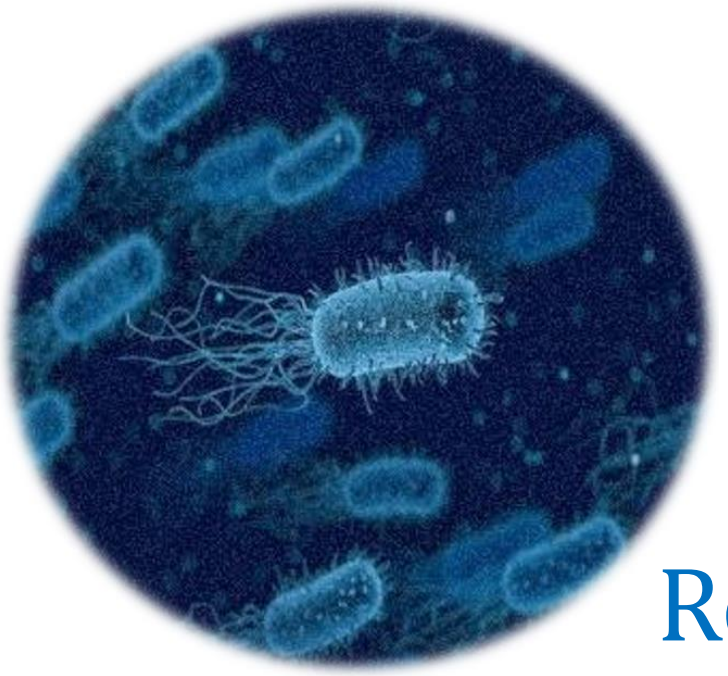

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Analyzing Dynamics of Tight Regulation: From Epidemics to Cells

Magdalena Djordjevic, IPB

I. Epidemic outburst under strong control measures
II. Tightly controlled gene expression within cells

Biological systems under weak control

Briefly consider two examples of weak (or absence of) control in biological dynamics:

- Unregulated (or weakly regulated) gene expression regulation.
- Inherent (without control measures) disease dynamics.

Argue that:

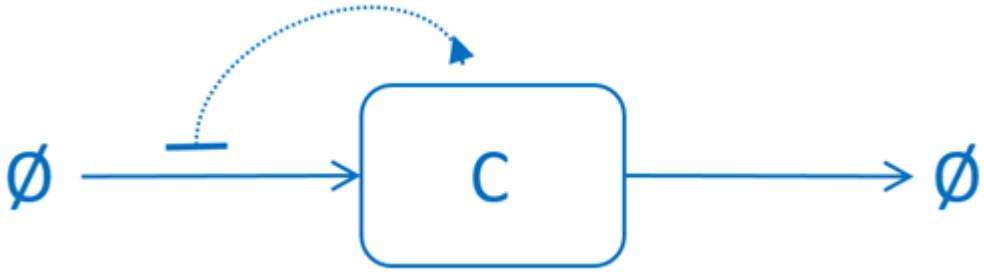
- Solving dynamics analytically for weakly regulated systems may be straightforward or even trivial and is well explored.
- In the opposite limit of tight regulation, not much has been done before. However, much analytical work can be done, which is, however, technically more complicated.

Un (or weakly) regulated gene expression

Proteins are synthesized from DNA and are subsequently degraded. If the process is unregulated, it can be described by:

$$\frac{dC}{dt} = \varphi - \lambda \cdot C$$

Simple linear differential equation!



Consider that the protein represses its expression (autoinhibition).
Protein expression then decreases with the increase in protein synthesis:

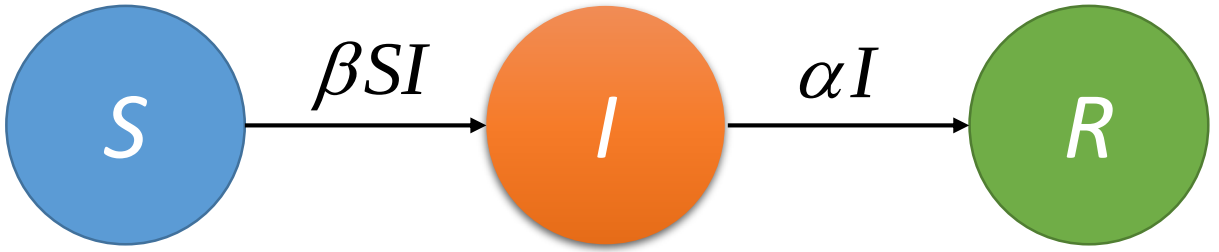
$$\varphi = \frac{\varphi_0}{1 + C/K_D}$$

In the weakly regulated limit ($K_D \gg C$), expression dynamics can also be solved analytically:

$$\frac{dC}{dt} = \varphi_0 - (\lambda + \varphi_0/K_D) \cdot C$$

Disease dynamics without control measures

A well-known SIR (Susceptible-Infected-Removed) infection model



$$S' = -\beta SI$$
$$I' = \beta SI - \alpha I$$
$$R' = \alpha I$$

Brauer, F. (2008). Compartmental models in epidemiology. In Mathematical epidemiology (pp. 19-79). Springer, Berlin, Heidelberg.

Inherent disease dynamics, i.e., not applicable when control measures, such as social distancing or vaccination, are introduced.

Analytical (closed-form) solutions are available:

Harko, T., Lobo, F. S., & Mak, M. (2014). Exact analytical solutions of the Susceptible-Infected-Recovered (SIR) epidemic model and of the SIR model with equal death and birth rates. Applied Mathematics and Computation, *236*, 184-194.

Part I

Analytical study of infection progression under strong social distancing

B Ilic, I Salom, M Djordjevic, MD, Nonlinear Dynamics, 1-21, 2023

MD, M. Djordjevic, B. Ilic, S. Stojku, I. Salom, Global Challenges 5, 2000101, 2021 (featured as a cover letter)

This work is supported by the Ministry of Science of the Republic of Serbia

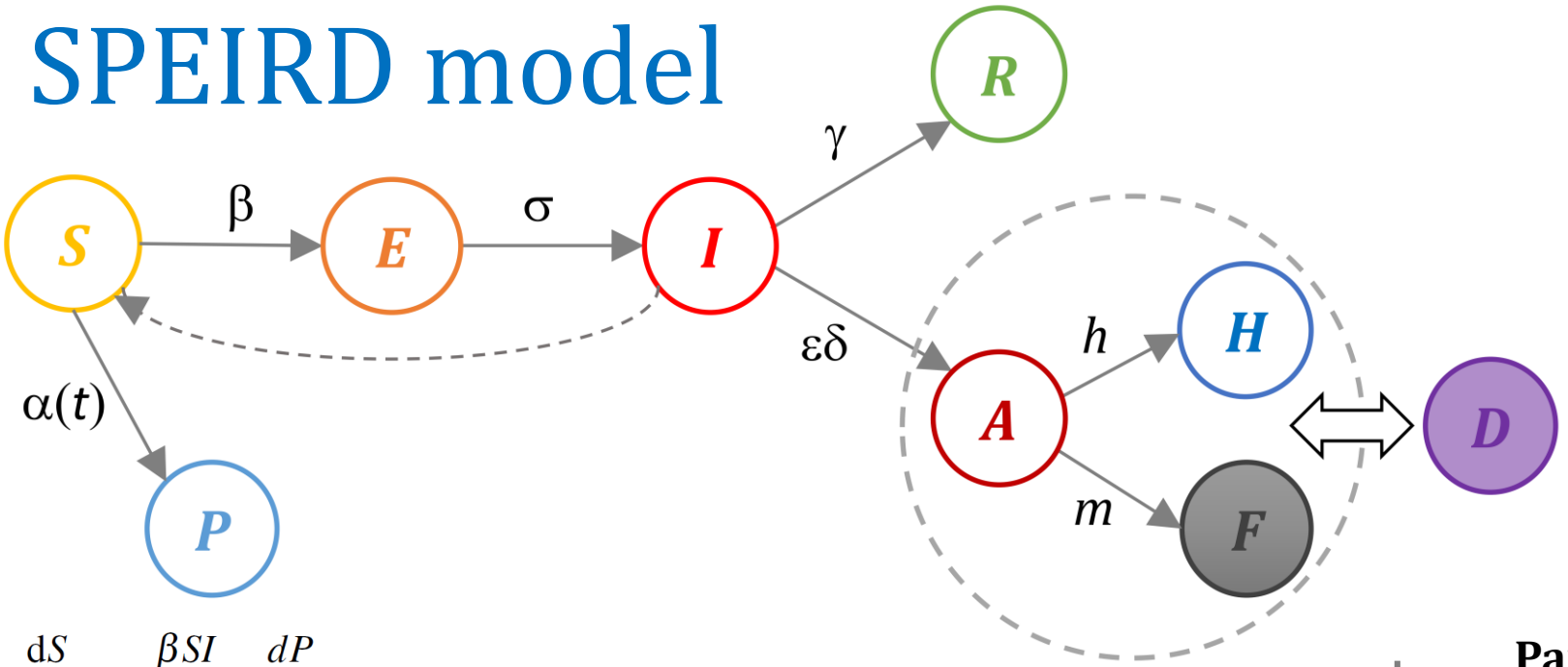
Motivation

- While there has been much computational work on the effect of intervention measures, such as vaccination or quarantine, the influence of social distancing on the epidemics' outbursts is not well understood.
- Understanding such influence is crucial in case of new pandemics, where effective pharmaceutical treatments are lacking, and well-timed social mitigation measures are crucial!

Goal

- Develop a realistic, analytically solvable framework for COVID-19 dynamics with social distancing measures.
- While based on COVID-19, our study has broad applicability to infection outbursts.
- Derive closed-form mathematical expressions for time-dependent epidemiological observables, including infected, detected cases and fatalities.
- Analytical solutions indicate simple quantitative relations between the model variables and epidemiological observables - give insights into cause-effect connections that underlie the outburst dynamics (obscured in numerical approaches).

SPEIRD model



S – susceptible
P – protected
E – exposed
I – infected
R – recovered
D – detected
A – active
H – healed
F – fatalities

$$\frac{dS}{dt} = -\frac{\beta SI}{N} - \frac{dP}{dt},$$

$$\frac{dP}{dt} = \frac{\alpha S}{1+(t_0/t)^n},$$

Gradual introduction of social distancing (Hill function).

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \sigma E,$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \varepsilon\delta I,$$

$$\frac{dR}{dt} = \gamma I,$$

$$\frac{dD}{dt} = \varepsilon\delta I,$$

Only a fraction of infected gets diagnosed.

$$\frac{dA}{dt} = \varepsilon\delta I - hA - mA$$

$$\frac{dF}{dt} = mA.$$

Analytically tractable!

Parameters:

N – total population number
β - transmission rate
α - social distancing strength
t_0 - timing of measures
σ - inverse of latency period
γ - inverse of infectious period
δ – detection time-scale
ε – detection efficiency
h – recovery rate of active cases
m – mortality rate

Analytical derivations of $I(t)$, $D(t)$ and $F(t)$

$$I(t) = \theta(t_0 - t) I_0 e^{\lambda_+ t} + \theta(t - t_0) I_0 e^{\lambda_+ t_0} e^{-\frac{\gamma+\varepsilon\delta+\sigma}{2}(t-t_0)} \times \frac{K\left(\frac{\gamma+\varepsilon\delta-\sigma}{\alpha}, \frac{2\sqrt{e^{-\alpha(t-t_0)}\beta\sigma}}{\alpha}\right)}{K\left(\frac{\gamma+\varepsilon\delta-\sigma}{\alpha}, \frac{2\sqrt{\beta\sigma}}{\alpha}\right)},$$

I_0 – Initial number of infected cases

$K(n,x)$ - Bessel function of the second kind

$$\lambda_+ = \frac{\sqrt{(\gamma+\varepsilon\delta-\sigma)^2+4\beta\sigma}-(\gamma+\varepsilon\delta+\sigma)}{2}$$

MD, M. Djordjevic, B. Ilic, S. Stojku, I. Salom, Global Challenges 5, 2000101, 2021

$$\frac{d^2F(t)}{dt^2} + (h+m)\frac{dF(t)}{dt} - m\varepsilon\delta I(t) = 0,$$

$$D(t) = \varepsilon\delta \int I(t)\, dt + C.$$

Analytical derivations of $F(t)$ and $D(t)$ are very involved due to a complex form of I(t)!

B Ilic, I Salom, M Djordjevic, MD, Nonlinear Dynamics, 1-21, 2023

$$K_n(x) \sim \sqrt{\frac{\pi}{2x}} e^{-x}\left(1+\mathcal{O}\left(\frac{1}{x}\right)\right) \qquad x = 2\sqrt{\beta\sigma}/\alpha \gg 1 \qquad \Gamma(s,x) = \int_x^\infty t^{s-1} e^{-t}\,dt$$

$$\begin{aligned}
F(t) = I_0\varepsilon\delta\frac{m}{h+m}\Bigg[&\theta(t_0-t)\left(\frac{e^{\lambda_+ t}-1}{\lambda_+}+\frac{e^{-(h+m)t}-e^{\lambda_+ t}}{h+m+\lambda_+}\right)\\
&+\theta(t-t_0)\left(\frac{e^{\lambda_+ t_0}-1}{\lambda_+}-e^{-(h+m)t}\frac{e^{(h+m+\lambda_+)t_0}-1}{h+m+\lambda_+}\right.\\
&+\frac{2}{\alpha}\left(\frac{2\sqrt{\beta\sigma}}{\alpha}\right)^{-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}+\frac{1}{2}} e^{\lambda_+ t_0+\frac{2\sqrt{\beta\sigma}}{\alpha}}\\
&\times\left\{\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{e^{-\alpha(t-t_0)}\beta\sigma}}{\alpha}\right)\right.\\
&-\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{\beta\sigma}}{\alpha}\right)+\left(\frac{2\sqrt{e^{-\alpha(t-t_0)}\beta\sigma}}{\alpha}\right)^{\frac{2(h+m)}{\alpha}}\\
&\times\left[\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma-2(h+m)}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{\beta\sigma}}{\alpha}\right)\right.\\
&\left.\left.\left.-\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma-2(h+m)}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{e^{-\alpha(t-t_0)}\beta\sigma}}{\alpha}\right)\right]\right\}\right)\Bigg]. \qquad (16)
\end{aligned}$$

$$\begin{aligned}
D(t) = \frac{I_0\varepsilon\delta}{\lambda_+}\Bigg(&\theta(t_0-t)e^{\lambda_+ t}+\theta(t-t_0)e^{\lambda_+ t_0}\\
&\times\left\{1+\frac{2\lambda_+}{\alpha}\left(\frac{2\sqrt{\beta\sigma}}{\alpha}\right)^{-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}+\frac{1}{2}} e^{\frac{2\sqrt{\beta\sigma}}{\alpha}}\right.\\
&\times\left[\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{e^{-\alpha(t-t_0)}\beta\sigma}}{\alpha}\right)\right.\\
&\left.\left.\left.-\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2},\tfrac{2\sqrt{\beta\sigma}}{\alpha}\right)\right]\right\}\Bigg)
\end{aligned}$$

B Ilic, I Salom, M Djordjevic, MD, Nonlinear Dynamics, 1-21, 2023

At saturation (the end of first epidemic wave):

$$\begin{aligned}
F_{fin} &\approx \frac{2I_0\varepsilon\delta}{\alpha}\frac{m}{h+m}\left(\frac{2\sqrt{\beta\sigma}}{\alpha}\right)^{-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}+\frac{1}{2}} e^{\lambda_+ t_0+\frac{2\sqrt{\beta\sigma}}{\alpha}}\\
&\times\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2}\right).
\end{aligned}$$

$$\begin{aligned}
D_{fin} &\approx \frac{2I_0\varepsilon\delta}{\alpha}\left(\frac{2\sqrt{\beta\sigma}}{\alpha}\right)^{-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}+\frac{1}{2}} e^{\lambda_+ t_0+\frac{2\sqrt{\beta\sigma}}{\alpha}}\\
&\times\Gamma\left(\tfrac{\gamma+\varepsilon\delta+\sigma}{\alpha}-\tfrac{1}{2}\right),
\end{aligned}$$

which can be further approximated:

$$\begin{aligned}
F_{fin}^{approx} &\approx 2D_0\frac{m}{h+m}e^{\frac{3}{2}}\sqrt{\frac{2\pi/\alpha}{\gamma+\varepsilon\delta+\sigma-\frac{3}{2}\alpha}}\lambda_+\\
&\times\left(\frac{2\lambda_++\gamma+\varepsilon\delta+\sigma}{\gamma+\varepsilon\delta+\sigma-\frac{3}{2}\alpha}\right)^{\frac{1}{2}-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}} e^{(t_0+\frac{2}{\alpha})\lambda_+}
\end{aligned}$$

$$\begin{aligned}
D_{fin}^{approx} &\approx 2D_0 e^{\frac{3}{2}}\sqrt{\frac{2\pi/\alpha}{\gamma+\varepsilon\delta+\sigma-\frac{3}{2}\alpha}}\lambda_+\\
&\times\left(\frac{2\lambda_++\gamma+\varepsilon\delta+\sigma}{\gamma+\varepsilon\delta+\sigma-\frac{3}{2}\alpha}\right)^{\frac{1}{2}-\frac{\gamma+\varepsilon\delta+\sigma}{\alpha}} e^{(t_0+\frac{2}{\alpha})\lambda_+}
\end{aligned}$$

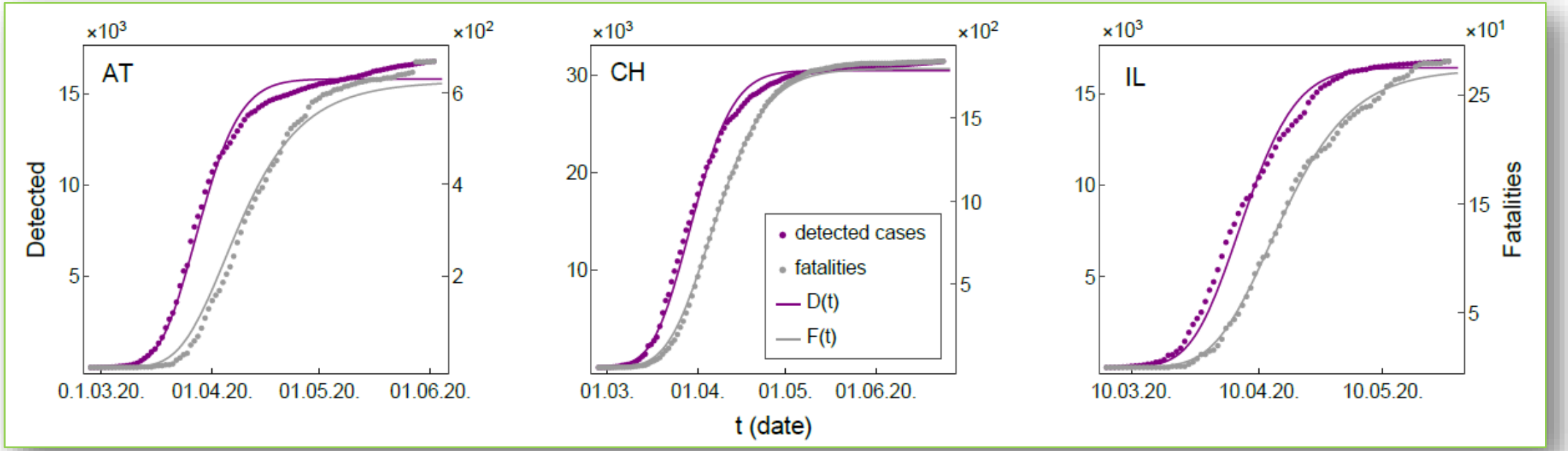
$$F_{fin}^{approx} = \frac{m}{m+h}D_{fin}^{approx}$$

$D(0) = D_0 = I_0\varepsilon\delta/\lambda_+$

Stirling's formula: $n! \approx \sqrt{2\pi n}\left(\frac{n}{e}\right)^n$

$4\beta\sigma \gg (\gamma+\delta\varepsilon-\sigma)^2$

Testing validity of analytical procedure



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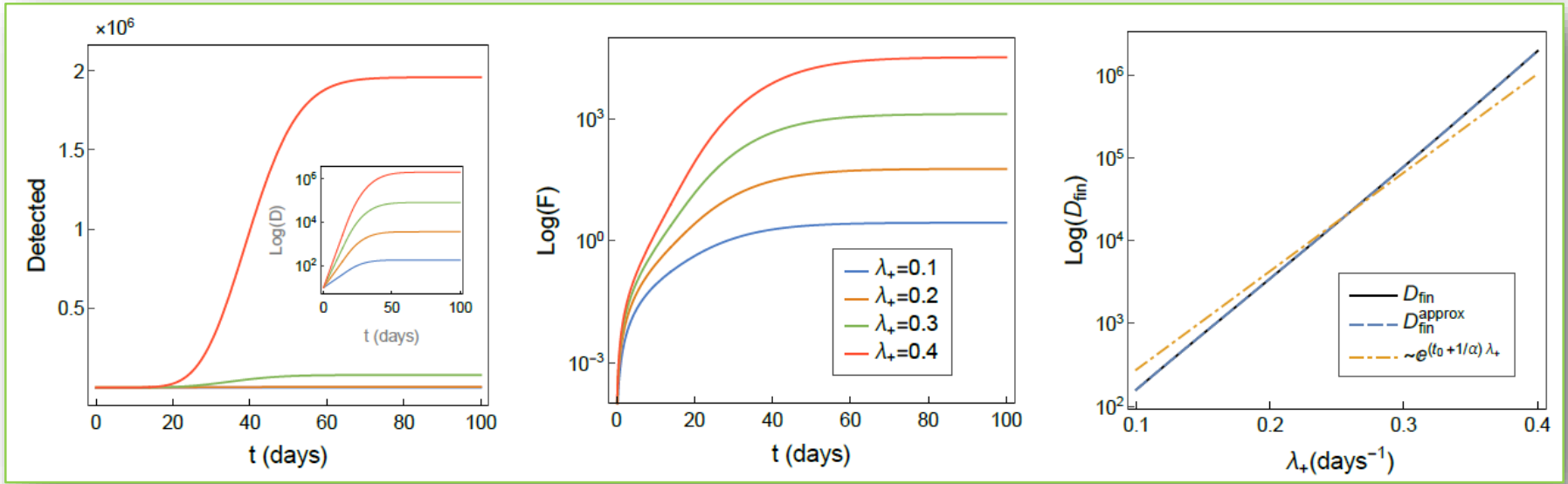
A good agreement between our analytical predictions and case counts.

Supports validity of our analytical approach.

How $D(t)$ and $F(t)$ depend on initial slope (λ_+)?

Basic reproduction number: $R_0 = \beta/\gamma = \frac{\lambda_+^2+\lambda_+(\gamma+\varepsilon\delta+\sigma)+(\gamma+\varepsilon\delta)\sigma}{\sigma\gamma}$



At saturation D and F is $\sim e^{t_\alpha \lambda_+}$, where $t_\alpha = t_0 + 1/\alpha$ is protection time.

Important quantity for assessing epidemic risks and public policy decision-making!

Analytic expression that quantifies interplay between t_0 and α!

Detected cases and fatalities are highly sensitive to λ_+.

The greater λ_+ is, the $D(t)$ and $F(t)$ curves are steeper, and saturation values become exponentially larger.

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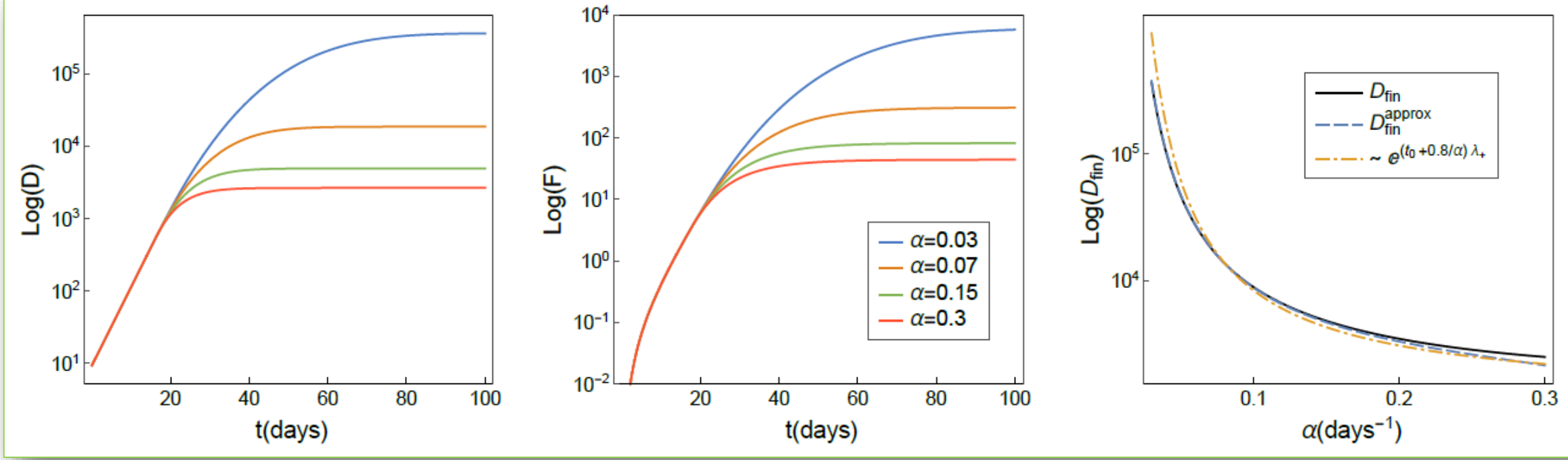
Effect of social distancing strength (α) on $D(t)$ and $F(t)$



Detected cases and fatalities are highly sensitive to α.

The greater α is, the lower saturation values of $D(t)$ and $F(t)$ are.

At saturation, D and F $\sim e^{(t_0+0.8/\alpha)\lambda_+} \approx e^{t_\alpha \lambda_+}$.

B Ilic, I Salom, M Djordjevic, MD, Nonlinear Dynamics, 1-21, 2023

MD, M. Djordjevic, B. Ilic, S. Stojku, I. Salom, Global Challenges 5, 2000101, 2021

Epidemic peak time, its duration and maximum of detected cases per day

B Ilic, I Salom, M Djordjevic, MD, Nonlinear Dynamics, 1-21, 2023

$dI/dt = 0 \quad d^2D/dt^2 = 0$ ⇒ Epidemic's peak time:

$$t_{max} = t_0 + \frac{1}{\alpha} \ln \left[\frac{16\beta\sigma}{(2(\gamma+\varepsilon\delta+\sigma)-\alpha)^2} \right]$$

Max of detected cases per day:

$$\left(\frac{dD}{dt}\right)_{max} = D_0 \lambda_+ e^{\lambda_+ (t_0 + \frac{2}{\alpha}) + \frac{1}{2}} \left(\frac{4\sqrt{\beta\sigma}}{2(\gamma+\varepsilon\delta+\sigma)-\alpha} \right)^{\frac{1}{2} - \frac{\gamma+\varepsilon\delta+\sigma}{\alpha}}$$

$d^2I/dt^2 = 0 \quad d^3D/dt^3 = 0$ ⇒ Infection tipping points:

$$t_{1,2} = t_0 + \frac{2}{\alpha} \ln \left(\frac{2\sqrt{\beta\sigma}}{\gamma+\delta\varepsilon+\sigma \mp \sqrt{\alpha\left(\gamma+\varepsilon\delta+\sigma-\frac{\alpha}{4}\right)}} \right)$$

$$\Delta t_{peak} = \frac{4}{\alpha} \ln \left(\frac{\gamma+\varepsilon\delta+\sigma+\sqrt{\alpha(\gamma+\varepsilon\delta+\sigma-\frac{\alpha}{4})}}{\gamma+\varepsilon\delta+\sigma-\alpha/2} \right)$$

$\alpha << (\gamma+\sigma)$

$$\Delta t_{peak} \approx \frac{4}{\sqrt{\alpha(\gamma+\varepsilon\delta+\sigma)}}$$

⇒ Duration of epidemic peak, Δt_{peak}, independent of transmission rate β!

Effects of λ_+ and α on $\left(\frac{dD}{dt}\right)_{max}$

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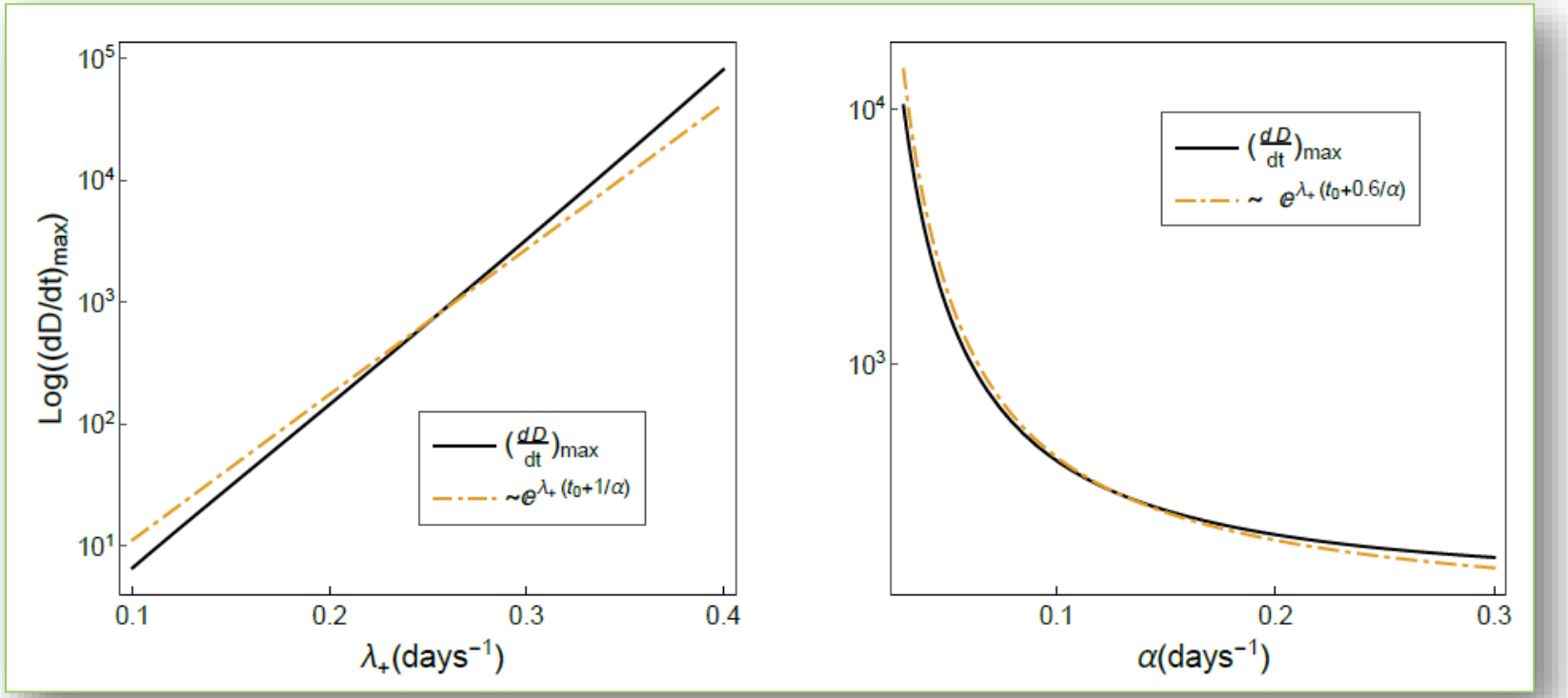
Protection time

$t_\alpha = t_0 + 1/\alpha$



$\left(\frac{dD}{dt}\right)_{max}$ has strong dependence $\sim e^{t_\alpha \lambda_+}$

Highlights importance of protection time.

Part I - Summary

- Demonstrated full analytical treatment of a compartmental epidemiological model incorporating social distancing measures.
- Model's accuracy validated against publicly available COVID-19 data.
- Analytical solutions reveal quantitative relations between model variables and epidemiological observables, offering insights into cause-effect connections (obscured in standard numerical approaches).
- Identified a quantitatively expressible interplay between social distancing strength and timing of implementation, leading to the concept of "protection time".
- Suggests that stringent measures can be often substituted by more relaxed ones introduced at earlier times - analytical expression to quantify this trade-off.
- The model is applicable beyond COVID-19, relevant to future epidemics.
- Highlighted the importance of well-timed control measures in the absence of vaccines or pharmaceutical treatments for emerging infectious diseases.

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Part II

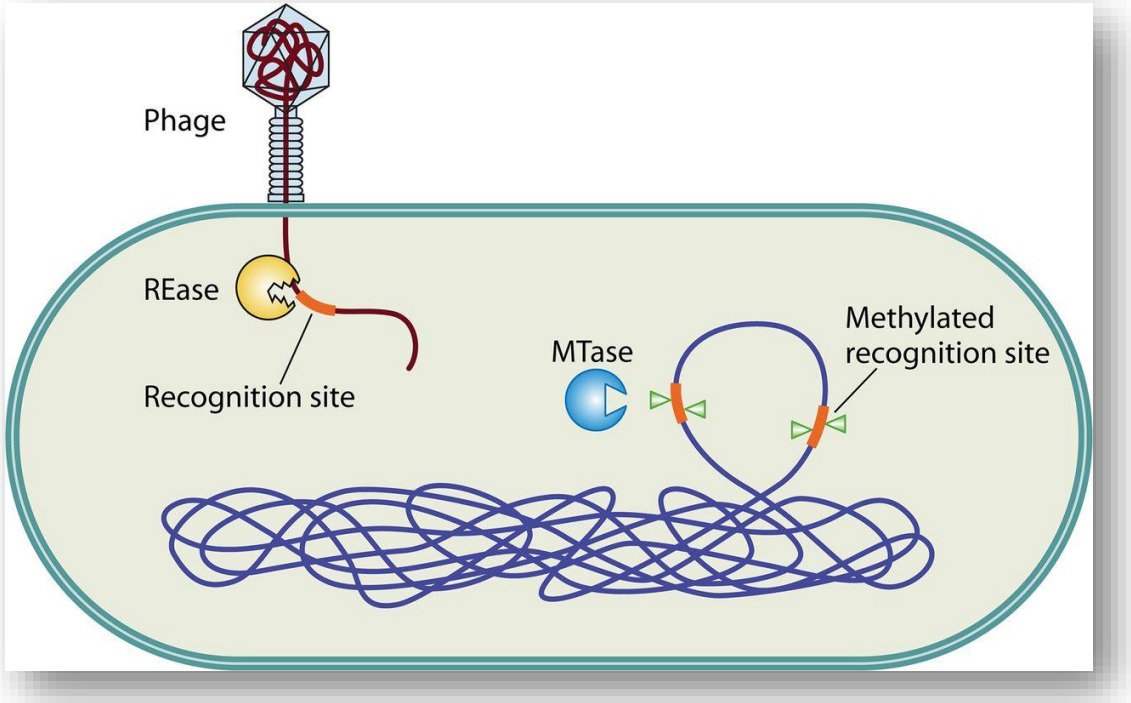
Bistability in the regulatory dynamics of bacterial restriction-modification systems

Magdalena Djordjevic, Lidija Zivkovic, Marko Djordjevic, in preparation (2023)

This work is supported by the Science Fund of the Republic of Serbia, project no. 7750294, q-bioBDS

Restriction-modification system

- Rudimentary Bacterial Defense System (BDS).
- Known to modulate barrier to horizontal gene transfer (HGT), providing protection against bacteriophages.
- Can bistability occur in restriction-modification (RM) systems?



Why bistability?

Bistability leads to antibiotic persistence in the toxin-antitoxin (TA) systems (another type of BDS).

The existence of bistability in RM systems could also lead to a subpopulation that can more easily acquire foreign genes (including virulence, antibiotic resistance, etc.).

We aim to analytically and numerically test this possibility, by studying different RM systems:

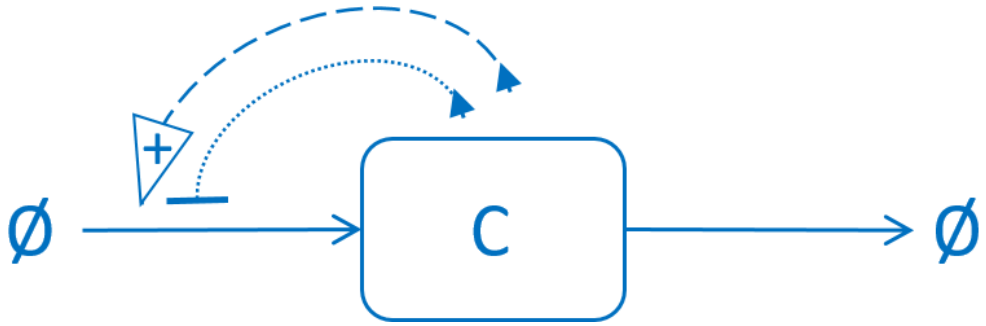
- Does currently measured experimental data in RM systems point to bistability?
- What characteristics in R, M and M/R dynamics can point to possible bistability?
- Can we predict which RM systems can exhibit bistability and under what conditions? Is this experimentally testable?

RM system control by C protein

- Many RM systems rely on specialized transcription factors called C (controller) proteins.
- C proteins play a vital role in the temporal regulation of RM gene expression, and function to indirectly modulate the horizontal gene transfer across the species.
- The dynamics of the C protein in different RM systems can be described by the same equations.
- The parameters in these equations vary between different RM systems.
- Internal parameters are fixed for a specific RM system.
- External parameters depend on the type of the system and external conditions.
- The goal is to develop an analytical model that describes the dynamics of the C protein independently of parameter values.
- Internal parameters will be fixed based on literature values for different RM systems.
- The study will investigate if the RM systems can exhibit bistability and under what external conditions.

C protein regulation

- Start from one transcription factor (control protein ”C”).
- C dimerizes and binds to its promoter as a dimmer.
- Binding leads to both positive and negative feedback.



- Total C generated by transcription ϕ diluted by cell division (λ):

$$\frac{dC_t}{dt} = n\phi(C) - \lambda C_t$$

- Dimmer formation (with $K_{d,1}$):

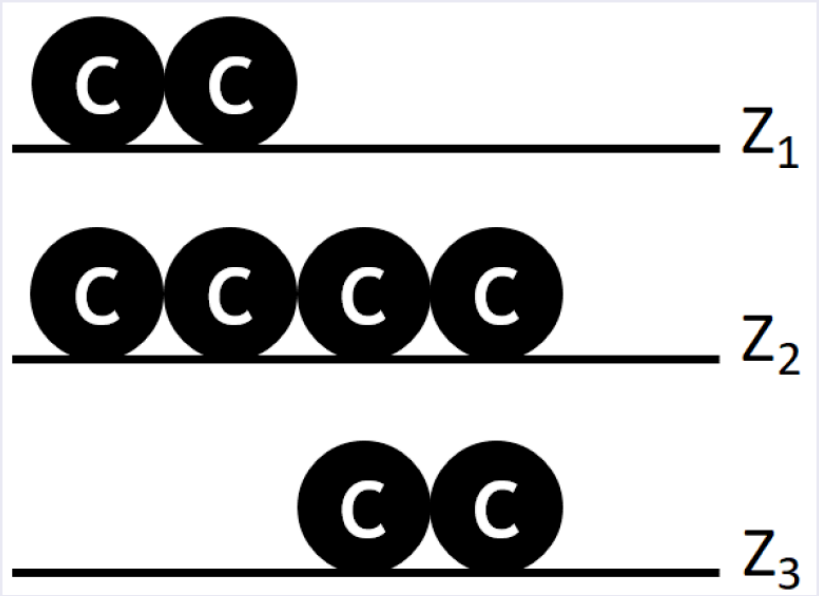
$$D = C^2 / K_{d,1}$$

$$C_t = C + 2D$$

$$C = \frac{K_{d,1}}{4}\left(\sqrt{1 + \frac{8C_t}{K_{d,1}}} - 1\right)$$

- Dimerization and transcription in quasi-equilibrium. n - copy number

Promoter configurations:



$K_{d,2}$	$K_{d,3}$	$K_{d,23}$
left	right	left and right

Table: C binding

weight	expression	effect
Z_1	$C^2/(K_{d,1}K_{d,2})$	activate
Z_2	$(\omega C^4)/(pK_{d,1}^2K_{d,2}^2)$	repress
Z_3	$C^2/(pK_{d,1}K_{d,2})$	repress

Table: Statistical weights

Transcription activity:

$$\phi(C) = \phi_l + \phi_m \frac{Z_1}{1 + Z_1 + Z_2 + Z_3}$$

$$\phi(C) = \phi_l + \phi_m \frac{C^2/(K_{d,1}K_{d,2})}{1 + C^2/(K_{d,1}K_{d,2}) + (\omega C^4)/(pK_{d,1}^2K_{d,2}^2) + C^2/(pK_{d,1}K_{d,2})}$$

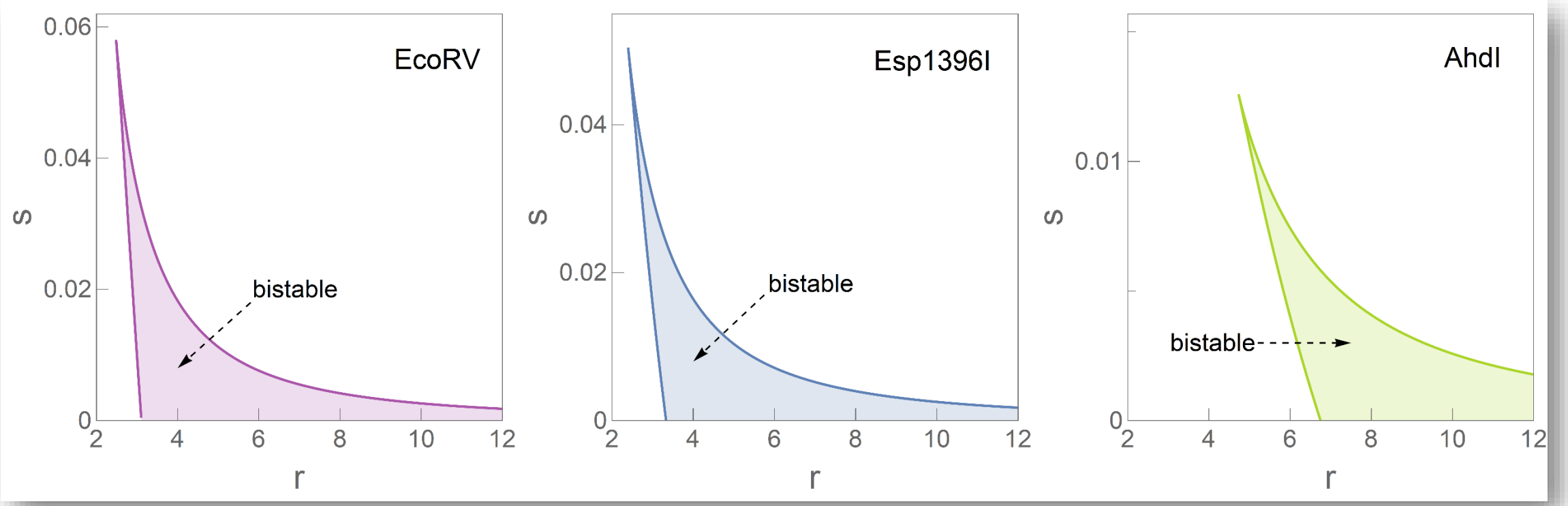
Rescalled C-protein dynamics:

$$\frac{d\widetilde{C}_t}{d\tau} = s + \frac{\widetilde{C}^2}{1+\widetilde{C}^2(1+1/p)+\omega/p\widetilde{C}^2} - \widetilde{C}_t \cdot r \text{ , with } \widetilde{C} = \alpha/4\left(\sqrt{1+8\widetilde{C}_t/\alpha}-1\right)$$

parameter	expression	interpretation	
α	$\sqrt{K_{d,1}/K_{d,2}}$	dimmer formation	Internal parameters
p	$K_{d,3}/K_{d,2}$	left to right binding strength	
ω	$K_{d,2}K_{d,3}/K_{d,23}$	binding cooperativity	
r	$(n\phi_m)/(\lambda\sqrt{K_{d,1}K_{d,2}})$	overall C expression strength	External parameters
s	ϕ_l/ϕ_m	promoter leakage	

- Complex system dynamics can be condensed to five parameters with clear biophysical interpretation directly related to experimentally measurable quantities.
- α, p, and ω are fixed for a given RM system, but change between different systems.
- r and s depend both on the system and external conditions (such as cell growth rate controlling λ, plasmid copy number n).

Stability diagrams for different RM systems



Analytical derivation of the stability diagram (highly nontrivial!)

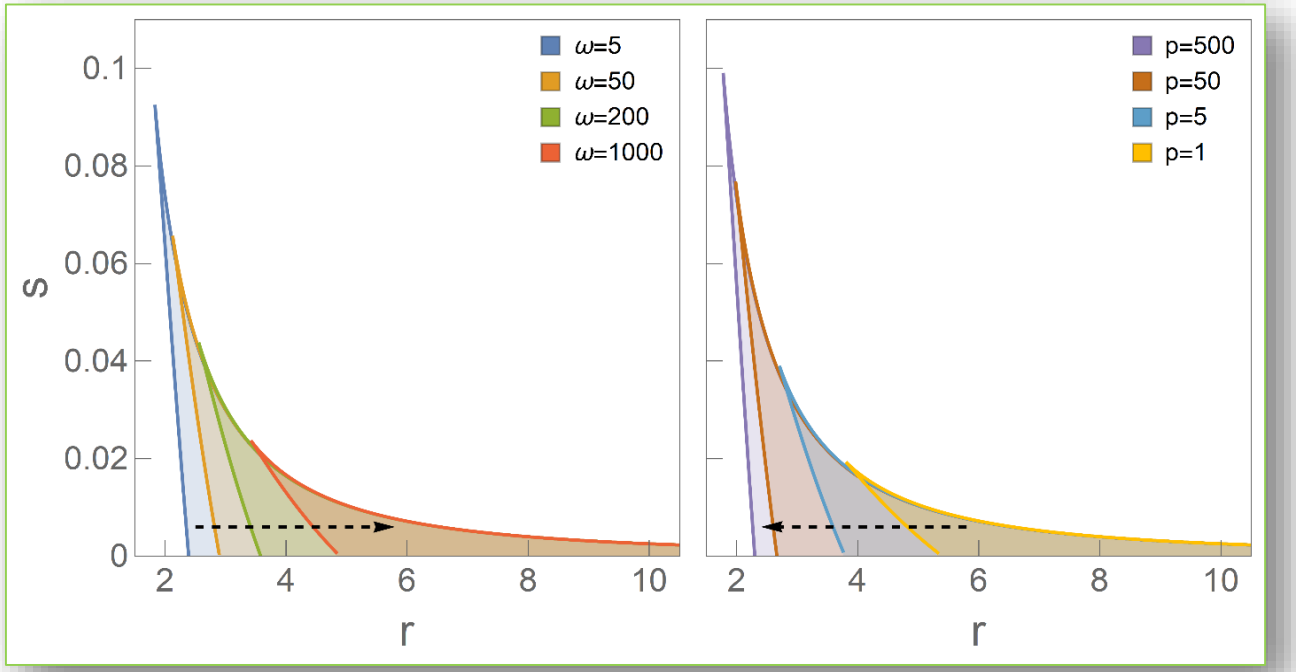
State of the art is to put the external parameters on a grid (r and s) so that for every grid point, stability has to be calculated - and then repeated for every combination of the internal system parameters (α, p, and ω).

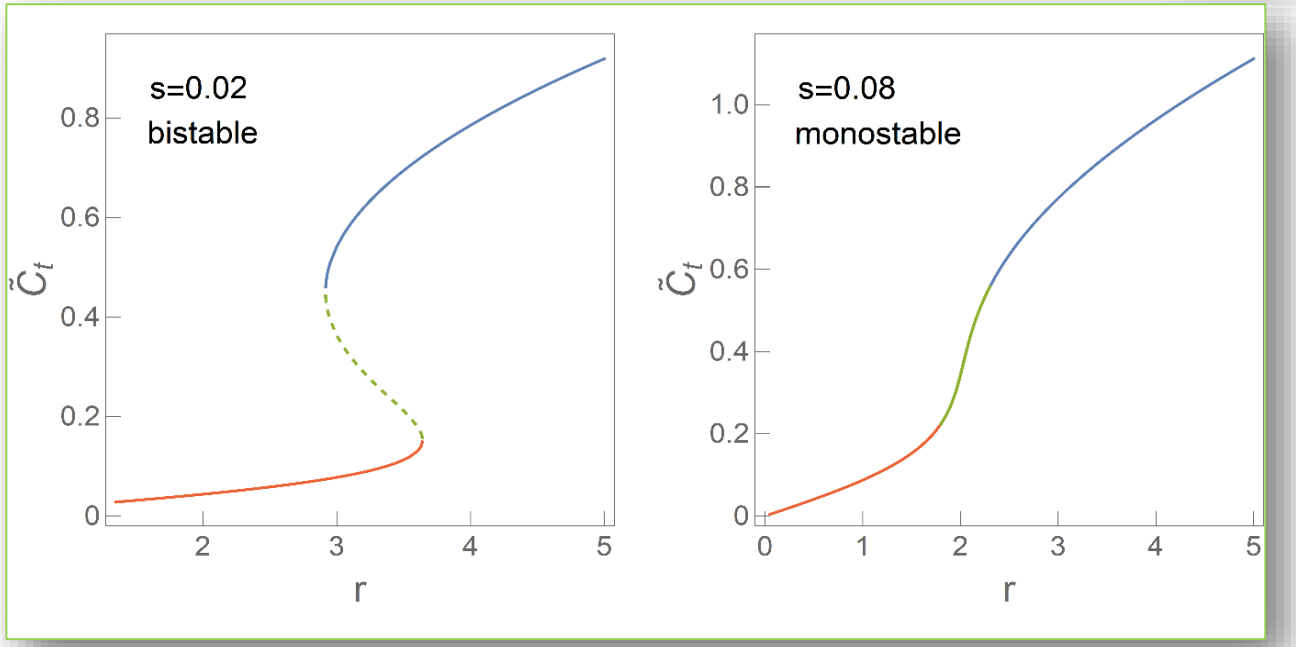
With the analytical derivation, one just has to re-plot the curves!

Bistability promoted by:

- small ω (cooperativity)
- large *p* (stronger activation binding)

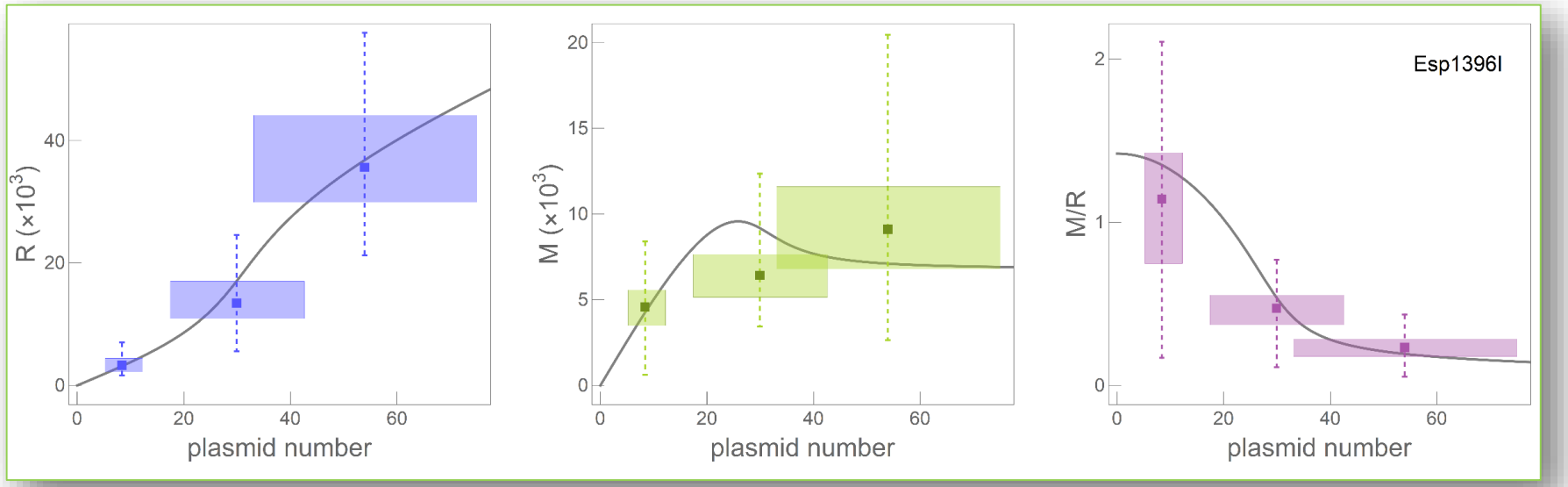
Intuition: Positive feedback promotes, and negative abolishes bistability!



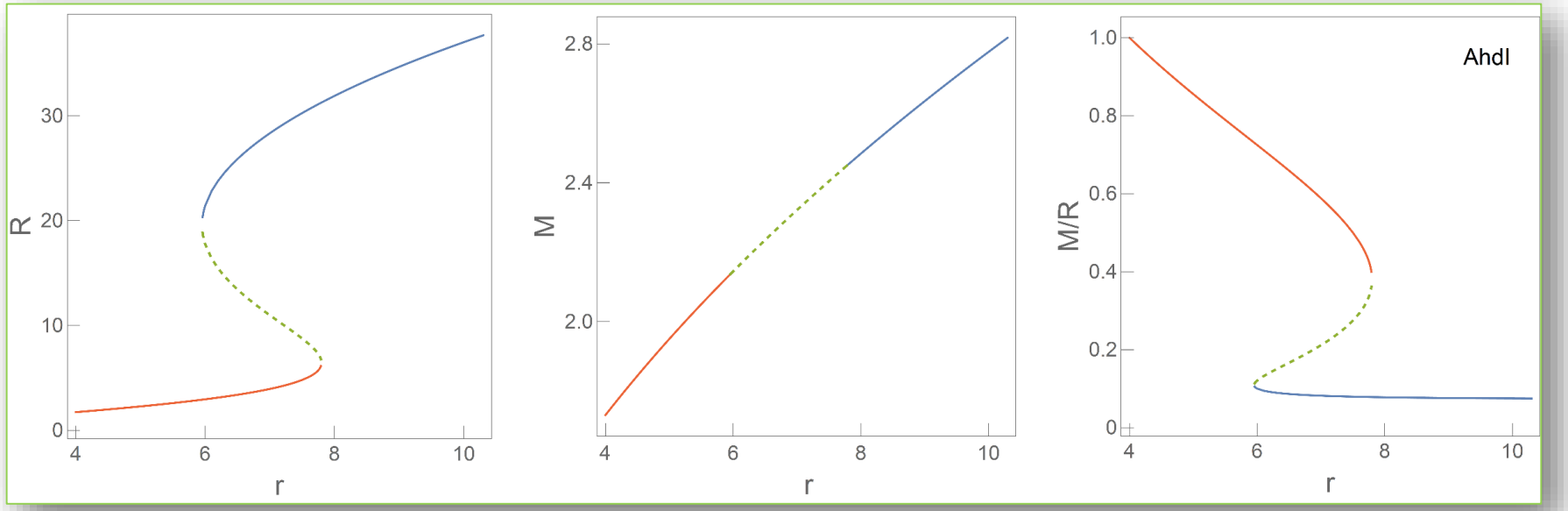


- Small promoter leakage (*s*).
- Intermediate expression strengths (*r*).

Comparison with available data and future predictions



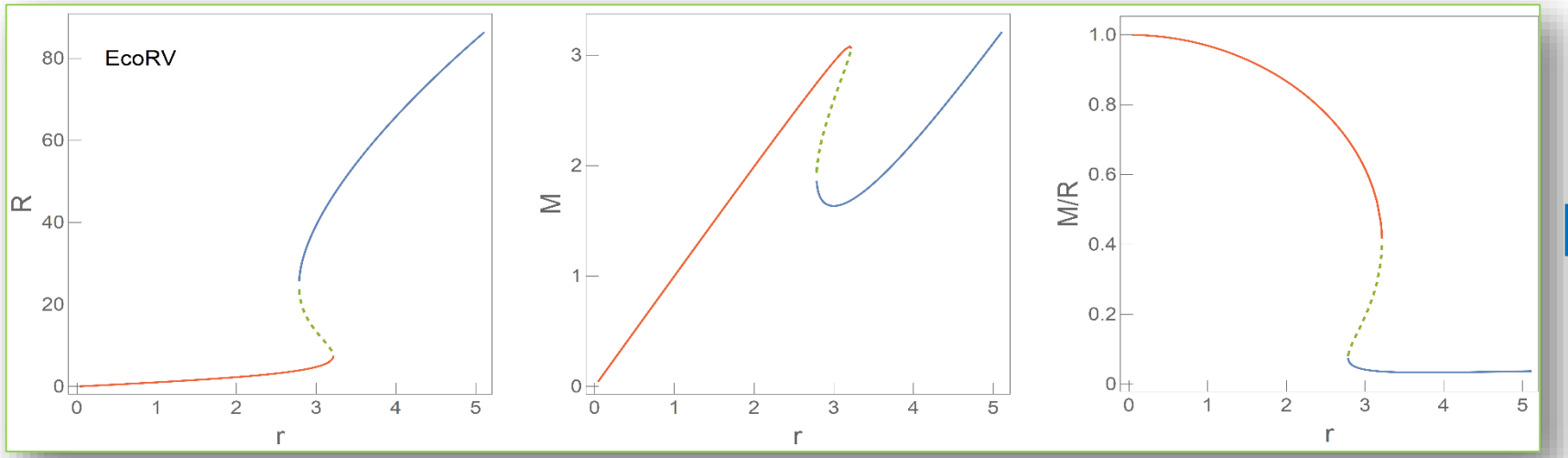
Esp1396I monostable.



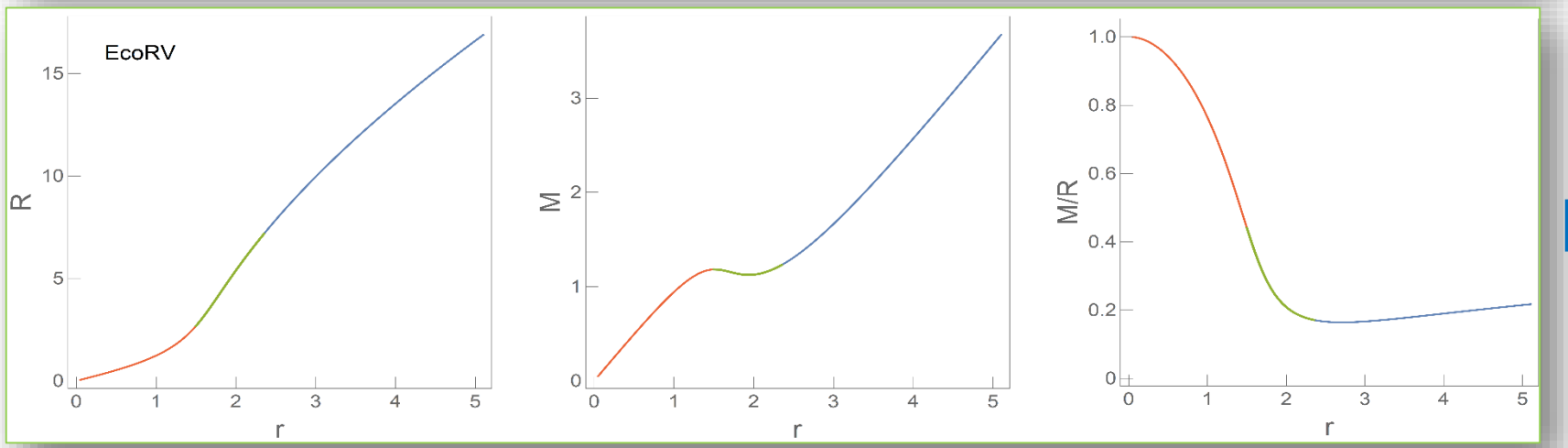
AhdI predicted bistable!

Future predictions for EcoRV

- EcoRV *s* value is not known from the experiment.
- However, despite quite different regulations, *R/M* dependence is predicted to be similar to AhdI and Esp1396I.



EcoRV bistable prediction



EcoRV monostable prediction

Part II - Summary

Developed analytical model directly applicable to diverse C-controlled RM systems:

- Behavior of a complex class of systems is condensed to just five parameters and a straightforward numerical procedure.
- Three experimentally directly measurable parameters (α, ω and p) are fixed for a given system.
- Re-plot equations with these three parameters to obtain a stability diagram and place your system in the diagram based on another two systems dependent parameters (r and s).
- Perform straightforward numerical calculations to obtain experimentally measurable quantities.

Explained experimental data and predict different qualitative dynamics of the system:

- Model agrees well with measured Esp1396I data, with the absence of bistability (at least under experimental conditions).
- For AhdI, a bistable regime is predicted.
- EcoRV shows similar qualitative behavior as Esp1396I and AhdI.
- Consequences of bistability in RM systems remain to be understood!
- Could RM system regulation lead to a subpopulation that readily acquires foreign genes (e.g., virulence, antibiotic resistance) similar to the possible roles of TA systems in antibiotic persistence?

Overall conclusion and outlook

- The tight regulation/control case may be highly relevant for biological system dynamics but appears underexplored in many cases.
- In the first example, we provided analytical solutions for disease dynamics.
- In the second example, we provided analytical derivations of the system stability diagrams typically investigated numerically.
- However, in the distinction to the limit of weak regulation, both the models and mathematical derivations are much more complex.
- **Outlook:** Explore more similar systems, such as bacterial toxin-antitoxin systems - somewhat similar to restriction-modification systems, but with an entirely different control.

Thank you for your attention!

$$\frac{d\widetilde{C}_t}{d\tau} = s + \frac{\widetilde{C}^2}{1+\widetilde{C}^2(1+1/p)+\omega/p\widetilde{C}^2} - \widetilde{C}_t \cdot r \text{ , with } \widetilde{C} = \alpha/4\left(\sqrt{1+8\widetilde{C}_t/\alpha}-1\right)$$