

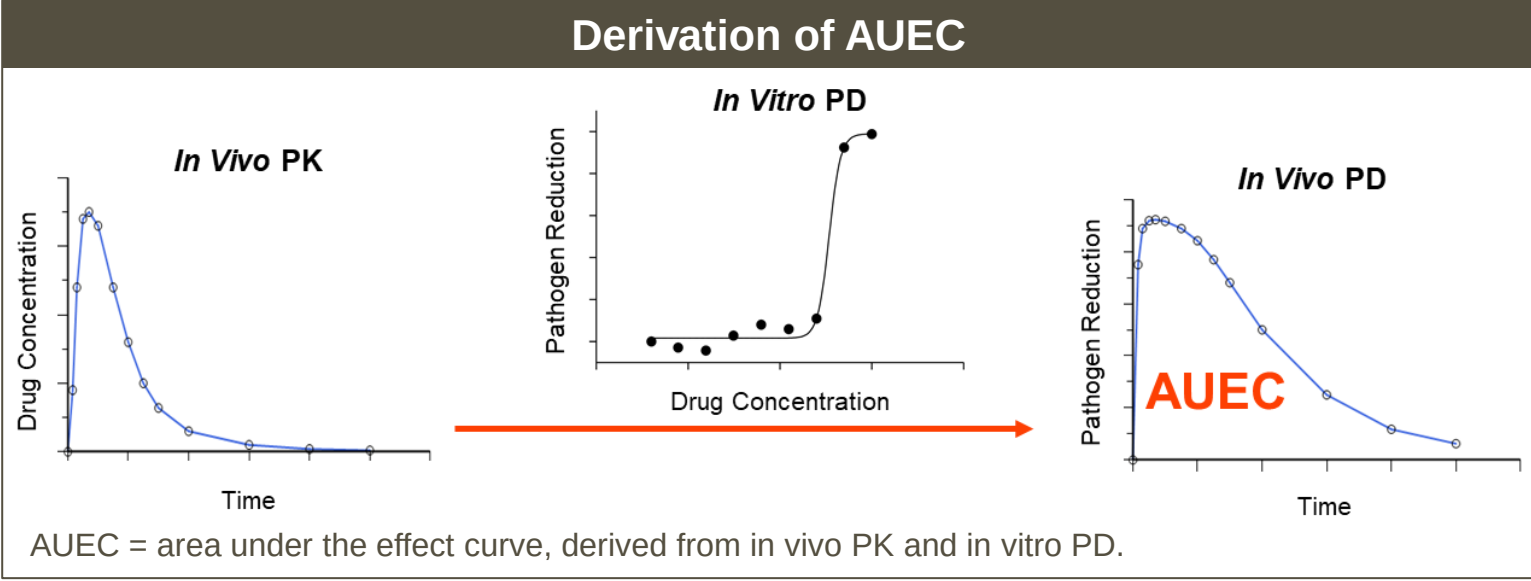
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Background and Objective

- Mechanistic approaches for predicting the therapeutic dose of anti-infectives can reflect various aspects of the infection in human but require extensive in vitro/in vivo experiments.
- Empirical approaches suggest a drug's efficacy is driven by an exposure- or time-dependent PKPD index (AUC, C_{max}, Time > MIC, Time > EC₅₀); they are simpler but lacking direct pharmacology input.
- Objective: to assess a new pharmacology-based PKPD index the area under the effect curve (AUEC), using simulated dose fractionation.

Derivation of AUEC



AUEC = area under the effect curve, derived from in vivo PK and in vitro PD.

Methods and Results

In vitro PD

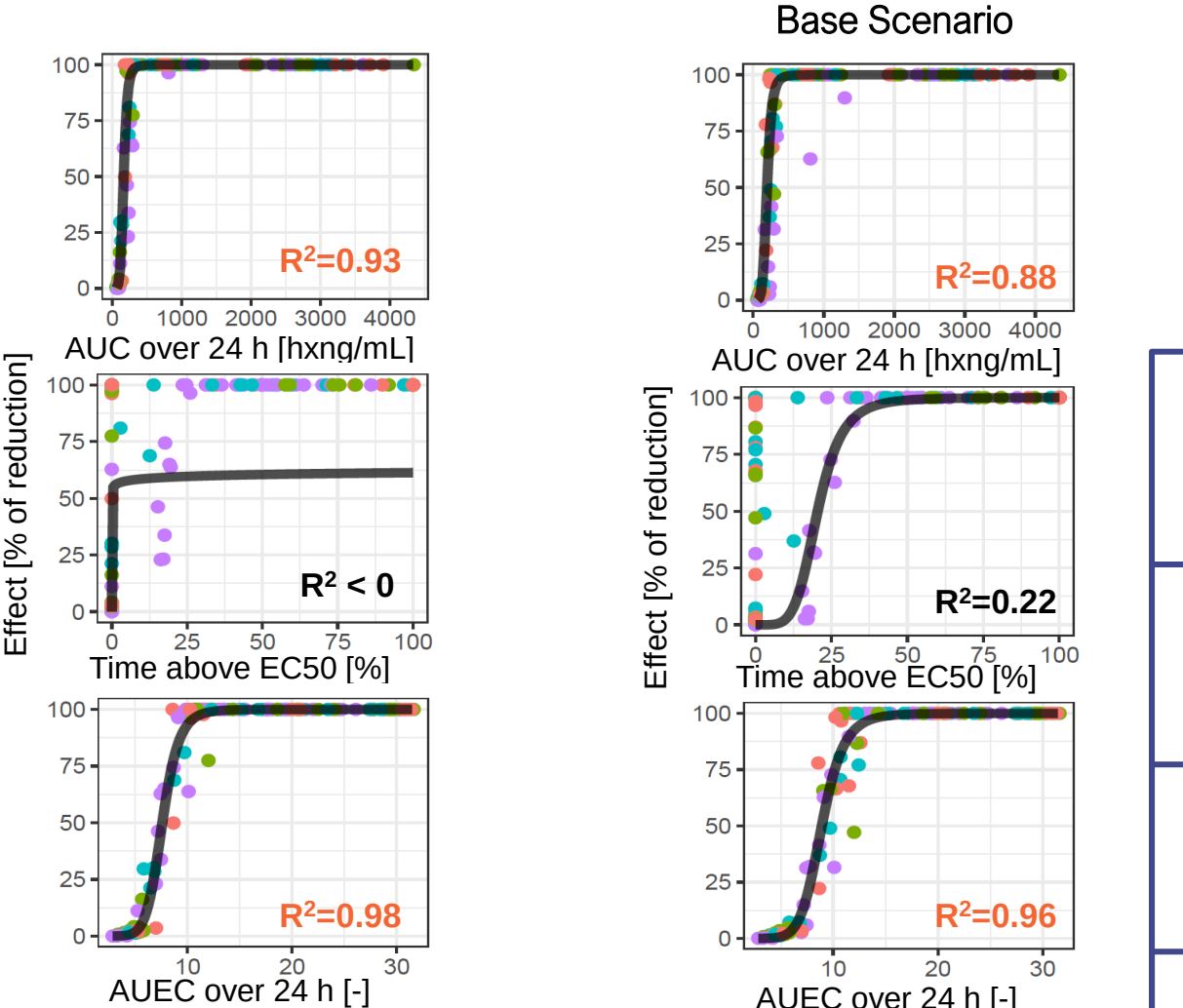
$$E_{\text{vitro}} = E_{\text{max}_{\text{vitro}}} \times C_{\text{vitro}}^{\text{yvitro}} / (EC_{50_{\text{vitro}}}^{\text{yvitro}} + C_{\text{vitro}}^{\text{yvitro}})$$

In vivo efficacy

$$dP/dt = P(t) \times \{k_{\text{net}} \times [P_{\text{max}} - P(t)/P_{\text{max}}] - E_{\text{max}_{\text{vivo}}} \times C(t)_{\text{vivo}}^{\text{yvivo}} / [EC_{50_{\text{vivo}}}^{\text{yvivo}} + C(t)_{\text{vivo}}^{\text{yvivo}}]\}$$

Dosing interval [h] 3 6 12 24

Base Scenario



Importance of dose range

In vitro-in vivo potency mismatch

Impact of PKPD slope

In vitro-in vivo slope mismatch

Base Scenario and its variations				
Scenario	R²			
	AUC	C _{max}	T>EC ₅₀	AUEC
Base	0.88	0.49	0.22	0.96
Dose range too high	0.36	< 0	0.79	0.76
Dose range too low	0.70	0.46	< 0	0.83
In vivo more potent	0.88	0.49	< 0	0.90
In vivo less potent	0.88	0.49	0.34	0.84
Steep PD	0.89	0.66	0.18	0.91
Shallow PD	0.89	0.54	< 0	0.97
In vivo steeper	0.88	0.49	0.22	0.91
In vivo shallower	0.88	0.49	0.22	0.91

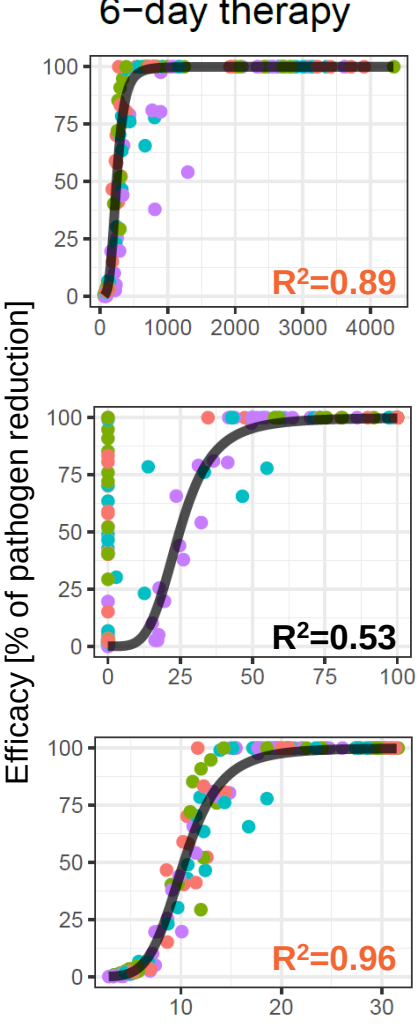
Acute infection

Shorter treatment

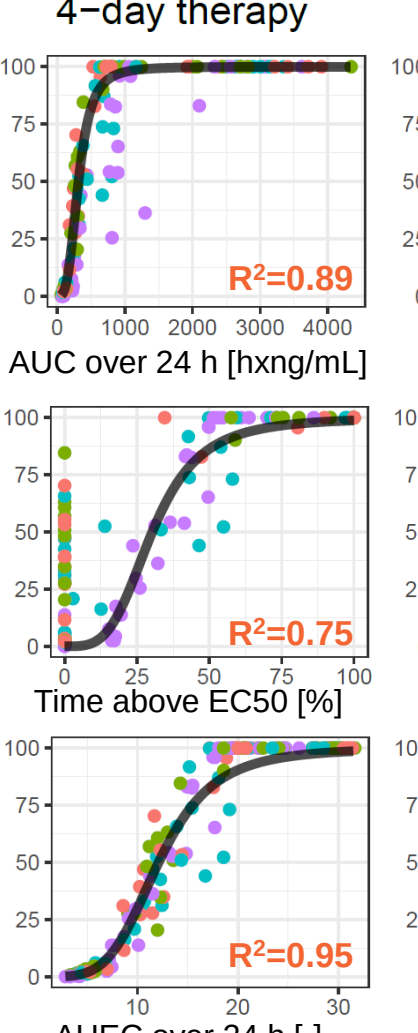
Base Scenario (and its variations)
Chronic infection, long treatment course, fully efficacious drug

Partially efficacious drug

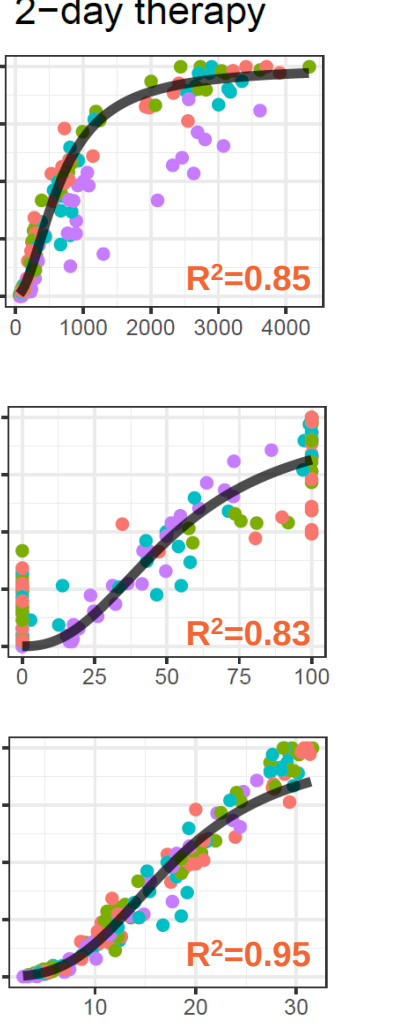
6-day therapy



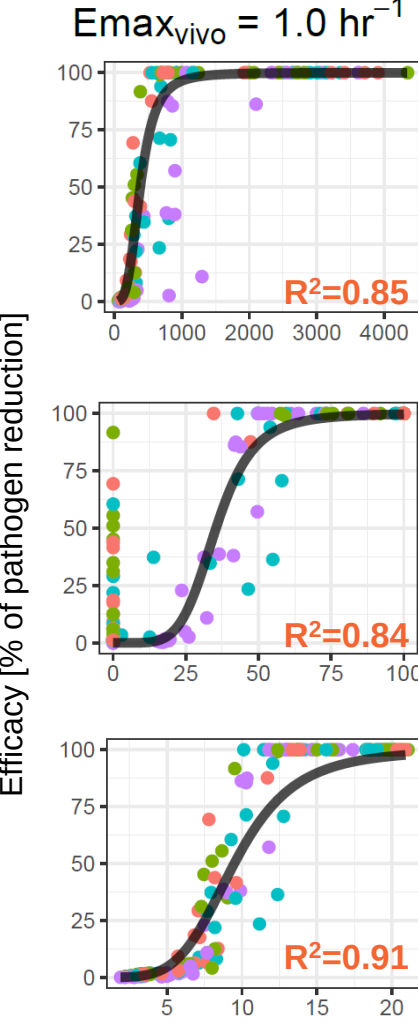
4-day therapy



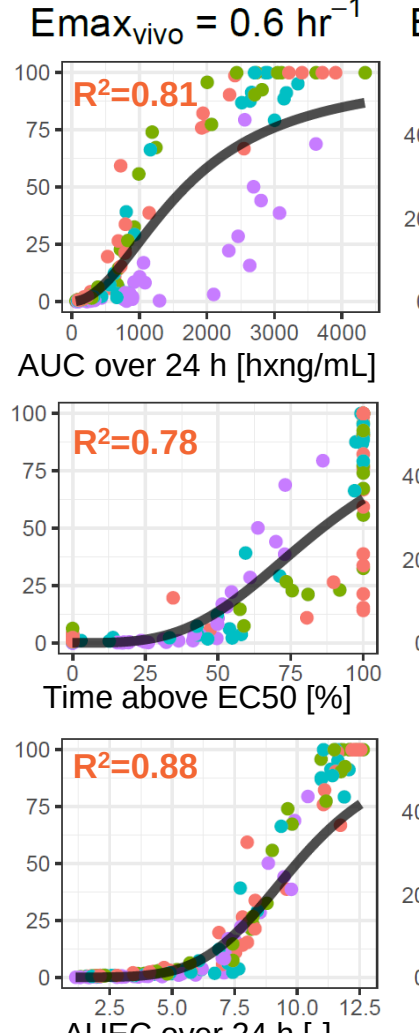
2-day therapy



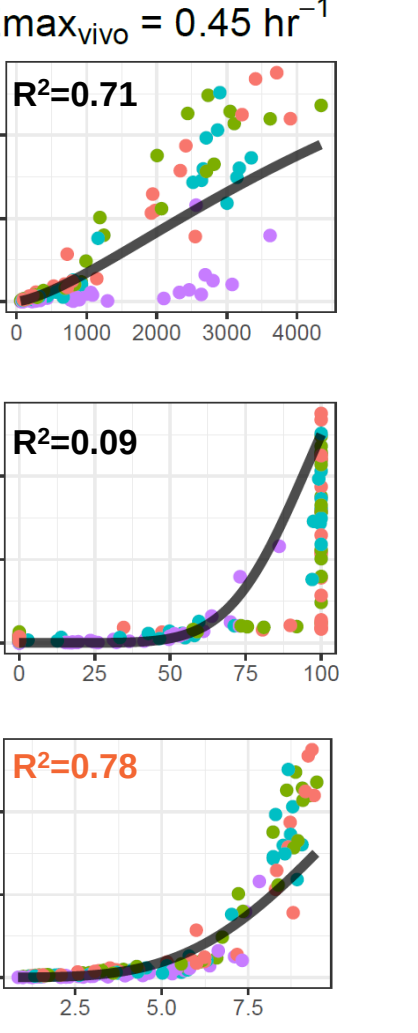
Emax_{vivo} = 1.0 hr⁻¹



Emax_{vivo} = 0.6 hr⁻¹



Emax_{vivo} = 0.45 hr⁻¹



Conclusions

- In all scenarios, AUEC shows strong correlation with *in vivo* efficacy.
- Dosing regimen had negligible impact on AUEC, suggesting better cross-species translation and needing less dose fractionation in animals.
- The AUEC concept is underpinned by the principle that pharmacology drives efficacy, hence applicable to indications beyond infections.
- This work is now published in full in CPT:PSP (<http://doi.org/10.1002/psp4.12811>) – QR code on the right.



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