LPA : Theory and Context

MCB Course, UBC
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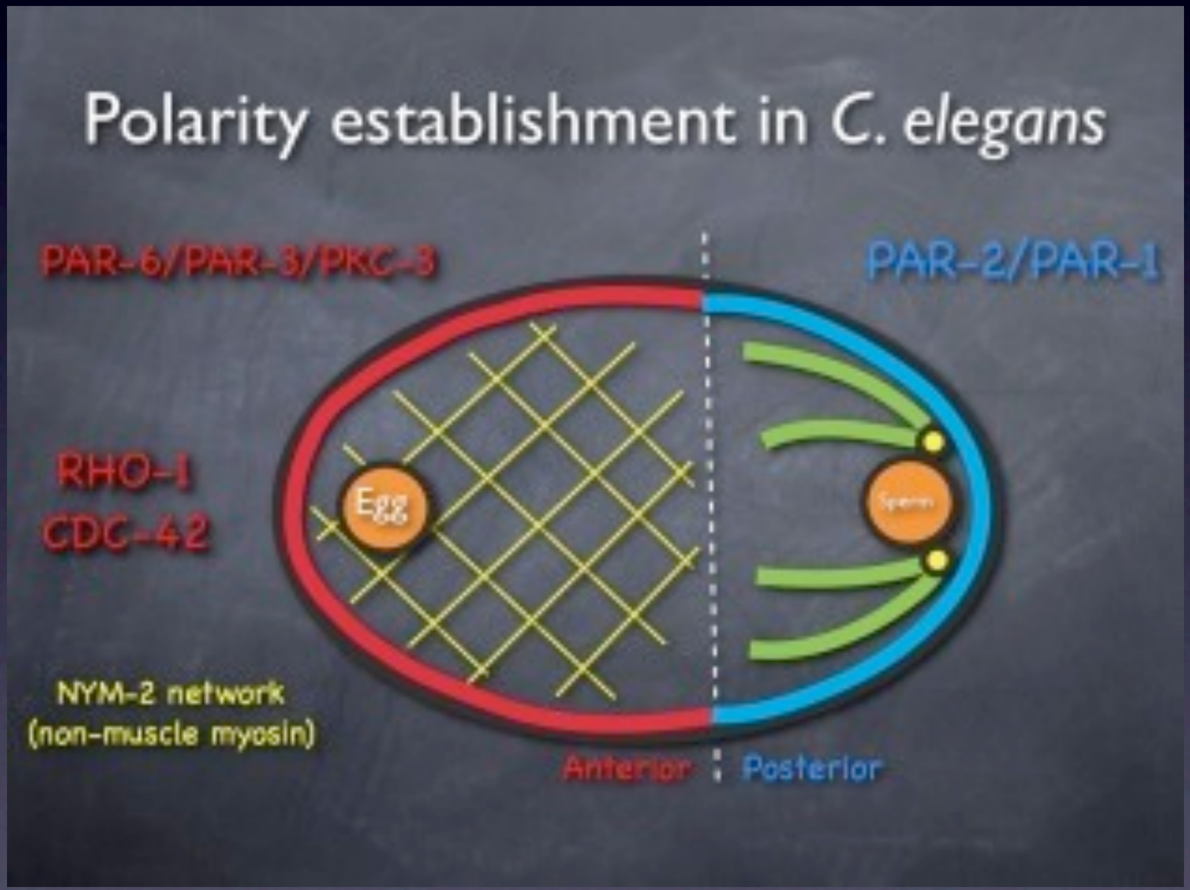
Topic of Discussion

- Pattern generation in biological systems.
- Exploring regimes of patterning behaviour in model parameter space.

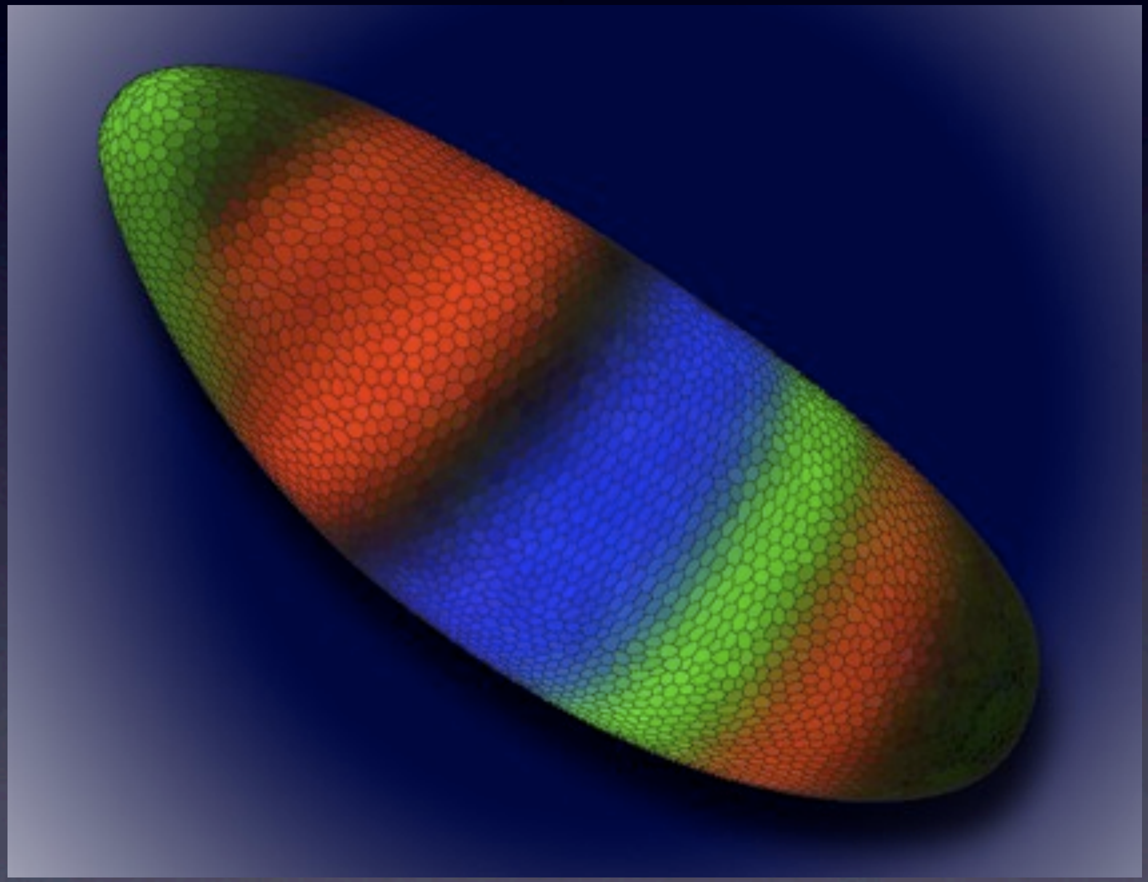
Examples

Cytokinesis Pre-Patterning



http://skoplab.weebly.com/research.html

Drosophila Gene Expression



http://www.lbl.gov/Science-Articles/Archive/sabl/2008/Feb/genome-mystery.html

Types of Patterns

- Temporal: Spatially homogeneous oscillations.
- Spatial: Temporally unchanging spatial pattern.
- Spatio-temporal: Blend of the above.
  - Travelling wave for example.

Modes of Pattern Generation

- Instability
  - Autonomous / spontaneous / noise induced.
  - Requires no stimulation.
- Excitability
  - Externally / stimulus driven.

Reaction Diffusion System

$$\frac{\partial \vec{u}}{\partial t}(x,t) = F(\vec{u}) + \boldsymbol{D}\triangle\vec{u}$$

Reaction: $F(\vec{u})$

Diffusion: $\boldsymbol{D}\triangle\vec{u}$

- A common framework for describing biological systems.
- $\vec{u}$ = concentration field

The Well Mixed System

$$\frac{d\vec{u}}{dt}(t) = F(\vec{u})$$

- "Reactants" ($\vec{u}$) are assumed spatially homogeneous.
- Only describes the temporal behaviour.

Well Mixed Steady State

$$F(\vec{u_0}) = 0$$

- Also called a 'fixed point' of F.
- Note: $\vec{u_0}$ is spatially homogeneous.
- QUESTION: When does a homogeneous state give way to patterning?

Well Mixed Stability

$$F(\vec{u_0}) = 0$$

Homogeneous Steady State (HSS)

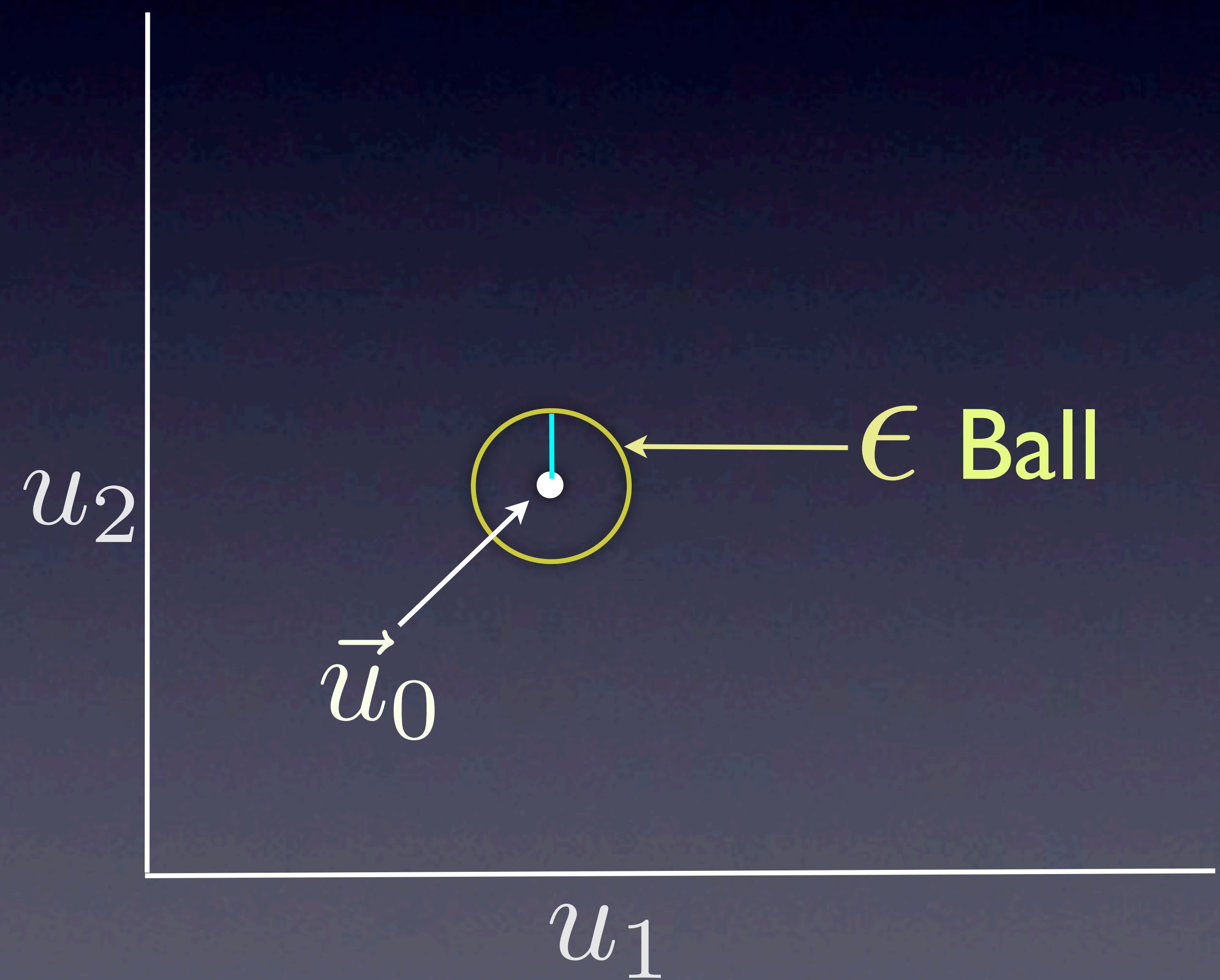
$$\vec{u} = \vec{u}_0 + \epsilon \vec{w}$$

Small Perturbation

- QUESTION: Does $\vec{w}(t)$ grow or decay?
  - Decay = stability
  - Growth = instability

Graphically

$$\vec{u} = (u_1, u_2)$$



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Linearized Equation

Jacobian

$$\frac{d\vec{w}}{dt}(t) = J_0 \vec{w}\,, \qquad J_0 = DF_{\vec{u}_0}$$

Linearization

- Taylor expand 'F' assuming ϵ is small
- J_0 is a n x n matrix

Stability

- Change of variables

$$J_0 \sim \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}$$

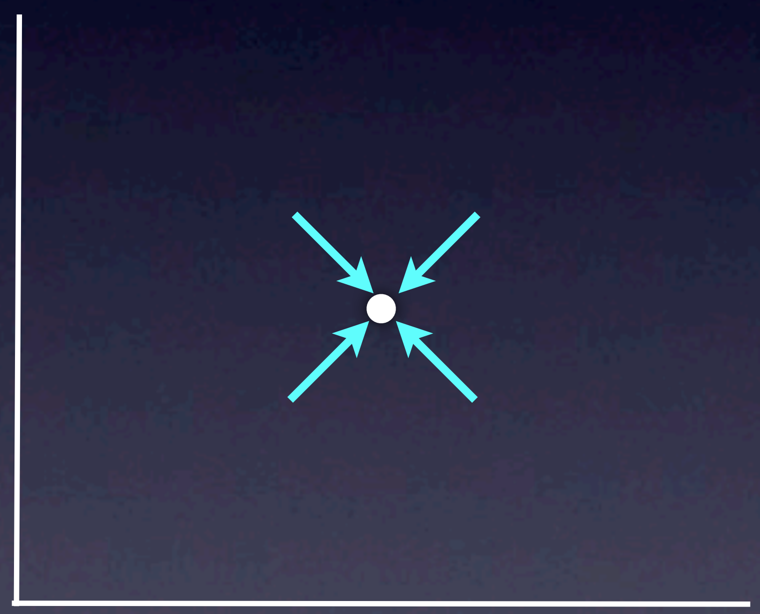
$$\vec{w}(t) \sim Const \begin{bmatrix} e^{\lambda_1 t} & 0 \\ 0 & e^{\lambda_2 t} \end{bmatrix}$$

Well Mixed Stability

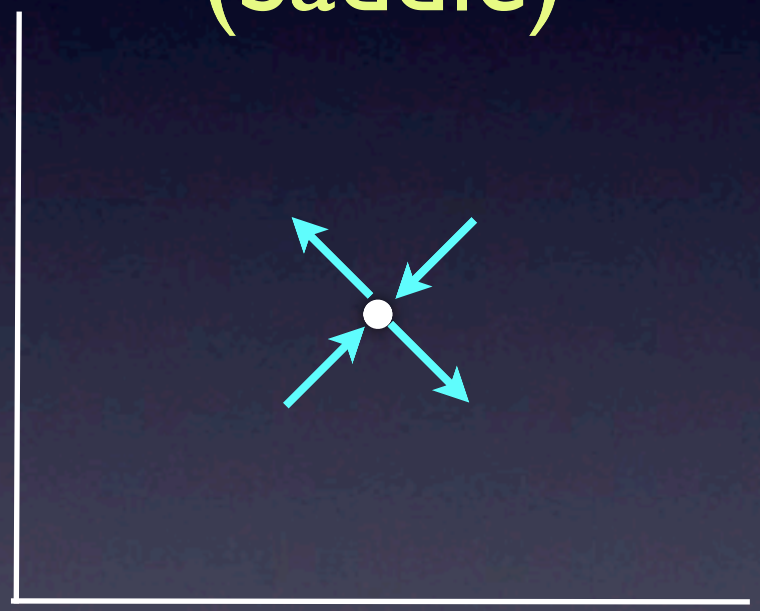
- $\mathcal{R}e(\lambda_i) > 0$ for 'i' implies growth of perturbation / instability, in the 'i' direction
- $\mathcal{R}e(\lambda_i) < 0$ indicates decay / stability in the 'i' direction

Well Mixed Stability

Stable



Unstable (Saddle)



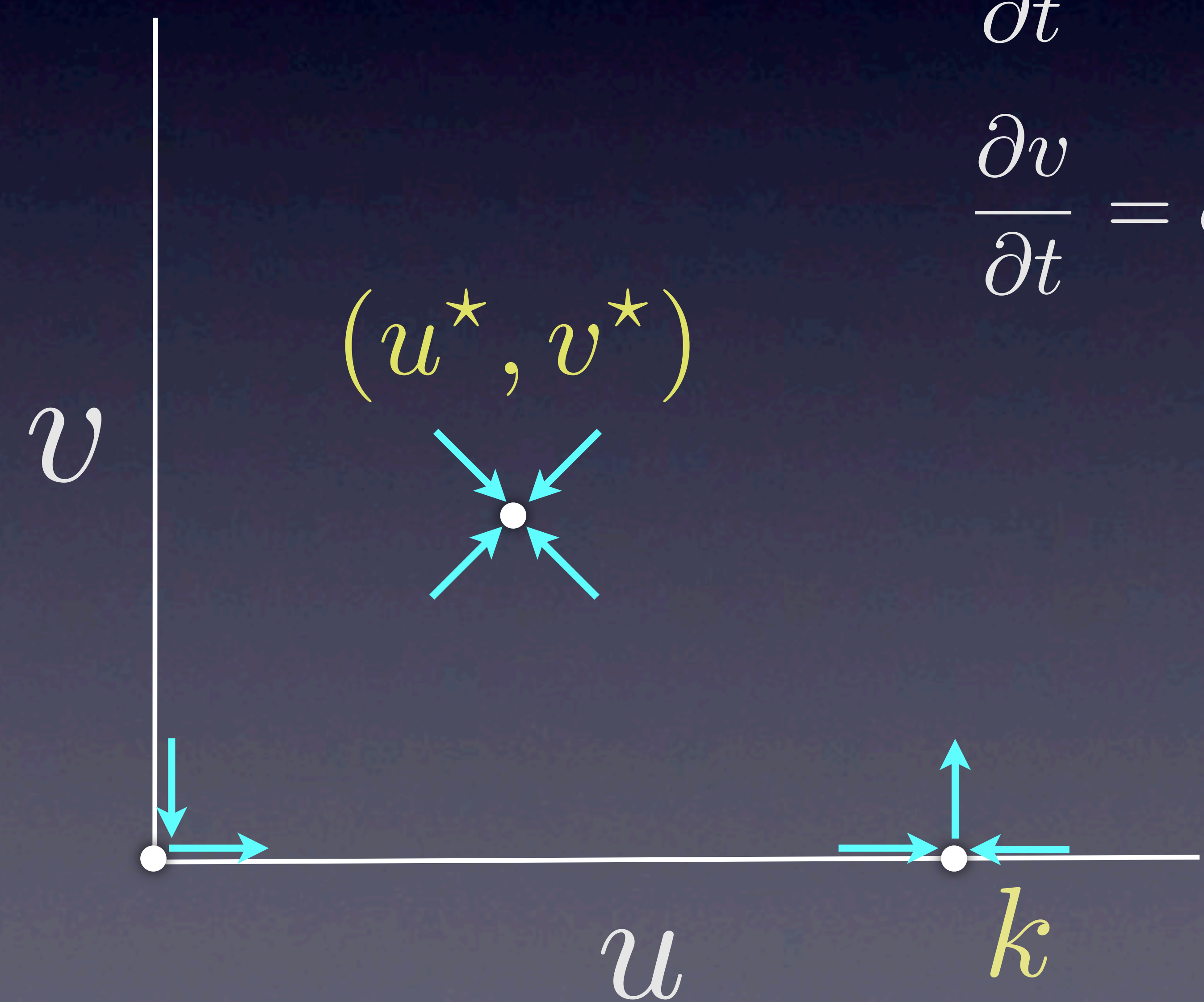
Unstable

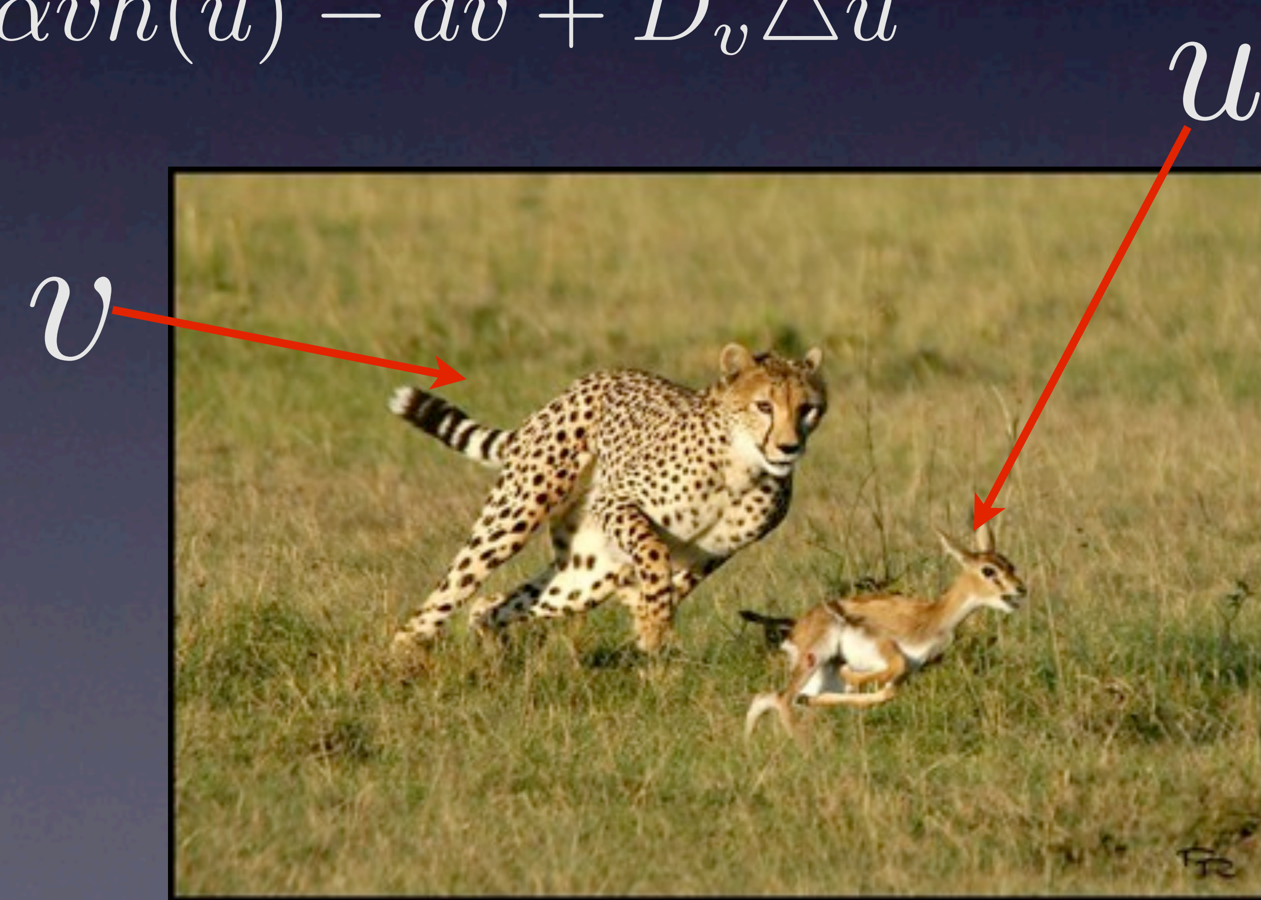
Example: Predator Prey

Logistic Growth — Predation

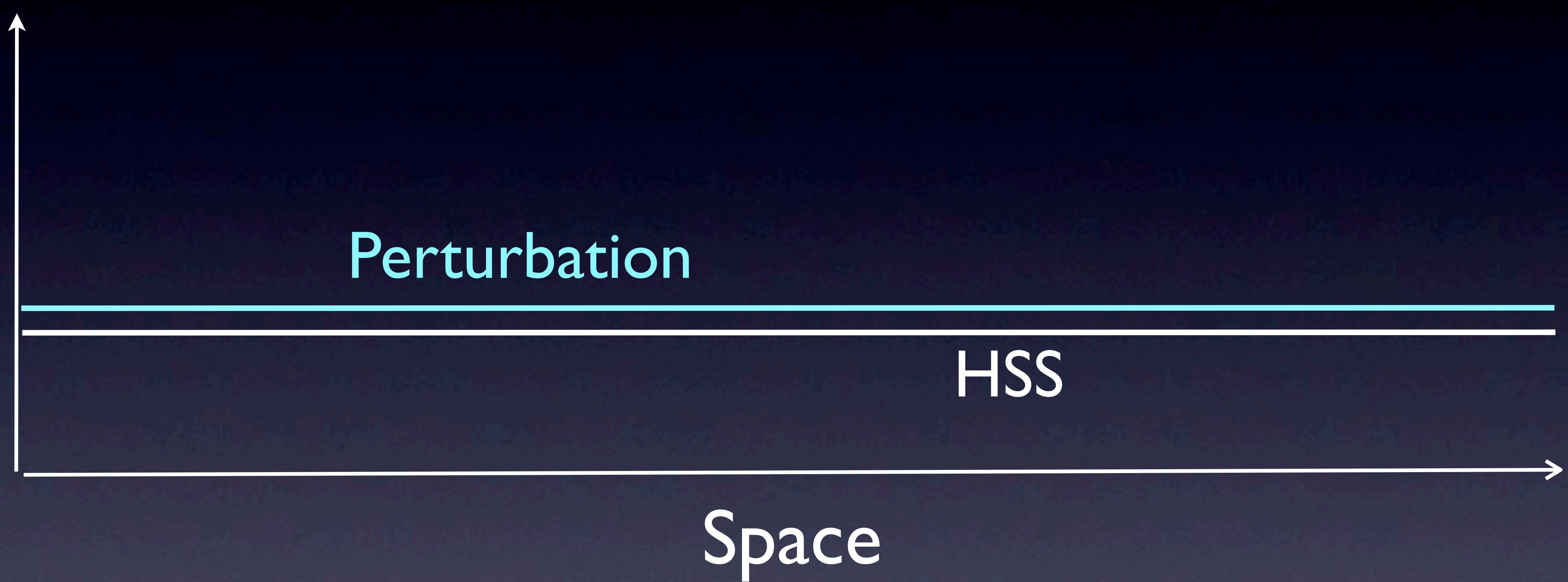
$$\frac{\partial u}{\partial t} = ru\left(1 - \frac{u}{k}\right) - vh(u) + D_u \triangle u$$

$$\frac{\partial v}{\partial t} = \alpha v h(u) - dv + D_v \triangle u$$



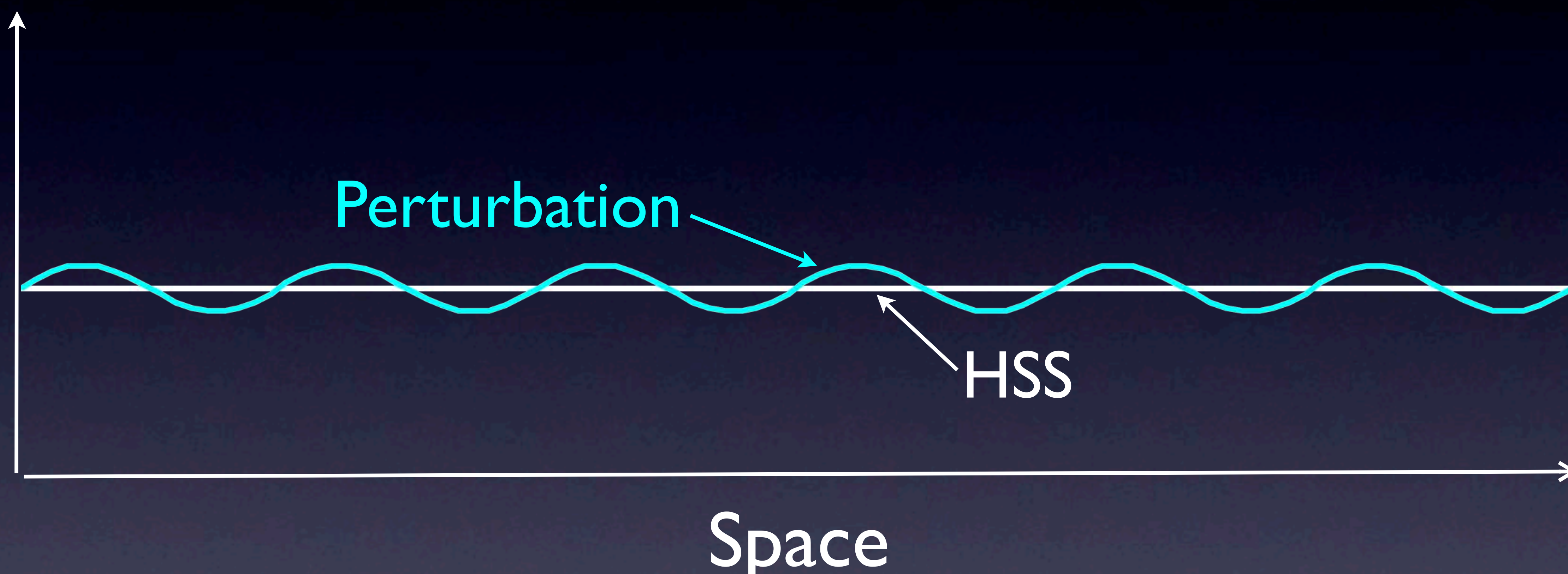


Well Mixed Analysis



- Determine stability with respect to SMALL homogeneous perturbation.
- Relies on linearization.

Spatial Instabilities (Turing Analysis)



- Determines stability of HSS with respect to SMALL periodic perturbation.

Periodic Perturbation

$$\frac{\partial \vec{u}}{\partial t}(x,t) = F(\vec{u}) + \boldsymbol{D}\triangle \vec{u}$$

$$\vec{u}(x,t) = \vec{u}_0 + \epsilon\, e^{ikx}\, \vec{w}(t)$$

- Consider a periodic perturbation of wave number 'k'

Turing Linearization

$$\frac{\partial \vec{w}}{\partial t} = J_0 \vec{w} - (k\pi)^2 \mathbf{D} \vec{w} \,, \qquad \mathbf{D} = \begin{bmatrix} D_1 & 0 \\ 0 & D_2 \end{bmatrix}$$

Define $J_k := J_0 - (k\pi)^2 \mathbf{D}$

Then $\dfrac{\partial \vec{w}}{\partial t} = J_k \, \vec{w}$

- ‘k’ is the perturbation wave number

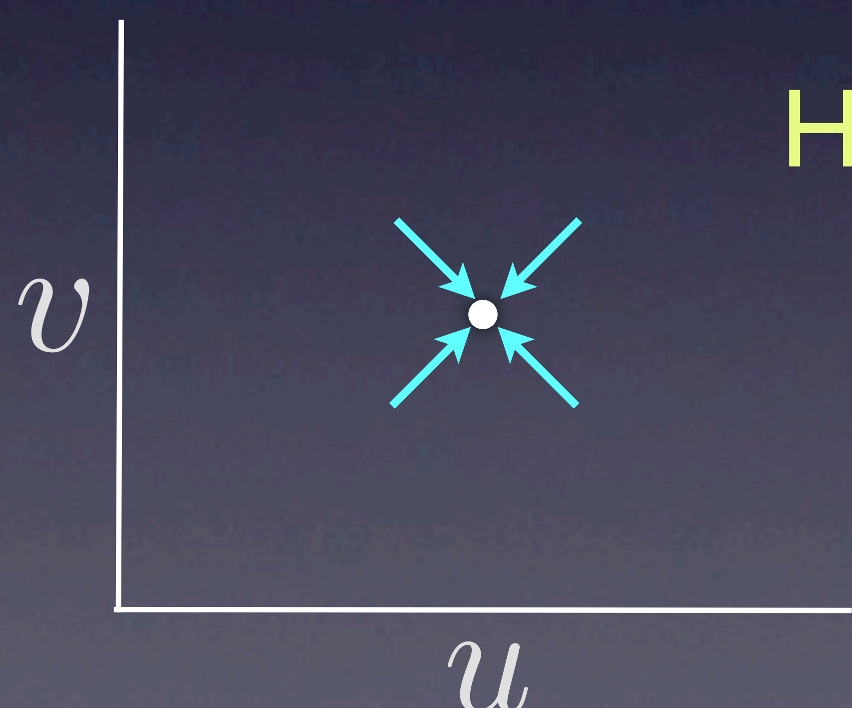
Turing Eigenvalues

- Eigenvalues $\{\lambda_i\}$ of J_k determine stability ***of that wave number***.
    - '-' eigenvalues indicate stability.
    - Any '+' eigenvalues indicate instability

Example: Schnakenberg

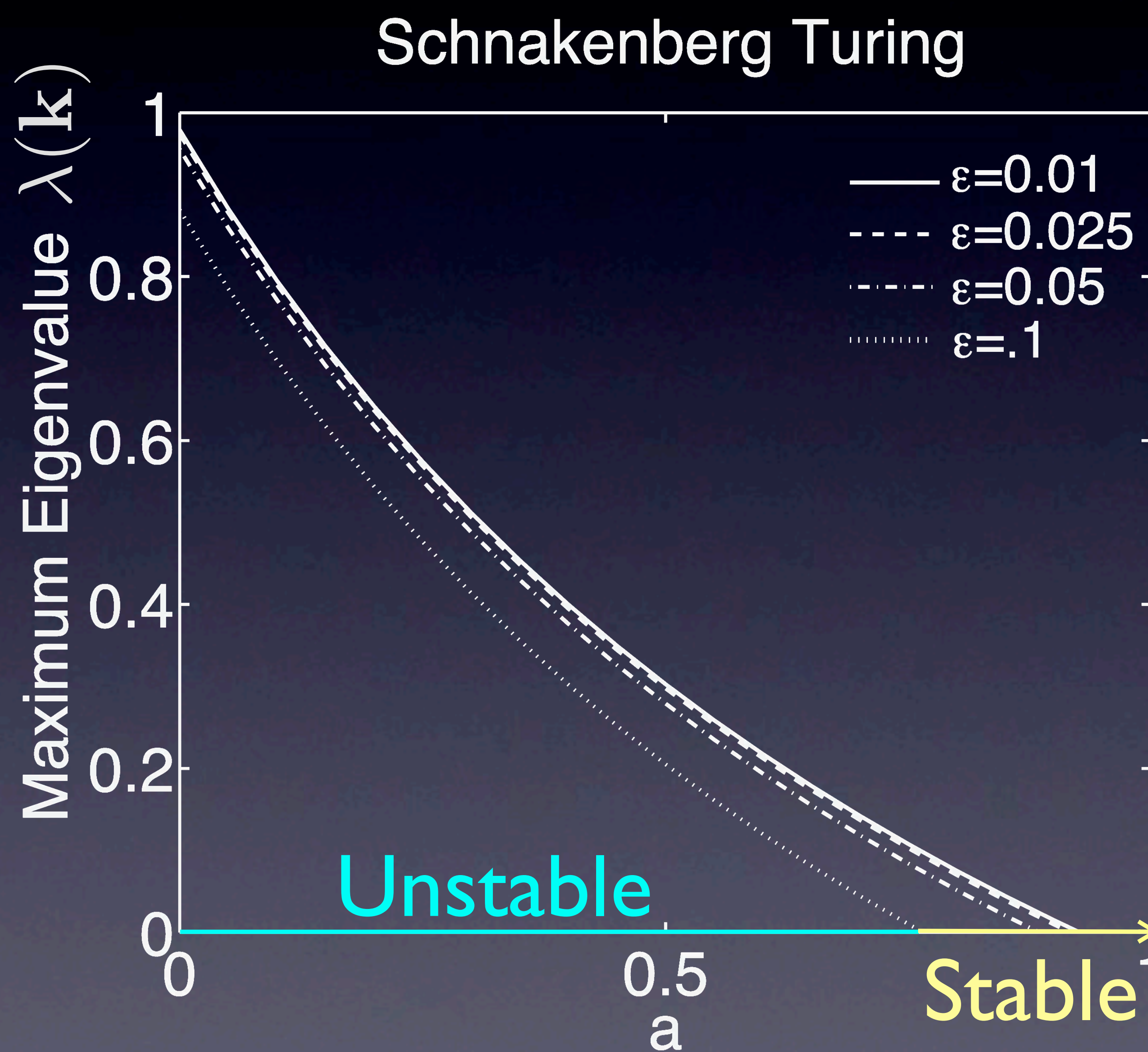
$$u_t(x,t) = a - u + u^2 v + \epsilon^2 \triangle u,$$
$$v_t(x,t) = b - u^2 v + D \triangle v.$$

HSS: $u_0 = a + b \,, \qquad v_0 = \dfrac{b}{(a+b)^2}$



- Activator (u) depleted substrate (v) model

Turing Analysis



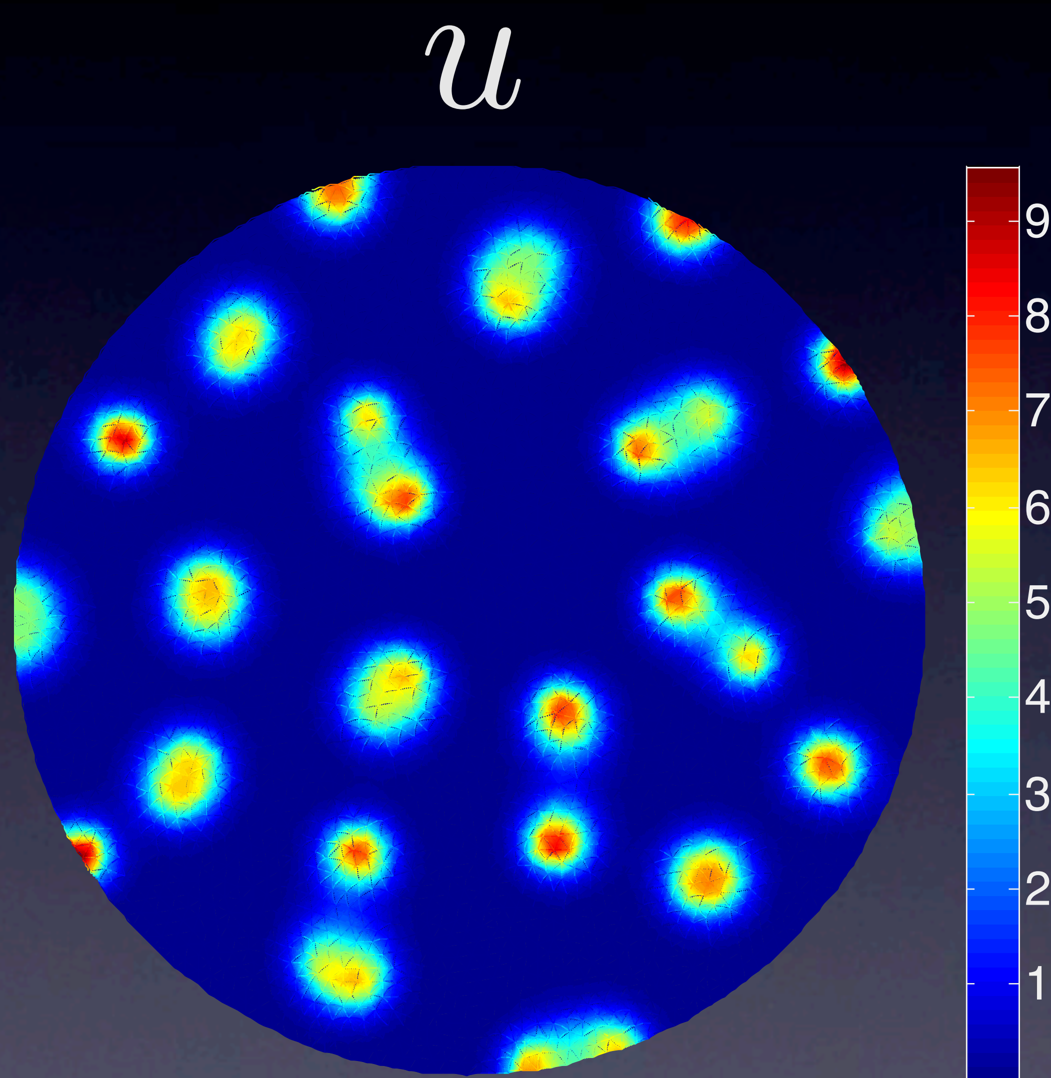
Snackenberg Simulation

$\epsilon = .1$

$D = 1$

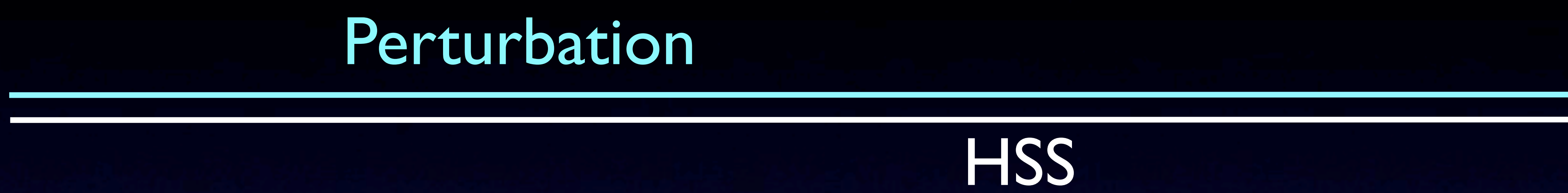
$a = 0$

$b = 1$

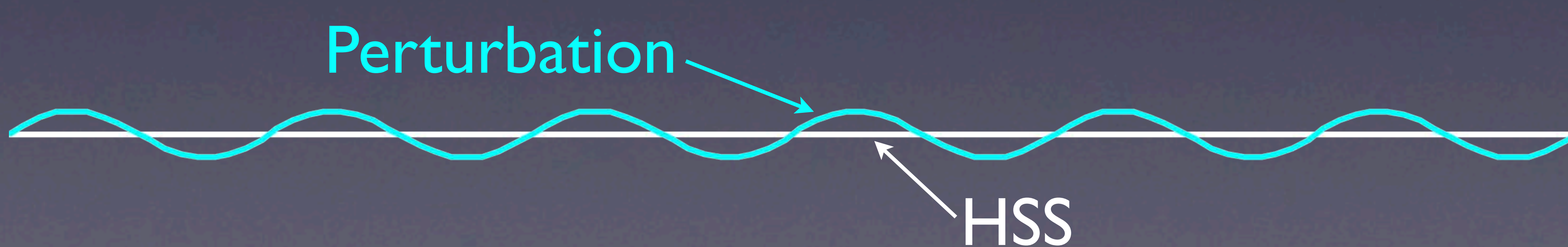


- Initial condition = $\vec{u}_0$ + .001 * random

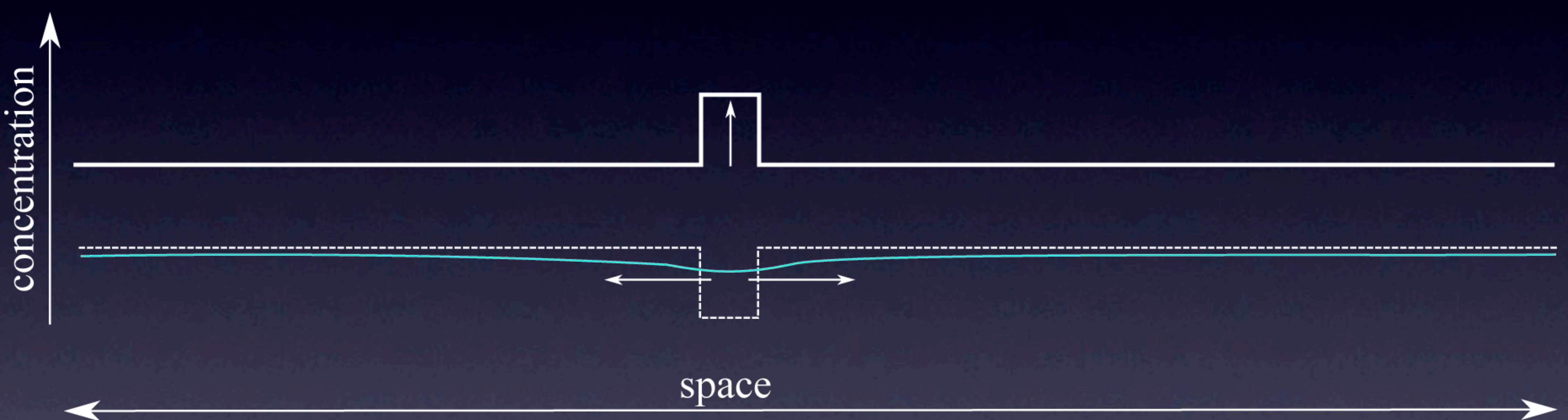
Recap



- Well mixed analysis
  - Stability to SMALL homogeneous perturbation
- Turing analysis
  - Stability to SMALL periodic perturbations.



Local Perturbation Analysis (LPA)

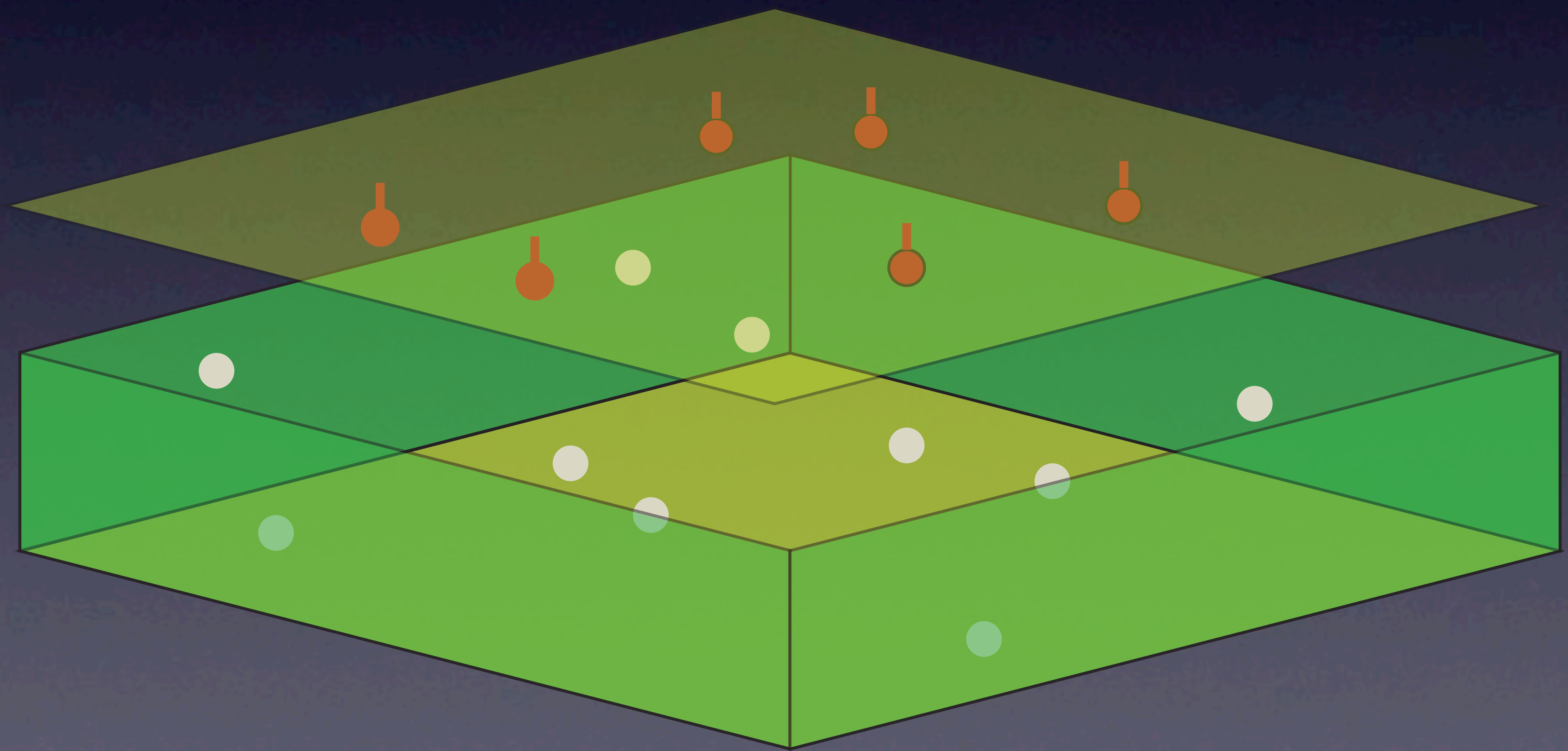


- Stability against ARBITRARILY TALL, localized perturbations

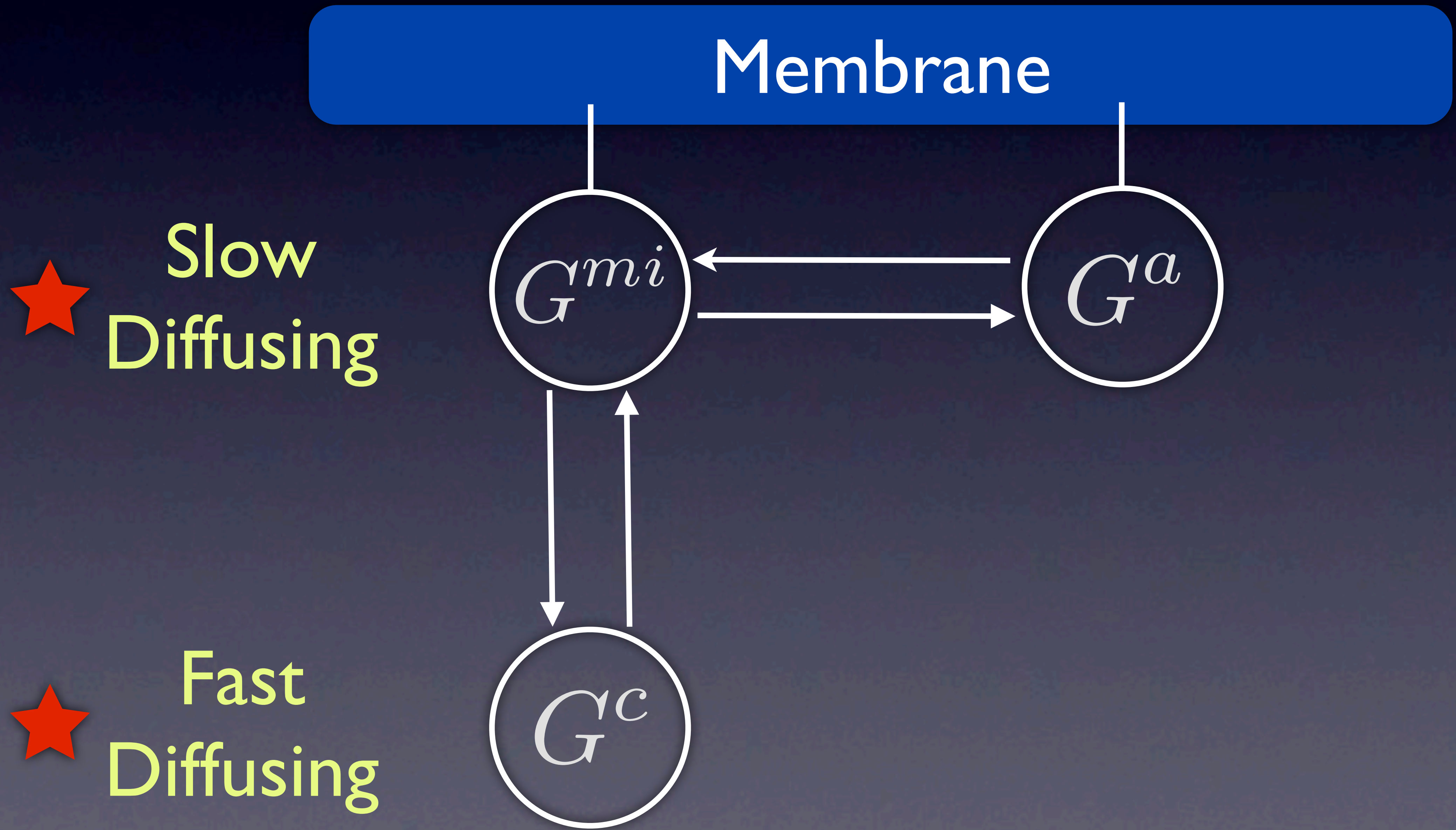
LPA Motivation

- Membrane Bound
- Cytosolic

Diffusing Chemicals



For Instance: GTPases



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LPA Setup

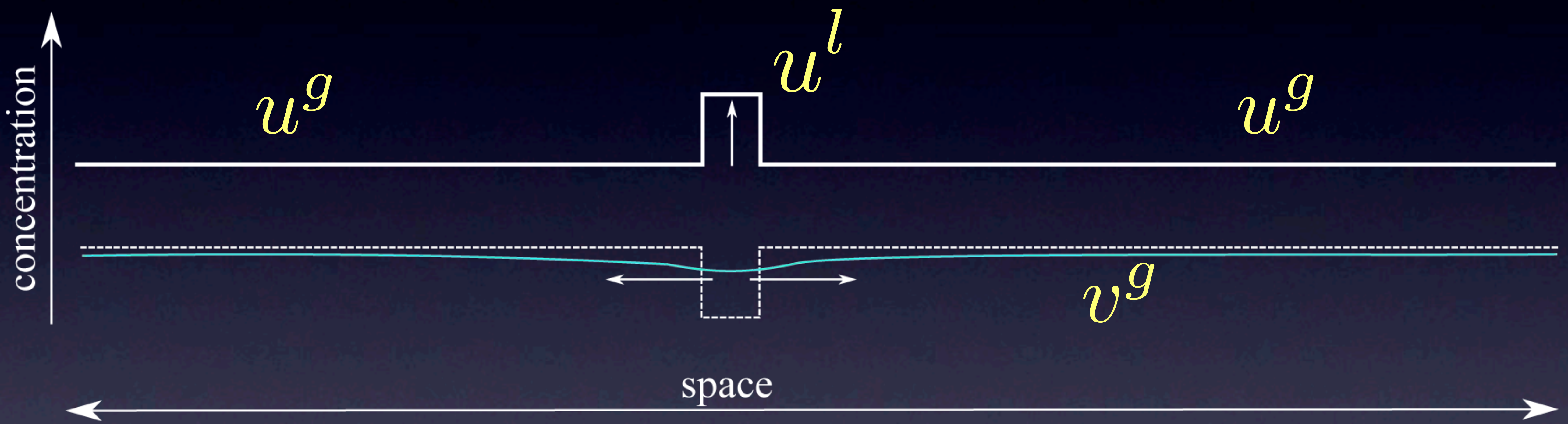
Slow Diffusing	$$\frac{\partial u}{\partial t}(x,t) = f(u,v;p) + \epsilon u_{xx}$$
Fast Diffusing	$$\frac{\partial v}{\partial t}(x,t) = g(u,v;p) + D v_{xx}$$

- Assume $f,\, g \sim O(1)$ ★
- ‘p’ is some generic parameter.

LPA Perturbation

- Consider the $\epsilon \ll 1$, $D \gg 1$ limit
- In this setting, apply a highly localized, ARBITRARILY TALL to the HSS.

Local Perturbation Analysis



- 'g' indicates a global variable, 'l' indicates local.

LP - System

Global: $$\frac{du^g}{dt}(x,t) = f(u^g, v^g; p),$$

Global: $$\frac{dv^g}{dt}(x,t) = g(u^g, v^g; p),$$

Local: $$\frac{du^l}{dt}(x,t) = f(u^l, v^g; p)$$

LP Analysis

- A bifurcation analysis of this system of 3 ***ODE's*** is referred to as a 'Local Perturbation Analysis' (LPA).

Nice Feature #1

- A system of ODE's is much easier to analyze than a system of PDE's.

LP - Jacobian

$$J_{LP} = \begin{bmatrix} f_u(u^g, v^g) & f_v(u^g, v^g) & 0 \\ g_u(u^g, v^g) & g_v(u^g, v^g) & 0 \\ 0 & f_v(u^l, v^g) & f_u(u^l, v^g) \end{bmatrix}$$

LP - Jacobian

$$J_{LP} = \begin{bmatrix} f_u(u^g, v^g) & f_v(u^g, v^g) & 0 \\ g_u(u^g, v^g) & g_v(u^g, v^g) & 0 \\ 0 & f_v(u^l, v^g) & f_u(u^l, v^g) \end{bmatrix}$$

$$\frac{du^g}{dt}(x,t) = f(u^g, v^g; p),$$
$$\frac{dv^g}{dt}(x,t) = g(u^g, v^g; p),$$
$$\frac{du^l}{dt}(x,t) = f(u^l, v^g; p)$$

- The well mixed Jacobian is embedded in the LP Jacobian

LP-Jacobian Structure

Well Mixed Jacobian

$$J_0 \sim \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}$$

LP Jacobian

$$J_{LP} \sim \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & f_u(u^l, v^g) \end{bmatrix}$$

Nice Feature #2

- The LP Jacobian inherits the 'well mixed' eigenvalues.
- So a LPA recovers linear stability properties such as:
  - Well mixed stability,
  - Limit cycle (Hopf) bifurcations,
  - Etc.

Detailed Example: Schnakenberg

$$\frac{du_g}{dt} = a - u_g + u_g^2\, v_g$$

$$\frac{dv_g}{dt} = b - u_g^2\, v_g$$

$$\frac{du_l}{dt} = a - u_l + u_l^2\, v_g$$

- LP System of ODEs

Schnakenberg LPA: Global Forms

$$\frac{du_g}{dt} = a - u_g + u_g^2 v_g$$

$$\frac{dv_g}{dt} = b - u_g^2 v_g$$

- Global forms only = well mixed system

Schnakenberg LPA: Global Forms

$$\frac{du_g}{dt} = a - u_g + u_g^2 v_g$$

$$\frac{dv_g}{dt} = b - u_g^2 v_g$$

Unique HSS

$$u_g = a + b \,, \qquad v_g = \frac{b}{(a+b)^2}$$

- Global forms only = well mixed system

Detailed Example: Schnakenberg

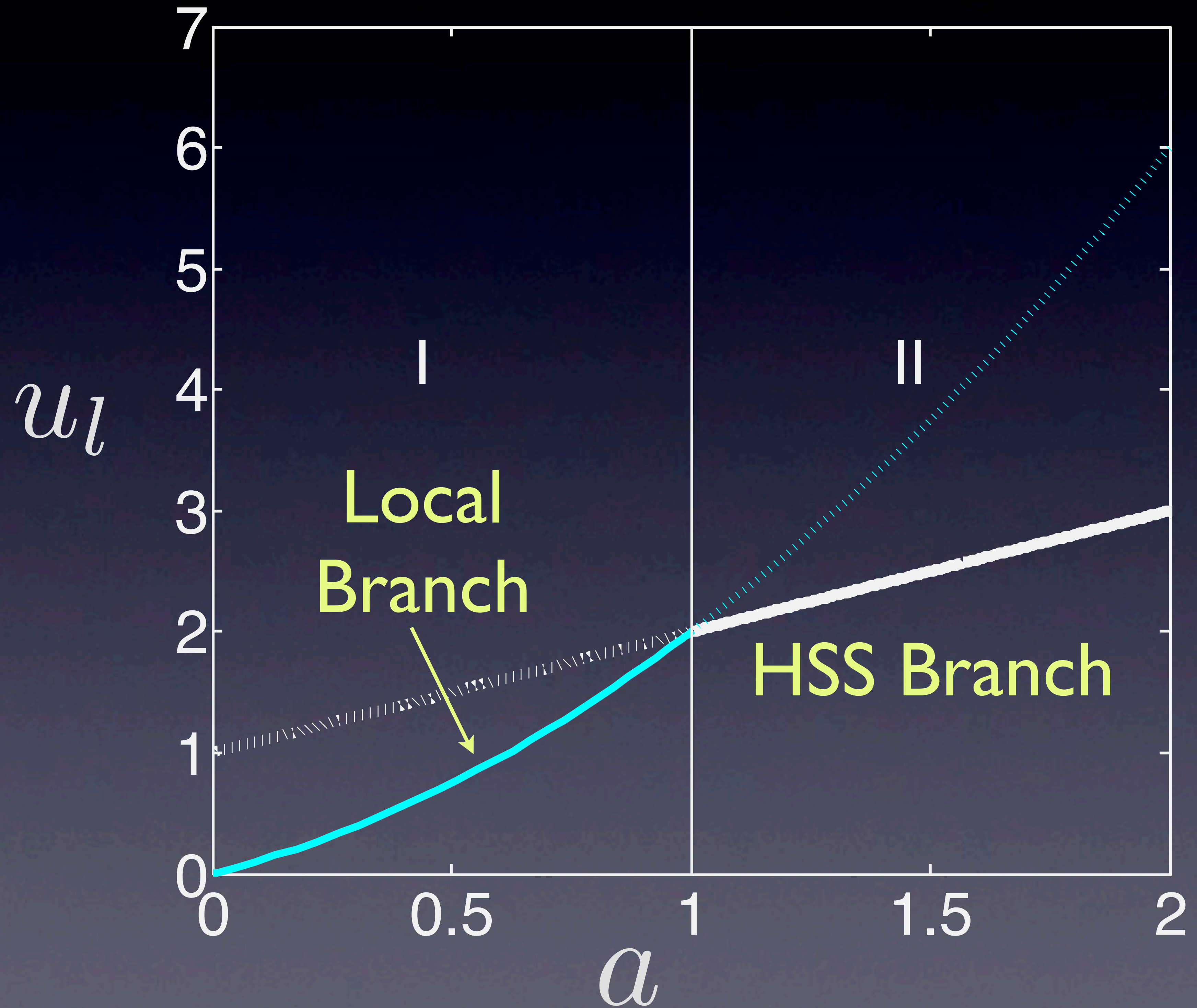
Consider: $$\frac{du_l}{dt} = a - u_l + u_l^2\, v_g = 0$$

FIX: $$u_g = a + b\,, \qquad v_g = \frac{b}{(a+b)^2}$$

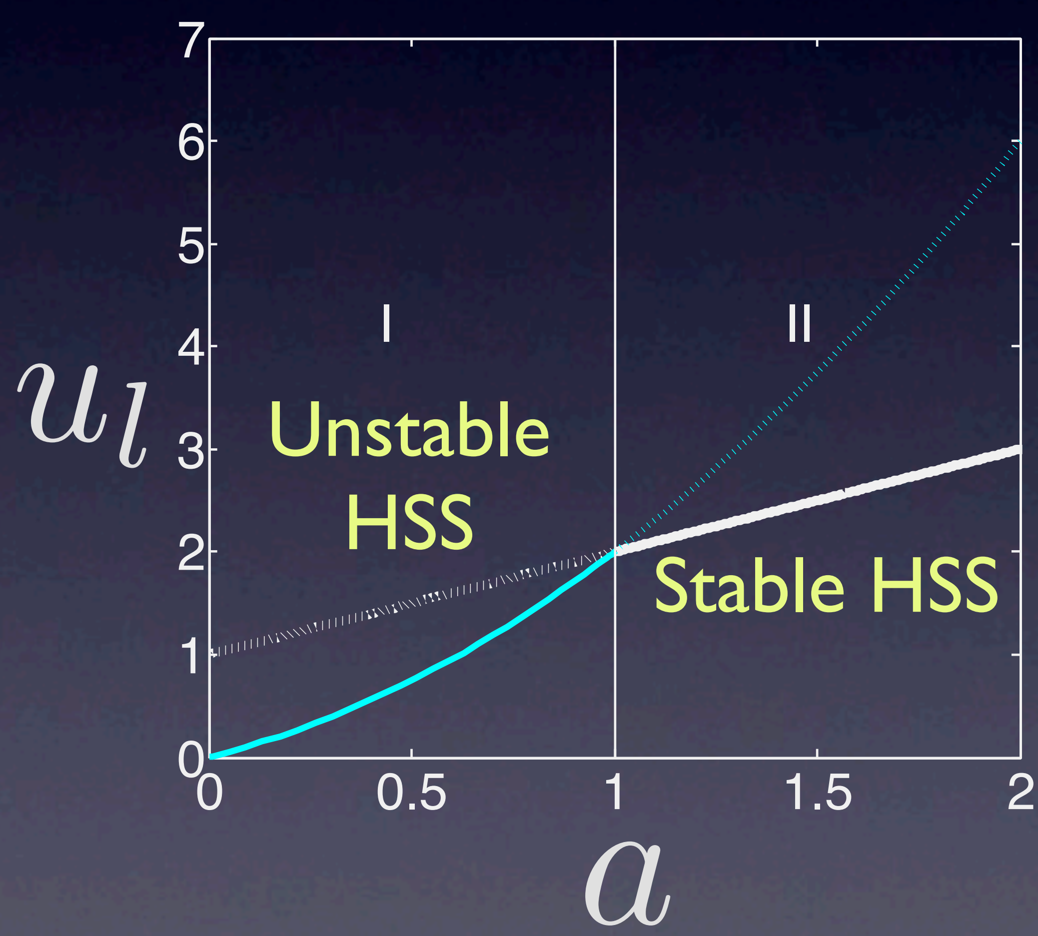
Solving for u_l: $$u_l^1 = a + b\,, \qquad u_l^2 = a + \frac{a^2}{b}$$

=HSS

Schnakenberg: LPA

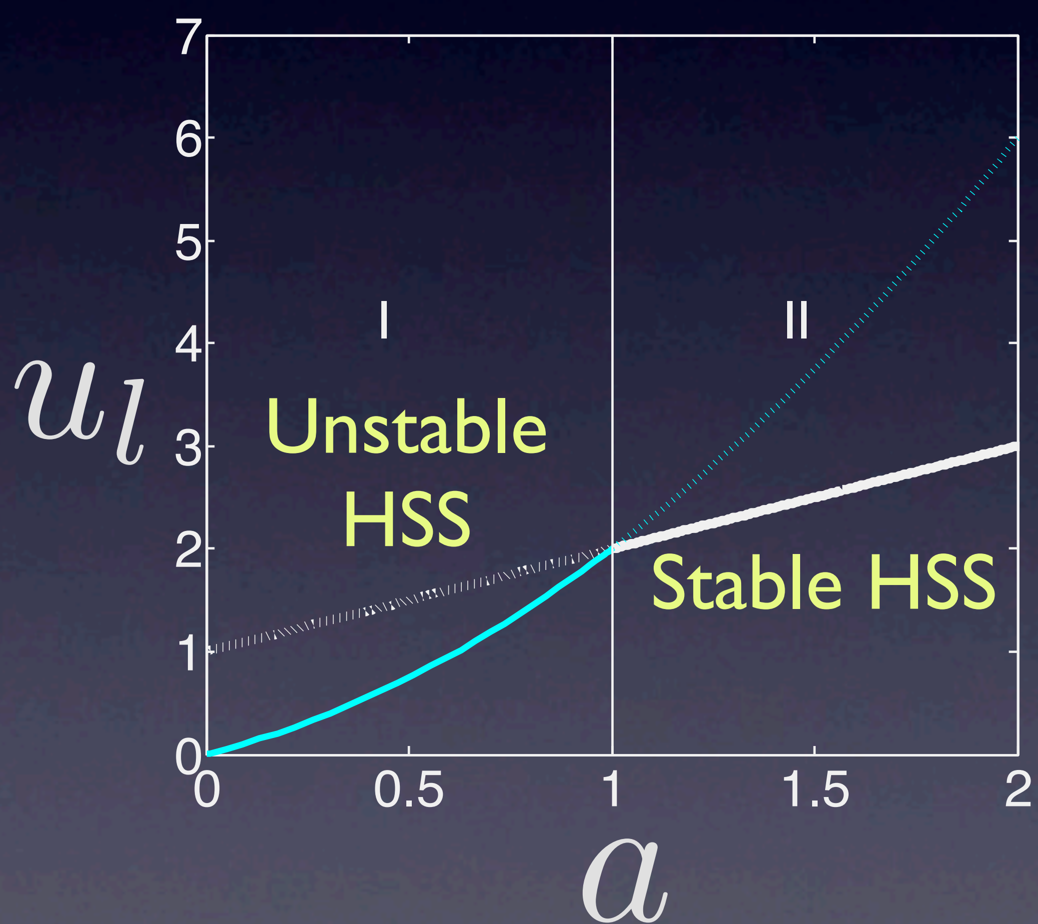


LPA Stability



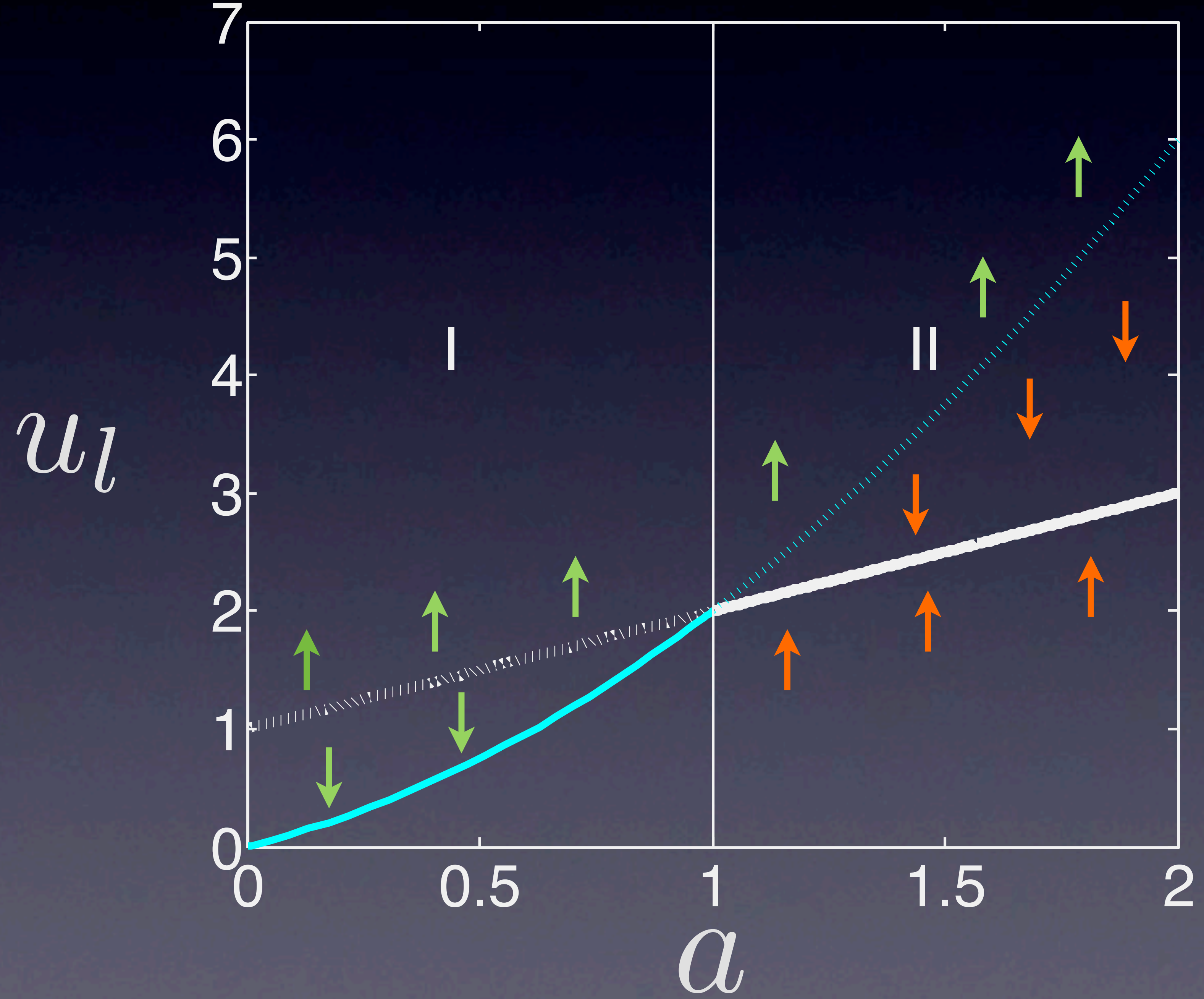
- Thick lines indicate the well mixed HSS.
    - Dashed (resp. full) indicate unstable (resp. stable)
- Thin lines indicate local states attainable ONLY BY THE LOCAL STATE u^l

LPA Stability



- Region I = Turing unstable
  - Patterning driven by small noise.
- Region II = $\delta - unstable$
  - Patterning driven by sufficiently large perturbation

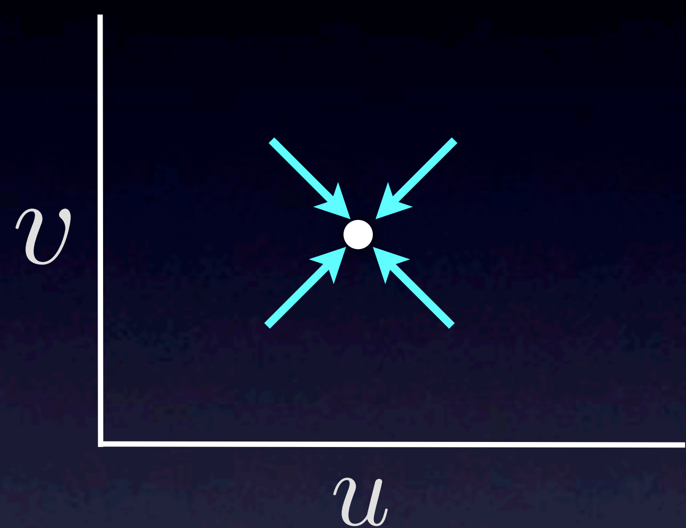
Interpretation



- Arrows indicate the growth or decay of a local perturbation of the HSS.
- The unstable ‘local branch’ indicates a threshold.

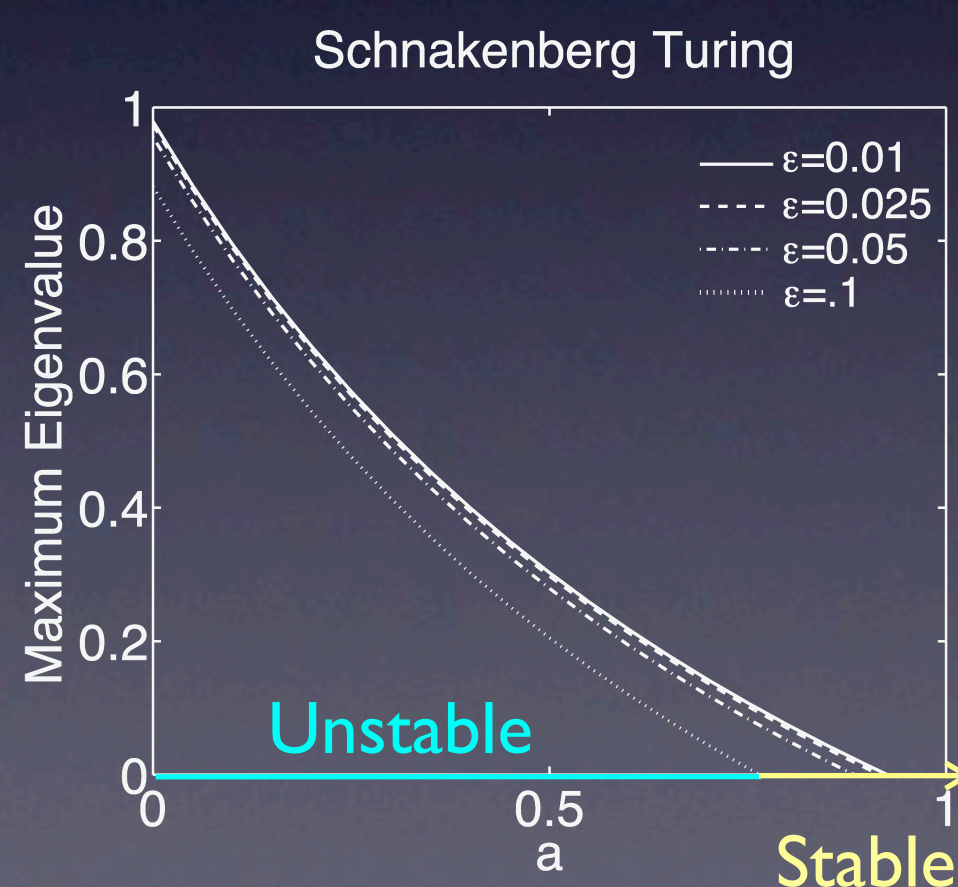
Tying it all together

Schnakenberg Recap

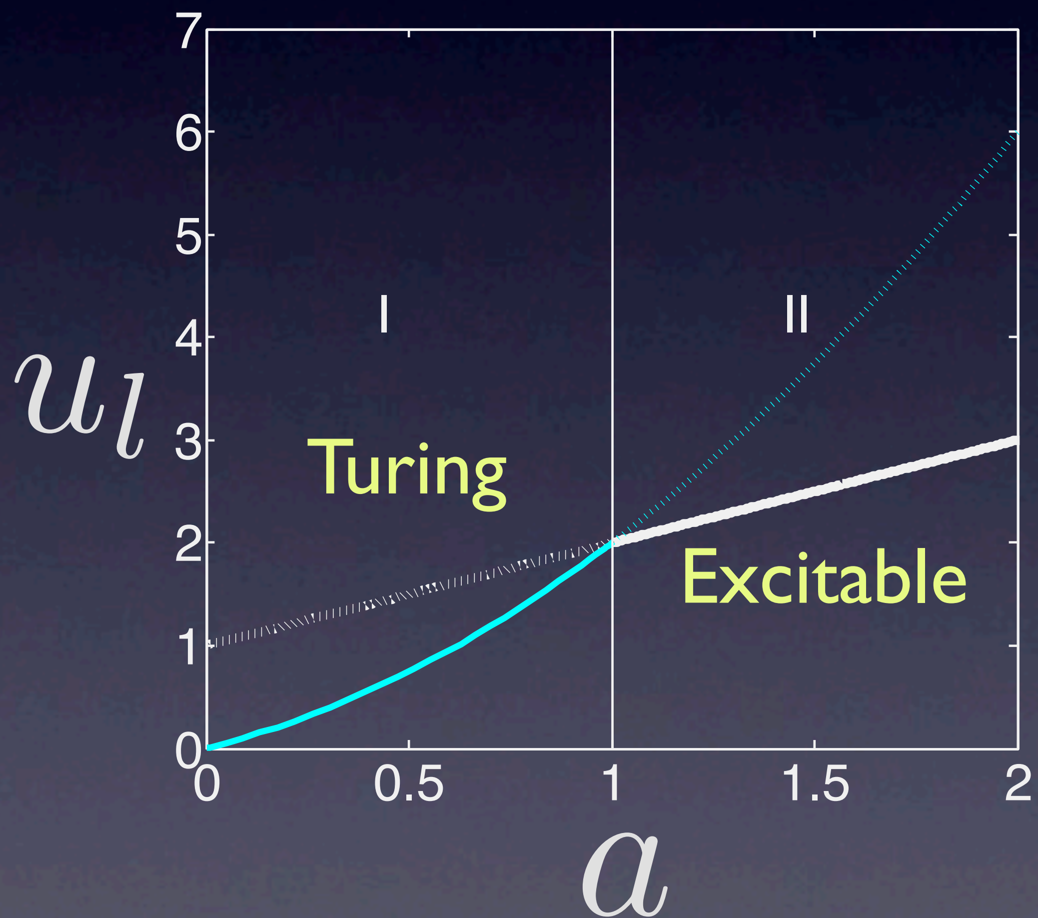


- The unique HSS of this system is stable.

- A Turing instability is present on a subset of [0,1].



Recap



- The LPA depicts the HSS.
- It indicates the Turing instability on [0,1].
- It also depicts excitable patterning on ‘a > 1’.

In summary

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- The LPA recovers information from well mixed and Turing analyses.

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- It detects threshold induced patterning not possible with other methods.

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- The LPA recovers information from well mixed and Turing analyses.
- It detects threshold induced patterning not possible with other methods.
- It does this using only ODE techniques and existing software.

What's Missing

- The method provides no diffusion information.
- It does not tell you the form of the resulting patterning.
- In the case of a Turing instability, it does not tell you the dominant wave number.