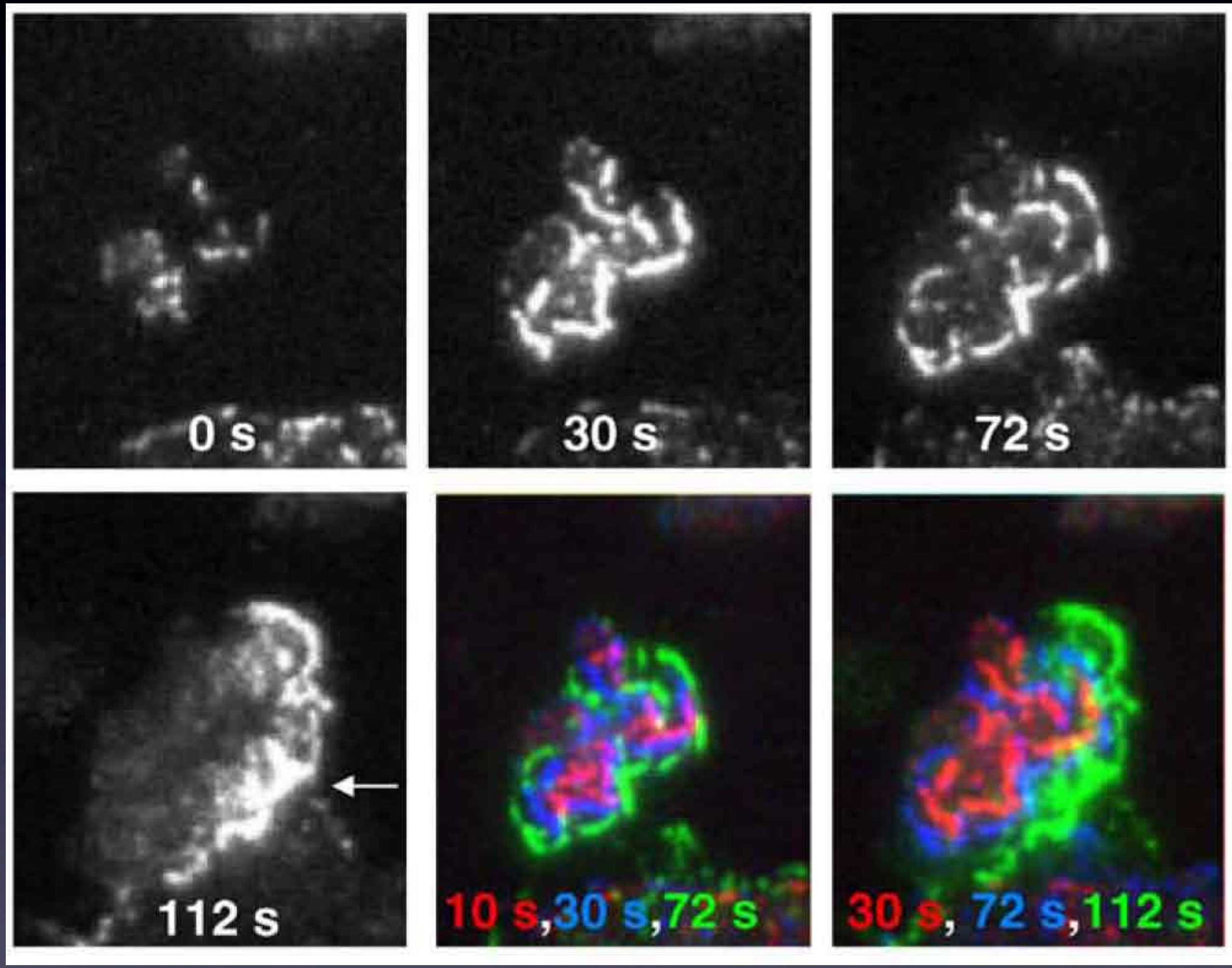
Wave Pinning, Actin Waves, and LPA

MCB 2012
William R. Holmes

Intercellular Waves



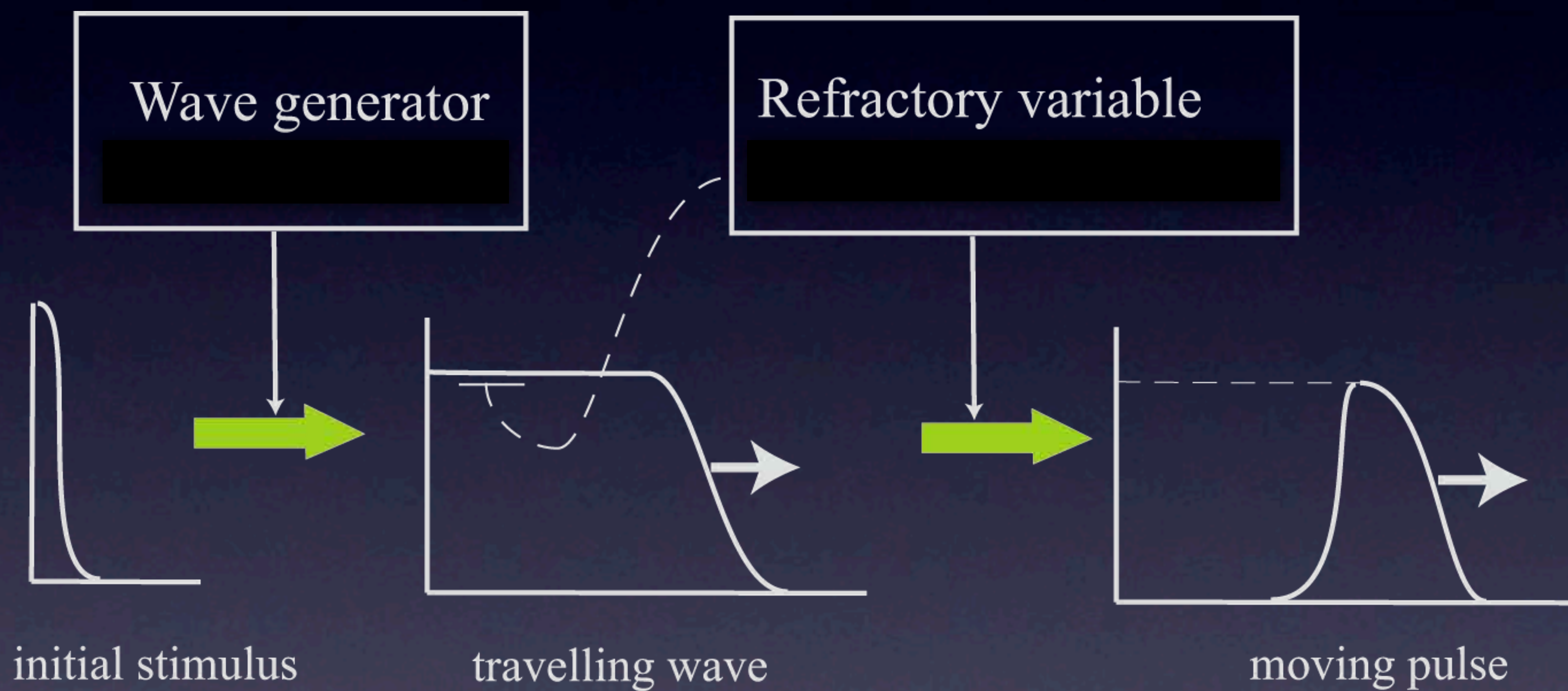
Weiner et al., 2007, PLoS Biology

- Dynamic Hem1 waves in neutrophils

Questions?

- How can such waves / pulses form?
- What molecular constituents play a role?

FitzHugh Nagumo Idea



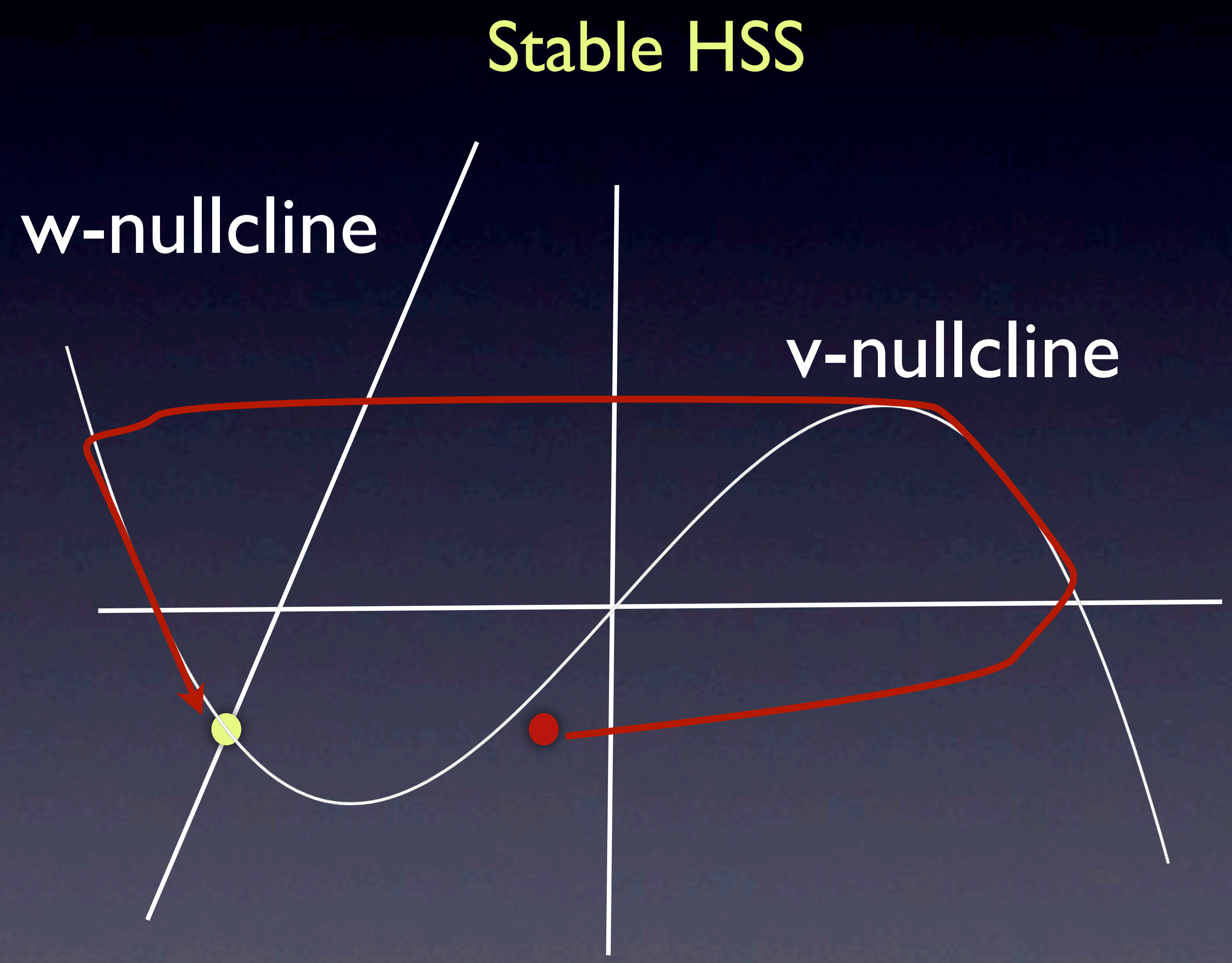
- Positive feedback induces a wave.
- Slower negative feedback yields a pulse.

FitzHugh Nagumo

$$v_t = v - v^3 - w + I + D_v \triangle v,$$
$$\tau w_t = v - bw - a$$

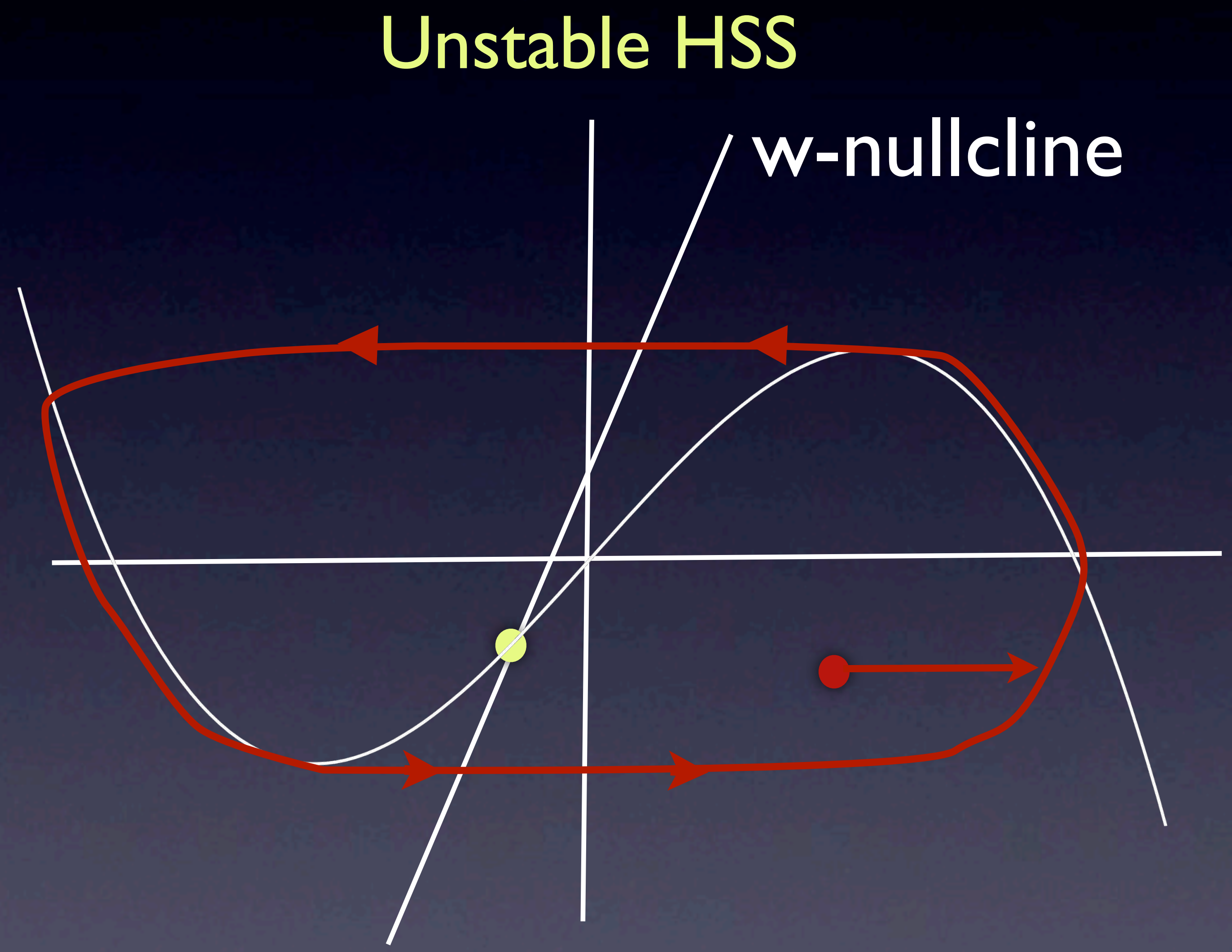
- Used to describe signal propagation in nerves.
- v = membrane voltage
- w = ion concentration

FitzHugh Nagumo



- Stable HSS leads to transient dynamics.

FitzHugh Nagumo



- Unstable HSS leads to a limit cycles and persistent dynamics

FN Feature

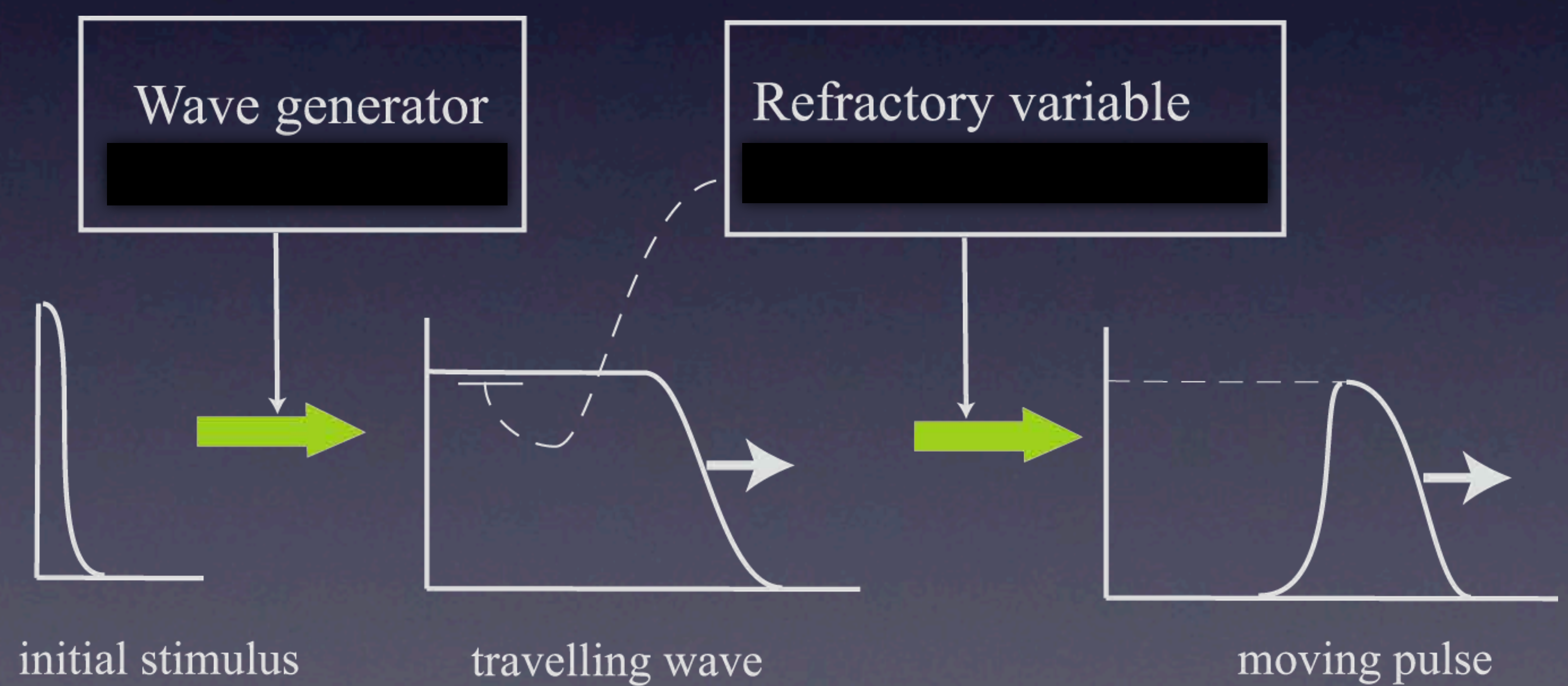
- Stable HSS = transient excitable dynamics
- Unstable HSS = unstable persistent dynamics

Relationship to cell dynamics

- Cells are not always all or nothing.
- Some cells exhibit dynamics even after a stimulus is removed.
  - Some cells are excitable and persistent.

FN Extionsion

- We will consider an augmentation of the standard FN framework.



Hypothesis

- We still consider a basic 'wave generator + refractory feedback' model.
- Wave Generator = Actin Regulators
- Refractory feedback = Actin

Hypothesis

- Polarity proteins such as GTPases or Phosphoinositides serve as a wave generator.
- Actin polymerization inactivates these proteins acting as a refractory feedback.

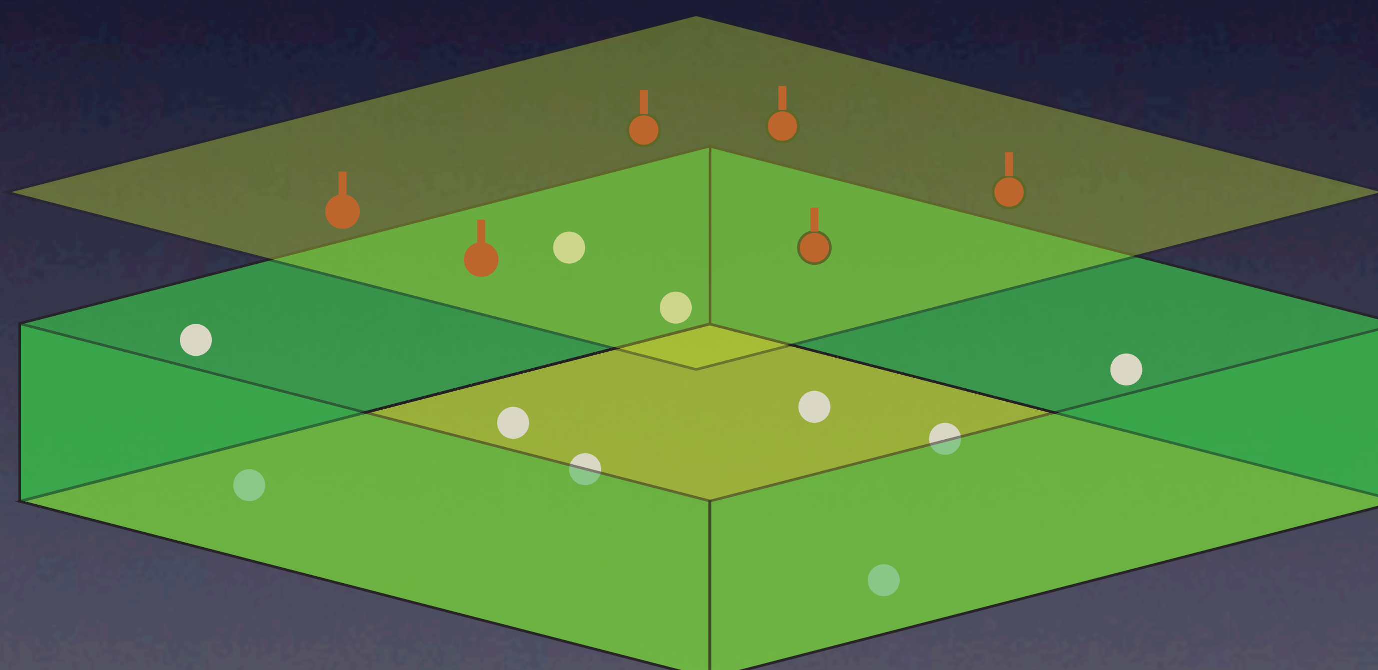
Wave Generator

- Consider a wave pinning (WP) model indicative of GTPase function.

Wave Generator : GTPases

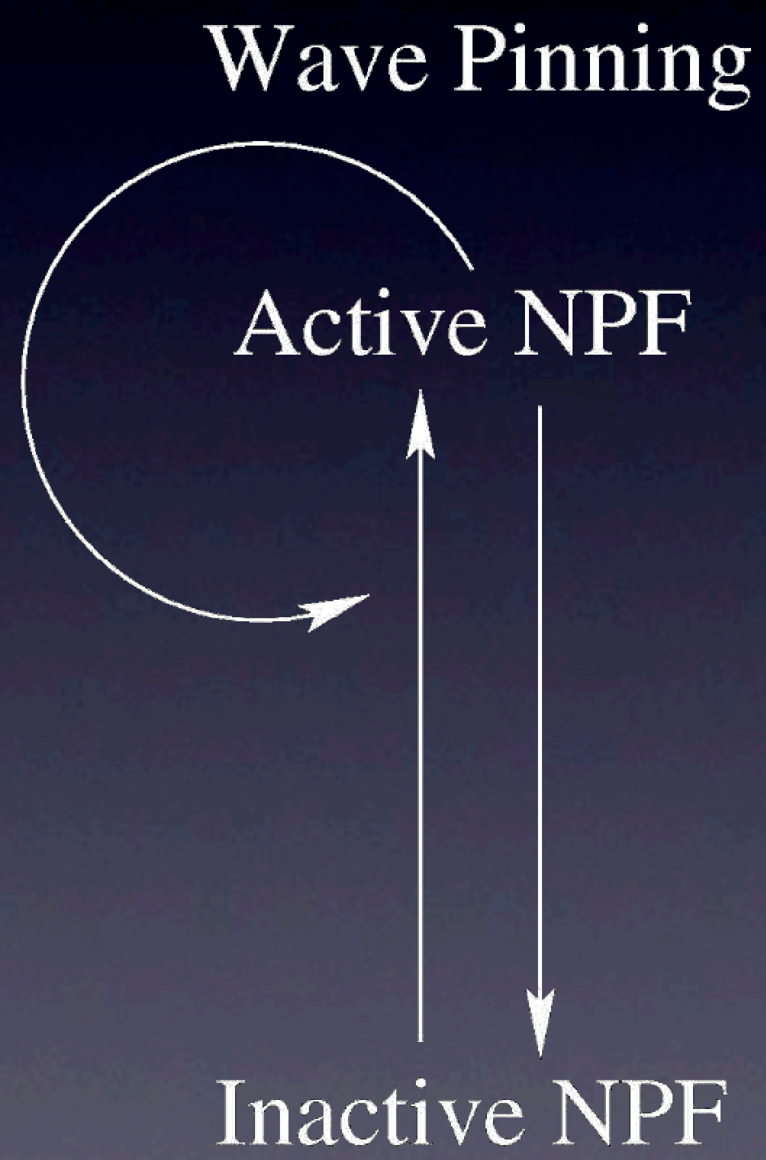
- NPF = actin nucleating protein
- Exists in 2 forms.
- Only the active NPF nucleates F-Actin

- Active NPF
- Inactive NPF



Model Features

- Primary features
  - Slow Fast Diffusion
  - Autocatalysis
  - Conservation

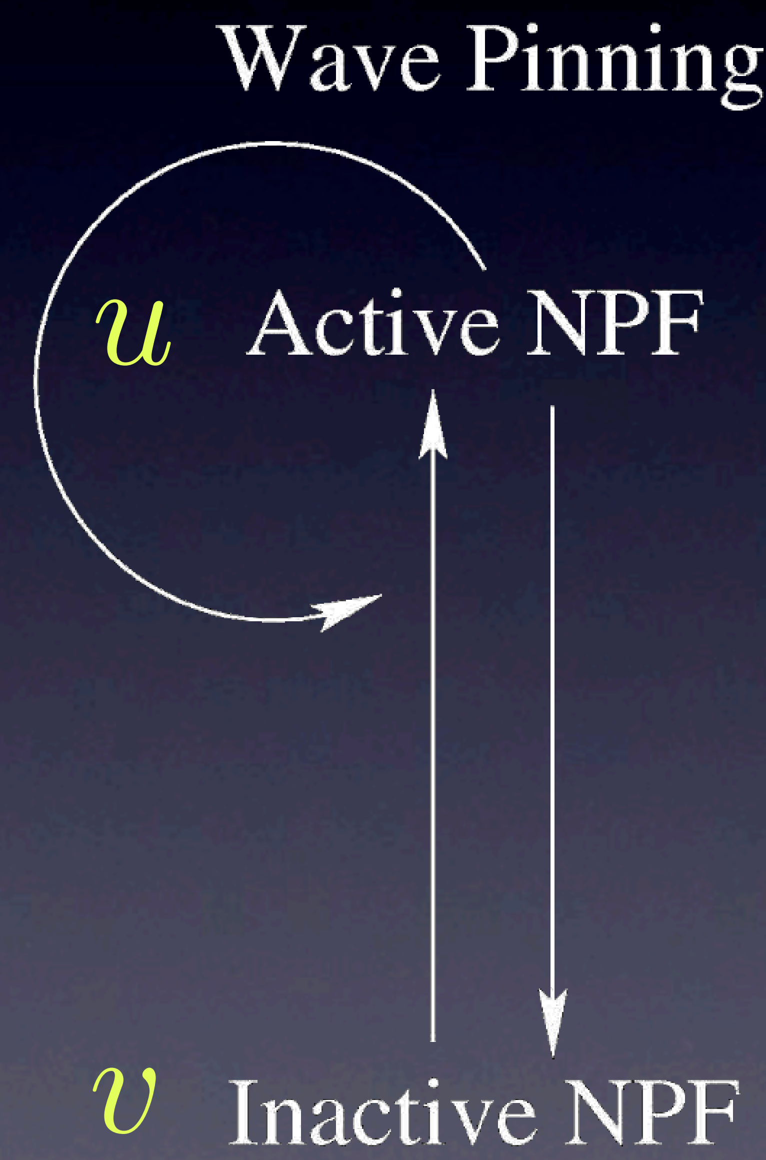


Wave Pinning: Equations

$$u_t(x,t) = f(u,v) + D_u \triangle u$$
$$v_t(x,t) = -f(u,v) + D_v \triangle v$$

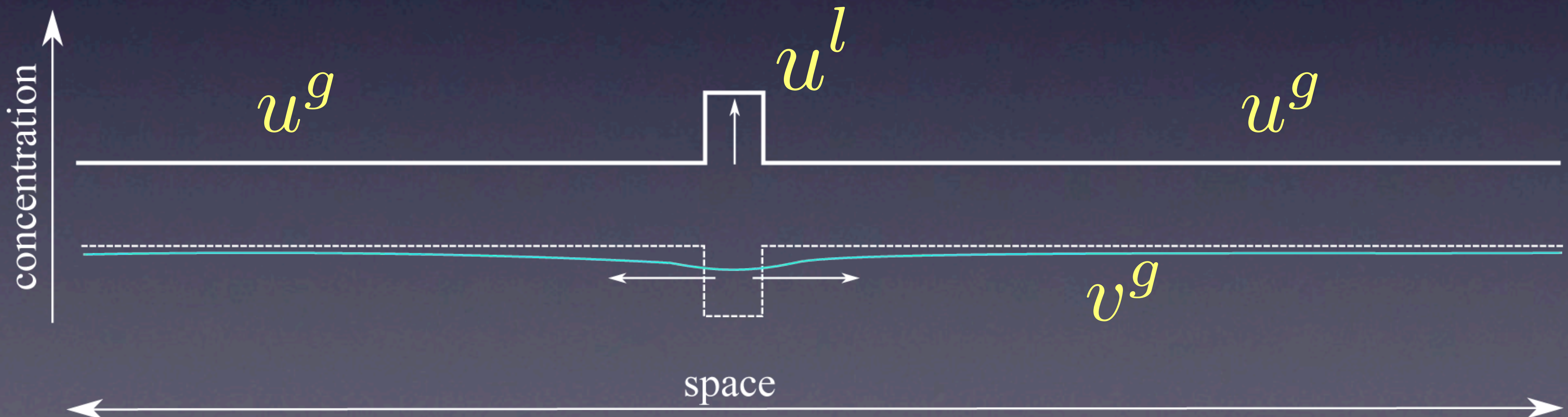
$$f(u,v) = v(k_0 + \frac{\gamma u^n}{K^n + u^n}) - \delta u$$

$$D_u \ll D_v$$



LPA Reduction

$$u^l_t(t) = f(u^l, v^g)$$
$$u^g_t(t) = f(u^g, v^g)$$
$$v^g_t(t) = -f(u^g, v^g)$$



Conservation Reduction

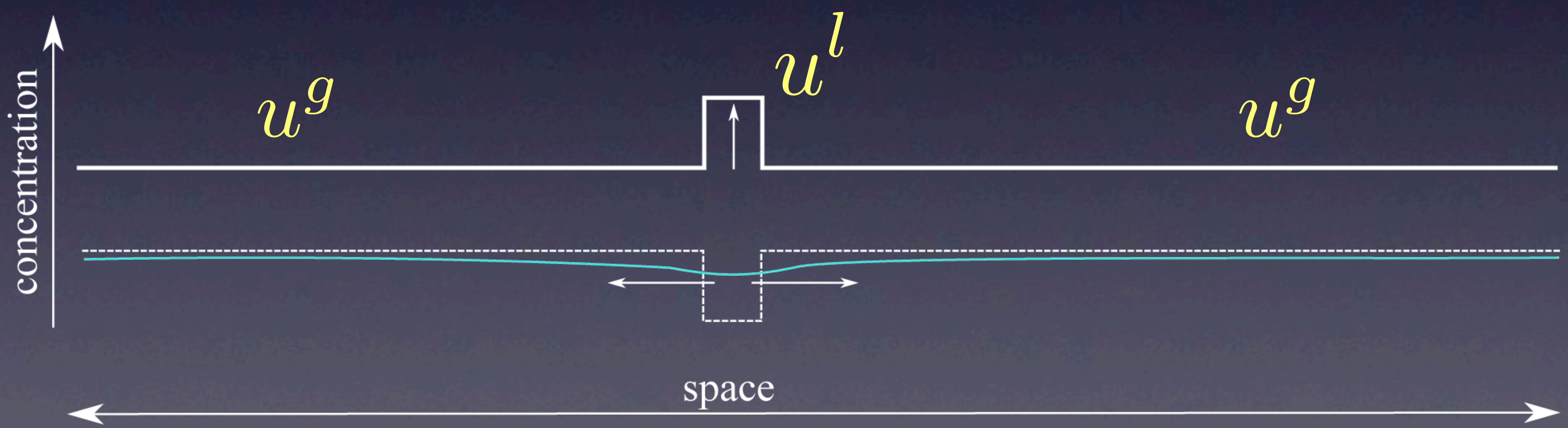
- Assume the perturbation is highly localized.

$$\int u^g(t) + v^g(t)\,dx \approx \int u(x,t) + v(x,t)\,dx = C$$

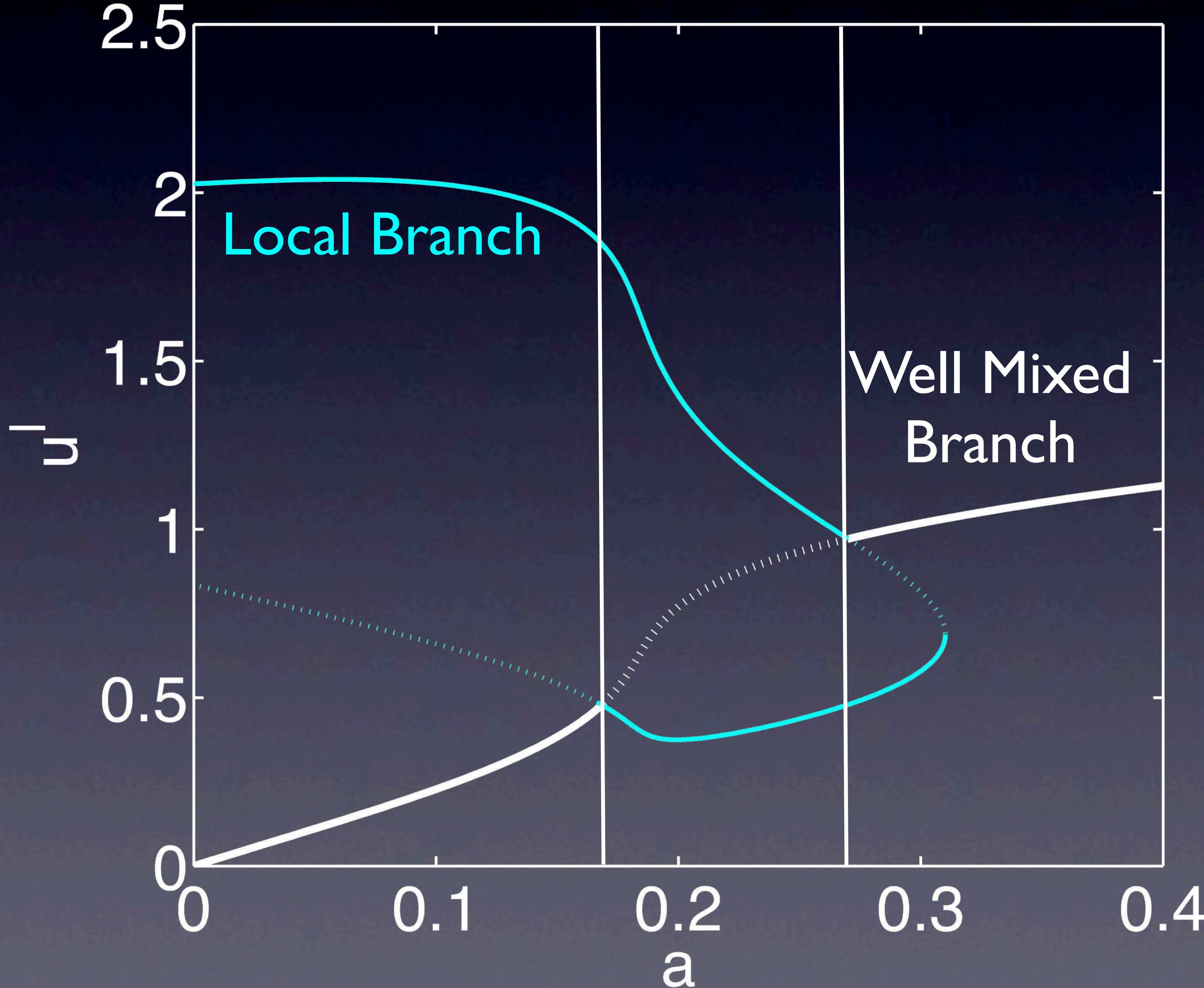
- So $v^g(t) = T - u^g(t)$

LPA System

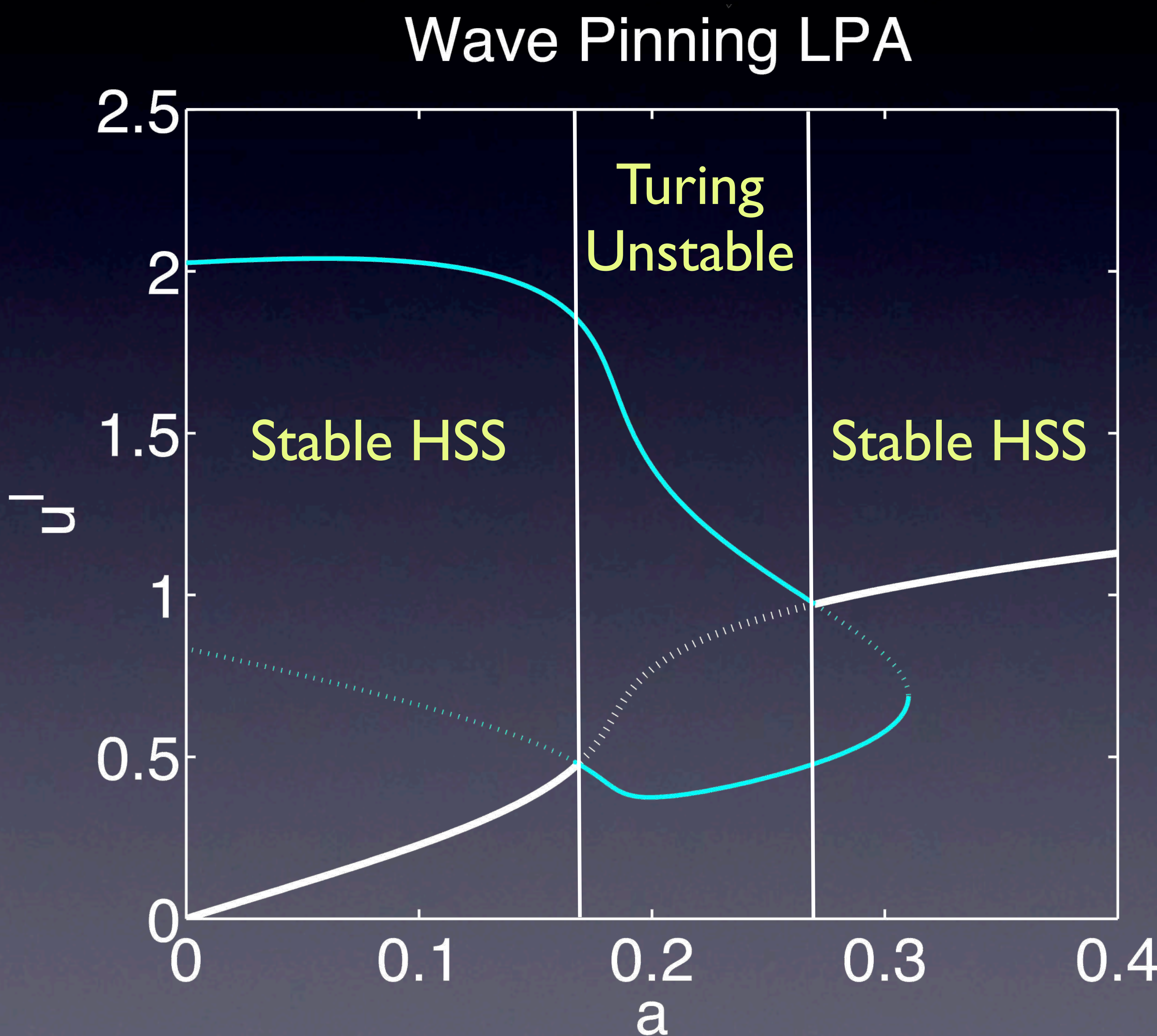
$$u_t^l(t) = f(u^l, T - u^g)$$
$$u_t^g(t) = f(u^g, T - u^g)$$



Wave Pinning LPA



Wave Pinning: Stability



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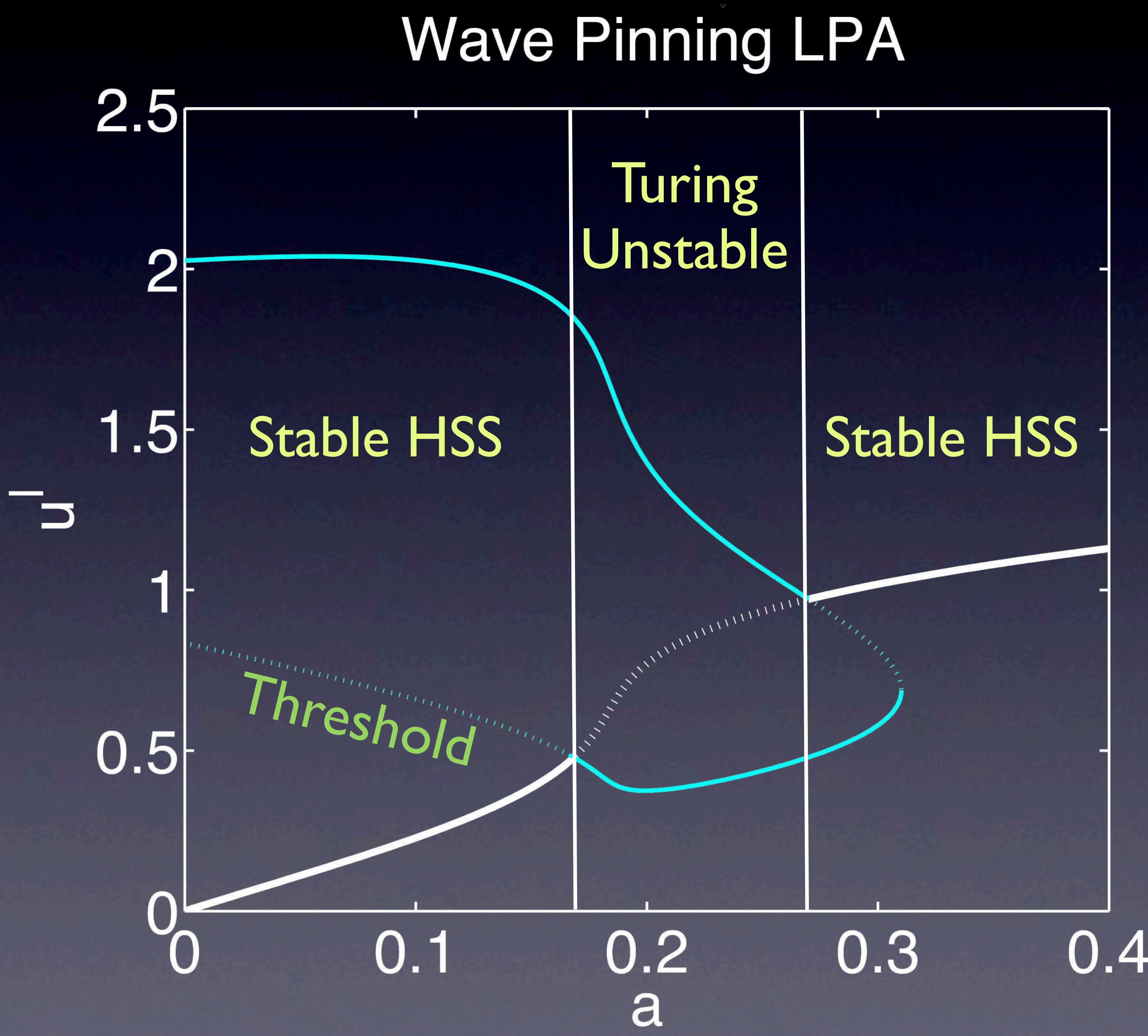
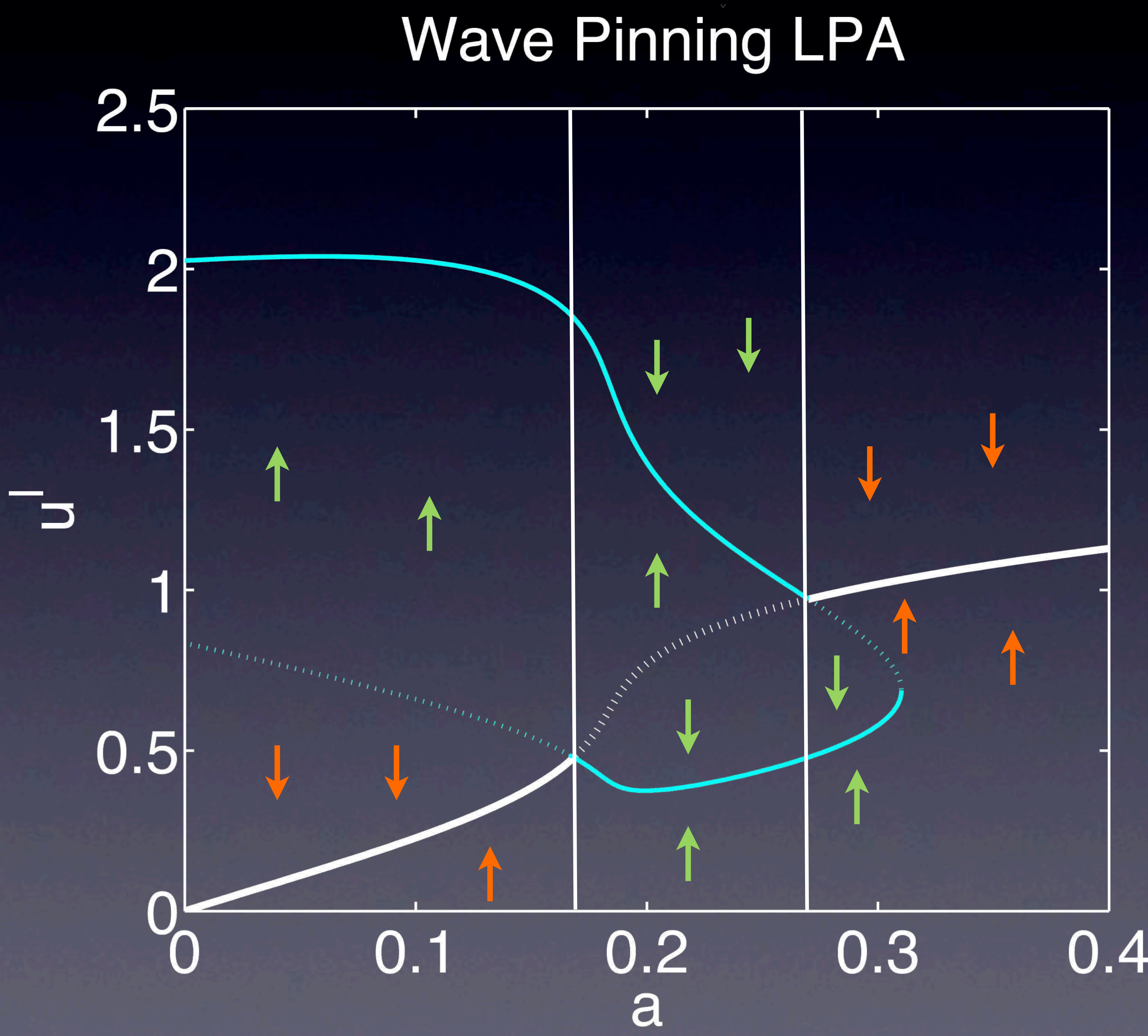
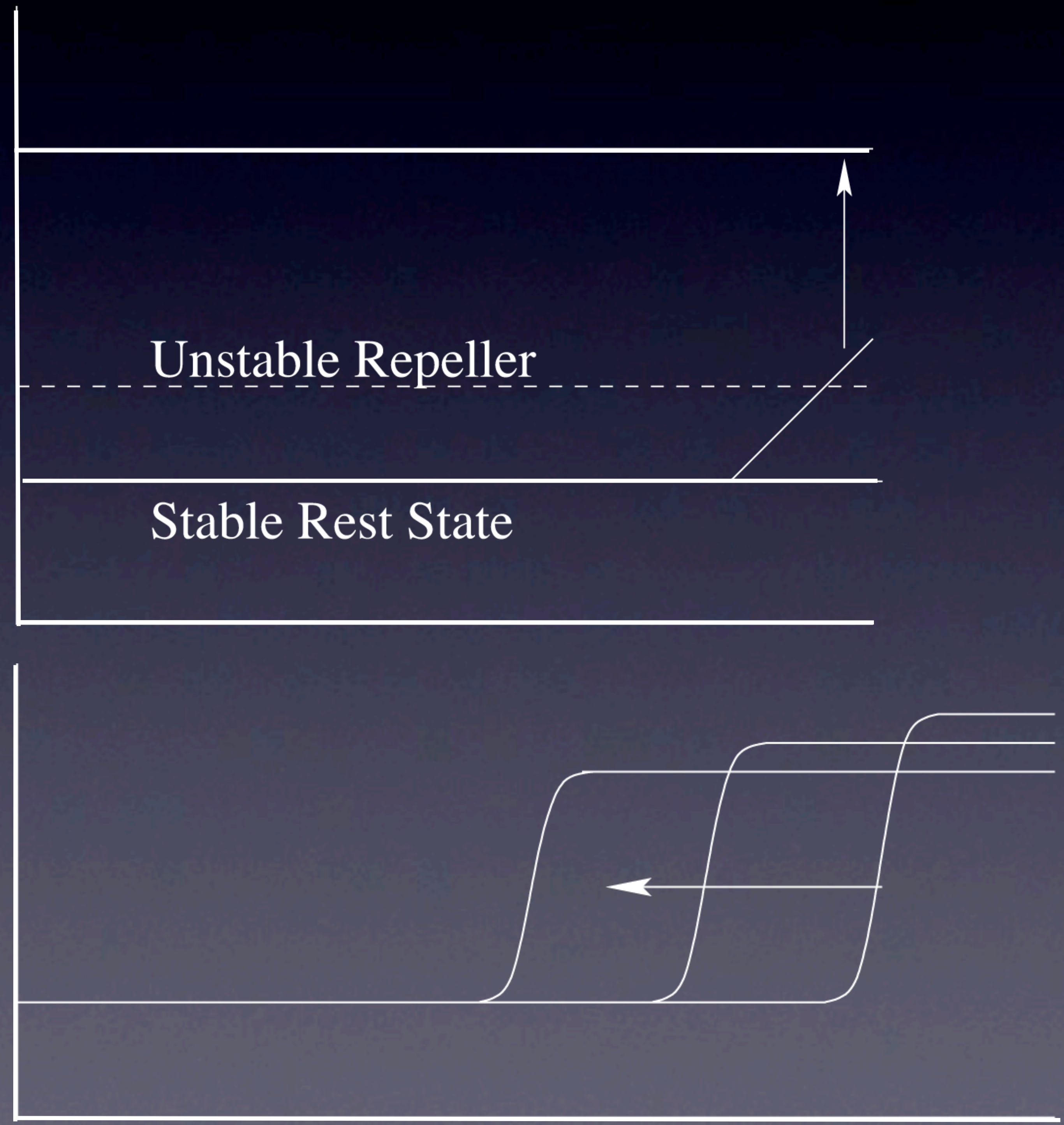


Wave Pinning: Stability



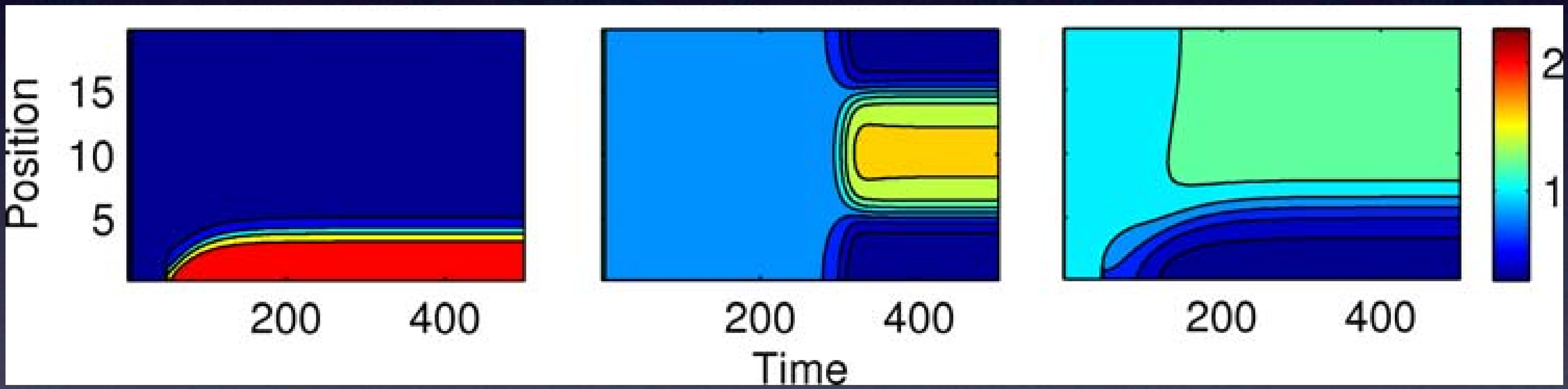
Wave Pinning

- + feedback yields a threshold response
- Conservation causes stalling.
- As the wave propagates, it depletes the inactive NPF



Wave Pinning: Simulations

Active NPF

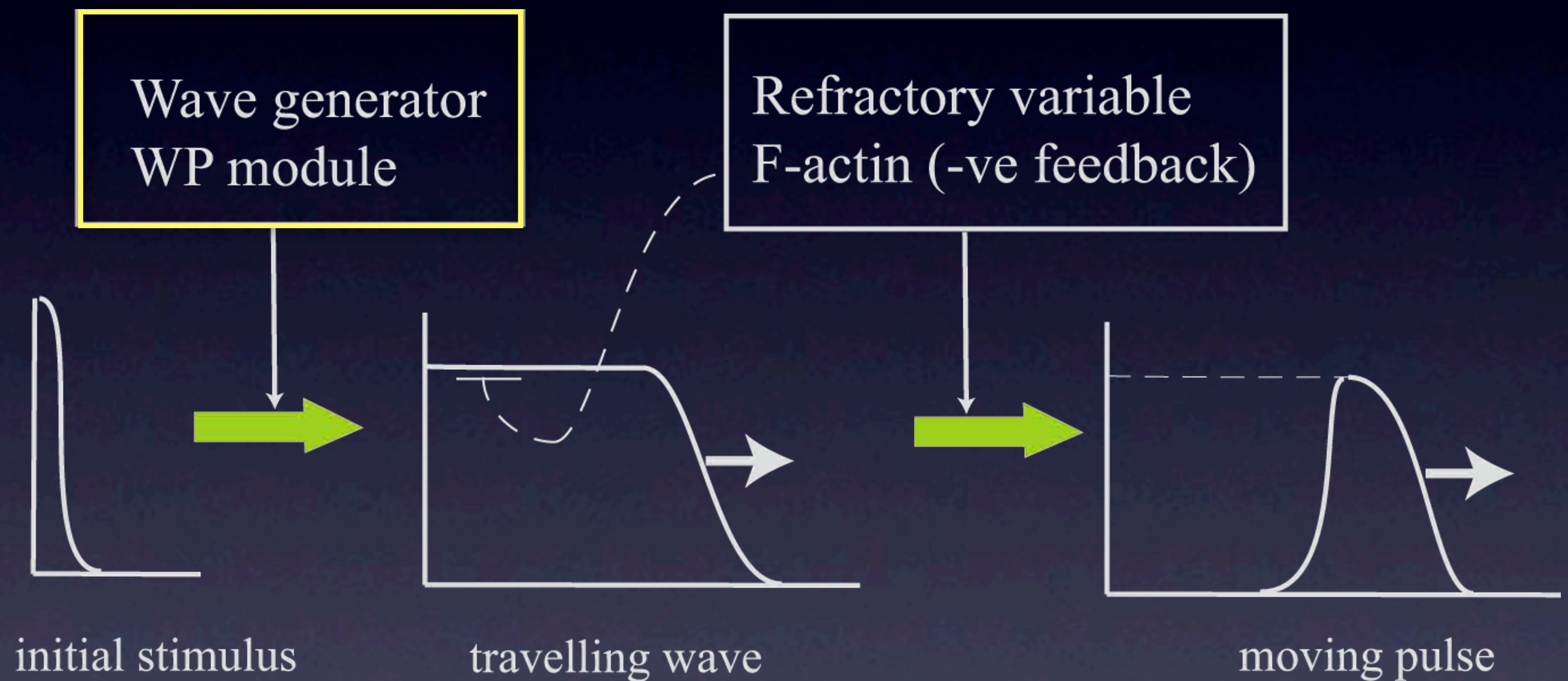


Wave Pinning + Perturbation

Turing Noise

Wave Pinning - Perturbation

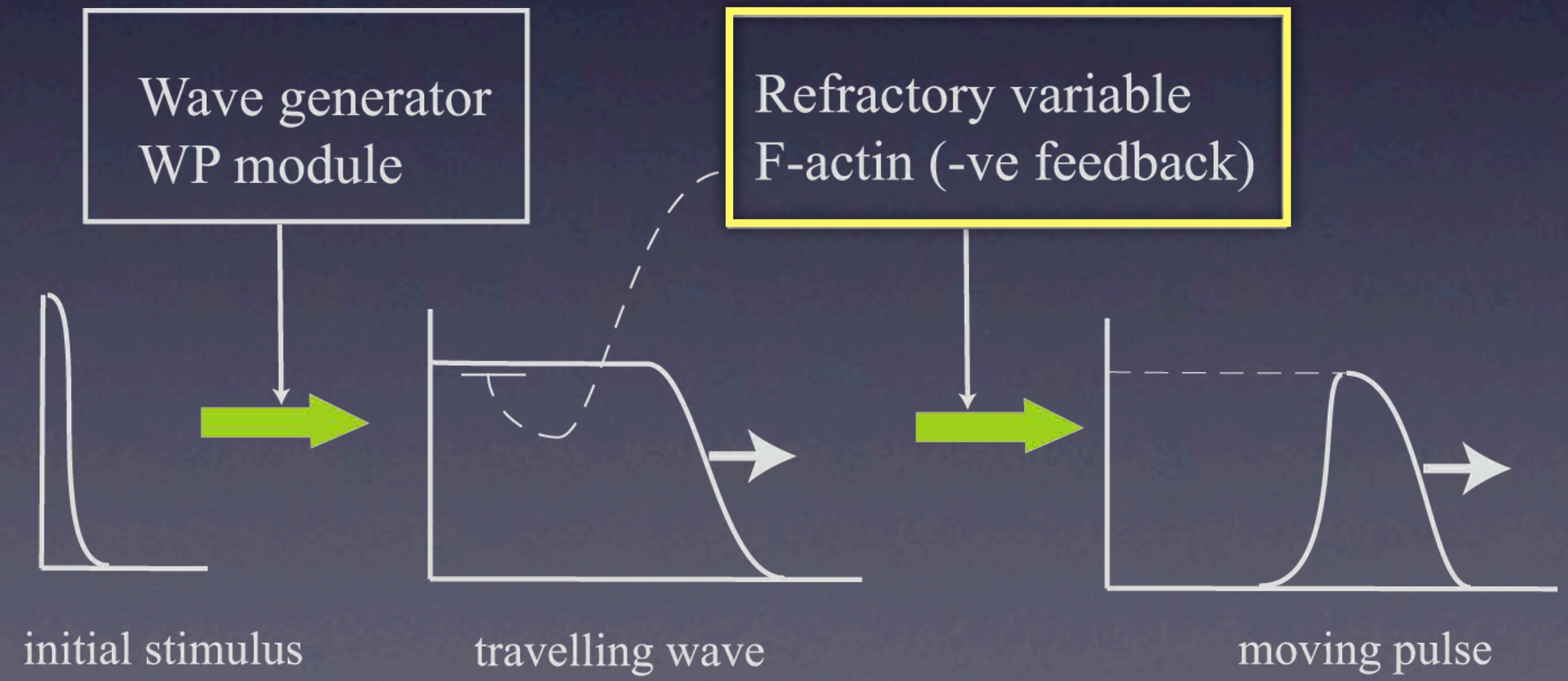
Wave Pinning: Wave Generator



- We will assume this WP model acts as a wave generator.

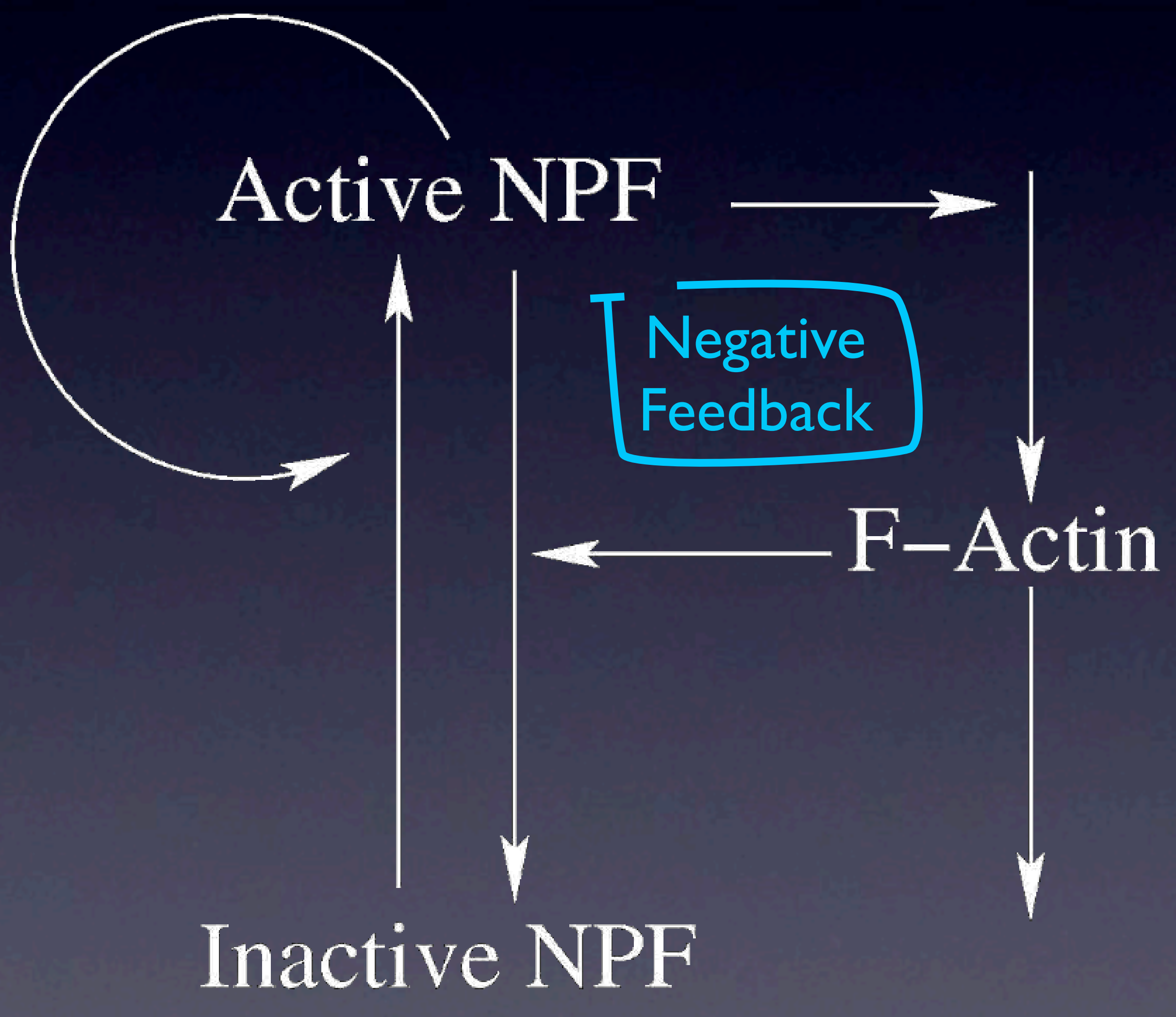
Refractory Feedback

- Polarity related proteins (GTPases) nucleate actin and initiate a wave.
- Growing actin 'inactivates' these proteins.



Actin Wave Model

- Active NPF promotes F-Actin.
  - Wave Generator
- F-Actin inactivates NPF
  - Refractory feedback



Actin Wave Model

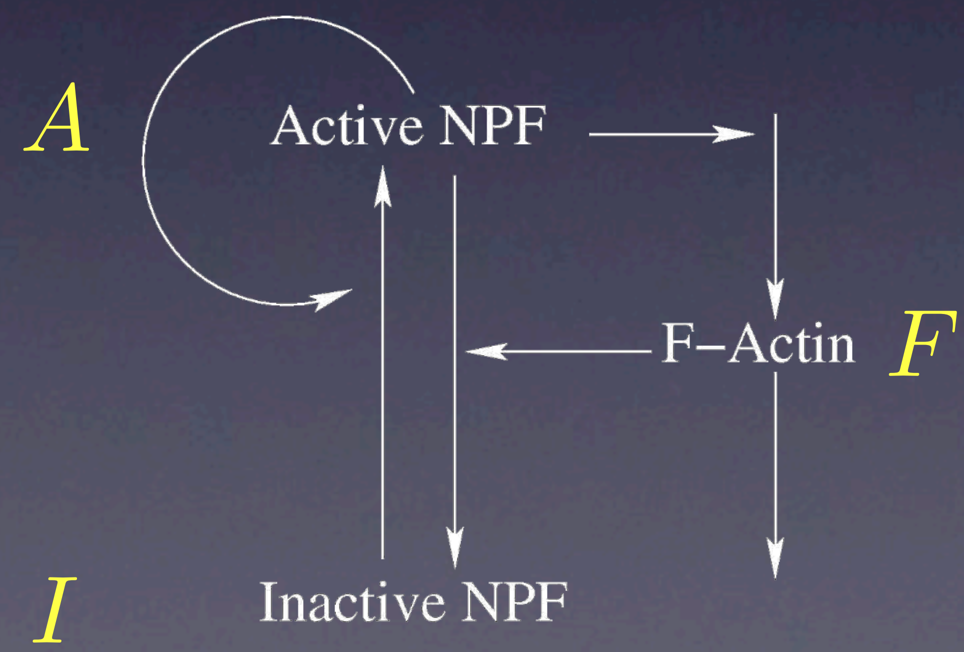
$$A_t = f + D_A \triangle A,$$
$$I_t = -f + D_I \triangle I$$

NPF Equations

$$f(A, I, F) = \left(k_0 + \frac{\gamma A^3}{A_0^3 + A^3} \right) I - \delta \left(s_1 + s_2 \frac{F}{F_0 + F} \right) A$$

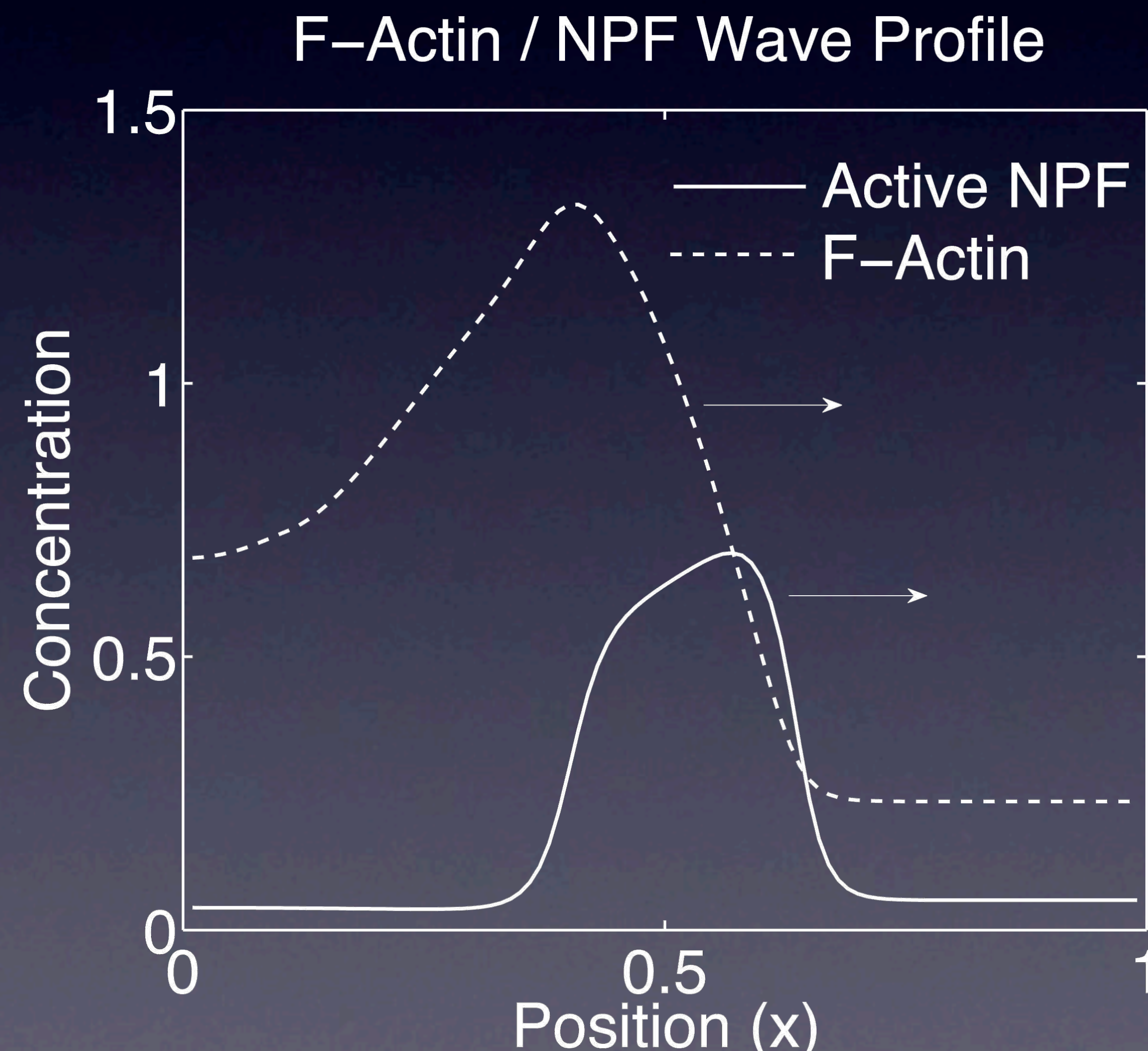
F-Actin Equations

$$F_t = \epsilon h$$
$$h(A, F) = k_n A - k_s F$$



Pulse Snapshot

- F-Actin wave trails NPF wave



Spatio-Temporal Behaviour

Pinned Wave

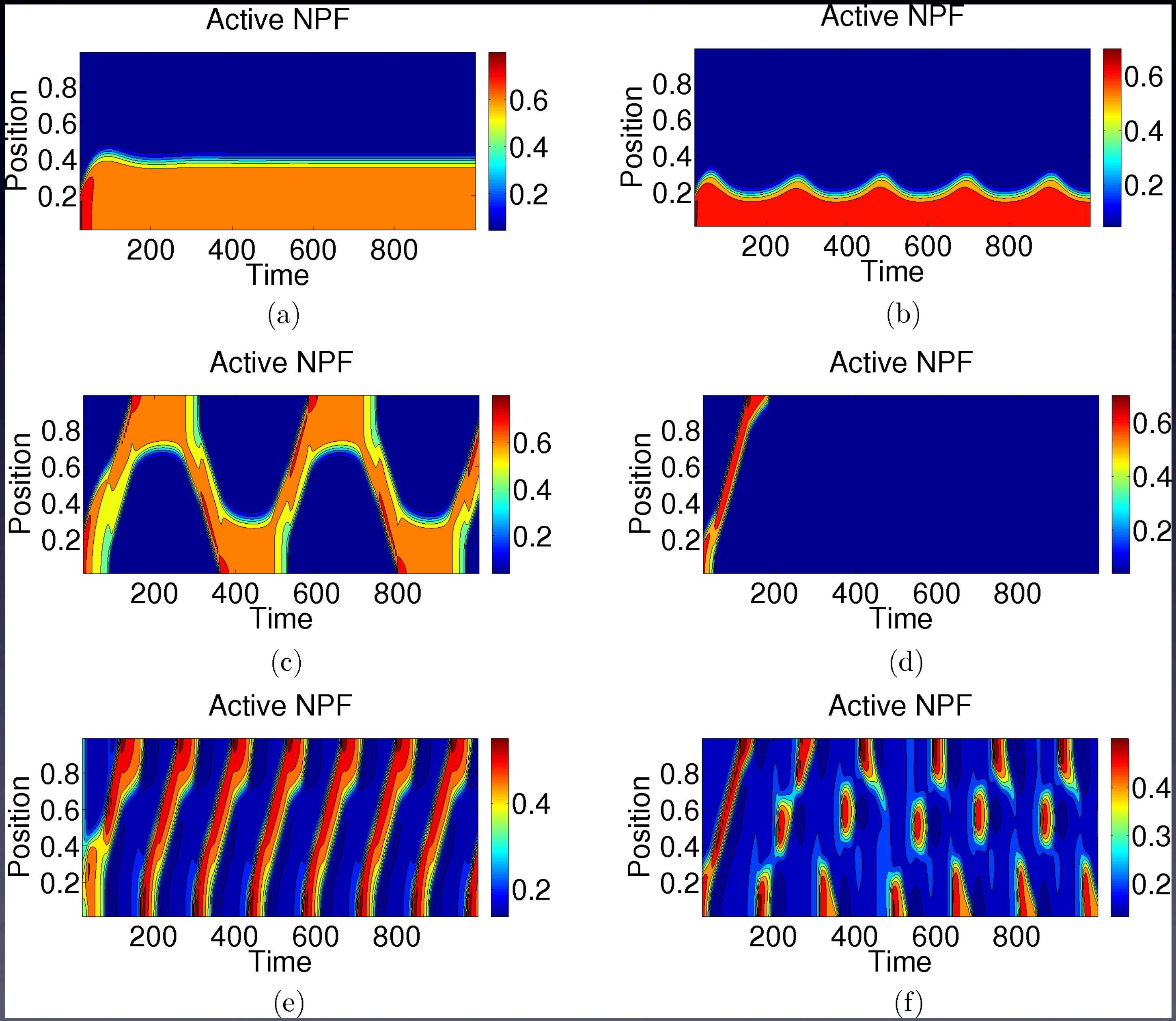
Oscillating Wave

Reflecting Pulse

Single Pulse

Pulse Train

Exotic



- Kymograph = (x,t) plot

Use LPA to map parameter space

Actin Wave LP-System

$$
\begin{aligned}
A^l_t &= f(A^l, I^g, F^l),\\
A^g_t &= f(A^g, I^g, F^g),\\
I^g_t &= -f(A^g, I^g, F^g),\\
F^l_t &= \epsilon h(A^l, F^l),\\
F^g_t &= \epsilon h(A^g, F^g)
\end{aligned}
$$

Actin Wave LP-System

$$A_t^l = f(A^l, I^g, F^l),$$

$$A_t^g = f(A^g, I^g, F^g),$$

$$I_t^g = -f(A^g, I^g, F^g),$$

$$F_t^l = \epsilon h(A^l, F^l),$$

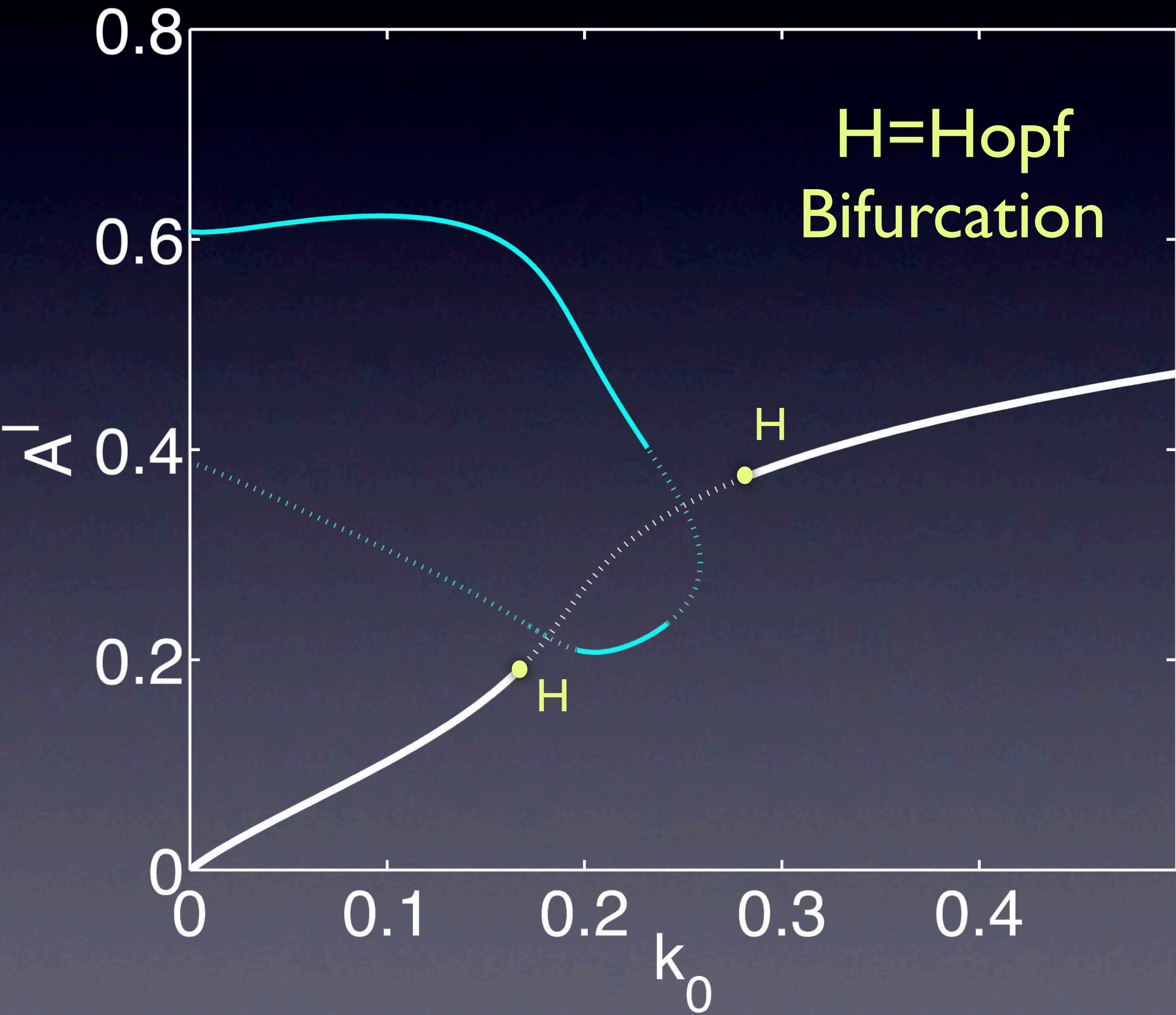
$$F_t^g = \epsilon h(A^g, F^g)$$

Actin Wave
LPA

- Applying NPF conservation.

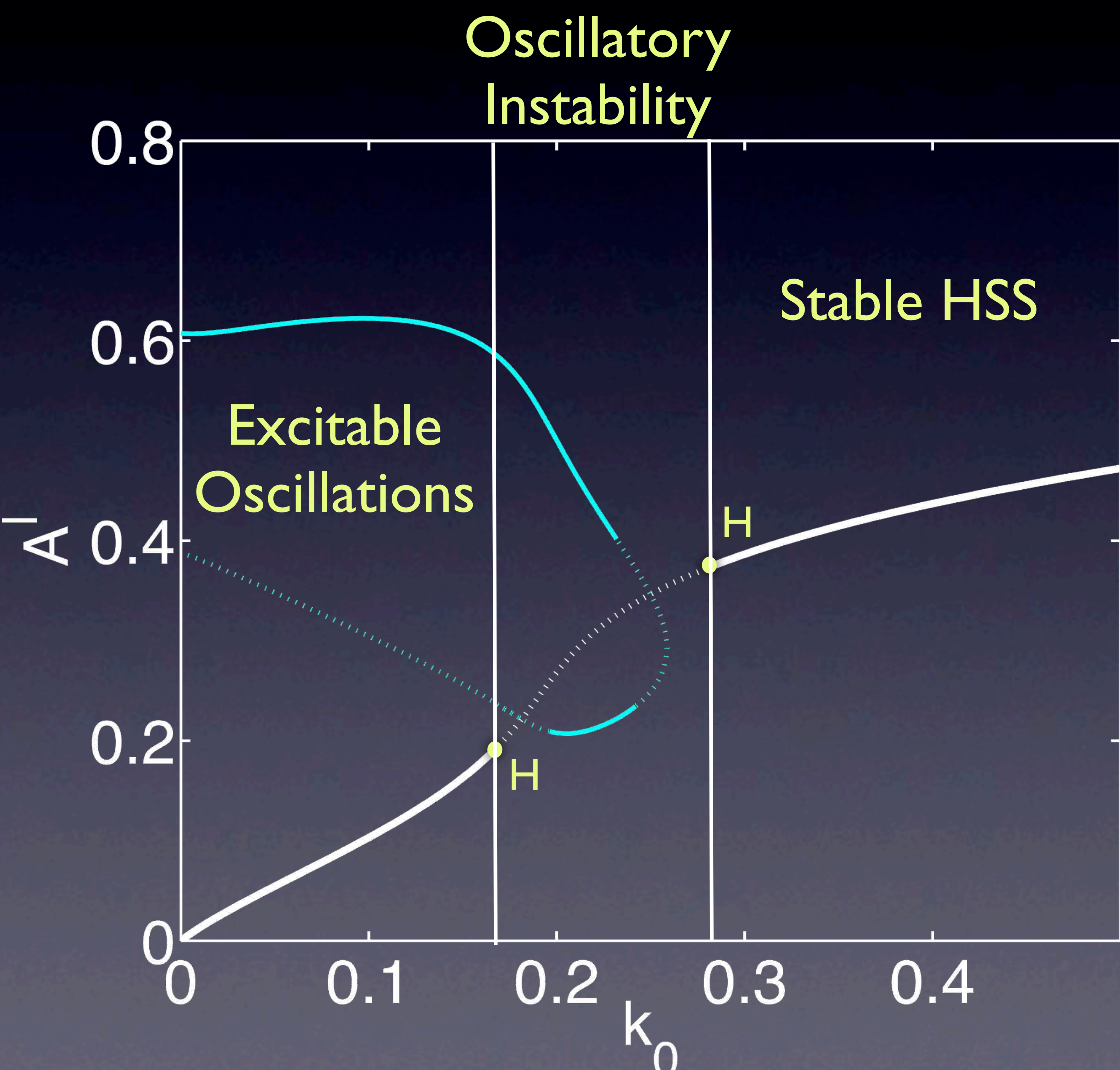
$$
\begin{aligned}
A_t^l &= f(A^l, C - A^g, F^l),\\
A_t^g &= f(A^g, C - A^g, F^g),\\
F_t^l &= \epsilon h(A^l, F^l),\\
F_t^g &= \epsilon h(A^g, F^g)
\end{aligned}
$$

Actin Wave LPA



- Branch Points are retained from wave pinning.
- Hopf bifurcations are new and indicate oscillations.

Actin Wave LPA

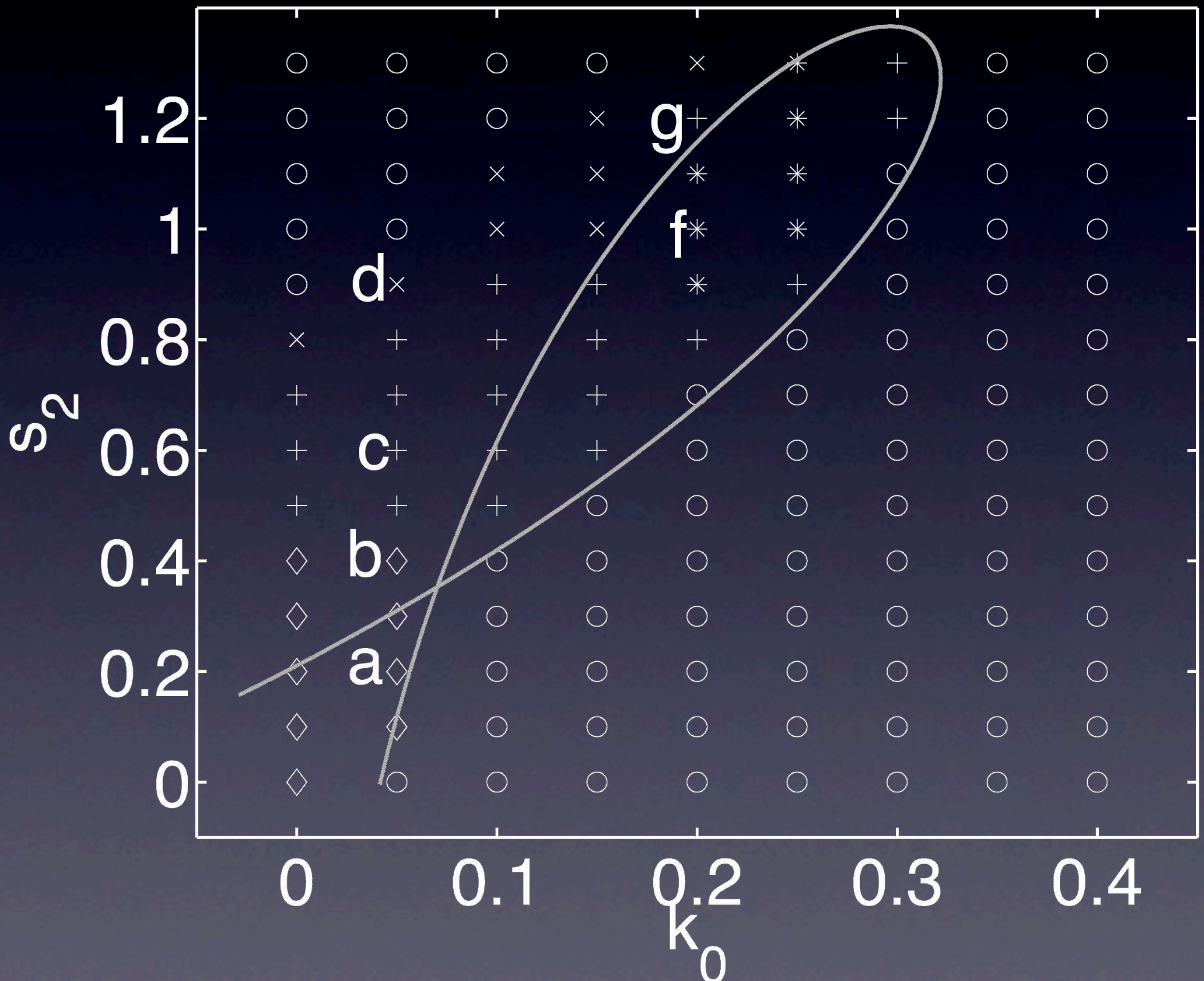


- Branch Points are retained from wave pinning.
- Hopf bifurcations are new and indicate oscillations.

Questions?

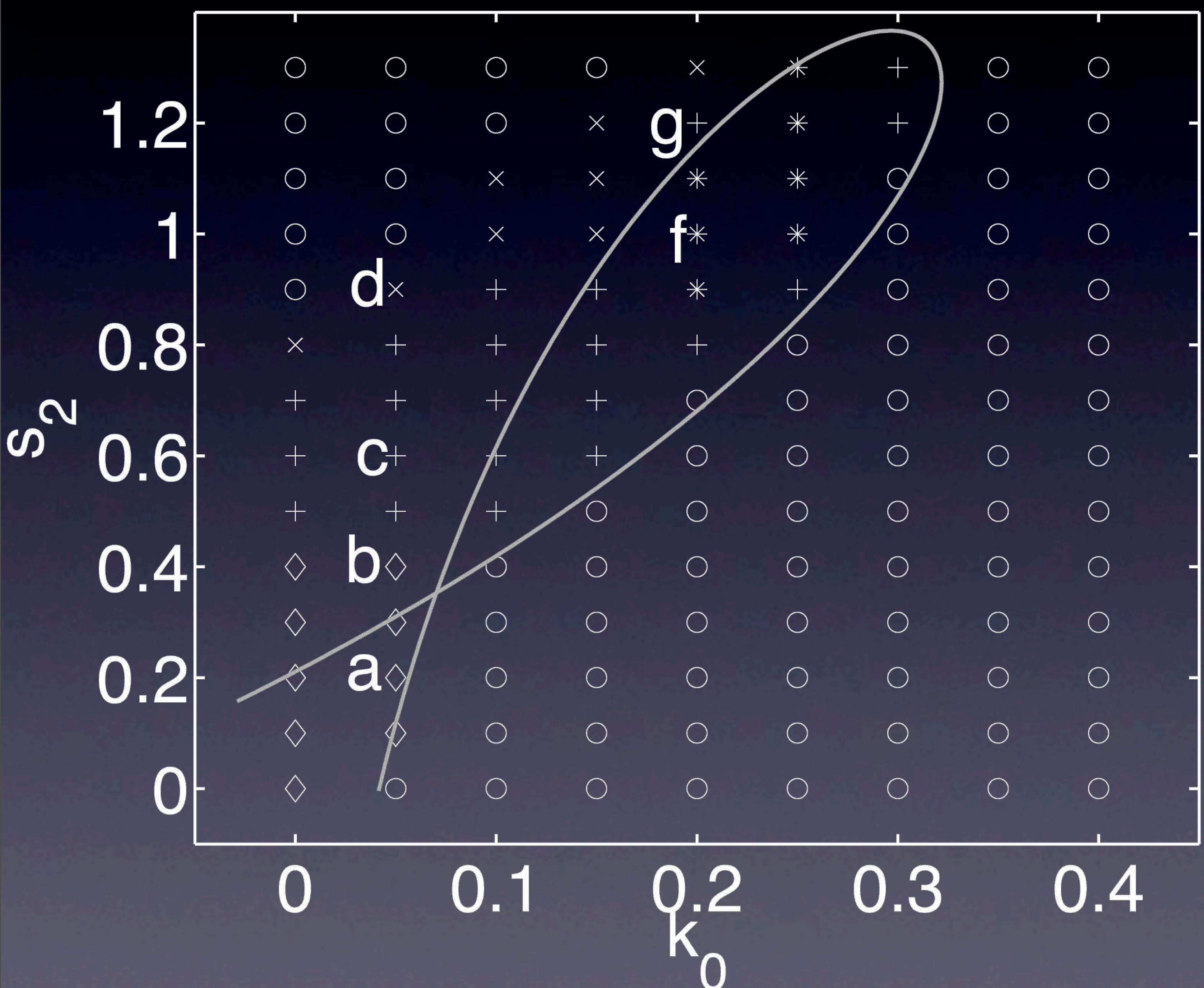
- How do the positive and negative feedback loops interact to initiate patterning?
- What role do they play in determining the resulting behaviour on a longer time scale?

LPA + Simulation



- Curve = 2 parameter Hopf continuation.
- Points = values used for PDE simulations.

LPA + Simulation



+ = Reflecting Waves

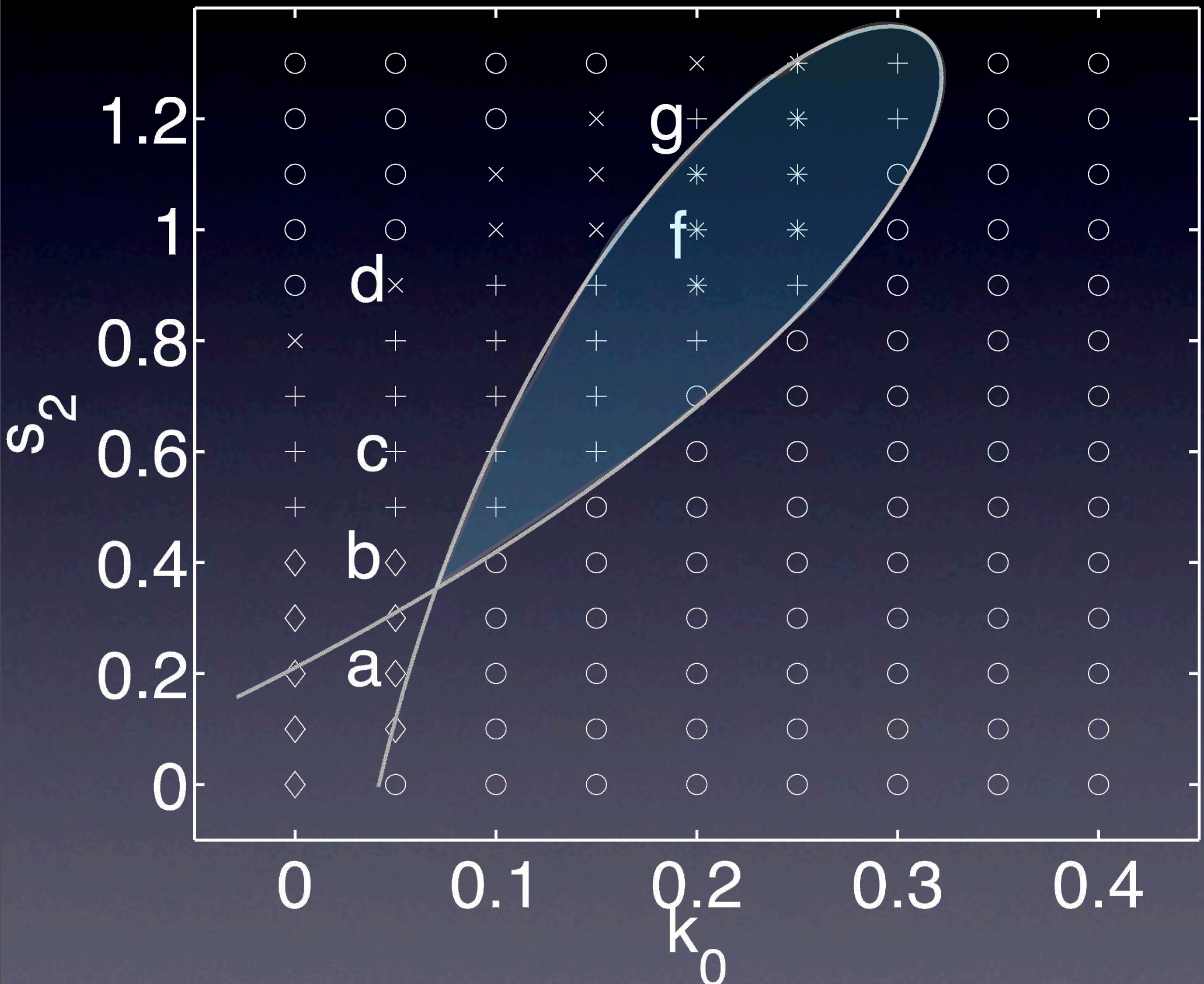
O = Reflecting Waves

* = Wave Trains

X = Single Wave

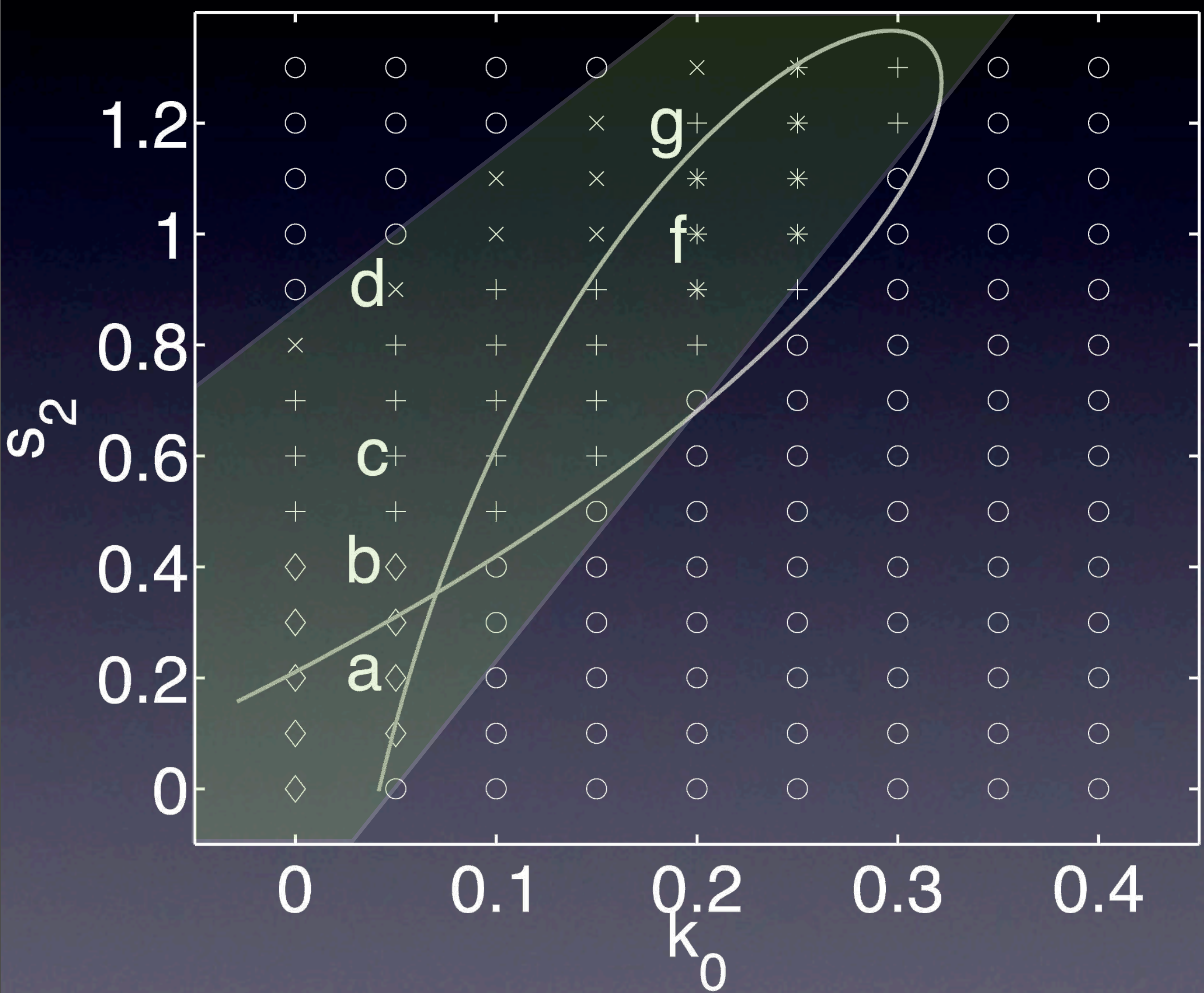
◊ = Single Wave

LPA + Simulation



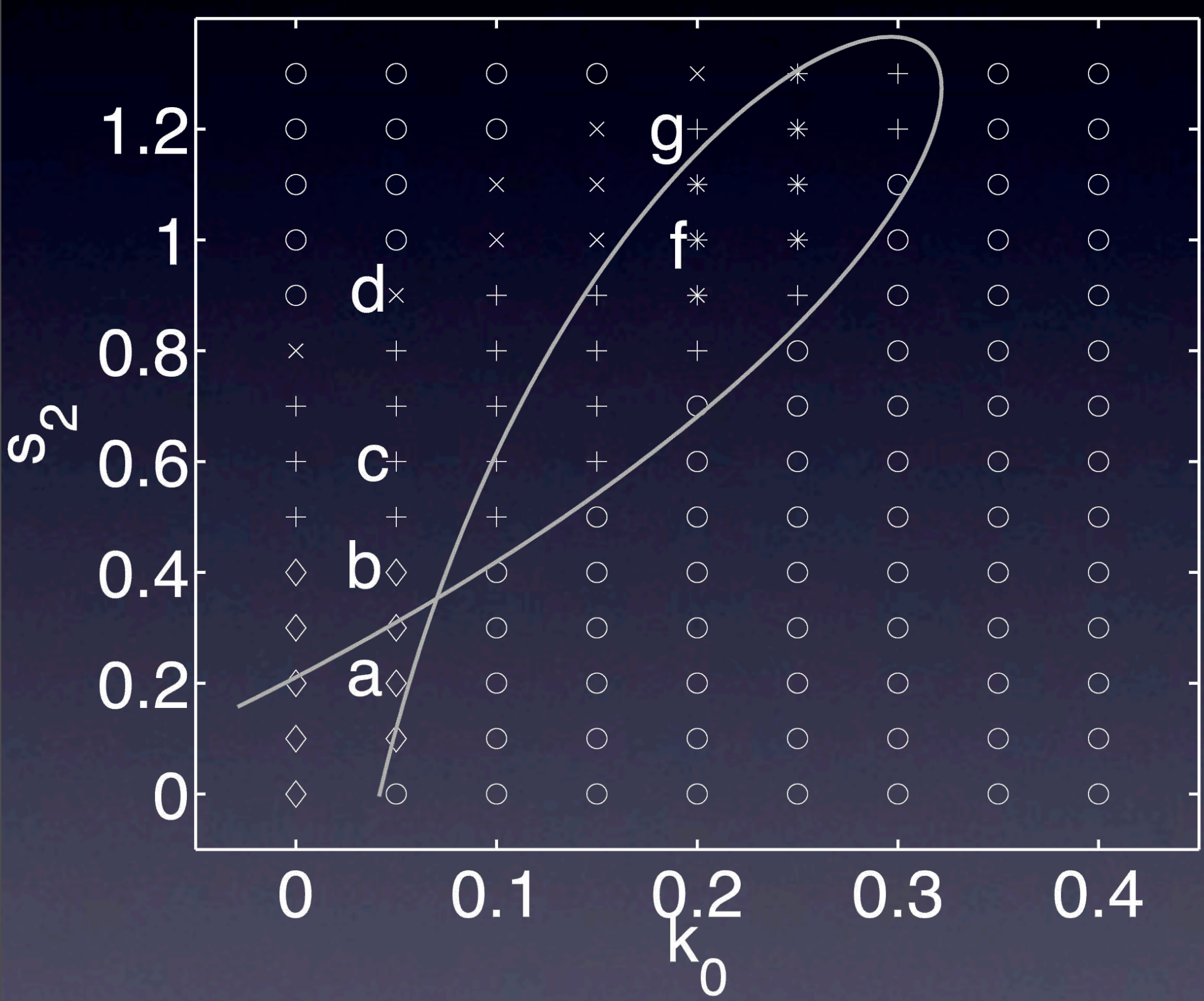
- Inside the fish tail, patterning arises from instability.
- Outside, from excitability.

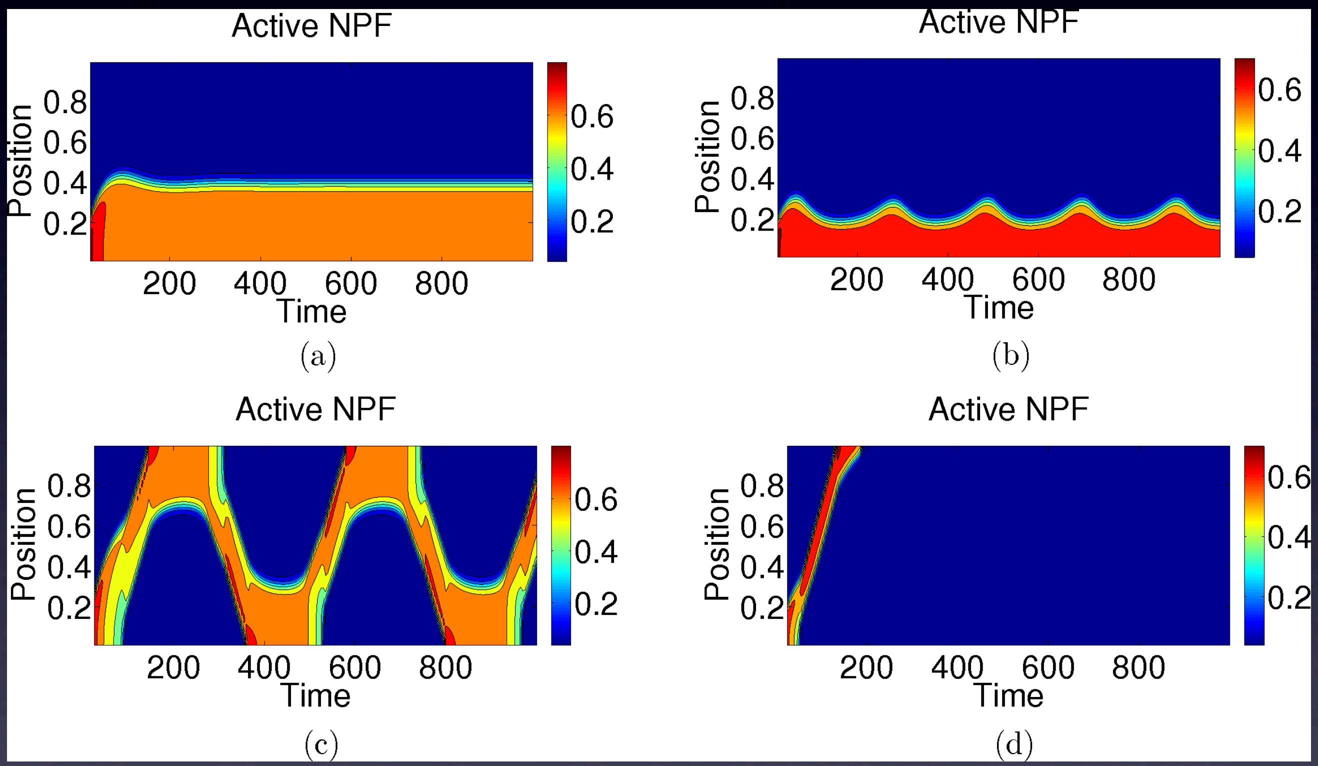
Patterning Region



- Feedback is necessary for patterning, but to much suppresses it.

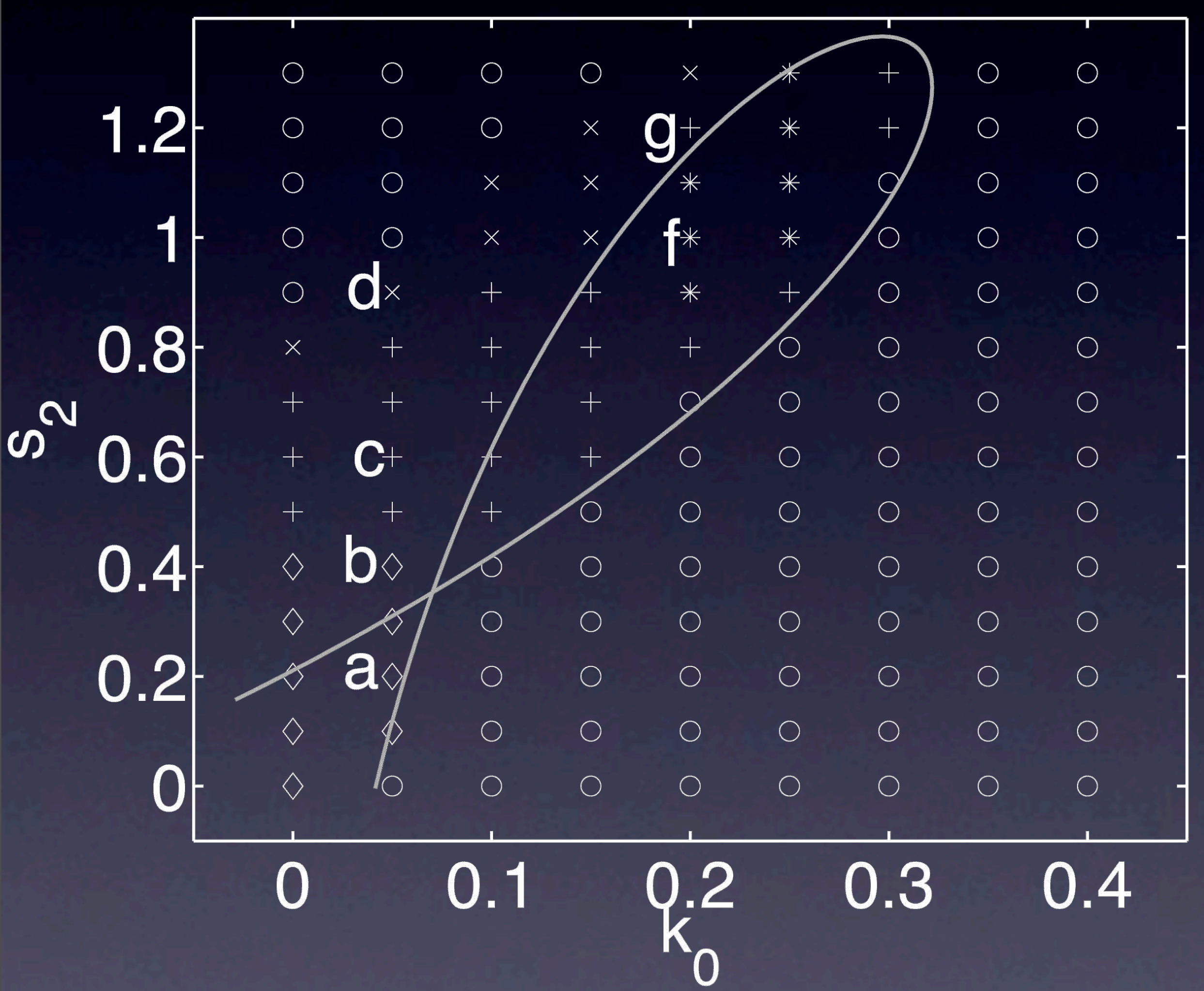
Static to Dynamic Transition

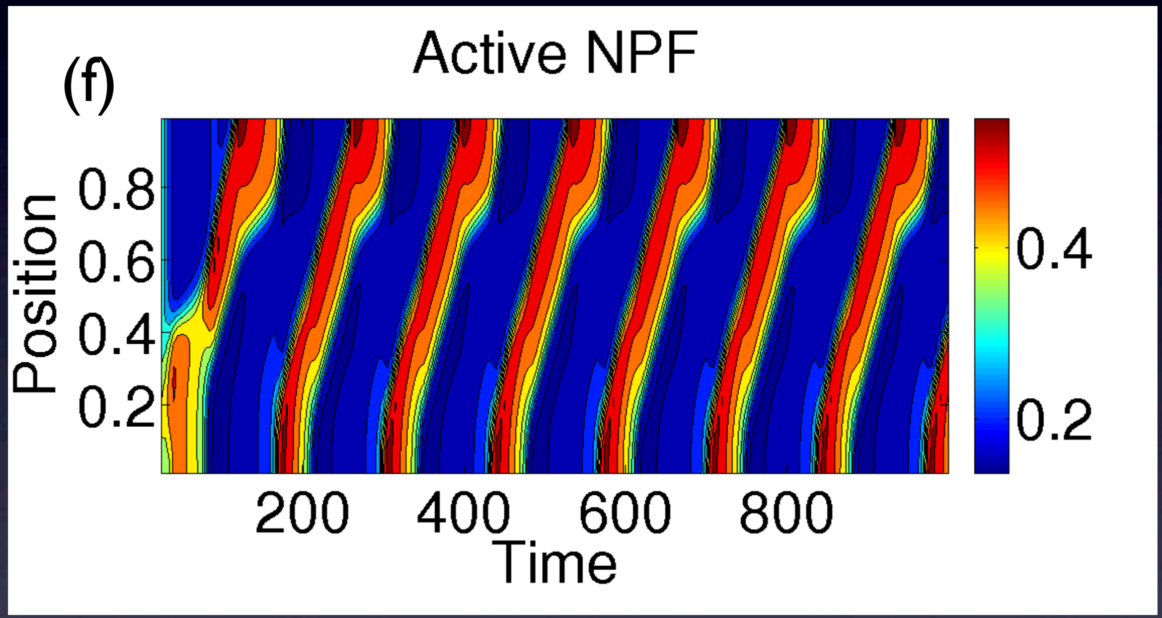




- Increasing feedback yields a progression from static, to dynamic, to no patterning.

Wave Trains





- Wave trains, indicative of target waves (in 2D), only occur inside the fish tail

Conclusions

- GTPase like kinetics coupled with F-actin feedback is capable of producing a wealth of static and dynamic behaviours.

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Conclusions

- The inclusion of a WP model (ie. conservation) as the ‘wave generator’ in the FitzHugh Nagumo framework yields substantially different behaviour.
  - Static to dynamic transition.
  - Reflecting waves vs wave trains.
  - Persistent patterning in excitable regimes.

Conclusions

- Increasing levels of feedback lead to a transition from static to dynamic behaviour and finally to the suppression of all patterning.