

# EXPLAINING THE UNEXPECTED MULTI-STATIONARITY IN A NONLINEAR MODEL OF PROLACTIN RESPONSE TO DOPAMINE D2 RECEPTOR ANTAGONISTS

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## Introduction

Prolactin (PRL) levels in plasma increase in response to dopamine D2 receptor antagonists. The PRL response shows tachyphylaxis to closely spaced drug doses. This PD response was modelled using the precursor pool model [1]. Stevens et al., modified the precursor pool model to include positive feedback (PF) of plasma PRL on its own synthesis in the lactotroph pool [2]. The PF was assumed to be zero if plasma PRL  $\leq$  baseline, and active for plasma PRL  $>$  baseline, through an “if condition”.

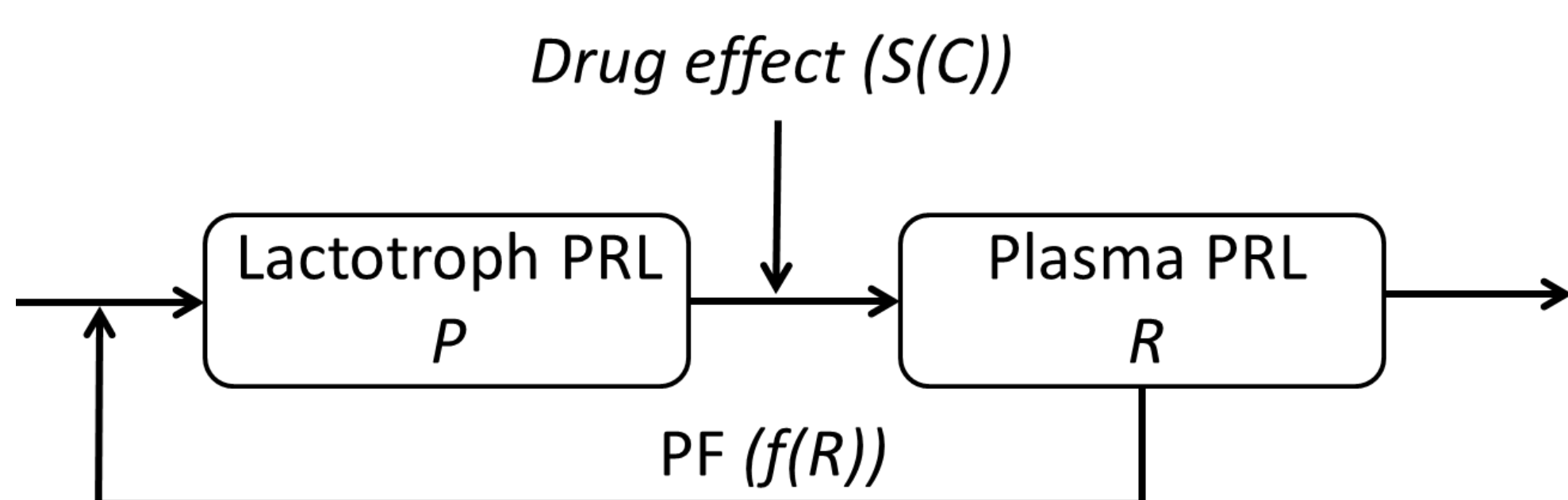


Figure 1. Schematic representation of the PRL pool model with PF. Drug effect and PF are both Emax functions.

## Model equations

$$\frac{dP}{dt} = k_s [1 + f(R)] - k_r \{1 + S(C)\} P,$$

$$\frac{dR}{dt} = k_r \{1 + S(C)\} P - k_{el} R.$$

$$S(C) = \frac{S_{max} C}{SC_{50} + C} \quad f(R) = \frac{E_{max}(R - R_0)}{EC_{50} + (R - R_0)}$$

The “if condition” states that  $f(R) = 0$  if  $R \leq R_0$

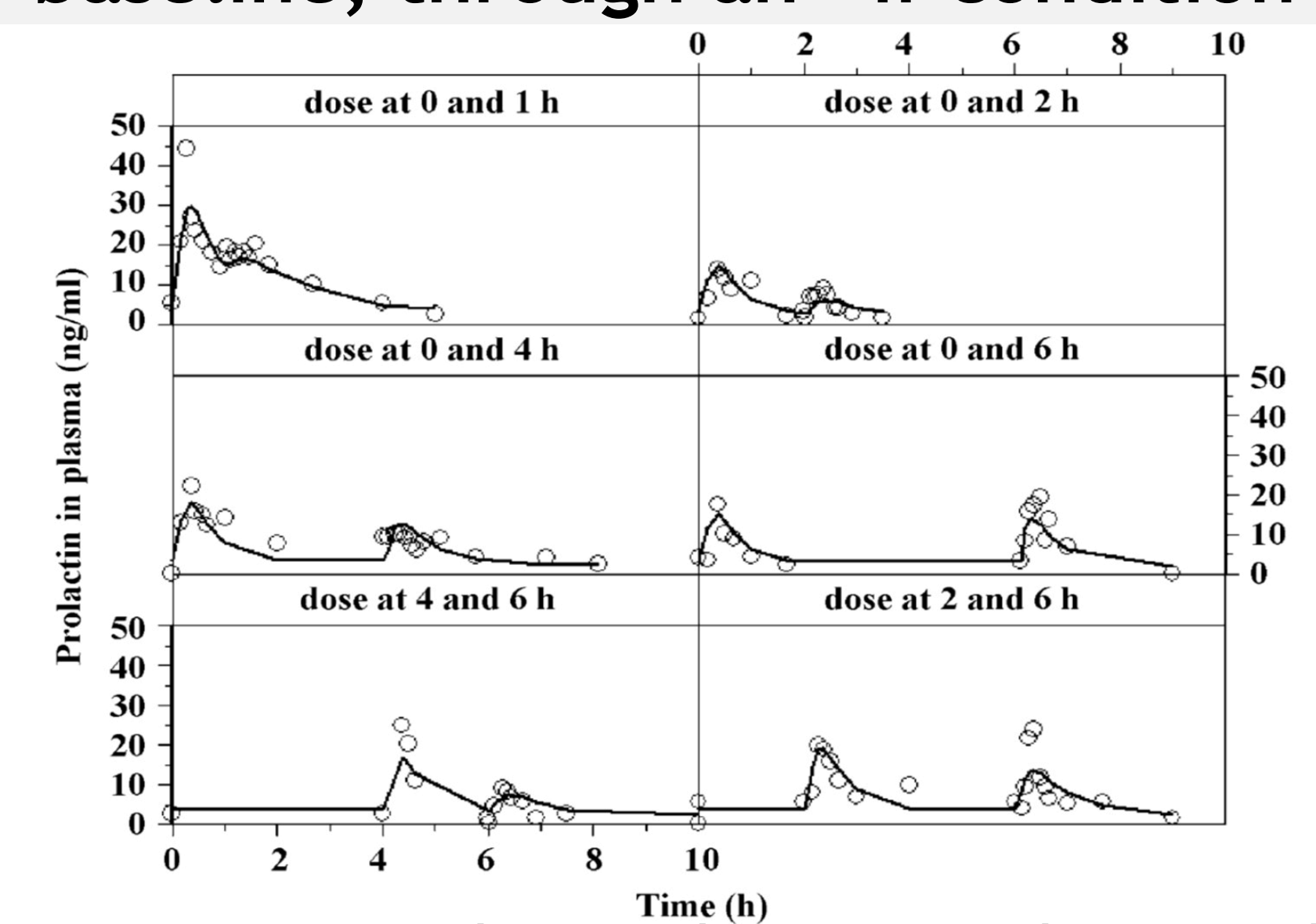


Figure 2. Sample rat plasma PRL data (circles) fitted with the PF model [2]. Model estimation used more extensive PK/PD datasets.

## Unexpected multistationarity

- $R_0 = k_s/k_{el}$  is the physiologically expected PRL baseline in plasma
- For certain drug doses the model predicts return to  $R_0$ , but for other doses it predicts a higher steady state  $R_1$  (Fig 3)
- The value of the steady state does not appear to increase (or decrease) linearly with dose

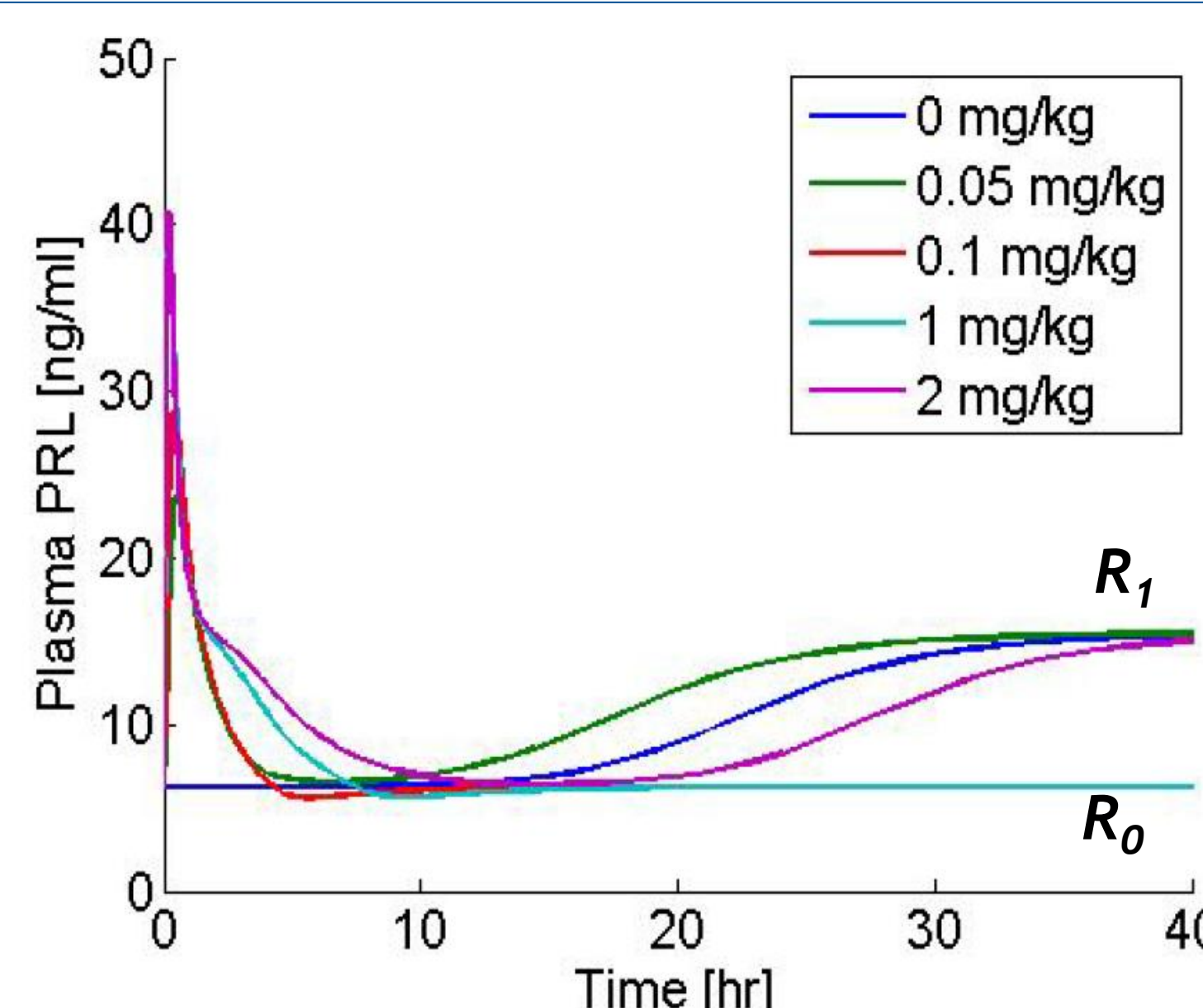


Figure 3. Simulation of the PF model shows that after the initial peak orbits relax to different steady states for different doses.

## Method

- Nondimensionalisation
- Finding steady states
- Phase plane analysis
- Determination of stability of steady states
- Parametric dependence of stability

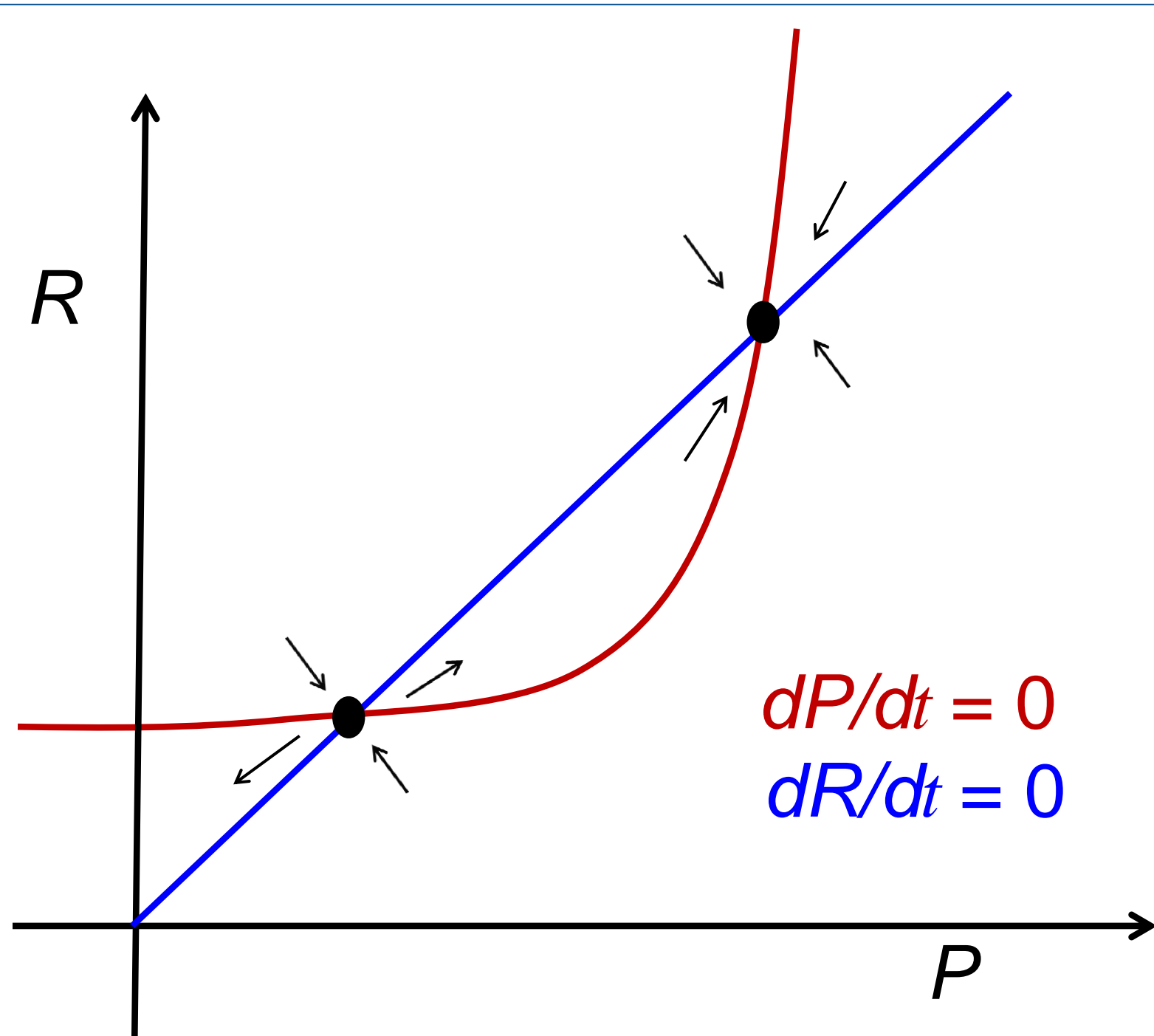


Figure 4. Phase diagram of the PF model without the “if condition” shows that the higher of the two steady states is stable and the lower (i.e. the desired) one is unstable.

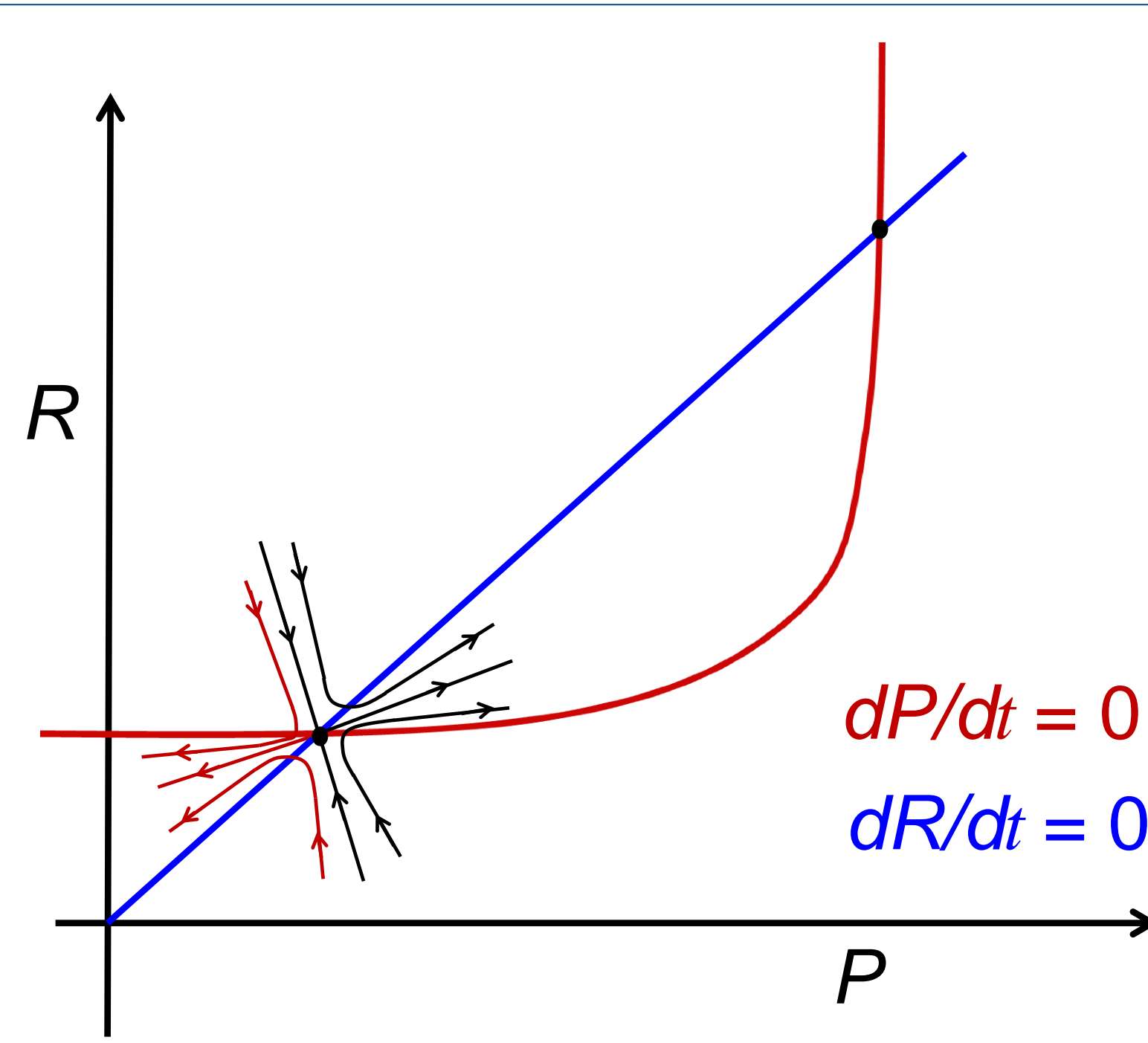


Figure 5. Orbits near the lower (desired) steady state show that orbits in red will eventually take negative values, thus necessitating an “if condition”.

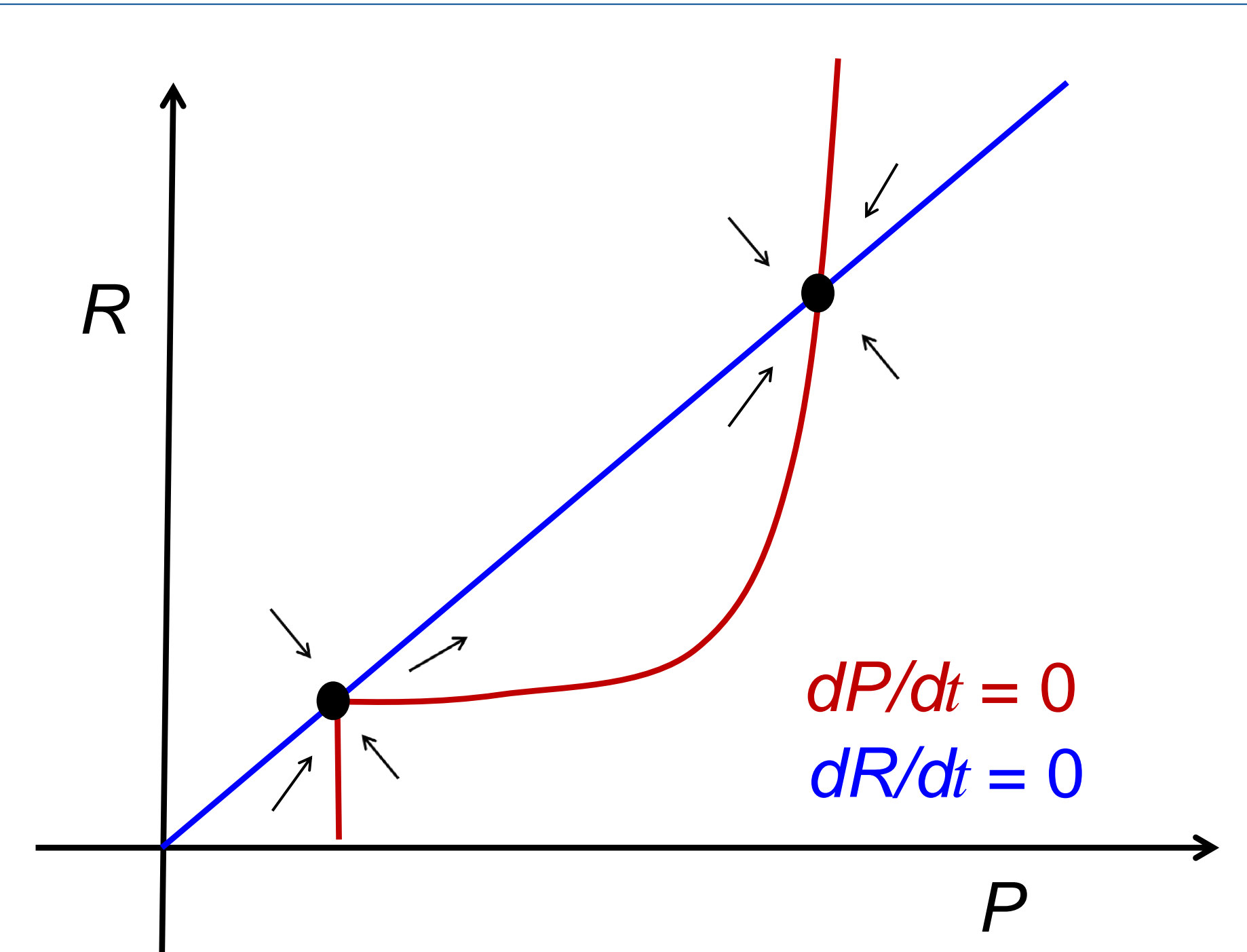


Figure 6. Phase diagram of the PF model with the “if condition” shows that the lower (desired) steady state is now stable from below.

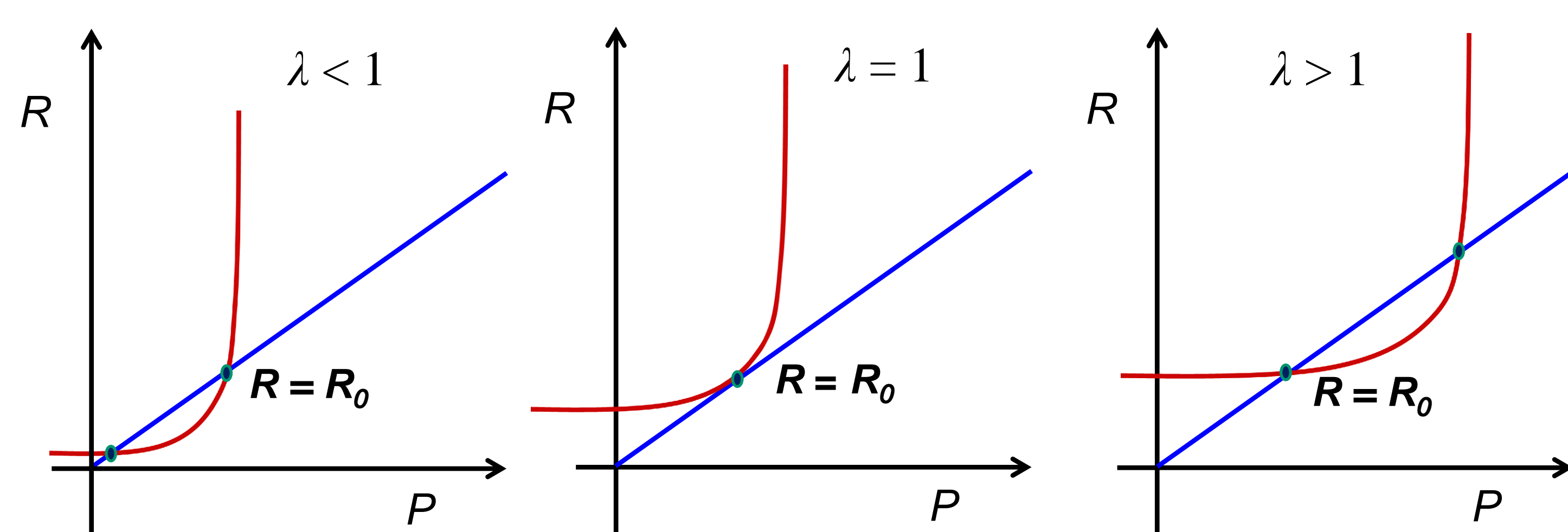


Figure 7. Phase diagrams for different values of the bifurcation parameter  $\lambda = R_0 E_{max} / EC_{50}$  show how stability of  $R_0$  depends upon  $\lambda$ .

## Results and conclusion

- The PF model has two steady states, namely  $R_0 = k_s/k_{el}$  and  $R_1 = R_0 + R_0 E_{max} / EC_{50}$
- The higher of the two steady states is always stable
- $R_0$  is stable if  $R_0 > R_1$ , i.e. if  $R_0 E_{max} / EC_{50} < 1$
- The lower (desired) steady state is stable from below
- Simulations predict lower or higher steady state depending upon whether the “if condition” is activated or not, respectively [3].

## References

- [1] Movin-Osswald G, Hammarlund-Udenaes M. *Journal of Pharmacology and Experimental Therapeutics*. 1995;274(2):921-927
- [2] Stevens J, Ploeger B, Hammarlund-Udenaes M, Osswald G, van der Graaf PH, Danhof M, et al. *Journal of Pharmacokinetics and Pharmacodynamics*. 2012;39(5):463-477.
- [3] Bakshi S, de Lange ECM, vd Graaf Piet H, Danhof M and Peletier LA, *CPT: Pharmacometrics and Systems Pharmacology*, Accepted. 2016.



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