Mathematical Biology - Reaction Diffusion Models and Turing Instability

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- In order to understand this diffusion via equations let us restrict attention to one spatial dimension (for simplicity)
- Consider a particle moving along the x-axis in a random fashion - let us suppose that in time $\triangle t$ the particle moves either $+\triangle x$ or $-\triangle x$.
  Denote by $p(x,t)$ the probability that a particle released at $x=0$, $t=0$ reaches position x at time t.

- At time $t - \triangle t$ the particle must have been at $x + \triangle x$ or $x - \triangle x$ so that

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- Expanding $p(x,t)$ in a Taylor Series we get

$$\begin{aligned} p(x,t) &= \frac{1}{2}\left[\begin{array}{c} p(x,t) - \triangle x\frac{\partial p}{\partial x} - \triangle t\frac{\partial p}{\partial t} + \frac{1}{2}(\triangle x)^2\frac{\partial^2 p}{\partial x^2} \\ +(\triangle x)(\triangle t)\frac{\partial^2 p}{\partial x \partial t} + \frac{1}{2}(\triangle t)^2\frac{\partial^2 p}{\partial t^2} + \ldots \end{array} \right] \\ &+\frac{1}{2}\left[\begin{array}{c} p(x,t) + \triangle x\frac{\partial p}{\partial x} - \triangle t\frac{\partial p}{\partial t} + \frac{1}{2}(\triangle x)^2\frac{\partial^2 p}{\partial x^2} \\ -(\triangle x)(\triangle t)\frac{\partial^2 p}{\partial x \partial t} + \frac{1}{2}(\triangle t)^2\frac{\partial^2 p}{\partial t^2} + \ldots \end{array} \right] \end{aligned}$$

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- Simplifying this we obtain

$$0 = -\triangle t\frac{\partial p}{\partial t} + \frac{1}{2}(\triangle x)^2\frac{\partial^2 p}{\partial x^2} + \frac{1}{2}(\triangle t)^2\frac{\partial^2 p}{\partial t^2} + \ldots$$

- So

$$\frac{\partial p}{\partial t} = \left(\frac{(\triangle x)^2}{2(\triangle t)} \right) \frac{\partial^2 p}{dx^2} + \frac{1}{2}(\triangle t) \frac{\partial^2 p}{\partial t^2} + \dots$$

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the one-dimensional diffusion equation.
- Extensions to higher-dimensions in space and more dependent variables are natural extensions.

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- More precisely in the absence of diffusion, linearly stable uniform steady states may persist but addition of diffusion may drive instabilities.
- Let us derive conditions under which this may happen.
- Most reaction-diffusion systems of biological interest can be non dimensionalised and scaled to take the general form

$$u_t = \gamma f(u,v) + \nabla^2 u \qquad v_t = \gamma g(u,v) + d\nabla^2 v \qquad (1)$$

[The scale factor γ can obviously be incorporated into the reaction kinetics f and g but we keep it separate for now.] We typically have two spatial variables x and y and may have more than two dependent variables u and v.

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- Set
$$u = u_0 + \hat{u},\ v = v_0 + \hat{v} \text{ with } |\hat{u}|,\ |\hat{v}| << 1$$
Then
$$\begin{aligned} \hat{u}_t &= \gamma[f_u \hat{u} + f_v \hat{v}] \\ \hat{v}_t &= \gamma[g_u \hat{u} + g_v \hat{v}] \end{aligned}$$
where all partial derivatives are evaluated at (u_0, v_0)

- If

$$\underline{\mathrm{w}} = \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \qquad \text{then} \qquad \underline{\mathrm{w}}_t = \gamma \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} \underline{\mathrm{w}}$$

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- We look for solutions $\underline{\mathrm{w}} \propto e^{\lambda t}$, where λ is an eigenvalue of the linearised matrix. Then

$$\begin{vmatrix} \gamma f_u - \lambda & \gamma f_v \\ \gamma g_u & \gamma g_v - \lambda \end{vmatrix} = 0 \tag{2}$$

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- For the roots of (2) to have negative real parts we require

$$f_u + g_v < 0 \quad (I)$$
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- If $u = u_0 + \hat{u}, \quad v = v_0 + \hat{v}$ then on linearisation we have

$$\tilde{u}_t = \gamma[f_u \tilde{u} + f_v \tilde{v}] + \nabla^2 \underline{\tilde{u}}$$

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- So, if $\underline{w} = \begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix}$, then

$$\underline{w}_t = \gamma \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} \underline{w} + D\nabla^2 \underline{w} \qquad D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix} \qquad (3)$$

This is a PDE. So to make progress we need to specify relevant boundary conditions.

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  This is a PDE. So to make progress we need to specify relevant boundary conditions.
- Frequently in biological applications zero flux conditions are appropriate (if in a particular application, some other boundary condition is more natural, then the analysis is easily modified).

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- Here k is an eigenvalue and the corresponding eigenfunctions give us a basis in which to expand a solution.

- If we denote by $\underline{\mathrm{w}}_k$ the eigenfunctions of the eigenvalue problem, we seek a solution of the original problem (3) of the form

$$\underline{\mathrm{w}}(x, y, t) = \Sigma_k c_k e^{\lambda_k t} \underline{\mathrm{w}}_k(x, y) \tag{4}$$

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- We wish to know whether any of the λ_k have positive real part (so that diffusion has caused instability).
- Substituting (4) into (3) and comparing eigenfunctions gives

$$\Sigma_k c_k \lambda_k e^{\lambda t} \underline{\mathrm{w}}_k = \gamma A \left(\Sigma_k c_k e^{\lambda_k t} \underline{\mathrm{w}}_k \right) + D\nabla^2 \left(\Sigma_k c_k e^{\lambda_k t} \underline{\mathrm{w}}_k \right)$$

where $A = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}$, the community matrix of the reaction part.

- This can be written:

$$\Sigma_k c_k \lambda_k e^{\lambda_k t} \underline{\mathsf{w}}_k = \gamma A \left(\Sigma_k c_k e^{\lambda_k t} \underline{\mathsf{w}}_k \right) - D \left(\Sigma_k c_k e^{\lambda_k t} k^2 \underline{\mathsf{w}}_k \right)$$

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- But $\underline{\mathrm{w}}_k$ are linearly independent.
  Hence $\lambda_k \underline{\mathrm{w}}_k = \gamma A \underline{\mathrm{w}}_k - k^2 D \underline{\mathrm{w}}_k$ or

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Non-trivial solutions $\lambda = \lambda_k$ exist if

- $$\det(\lambda I - \gamma A + k^2 D) = 0, \quad \text{i.e.}$$

$$\begin{vmatrix} \lambda - \gamma f_u + k^2 & -\gamma f_v \\ -\gamma g_u & \lambda - \gamma g_v + dk^2 \end{vmatrix} = 0$$

- So for non-trivial solutions we require:

$$\lambda^2 + \lambda[k^2(1+d) - \gamma(f_u + g_v)] + h(k^2) = 0 \tag{5}$$

with $h(k^2) = dk^4 - \gamma(df_u + g_v)k^2 + \gamma^2(f_u g_v - f_v g_u)$

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- This can happen if either the coefficient of λ is negative or if $h(k^2) < 0$ for some k.
  The former is impossible as we have already required $f_u + g_v < 0$ (condition I)
- Now since $f_u g_v - f_v g_u > 0$ (condition II)
  $h(k^2)$ can only possibly be negative if

$$df_u + g_v > 0 \quad (III) \quad (\implies d \neq 1 \quad \text{by I})$$

- Now observe that

$$\begin{aligned} h(k^2) &= d\left[k^4 - \tfrac{\gamma}{d}(df_u + g_v)k^2 + \tfrac{\gamma^2}{d}(f_u g_v - f_v g_u)\right] \\ &= d\left[\left(k^2 - \tfrac{\gamma}{2d}(df_u + g_v)\right)^2 + \tfrac{\gamma^2}{d}(f_u g_v - f_v g_u)\right. \\ &\quad \left. - \tfrac{\gamma^2}{4d^2}(df_u + g_v)^2\right] \end{aligned}$$

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- Therefore the minimum value of h occurs at $k^2 = \frac{\gamma}{2d}(df_u + g_v)$. This is the wavenumber of the first mode to become unstable.
- Consequently $h_{\min} = \gamma^2(f_u g_v + f_v g_u) - \frac{\gamma^2}{4d}(df_u + g_v)^2$ and so for instability we need $h_{\min} < 0$, i.e.

$$(df_u + g_v)^2 > 4d(f_u g_v - f_v g_u) \quad (IV)$$

((I) and (III) $\implies d \neq 1$)

- Thinking of the diffusion constant d as a parameter, we see that there is a critical value of $d = d_c$ which leads to instability.

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- By (IV) d_c satisfies

$$(d_c f_u + g_v)^2 = 4d_c(f_u g_v - f_v g_u)$$

and the wavenumber of the first unstable mode satisfies

$$k^2_{\text{crit}} = \frac{\gamma}{2d_c}(d_c f_u + g_v) = \frac{\gamma}{2d_c} 2\sqrt{d_c}\sqrt{f_u g_v - f_v g_u}$$

$$= \gamma \left[\frac{f_u g_v - f_v g_u}{d_c} \right]^{\frac{1}{2}}$$

- Consider the diffusion-driven activator-inhibitor system

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- For homogeneous steady solutions $u = u_0$, $v = v_0$ with

$$\frac{u_0^2}{v_0} = bu_0, \quad u_0^2 = v_0 \implies u_0 = \frac{1}{b} \quad v_0 = \frac{1}{b^2}$$

- Reaction kinetics terms are

$$f = \frac{u^2}{v} - bu \quad g = u^2 - v$$

so

$$\begin{aligned} f_u &= \frac{2u}{v} - b & f_v &= \frac{-u^2}{v^2} \\ g_u &= 2u & g_v &= -1 \end{aligned}$$

At the steady state

$$f_u = b \quad f_v = -b^2 \quad g_v = \frac{2}{b} \quad g_v = -1$$

- For stability in the absence of diffusion

$$\left.\begin{array}{lll} f_u + g_v < 0 & \Longrightarrow \; b - 1 < 0 & \Longrightarrow \; b < 1 \\ f_u g_v - f_u g_v > 0 & \Longrightarrow \; -b + 2b > 0 & \Longrightarrow \; b > 0 \end{array}\right\}$$

therefore $0 < b < 1$

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  therefore $0 < b < 1$

- Diffusion-driven instability necessitates

$$df_u + g_v > 0 \implies db - 1 > 0 \implies db > 1$$

$$\text{and } (df_u + g_v)^2 > 4d(f_u g_v - f_v g_u)$$

- For stability in the absence of diffusion

$$\left.\begin{array}{lll} f_u + g_v < 0 & \Longrightarrow \; b - 1 < 0 & \Longrightarrow \; b < 1 \\ f_u g_v - f_u g_v > 0 & \Longrightarrow \; -b + 2b > 0 & \Longrightarrow \; b > 0 \end{array}\right\}$$

  therefore $0 < b < 1$

- Diffusion-driven instability necessitates

$$df_u + g_v > 0 \implies db - 1 > 0 \implies db > 1$$

$$\text{and } (df_u + g_v)^2 > 4d(f_u g_v - f_v g_u)$$

-

$$\implies (db - 1)^2 > 4db$$

if $X = db \implies (X-1)^2 > 4X \implies X^2 - 6X + 1 > 0$

- So $(X-3)^2 > 8$ so $X - 3 > 2\sqrt{2}$ or $X - 3 < -2\sqrt{2}$

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- Hence for diffusion to be unstable we require $0 < b < 1$ and $db > 3 + 2\sqrt{2}$

  We also know that the critical wavenumber k_c satisfies

$$k_c^2 = \left[\frac{f_u g_v - f_v g_u}{d}\right]^{\frac{1}{2}} = \left(\frac{b}{d}\right)^{\frac{1}{2}}$$

  But at this point $db = 3 + 2\sqrt{2}$ so $\frac{b}{d} = \frac{3+2\sqrt{2}}{d^2}$ and so

$$k_c^2 = \left[\frac{3 + 2\sqrt{2}}{d^2}\right]^{1/2} = \frac{1 + \sqrt{2}}{d}$$

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- Suppose that $A_i, i = 1, \ldots, n$, is a family of $n \times n$ stable matrices. Consider the **switching system**

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- If there exists $P > 0$ so that

$$A_i^T P + P A_i \leq 0, \qquad \text{for all } i \in \{1, 2, ...n\}, \tag{7}$$

then the quadratic function $V(x) = x^T P x$ is a **Common Lyapunov function** (CLF) for the switching system (6).

- Shorten and Narendra derived necessary and sufficient conditions for the existence of a CLF for a finite number of stable second order systems.
- A pair of 2×2 stable matrices A_1 and A_2 have a common Lyapunov function with strict inequality in (7) if, and only if, the matrices $A_1 {A_2}^{-1}$ and $A_1 A_2$ have no negative real eigenvalues.

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- We will apply the notion of CLF to the stable matrices A and $-D$ where A is the linearised **reaction matrix** and D is the **diffusion matrix** in a reaction diffusion system.
- Even when one matrix is diagonal, the existence of CLFs is subtle as illustrated by the following example.

- Consider the following stable matrices supposed to arise from linearising a reaction system around a steady state:

$$A_1 = \begin{pmatrix} -1 & 0.2 \\ 0 & -1 \end{pmatrix}, \quad A_2 = \begin{pmatrix} -2 & 6 \\ 0 & -3 \end{pmatrix}, \quad A_3 = \begin{pmatrix} 2 & -1 \\ 8 & -3 \end{pmatrix}$$

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- A_3 and $-D$ have no CLF (since $-A_3D^{-1}$ has eigenvalues $-1, -0.4$).
- $$P = \begin{pmatrix} 3 & 1 \\ 1 & 5 \end{pmatrix}$$ is a CLF for A_2 and D.

- The system

$$\frac{dx}{dt} = Ax$$

is **reactive** i.e. exhibits initial growth, when $A + A^T$ has a positive eigenvalue, equivalently when I **is not** a Lypaunov matrix for A.

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- Therefore DDI implies A is reactive (see Neubert, Caswell and Murray) and reactivity is **necessary** for DDI.

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- If A and $-D$ have a CLF, then similarly DDI is not possible since

$$\begin{cases} A^T P + PA < 0 \text{ and} \\ (-D)P + P(-D) < 0 \end{cases} \implies (A - k^2 D)^T P + P(A - k^2 D)P < 0$$

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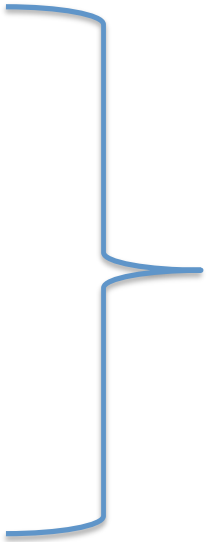
  for all k.
- Whilst simple, this result is **very powerful** in applications. Why? Testing whether pairs of matrices share a CLF is determined using **SEMI-DEFINITE PROGRAMMING** e.g. using cvx in Matlab - even in high dimensions!

To load cvx: Check out Steve Boyd at Stanford

```
cvx_setup
```

To run cvx: Key in A and D. Then run:

```
cvx_begin sdp
variable P(n,n) symmetric
A'*P+P*A<zeros(n);
-D'*P-P*D<zeros(n);
P>=eye(n);
cvx_end
```



Matlab Code

A simple inhibitor-activator PDE model describing the regenerative growth of Hydra:

$$\begin{cases} \frac{\partial a}{\partial t} &= \rho\rho_0 + c_1\rho\frac{a^2}{h} - \mu a + d_1\nabla_x^2 a \\ \\ \frac{\partial h}{\partial t} &= c_2\rho^{'}a^2 - \nu h + d_2\nabla_x^2 h. \end{cases}$$

$a(x,t)$ and $h(x,t)$ are the activator and inhibitor concentrations at position x and time t.

The parameters

- Set 1: $c_1 = 0.005$, $c_2 = 0.035$, $d_1 = 0.03$, $d_2 = 0.45$, $\rho^{'} = 0.075$ and $\rho = \rho_0 = 3.2$.
- Set 2: $c_1 = 0.05$, $c_2 = 0.025$, $d_1 = 0.03$, $d_2 = 0.45$, $\rho^{'} = 0.00075$ and $\rho = \rho_0 = 3.2$

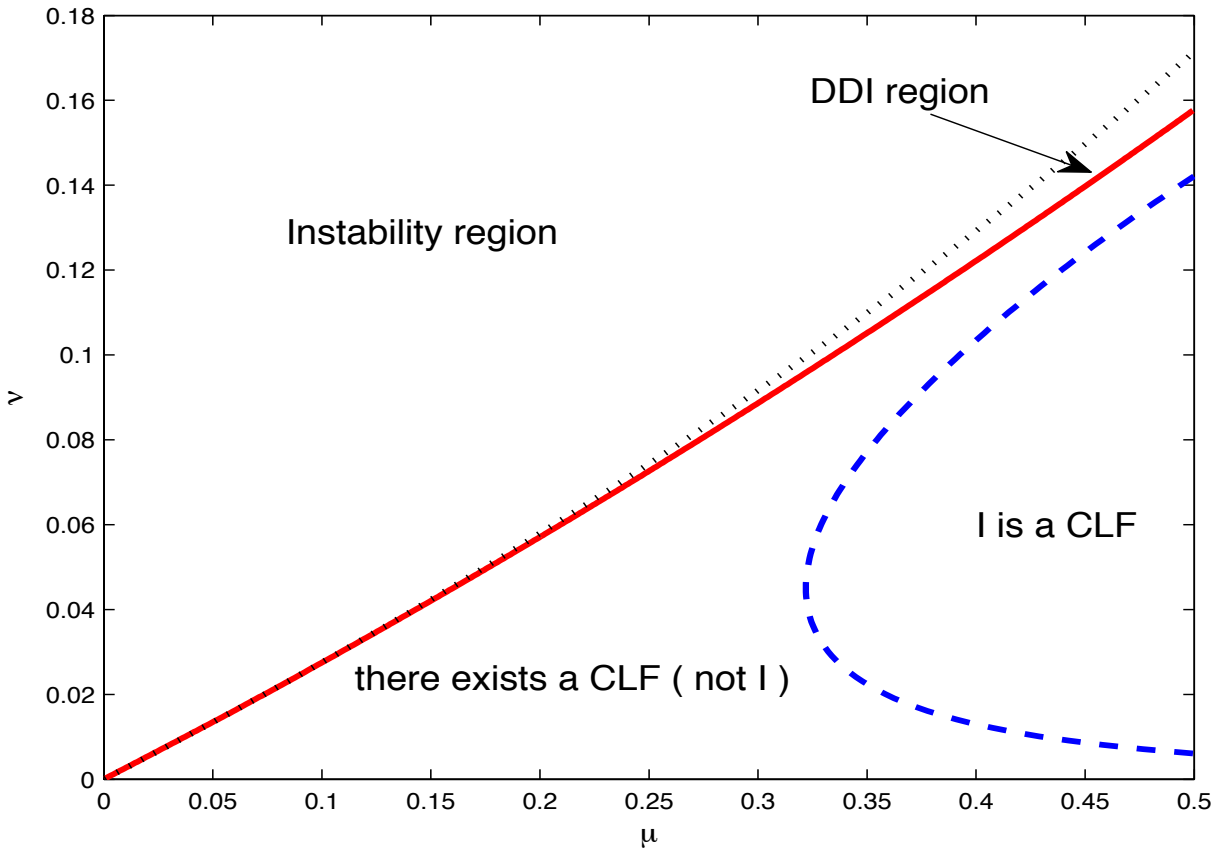


Figure: For Set 1: Parameters (μ, ν) where there is DDI, I is a CLF and there is a CLF.

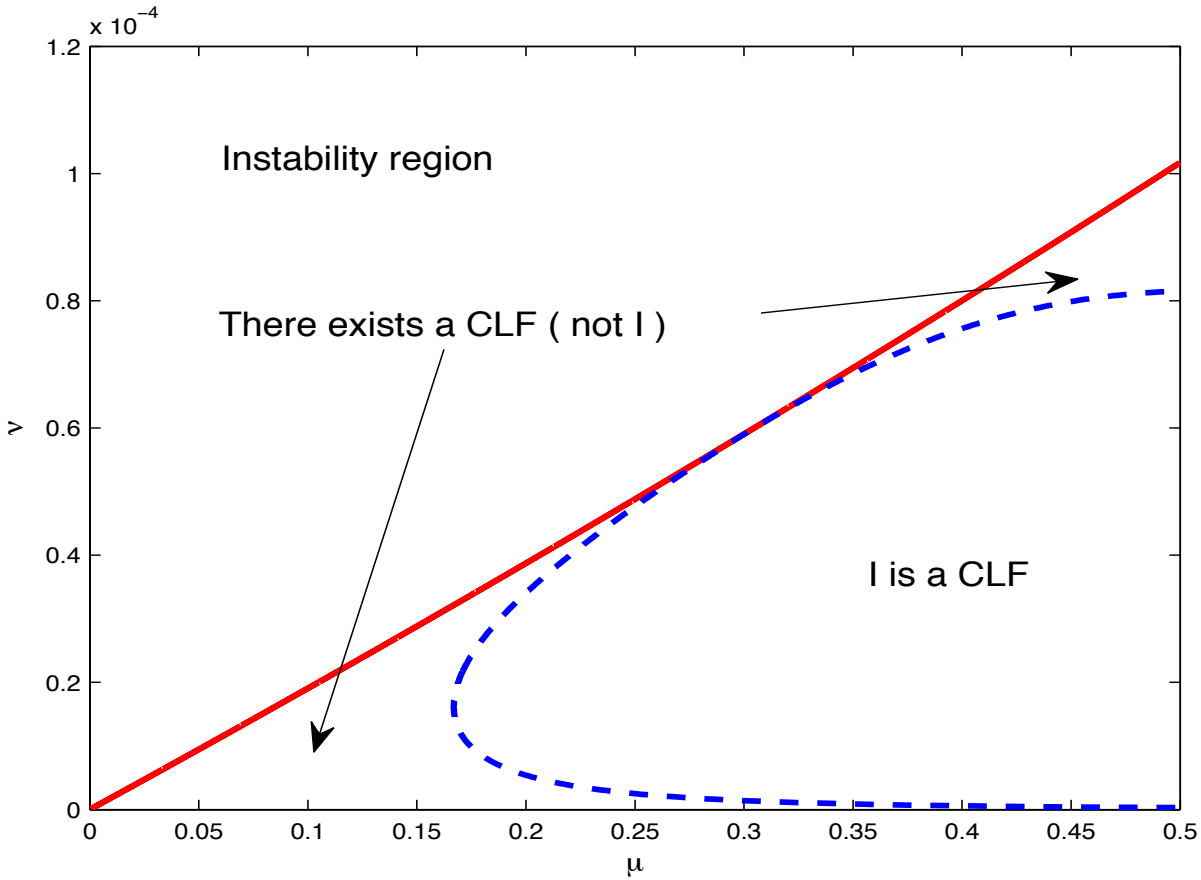


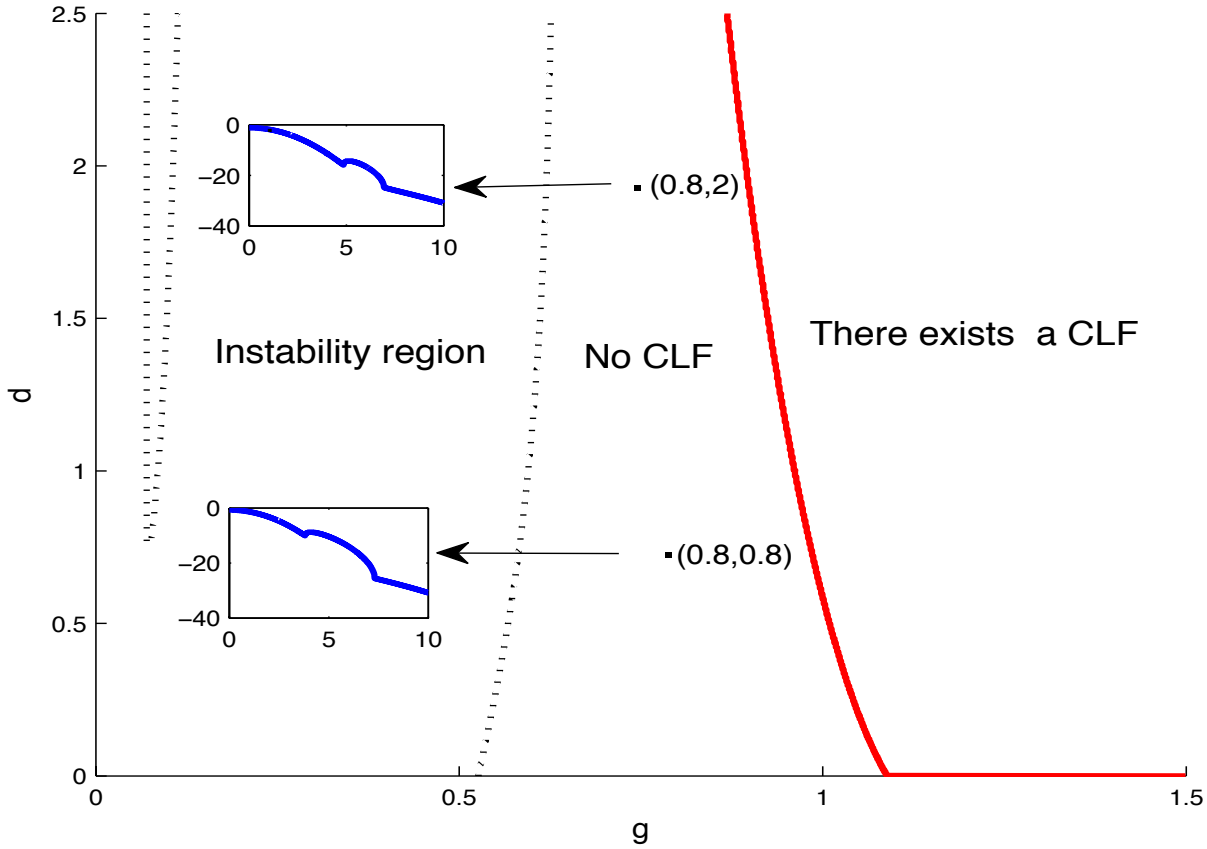
Figure: For Set2: Parameters (μ, ν) where I is a CLF and there is a CLF. Here there is no DDI

Here we consider a three dependent variable model (and so the well known parameter test for DDI does not apply). It describes a spatial model for the interaction of a host (u), a parasite (v) and a hyper-parasite (w).

$$\begin{aligned}
\frac{\partial u}{\partial t} &= \tau[u(1-\frac{u}{K})-uv]+d_1\nabla^2 u \\
\frac{\partial v}{\partial t} &= \tau\mu[\frac{uv}{1+\gamma}-\frac{vw}{1+\gamma v}]+d_2\nabla^2 v \\
\frac{\partial w}{\partial t} &= \tau d[v-w]+d_3\nabla^2 w.
\end{aligned}$$

The parameters

$d_1 = 0.02$, $d_2 = 0.2$, $d_3 = 1$, $\mu = 15$, $K = 10$ and $\tau = 1$.


2.5
2
1.5
1
0.5
0
d
0
0.5
1
1.5
g
0
−20
−40
0
5
10
(0.8,2)
Instability region
No CLF
There exists a CLF
(0.8,0.8)

In our set up, indeed in the standard Turing instability framework, D is supposed to be diagonal. However, this is not an essential ingredient of our approach and the CLF-based approach still applies. This is useful for applications where other "movement" mechanisms are invoked.
For example, a common movement mechanism is based on "chemotaxis" which mathematically brings in cross-derivatives.
A simple model in which this arises is in the Schnakenberg diffusion-chemotaxis model:

$$\begin{aligned}\frac{\partial u}{\partial t} &= \gamma(a - u + u^2 v) + \nabla^2 u - \alpha \nabla.(u \nabla v),\\ \frac{\partial v}{\partial t} &= \gamma(b - u^2 v) + d\nabla^2 v\end{aligned}$$

Linearisation around the equilibrium $(a+b, b/(a+b)^2)$ leads to the reaction-diffusion-chemotaxis matrix pencil:

$$A - ||\omega||^2 D_\alpha,$$

where

$$A = \begin{pmatrix} \frac{b-a}{a+b} & (a+b)^2 \\ \frac{-2b}{a+b} & -(a+b)^2 \end{pmatrix}, \quad D_\alpha = \begin{pmatrix} 1 & -\alpha(a+b) \\ 0 & d \end{pmatrix}.$$

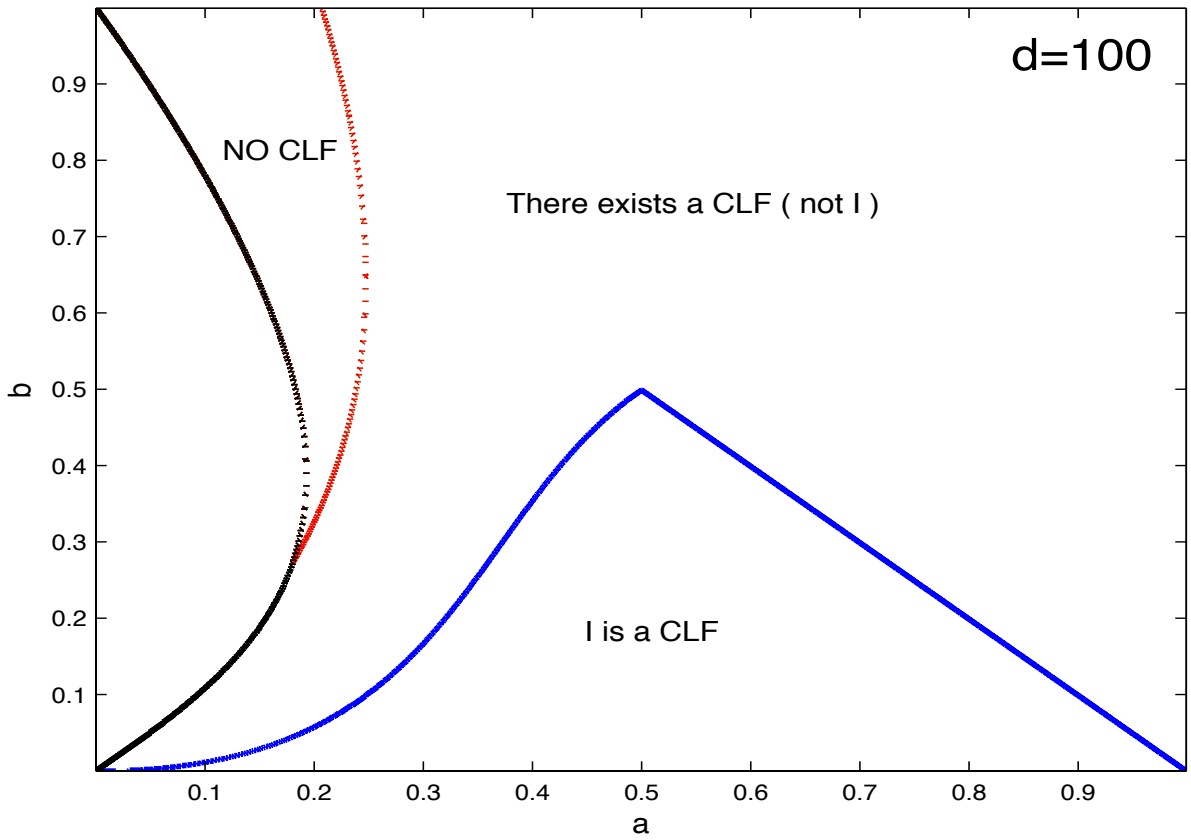


Figure: The parameter used here are $d = 100$,$\gamma = 1$ and $\alpha = 20$.

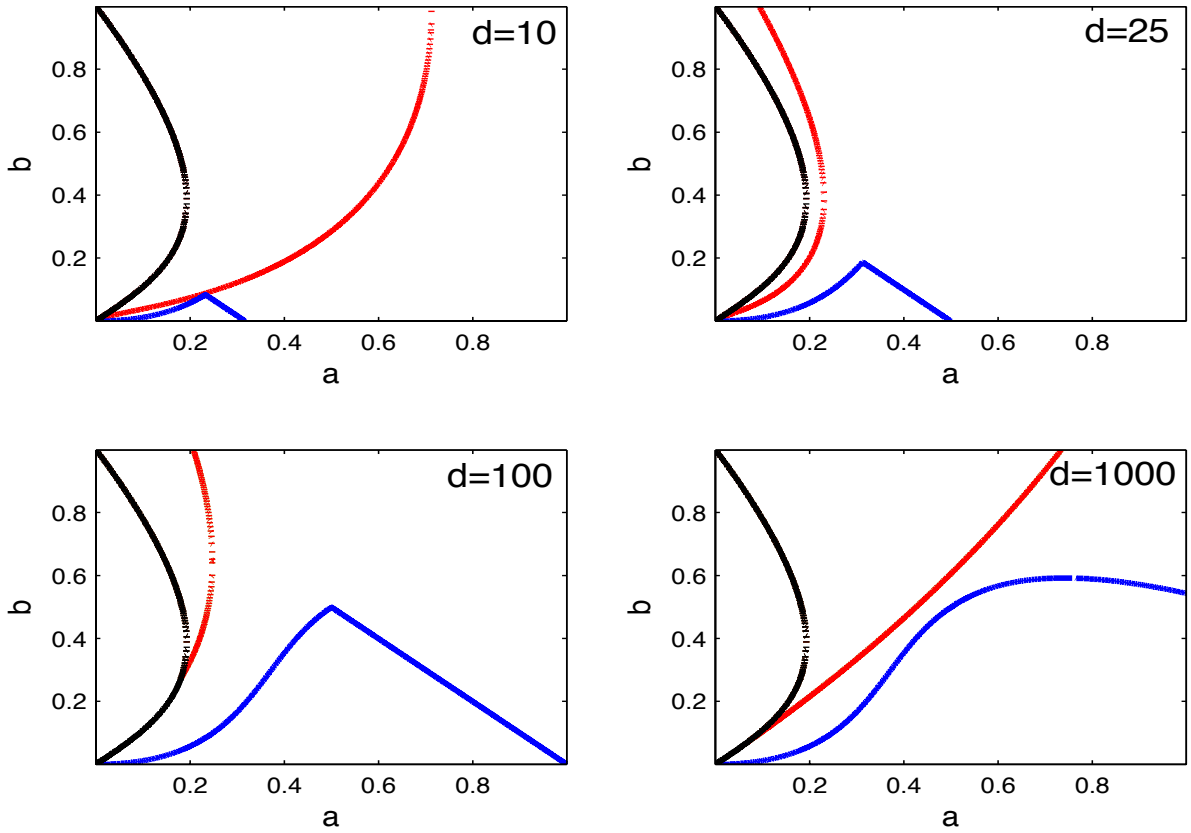


Figure: To the right of the red curve no pattern formation is possible as the diffusion coefficient d is increased: $d = 10$, 25, 100 and 1000.

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- It provides a more systematic search for parameter domains on which pattern formation is possible compared to ad hoc methods based on computing the dispersion relation for specific parameters
- It is a simple, but powerful, generalisation of the "reactivity is necessary" results of Neubert et al.