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NEUTRALISING ANTIBODIES PREVENT PRRSV VIREMIA REBOUND: EVIDENCE FROM A DATA-SUPPORTED MODEL

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In collaboration with
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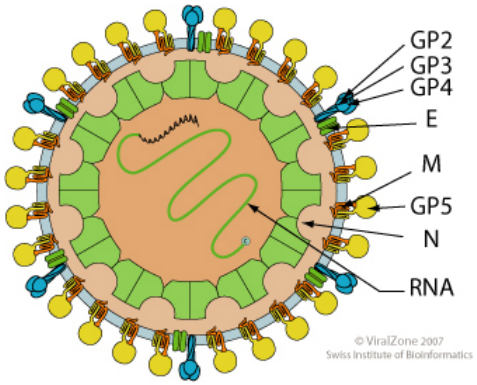
Context

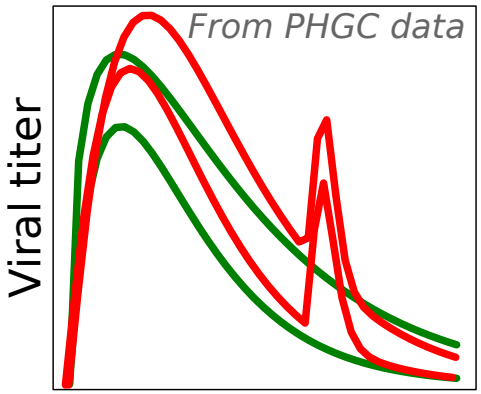
Porcine Reproductive and Respiratory Syndrome virus (PRRSv):



- Targets the porcine antigen presenting cells (APC)
- Wide variability in virulence & susceptibility
- Numerous vaccines, but only partially protective

⇒ Need to better understand the immune response

Viral titer rebounds:

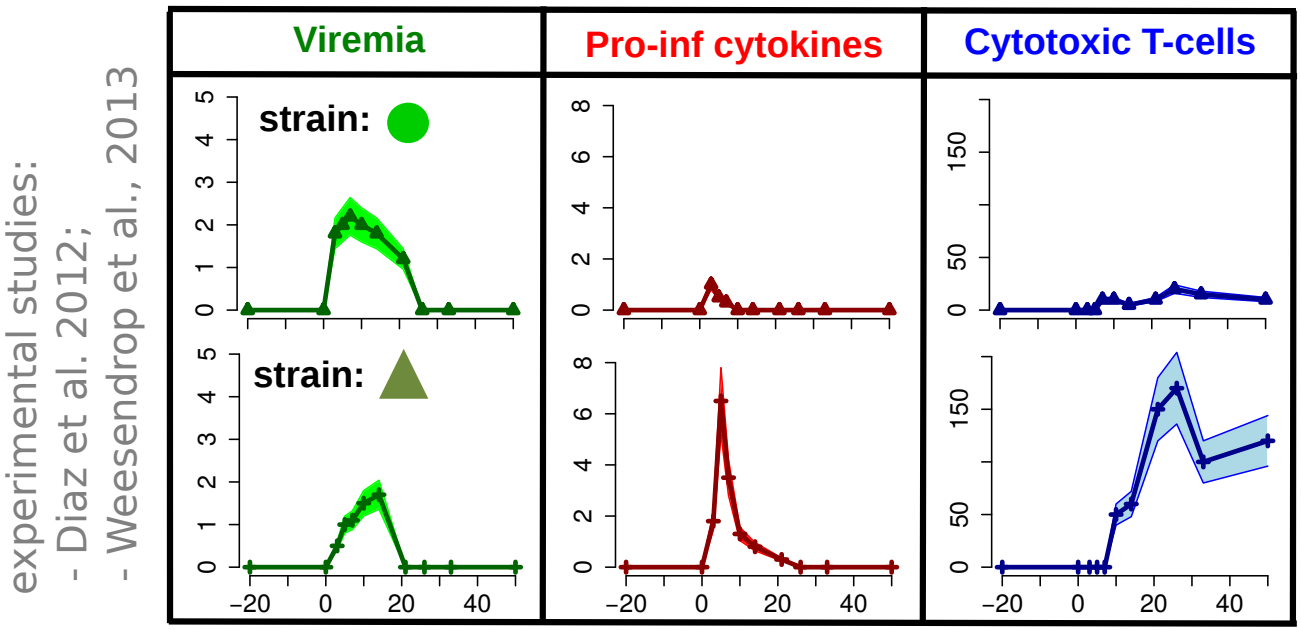


- Mechanisms unclear (immune response, viral mutation, re-exposure over infection)
- Issue for the infection control (vaccination, genetic selection, population dynamics)

⇒ What immune mechanisms can cause rebounds ?

Linking immune response & infection dynamics

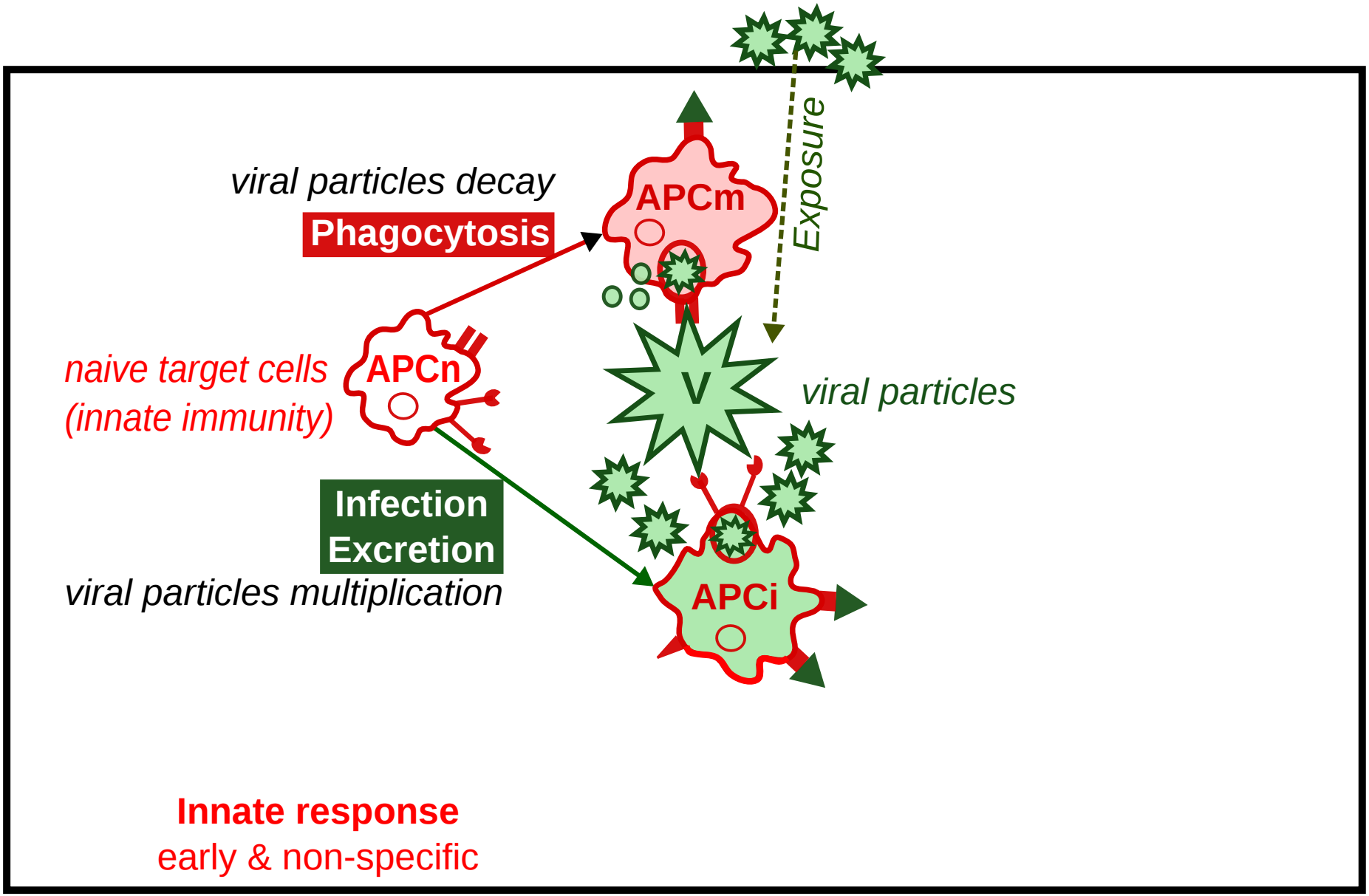
– Contrasted immune reponses can result in similar infection dynamics:



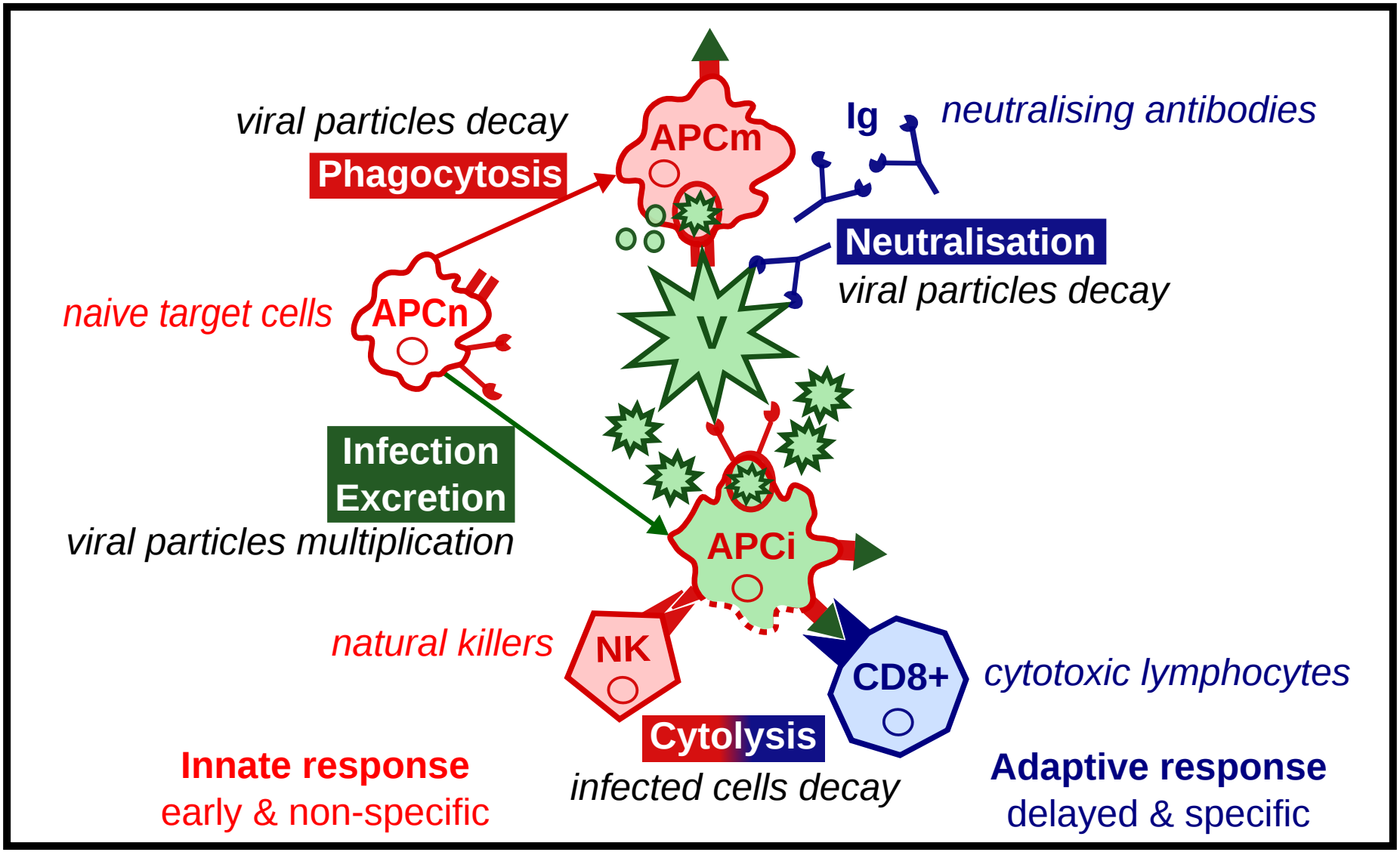
– Fragmented & partial view from the experimental studies
– High variability & complex system

→ ORIGINAL MODEL: Integrative view of the within-host dynamics

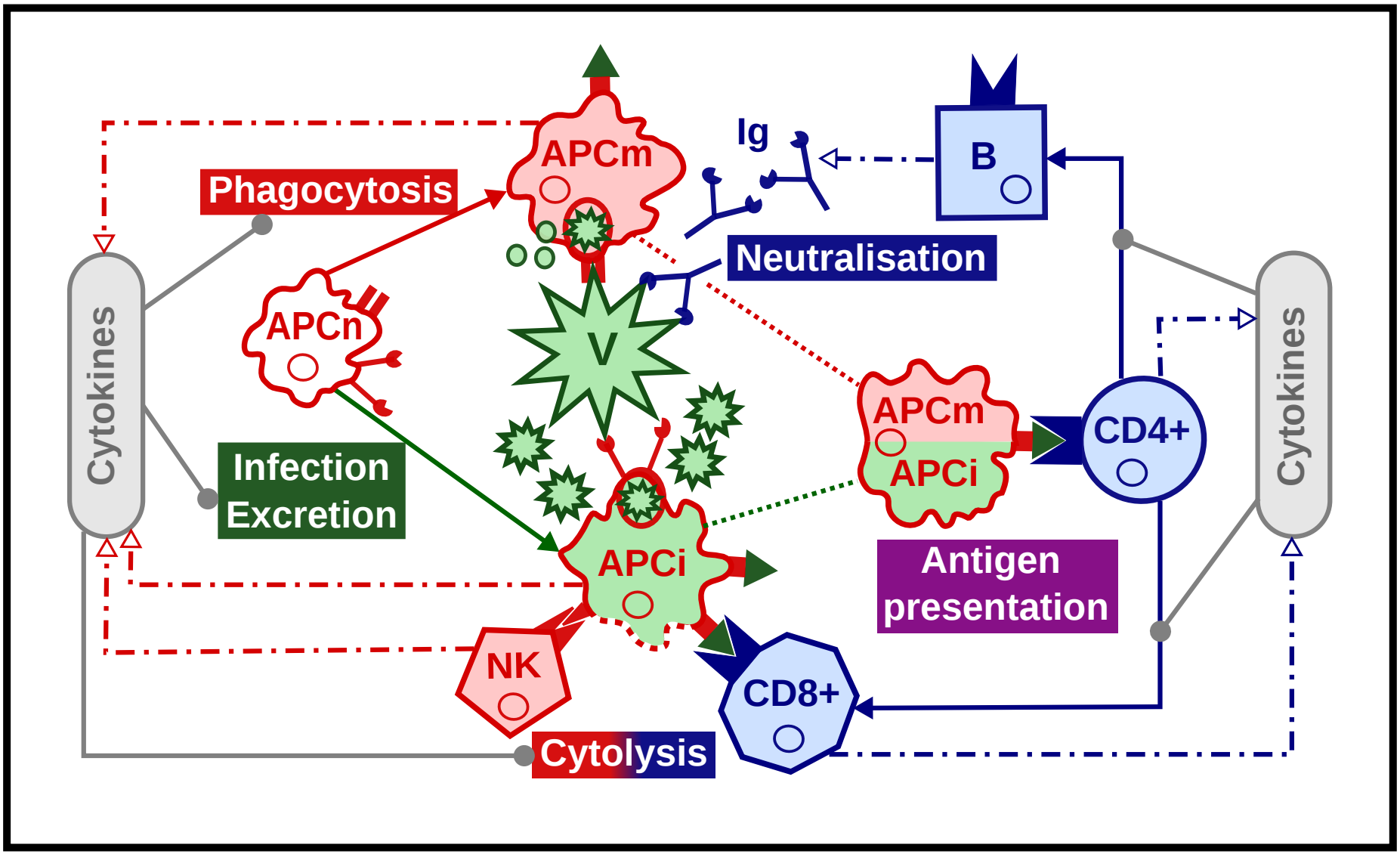
(1) initiation of infection & immune response



(2) virus-immune response interactions

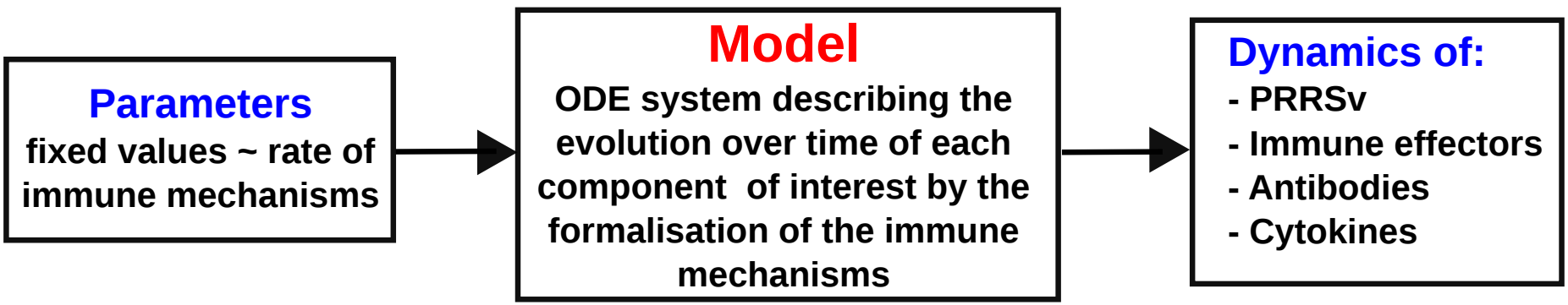


(3) immune response activation & regulations



Model - overview

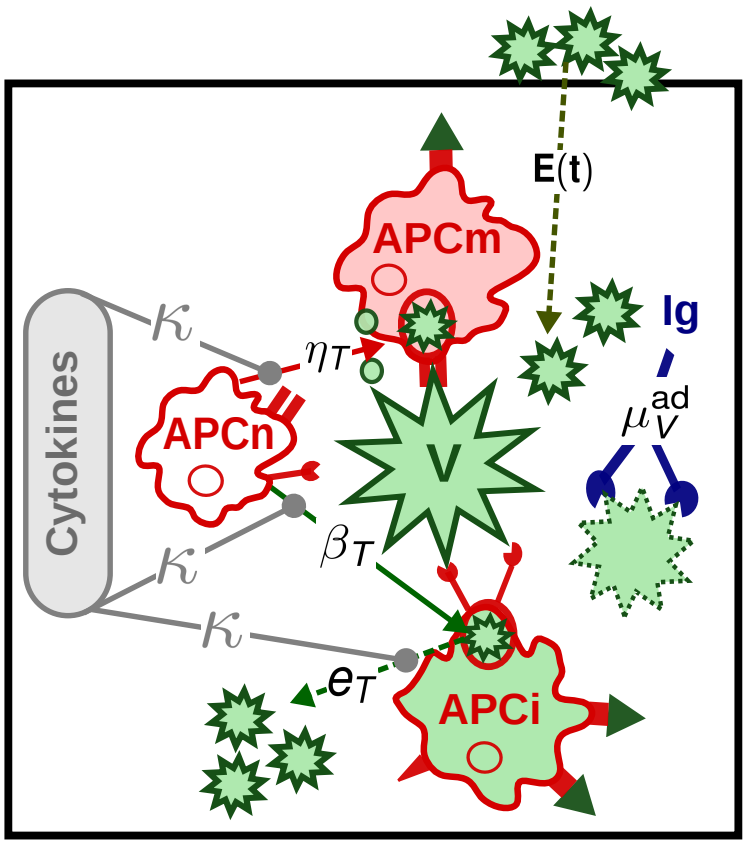
Integrative and detailed view of the within-host dynamics



- evolution over time of PRRSv, innate and adaptive components
- deterministic system of 19 ODE involving 50 parameters
- mechanisms at between-cell scale, variability $\sim$ parameter values

Model - equations

example of viral dynamics:



$$\dot{\mathbf{V}} = + \underbrace{E(t)}_{\text{exposure}}$$

$$- \underbrace{\eta_T \, \mathbf{V} \, (\mathrm{APC}_n + \mathrm{APC}_m) \, \kappa^-() \, [1 + \kappa^+()]}_{\text{phagocytosis}}$$

$$- \underbrace{\beta_T \, \mathbf{V} \, (\mathrm{APC}_m + \mathrm{APC}_n) \, \kappa^-() \, [1 + \kappa^+()]}_{\text{infection}}$$

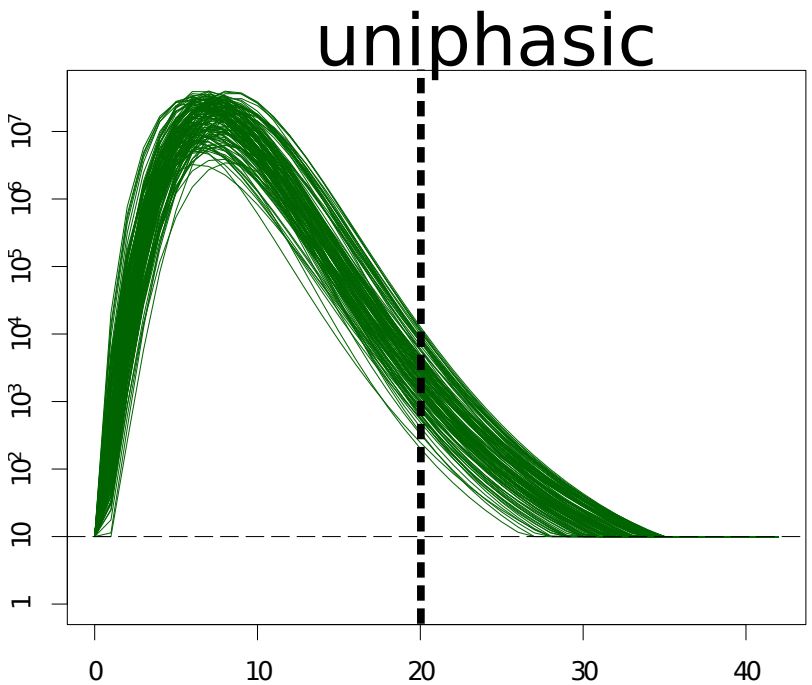
$$+ \underbrace{e_T \, \mathrm{APC}_i \, \kappa^-()}_{\text{excretion}}$$

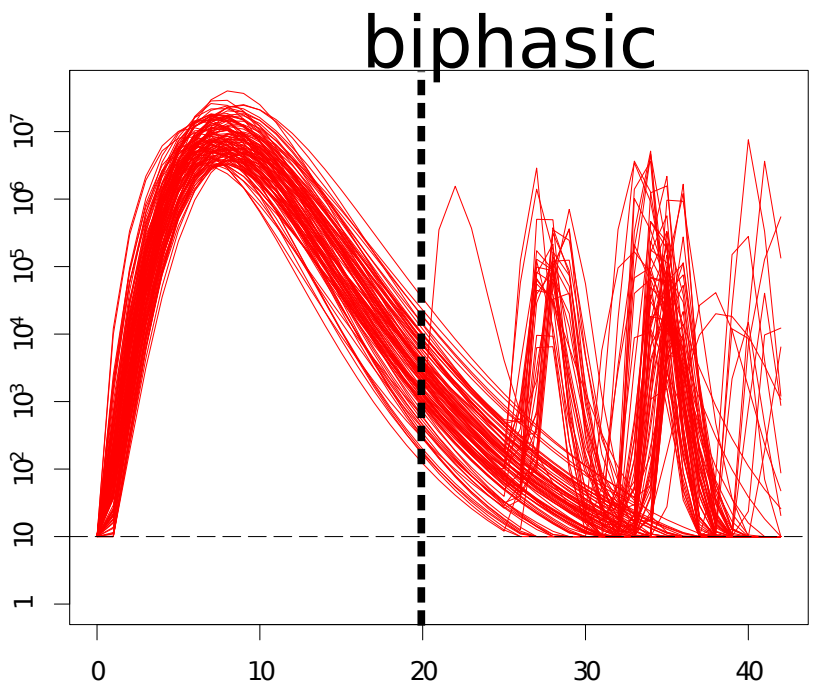
$$- \underbrace{\mu_V^{ad} \, \mathbf{V} \, \mathrm{I_g}}_{\text{neutralisation}}$$

$$- \underbrace{\mu_V^{nat} \, \mathbf{V}}_{\text{natural decay}}$$

What prevents rebounds?

Data. **300 pigs (genomic variability), NVSL strain (high virulence)**





Method.

(1) Model fitting

(2) Identify the underlying mechanisms (ex. of antibodies)

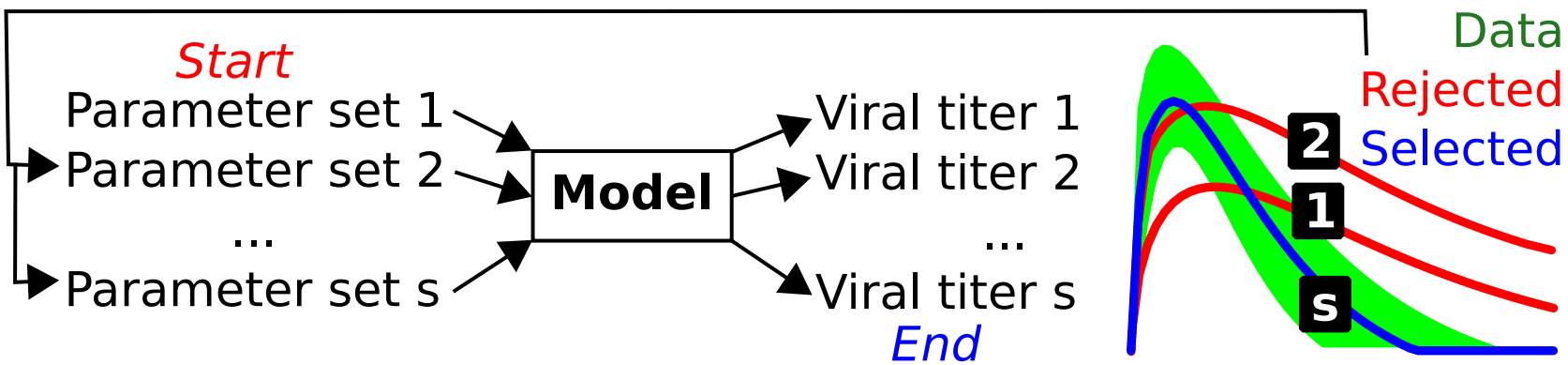
What prevents rebounds?

Data.

Method.

(1) Model fitting

1. Selection of parameters: linked to between-host variability (14/50)
2. Check if the model can generate the data
3. Fitting method. 600 times the fitting process / profile:



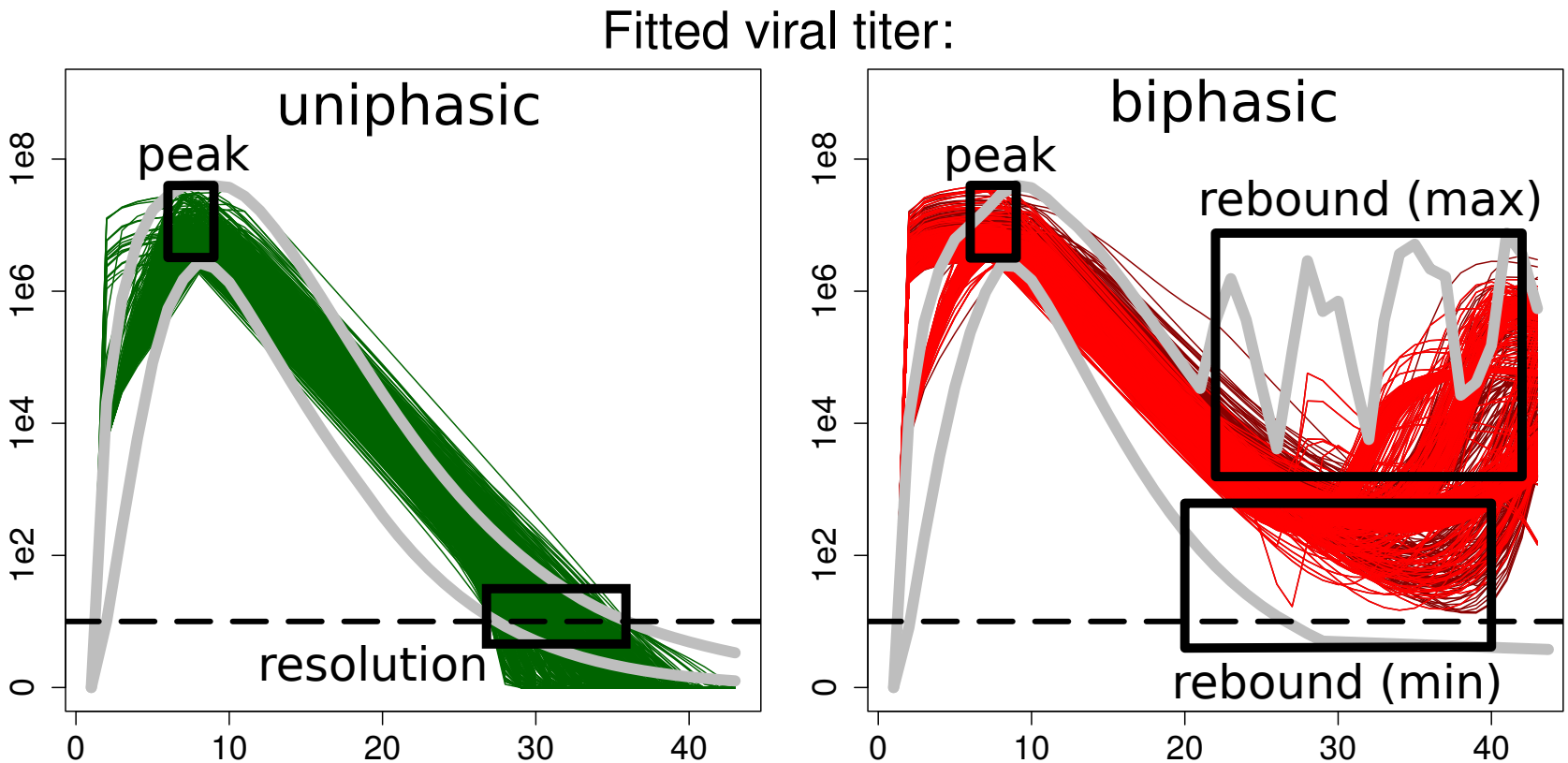
(2) Identify the underlying mechanisms (ex. of antibodies)

What prevents rebounds?

Data.

Method.

(1) Model fitting



(2) Identify the underlying mechanisms (ex. of antibodies)

What prevents rebounds?

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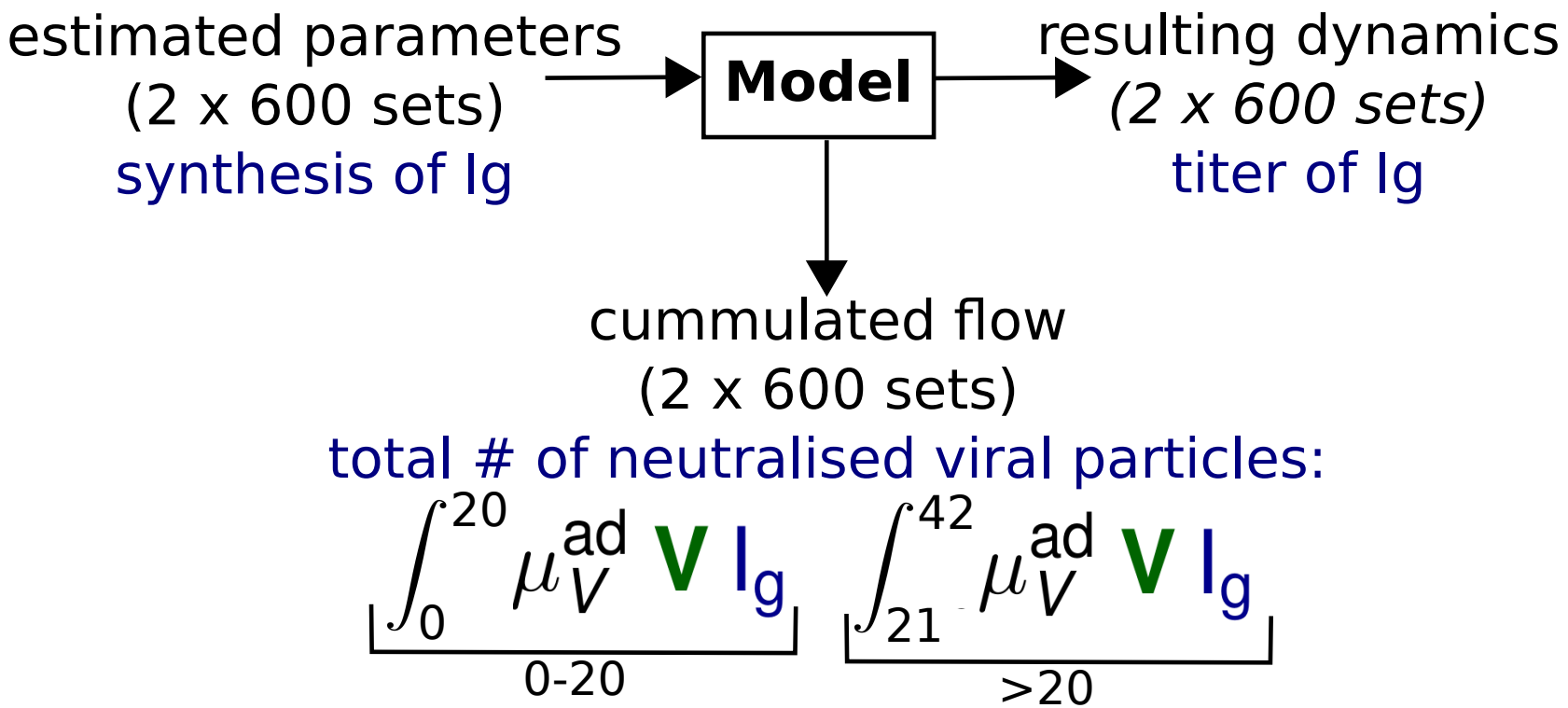
(1) Model fitting

(2) Identify the underlying mechanisms (ex. of antibodies)

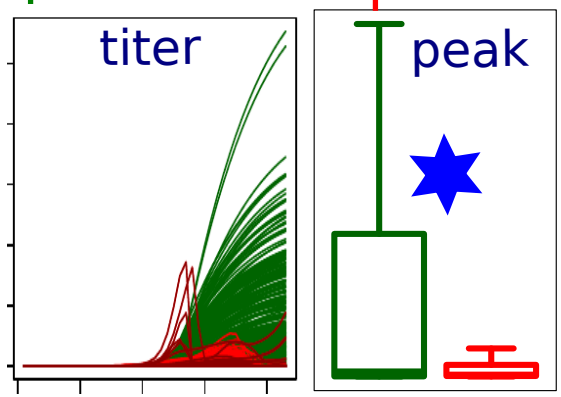


What prevents rebounds?

estimated parameters
uniphasic *vs* biphasic

→ **Model** →

resulting dynamics
uniphasic *vs* biphasic



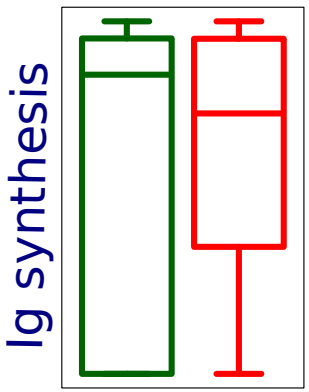
↓

cummulated flows
uniphasic *vs* biphasic

(1) Rebounds due to a lack of antibodies synthesis

What prevents rebounds?

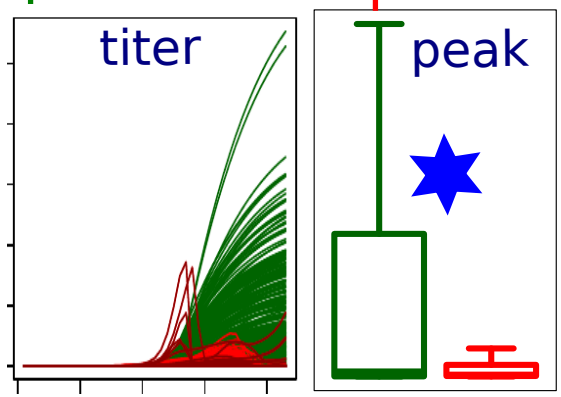
estimated parameters
uniphasic *vs* biphasic



Model

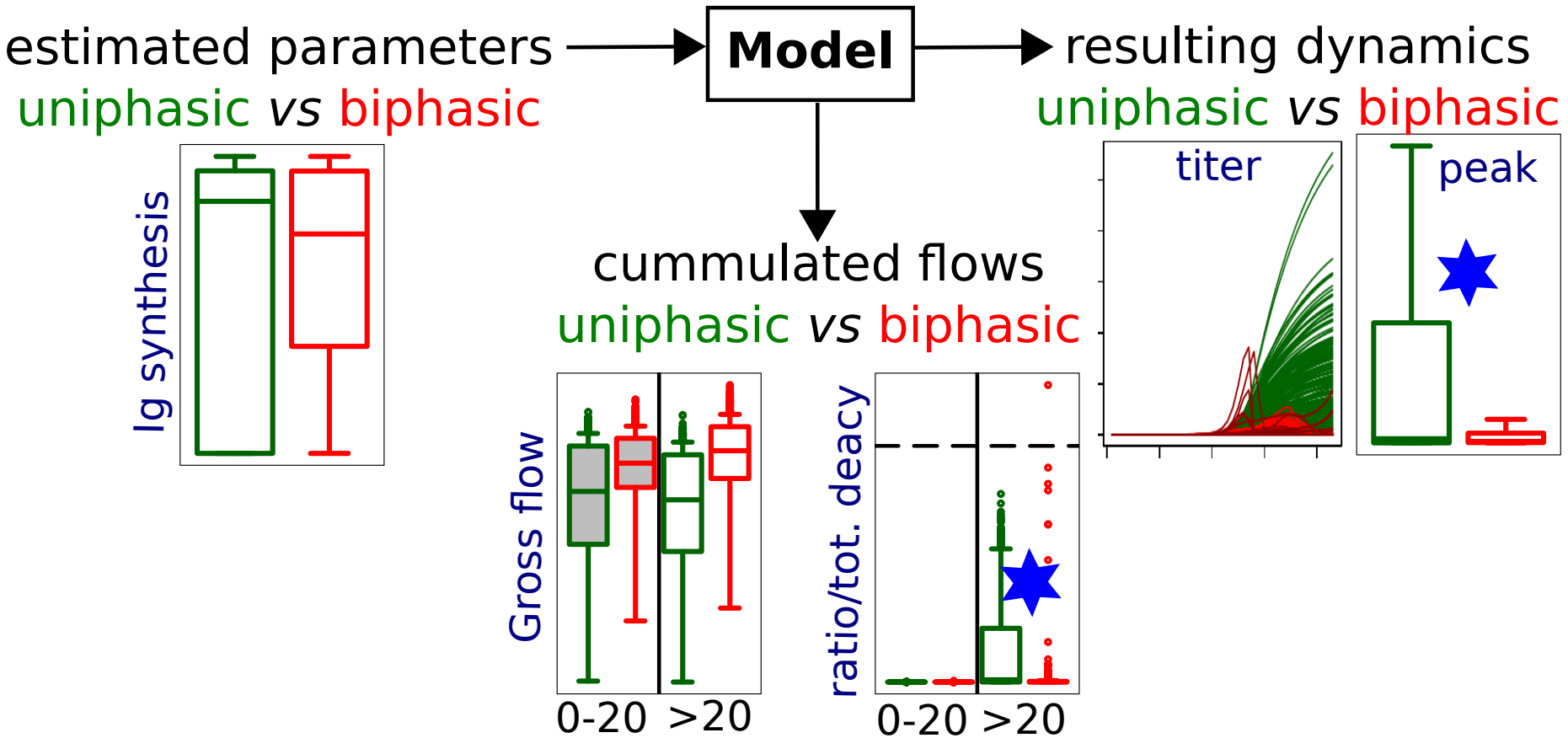
cummulated flows
uniphasic *vs* biphasic

resulting dynamics
uniphasic *vs* biphasic



(2) Lower Ig titer despite similar synthesis !?!?!

What prevents rebounds?



(3) Rebounders need more neutralising antibodies !!!

→ **strength of neutralisation determines infection profiles?**

What prevents rebounds?

Influence of pomoting / inhibiting neutralisation efficiency on profile

Method: vary μ_V^{ad}			Results: % of profile inversion		
levels	uniphasic	biphasic	levels	uni $\rightarrow$ bi	bi$\rightarrow$ uni
L_1	$\times 0.1$	$\times 10$	L_1	0	85
$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$		
L_6	$\times 0.001$	$\times 1000$	L_6		

$\Downarrow$

strength of neutralisation do not determines infection profile
... BUT ...
high neutralisation can prevent rebounds !

Conclusion

Strengths:

- Model: can reproduce the variability within and between PRRSv profiles
- Approach: powerfull to identify underlying mechanisms

Expe.: only dynamics $\rightarrow$ *expensive & partial view*

- Results: new insights to explain PRRSv within-host dynamics

$\rightarrow$ *prospects for infection control (vaccination & host genetic selection)*

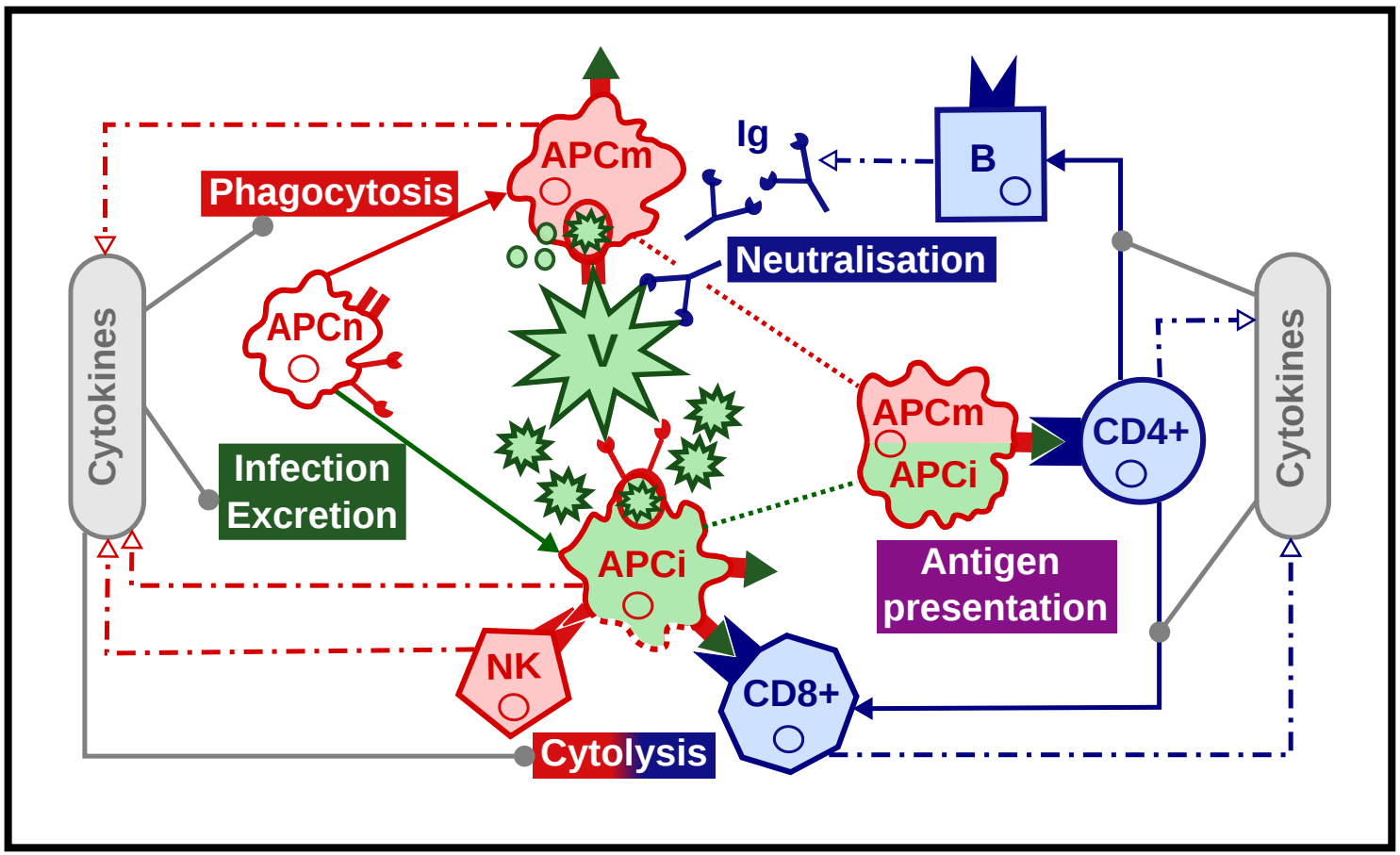
Limits:

- Only fitted on viral titer (1 model variable / 19)
- No validation of fixed parameters & ranges

Prospects:

- Model simplification (Stefano's method)
- Exploration of other hypotheses (viral mutation, re-exposure)

Thank you!


APCm
Ig
B
Phagocytosis
Neutralisation
APCn
V
Cytokines
Cytokines
APCm
APCi
CD4+
Infection
Excretion
APCi
Antigen
presentation
NK
CD8+
Cytolysis