 mg/L	100 %	0 %	10 %
□	+25 %	1250 mg (18.4 mg/kg)	8 hours	1.5 hours	669 mg/L.hr	18.5 mg/L	100 %	20 %	15 %
□	+50 %	1500 mg (22.1 mg/kg)	8 hours	1.5 hours	803 mg/L.hr	22.2 mg/L	100 %	85 %	21 %

Summary | Generate PDF

* *P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity); Tox: Probability of nephrotoxicity, based on Lodise et al. Clin Infect Dis 2009.*

# doses 12 starting at dose # later at 09/25/2019 22:28 Add doses

PK | Fit info | Exposure | Covariates

Time	TDM	Prediction	Weight	Fit
08/16/2019 14:34	14	13.02 mg/L	100%	✓
08/17/2019 06:04	16	15.15 mg/L	100%	✓
08/17/2019 22:18	16	14.69 mg/L	100%	✓

Model:	Thomson AH, JAC 2009 (general)
Fitting method:	MAP Bayesian
Weighting scheme:	Linear gradient
Model fit:	Good

Drug monitoring

Edit doses/TDM

	Dose	Interval	Start time ▲	Inf. length	TDM	Since dose	Comments
1	1750 mg		08/25/2019 09:11	2 hours			08/22/2019 10:51 faldaszj co... (1)
2	1000 mg	6 h 52 m	08/25/2019 16:03	1 hours			

- cloud-based web-application
- based on pharmacology models
- integrated clinical workflow

What is a medical device?

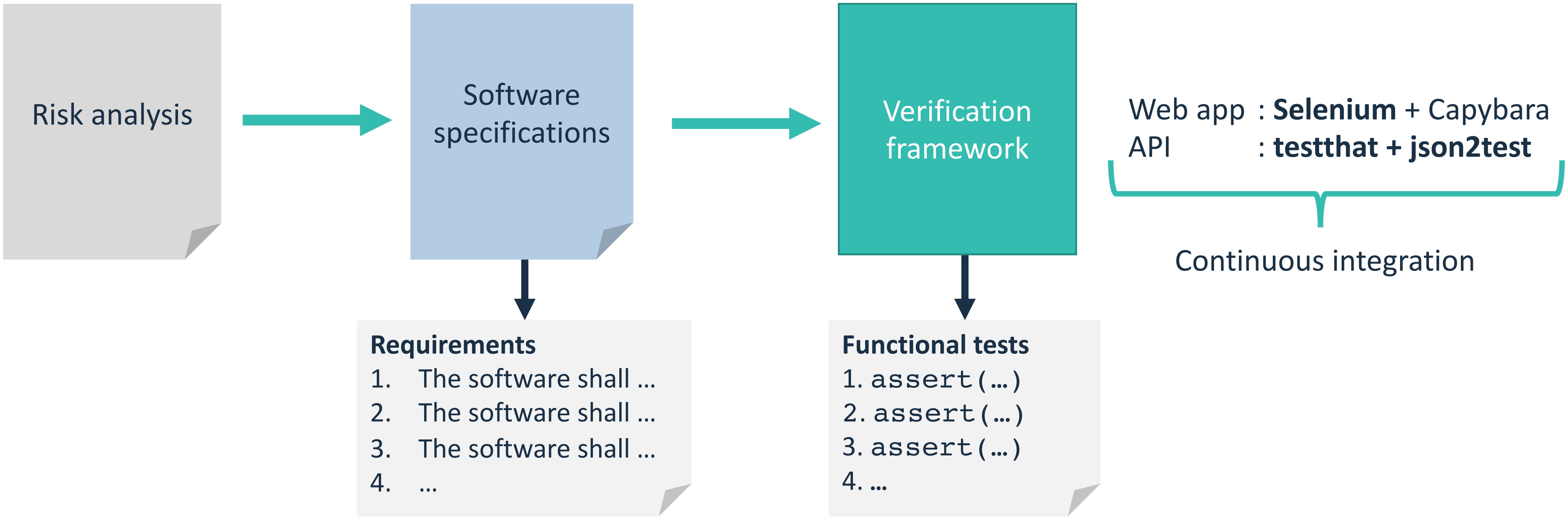
What is software as a medical device?

Clinical Decision Support (**CDS**)

Regulatory process: stages

1. **pre-development**
   - decide which class medical device
     - what claims are you making?
     - what are the risks involved?
   - set up quality system (US: 21 CFR 820, EU: 93/42/EC)
2. **product development**
   - under design controls
3. **verification**
   - Applying test framework
4. **validation**
   - File with FDA (510k)
5. **release**

Regulatory process: documents



Risk analysis

Software specifications

Verification framework

Web app : **Selenium** + Capybara
API : **testthat + json2test**

Continuous integration

Requirements

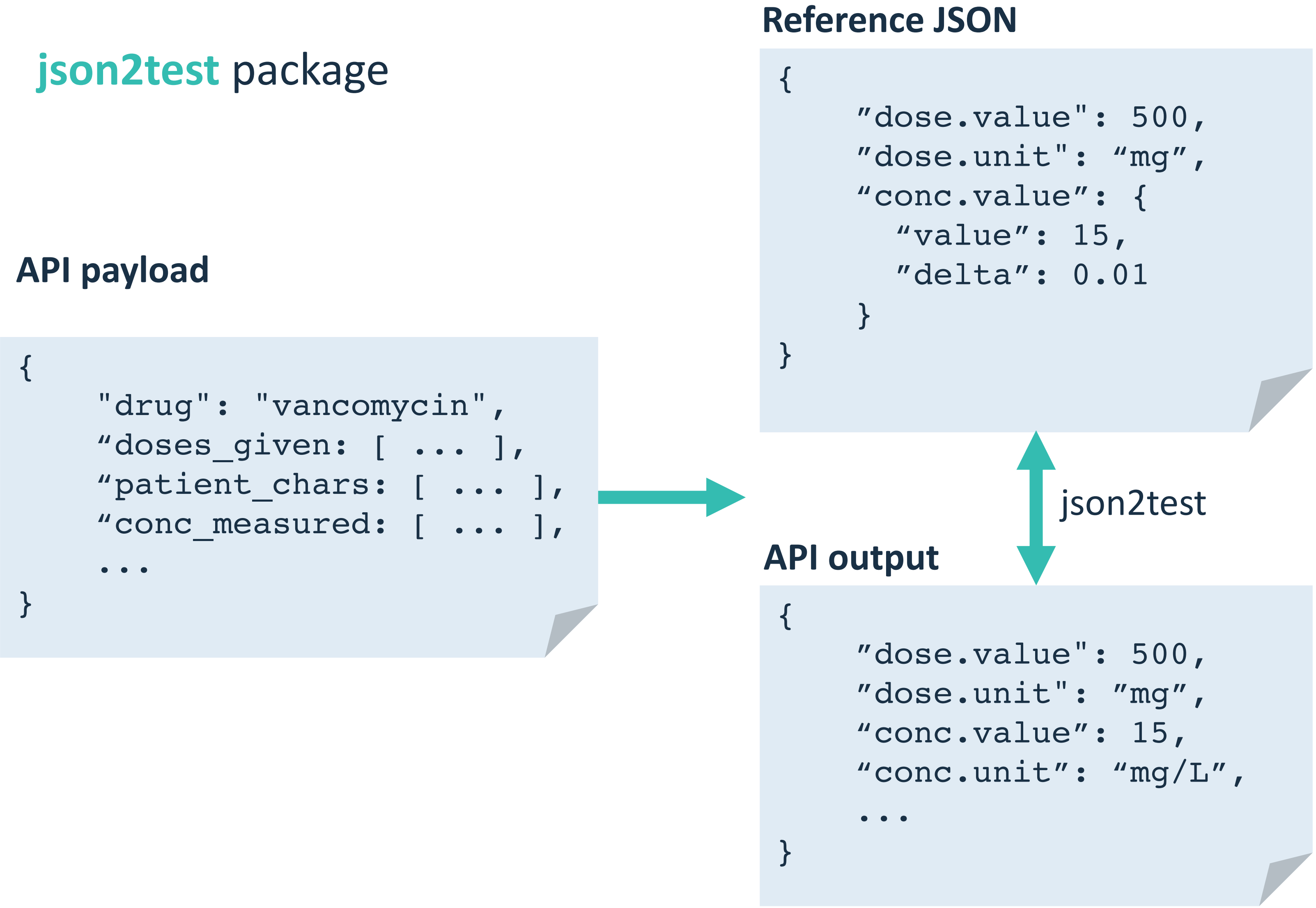
1. The software shall …
2. The software shall …
3. The software shall …
4. …

Functional tests

1. `assert(…)`
2. `assert(…)`
3. `assert(…)`
4. …

See also talk Ellis Hughes: https://thebioengineer.github.io/validation/

json2test package



Reference JSON

```
{
     ”dose.value": 500,
     ”dose.unit": “mg”,
     “conc.value”: {
       “value”: 15,
       ”delta”: 0.01
     }
}
```

API payload

```
{
     "drug": "vancomycin",
     “doses_given: [ ... ],
     “patient_chars: [ ... ],
     “conc_measured: [ ... ],
     ...
}
```

API output

```
{
     ”dose.value": 500,
     ”dose.unit": ”mg”,
     “conc.value”: 15,
     “conc.unit”: “mg/L”,
     ...
}
```

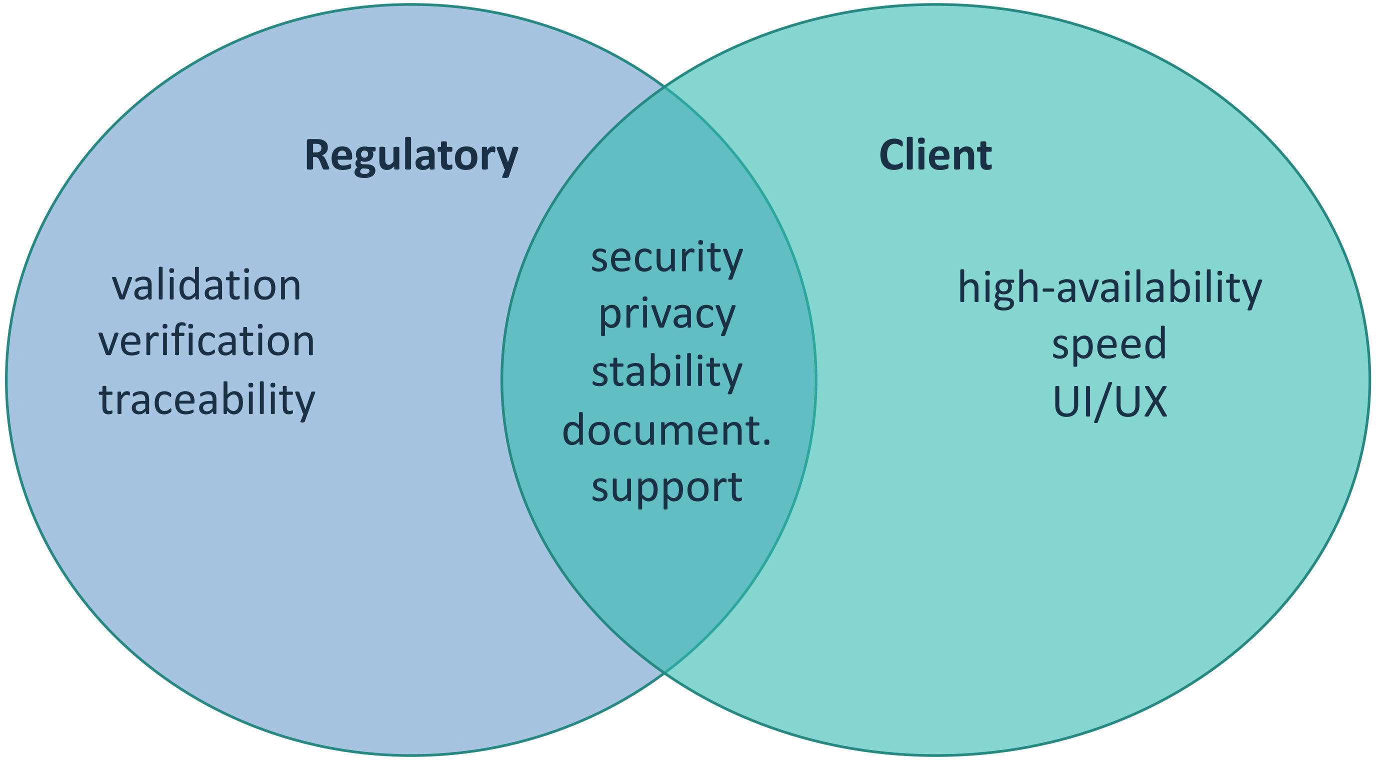
Benefits

- no writing test scenarios, just specify relevant reference values
- faster implementation

https://github.com/InsightRX/json2test

Other requirements

Client requirements



Regulatory

validation
verification
traceability

security
privacy
stability
document.
support

Client

high-availability
speed
UI/UX

Computations

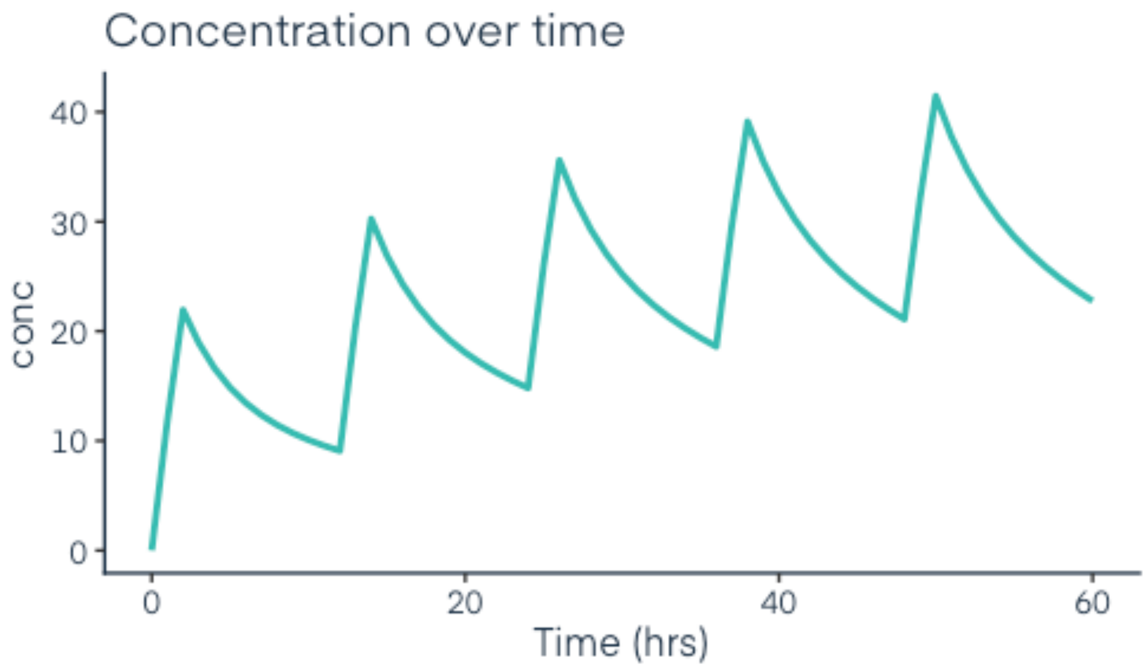
Architecture

Scaleability

API frameworks

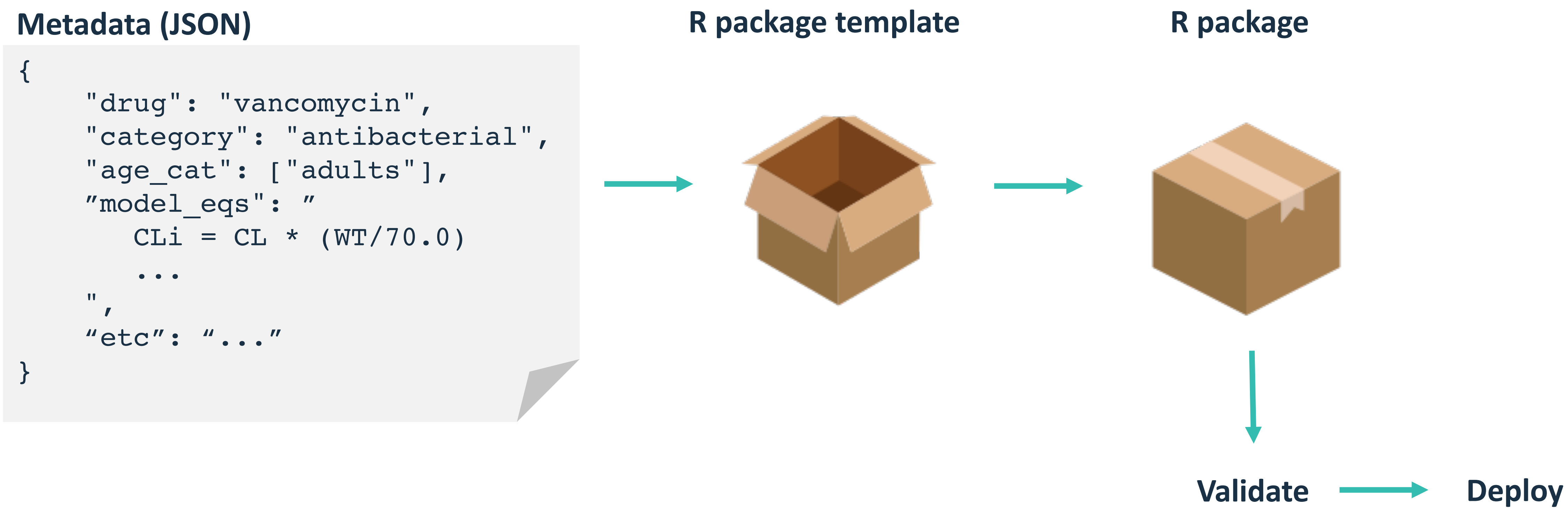
Computations

- Models are systems of differential equations
- Open source package PKPDsim
- Compiled code (Rcpp)
- In-house developed: beneficial for regulatory



https://github.com/InsightRX/PKPDsim

PKPDsim package: models as packages



Metadata (JSON)

```
{
    "drug": "vancomycin",
    "category": "antibacterial",
    "age_cat": ["adults"],
    ”model_eqs": ”
       CLi = CL * (WT/70.0)
       ...
    ",
    “etc”: “...”
}
```

R package template

R package

Validate → **Deploy**

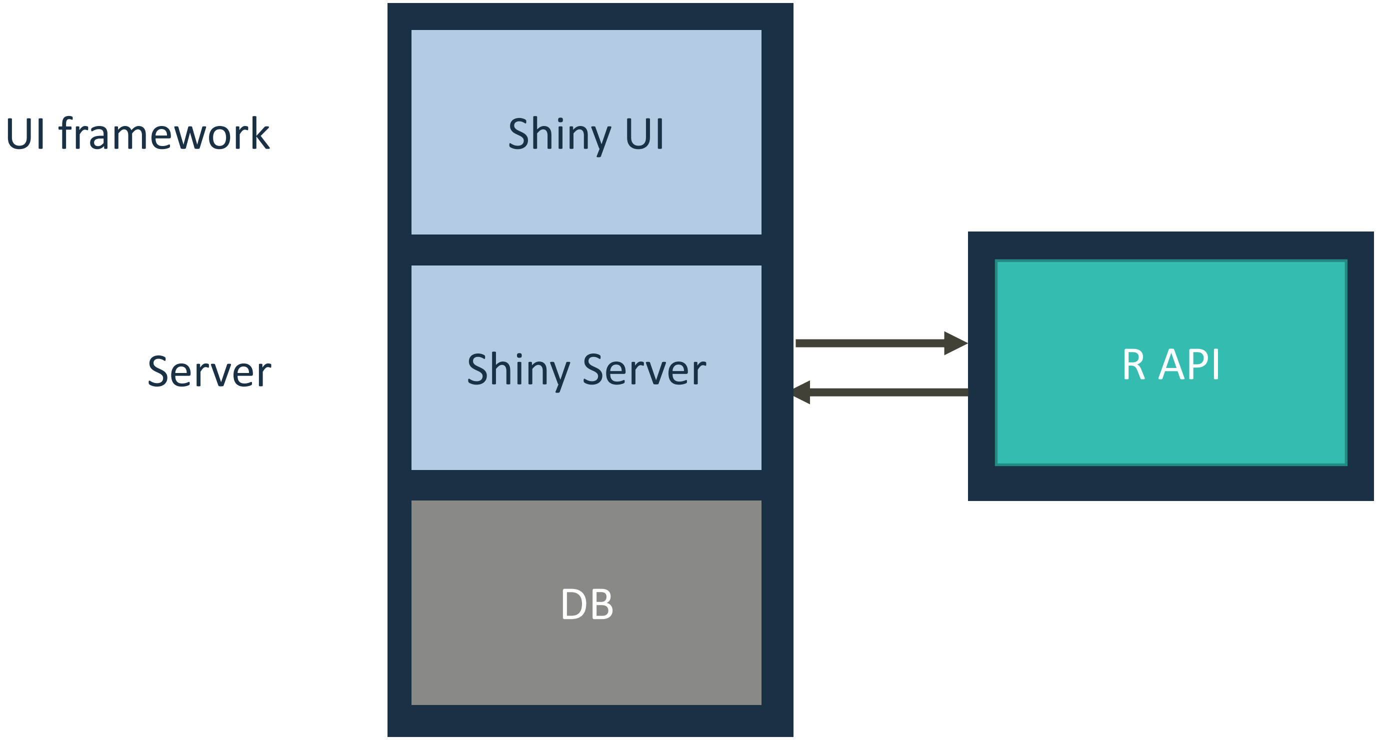
Benefits

- Easy to add / update models
- Generate documentation from metadata

https://github.com/InsightRX/PKPDsim

Architecture

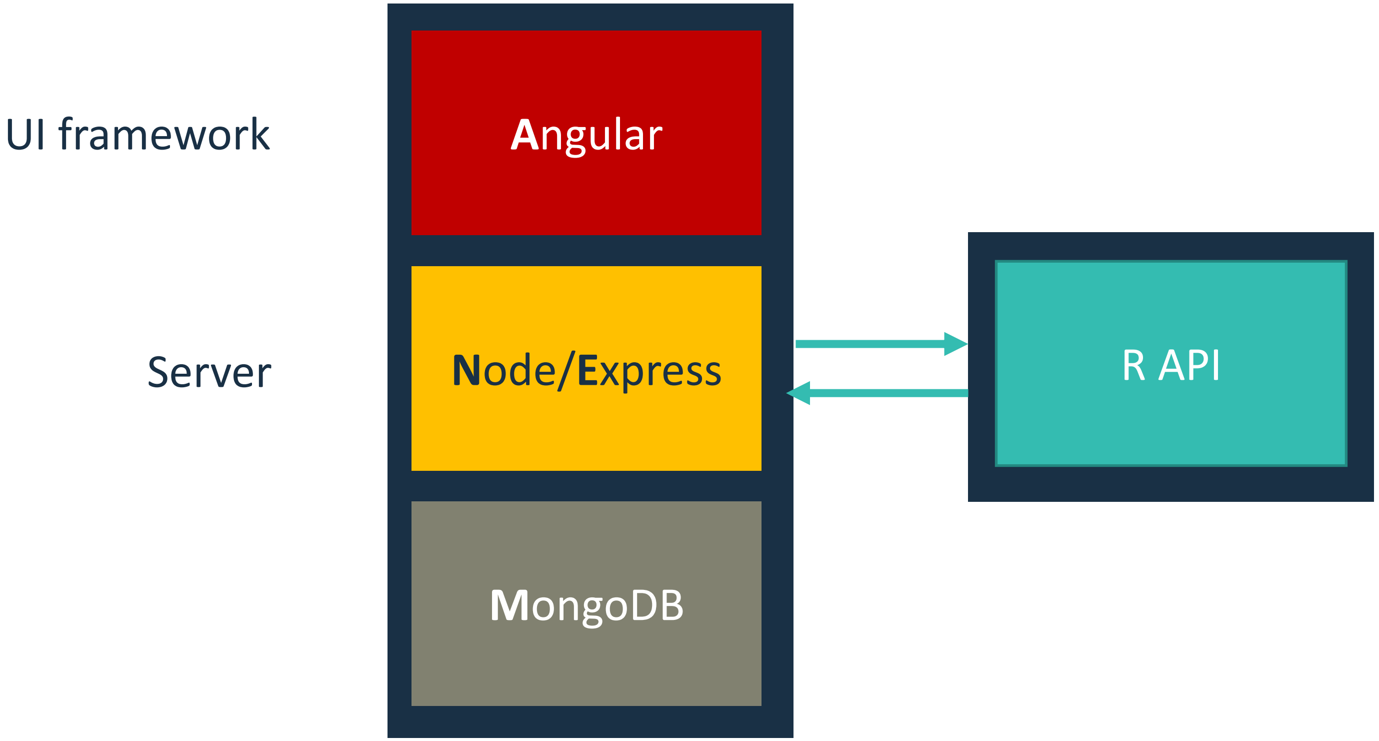
Architecture



Considerations

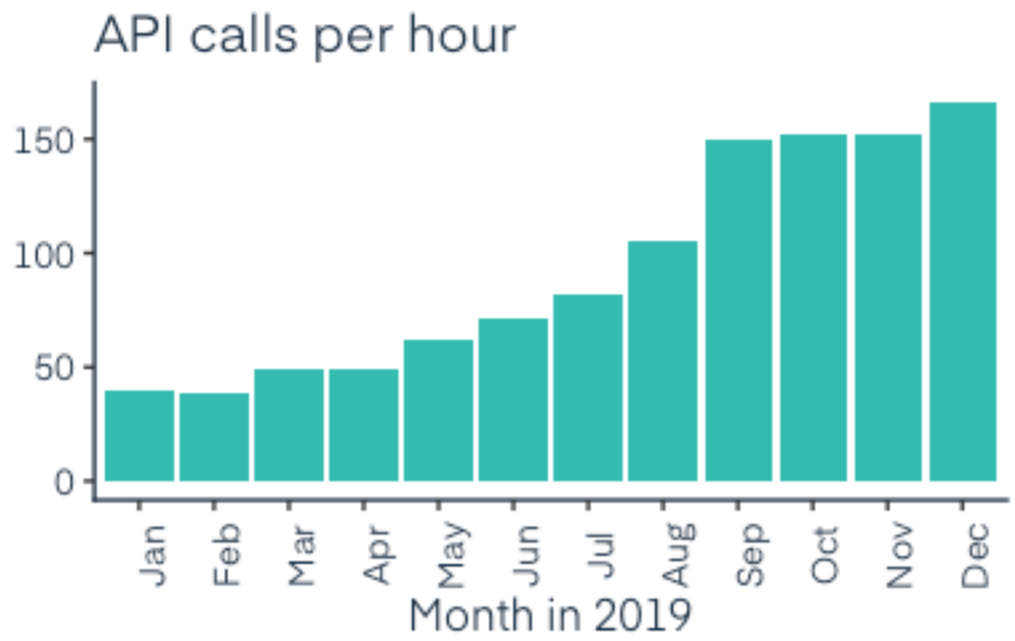
- Complexity
- Future
- Know-how
- Personnel
- Funds

Architecture

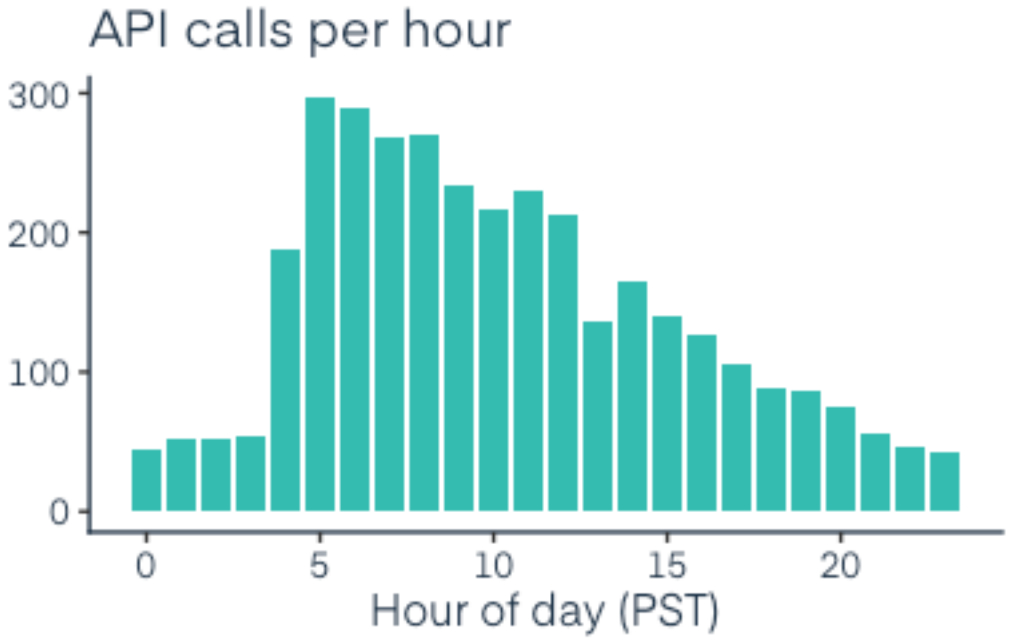


Scaleability

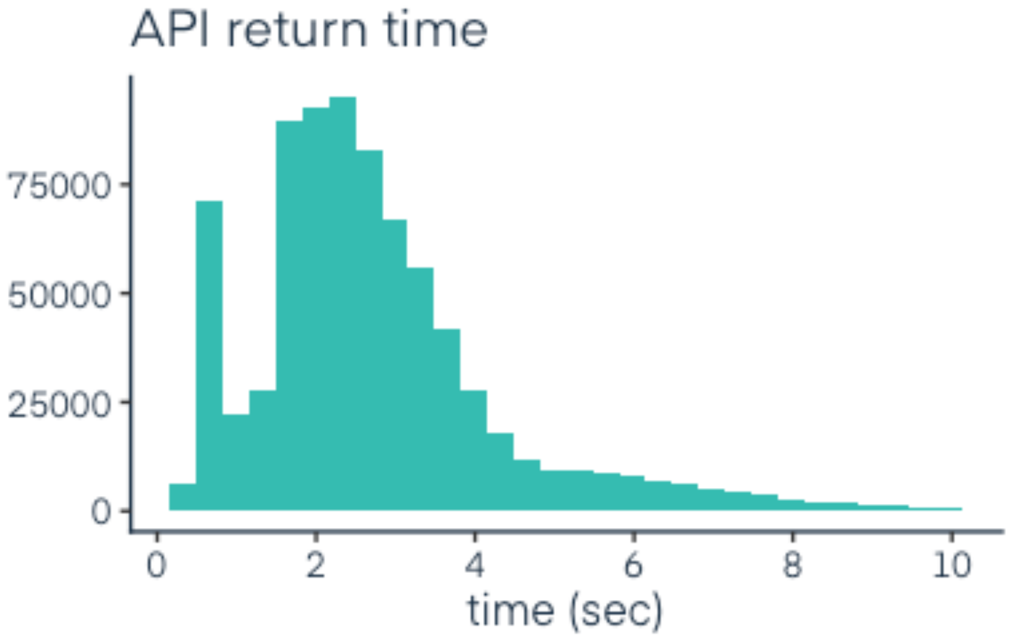
API requirements



API requirements



API requirements



API frameworks

API frameworks

1. **Custom**, written in NodeJS
2. **OpenCPU**, exposes R packages as APIs
   - initially AWS::EC2
   - later using AWS::Fargate (Docker, “infrastructure-as-code”)
3. **Plumber**
   - use inline comments to expose functions as API calls
   - deploy to cloud server / docker, or to RStudio **Connect**
4. **AWS::Lambda**
5. **…**

Take-home messages

- Medical device in R? Yes!
- Functional testing is important
- Store as much in metadata (vs code) as possible
- Write your own (core) code!

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Users of our open-source packages

🐦 @ronpirana
@InsightRX

Insight RX

Precision dosing done right.

www.insight-rx.com | info@insight-rx.com