ANALYSIS OF BIOLOGICAL NETWORKS USING HYBRID SYSTEMS THEORY

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INTRODUCTION

- **Biochemical networks implement & control of cellular functions**
  - ◇ Metabolism
  - ◇ DNA synthesis, gene regulation
  - ◇ Movement & information processing
- **A major goal of molecular cell biologists & bioengineers:**
  - ◇ Understanding how networks are integrated & regulated
  - ◇ How network regulation can be influenced (e.g., for therapeutic purposes)
- **Qualitative & quantitative tools:**
  - ◇ Experimental techniques (e.g., measurements of gene expression patterns)
    - ⋆ Biochemical intuition alone insufficient due to sheer complexity
  - ◇ Mathematical and computational tools:
    - ⋆ Qualitative and quantitative insights
    - ⋆ Reduce trial-and-error experimentation
    - ⋆ Lead to testable predictions of certain hypotheses

MODELING OF BIOLOGICAL NETWORKS

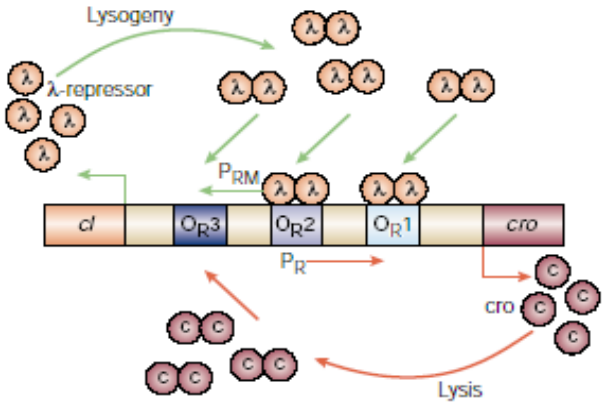
- **Biological networks are intrinsically dynamical systems:**
  - ◇ Drive adaptive responses of a cell in space & time
  - ◇ Behavior determined by "biochemical kinetics" or "rate equations"
    - ⋆ Variables: concentrations of network components (proteins, metabolites)
    - ⋆ Dynamics describe rates of production & decay of network components
- **Dynamic models of biological networks:**
  - ◇ Systems of continuous-time nonlinear ordinary differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, \cdots, x_n) \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \cdots, x_n) \end{aligned}$$

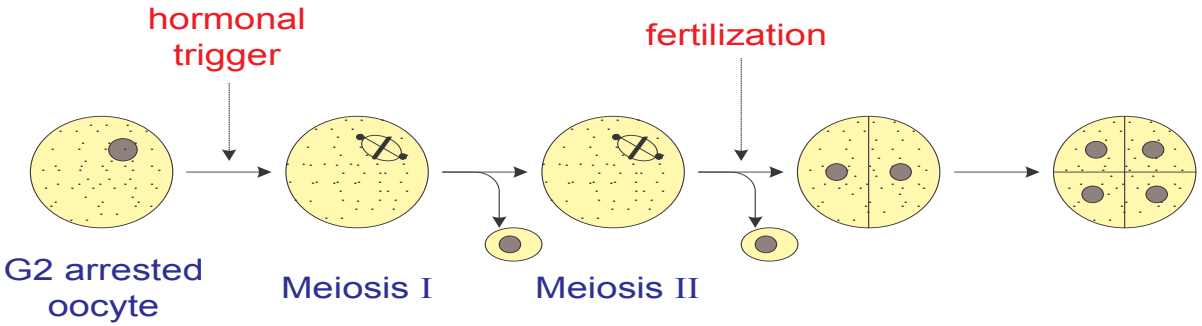
    - ⋆ Applying analytical techniques of nonlinear dynamics
    - ⋆ Combining mathematical analysis & computational simulation

COMBINED DISCRETE-CONTINUOUS DYNAMICS IN BIOLOGICAL NETWORKS

- **Discrete events superimposed on continuous dynamics:**
  - ◇ Switching between multiple qualitatively different modes of behavior
- **Examples of hybrid dynamics:**
  - ◇ At the molecular level:
    - ⋆ Inhibitor proteins turning off gene transcription by RNA polymerase
    - ⋆ e.g., genetic switch in λ-bacteriophage between lysis & lysogeny modes



  - ◇ At the cellular level:
    - ⋆ Cell growth and division in a eukaryotic cell: sequence of four processes, each continuous, triggered by certain conditions or events



COMBINED DISCRETE-CONTINUOUS DYNAMICS IN BIOLOGICAL NETWORKS

- **Examples of hybrid dynamics (cont'd):**
  - ◇ At the inter-cellular level:
    - ⋆ Cell differentiation viewed as a switched system
  - ◇ Switched dynamics can be the result of external intervention:
    - ⋆ Re-engineering the network by turning on/off certain pathways
- **Defining characteristic:**

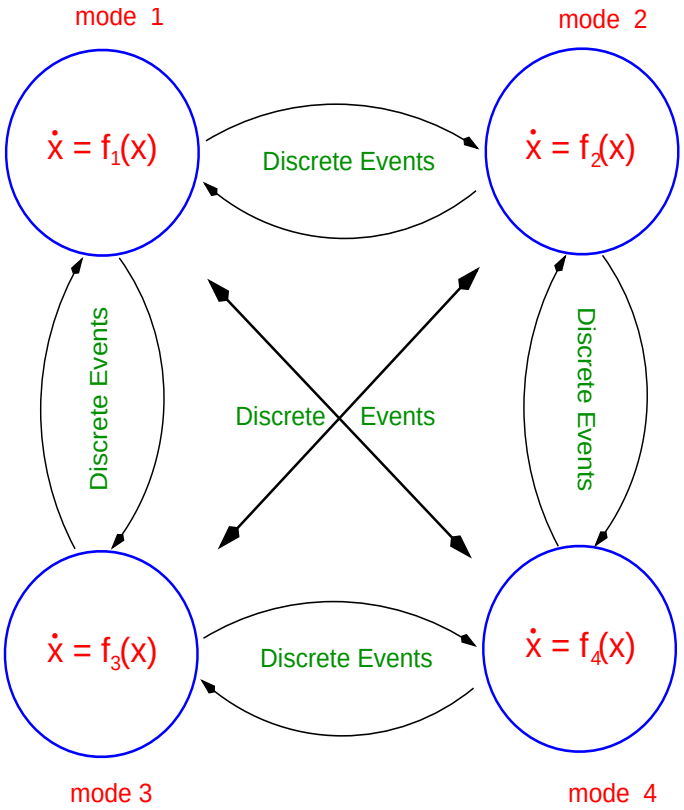
  Intervals of continuous dynamics interspersed by discrete transitions

- **A hybrid systems approach needed for:**
  - ◇ Modeling, simulation & analysis
  - ◇ Controlling/modifying the network behavior

A HYBRID SYSTEMS FRAMEWORK FOR ANALYSIS & CONTROL OF BIOLOGICAL NETWORKS

- **Mathematical models:**

$$\frac{dx(t)}{dt} = f_i(x(t), p)$$
$$i(t) \in \mathcal{I} = \{1, 2, \cdots, N < \infty\}$$



Multimodal representation

- $x(t) \in \mathbb{R}^n$: vector of continuous state variables
- $i(t) \in \mathcal{I}$: discrete variable "switching signal"
- N : total number of modes/subsystems
- p : model parameters "genetically controlled"
- $f_i(x)$: nonlinear rate expressions

⋆ Each mode governed by continuous dynamics

⋆ Transitions between modes governed by discrete events

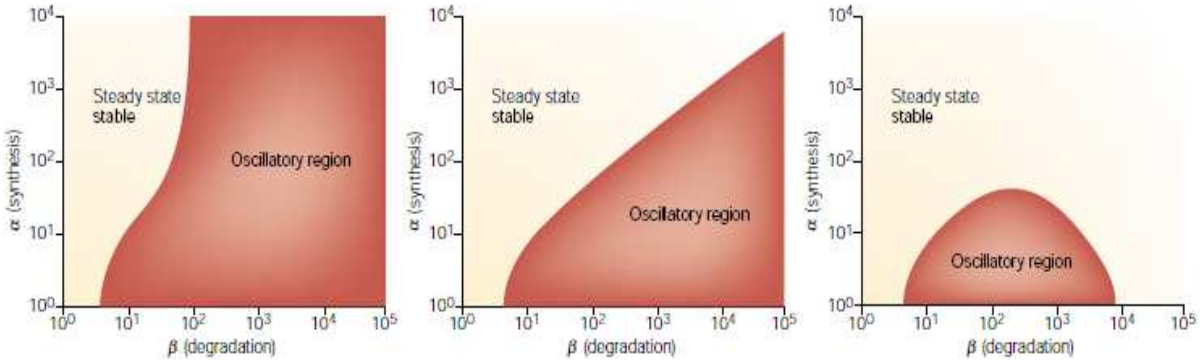
⋆ Switching classifications: autonomous vs. controlled

ANALYSIS OF MODE TRANSITIONS IN BIOLOGICAL NETWORKS

- **Changing network dynamics:**
  - ◇ Changes in model parameters
    - ⋆ Rate constants
    - ⋆ Total enzyme concentrations

Changing gene expression $\Longrightarrow$ changes in parameter values $\Longrightarrow$ mode switches

- **Bifurcation analysis:**
  - ◇ Dependence of attractors of a vector field on parameter values
    - ⋆ Single steady-state, multiple steady-states, limit cycles, etc.
  - ◇ Partitioning parameter space into regions where different behaviors observed



  - ◇ **Does not account for the dynamics of switching between modes**
    - ⋆ **Example: switching from an oscillatory to a multi-stable mode**

DYNAMICAL ANALYSIS & CONTROL OF MODE TRANSITIONS IN BIOLOGICAL NETWORKS

- **Objective:**

  Development of a hybrid dynamical systems approach:

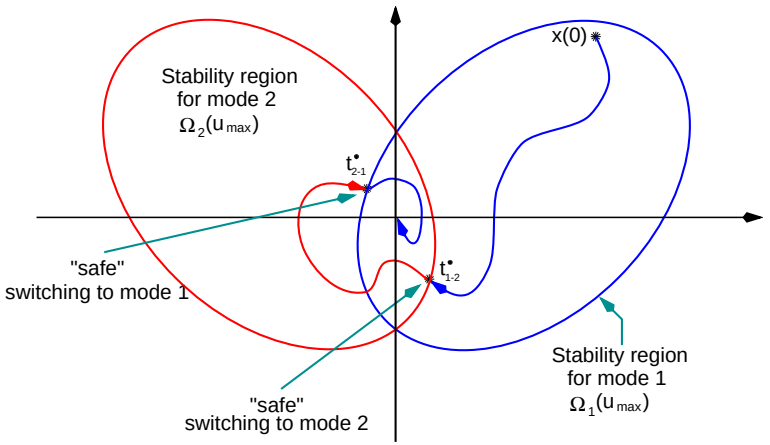
  - ◇ Account for the transients of mode switching
  - ◇ Determine when (where in state-space) mode transitions are feasible.
    - ⋆ Supplements bifurcation analysis

- **Control implications:**

  - ◇ Identify limitations on our ability to manipulate network behavior

- **Central idea:**

  - ◇ Orchestrating switching between stability regions of constituent modes



(El-Farra and Christofides, AIChE J., 2003)

MATHEMATICAL CONCEPTS AND TOOLS FROM NONLINEAR DYNAMICAL SYSTEMS

$$\frac{dx}{dt} = f(x), \quad f(0) = 0$$

- **Lyapunov functions:** main tool for studying stability of nonlinear systems
  - ◇ Positive-definiteness: $V(0) = 0$, $V(x) > 0$ for all $x \neq 0$
  - ◇ Negative-definite time-derivative: $\dot{V} = \dfrac{\partial V}{\partial x} f(x) < 0$ (asymptotic stability)
- **Domain of attraction of an equilibrium state:**
  - ◇ Set of points starting from where trajectories converge to equilibrium state
  - ◇ Estimates can be obtained using Lyapunov techniques

$$\Omega = \{x \in \mathbb{R}^n : \dot{V}(x) < 0 \ \& \ V(x) \leq c\}$$

  - ◇ Larger estimates obtained using a combination of several Lyapunov functions

METHODOLOGY FOR ANALYSIS & CONTROL OF MODE SWITCHINGS IN BIOLOGICAL NETWORKS

- Identification of the different modes of the network
  - ◇ A different set of differential equations for each mode
  - ◇ Same equations with different parameters
- Characterization of the steady-state behavior of each mode
- Characterization of the domains of attraction of the steady-states
  - ◇ Lyapunov techniques
  - ◇ Boundaries of stability regions represent switching surfaces
- Analysis of the overlap of the stability regions of the various modes
  - ◇ Monitoring the evolution of the state trajectory
  - ◇ A transition is feasible if state resides within stability region

AN EXAMPLE FROM CELL-CYCLE REGULATION

- **Simplified network model:** (Novak & Tyson, *J. Thoer. Biol.*, 1993)
  - ◇ Reactions based on cyclin-dependent kinases and their associated proteins

$$\begin{aligned}\frac{du}{dt} &= \frac{k_1'}{G} - \left(k_2' + k_2'' u^2 + k_{wee}\right) u + \left(k_{25}' + k_{25}'' u^2\right)\left(\frac{v}{G} - u\right) \\ \frac{dv}{dt} &= k_1' - (k_2' + k_2'' u^2) v\end{aligned}$$

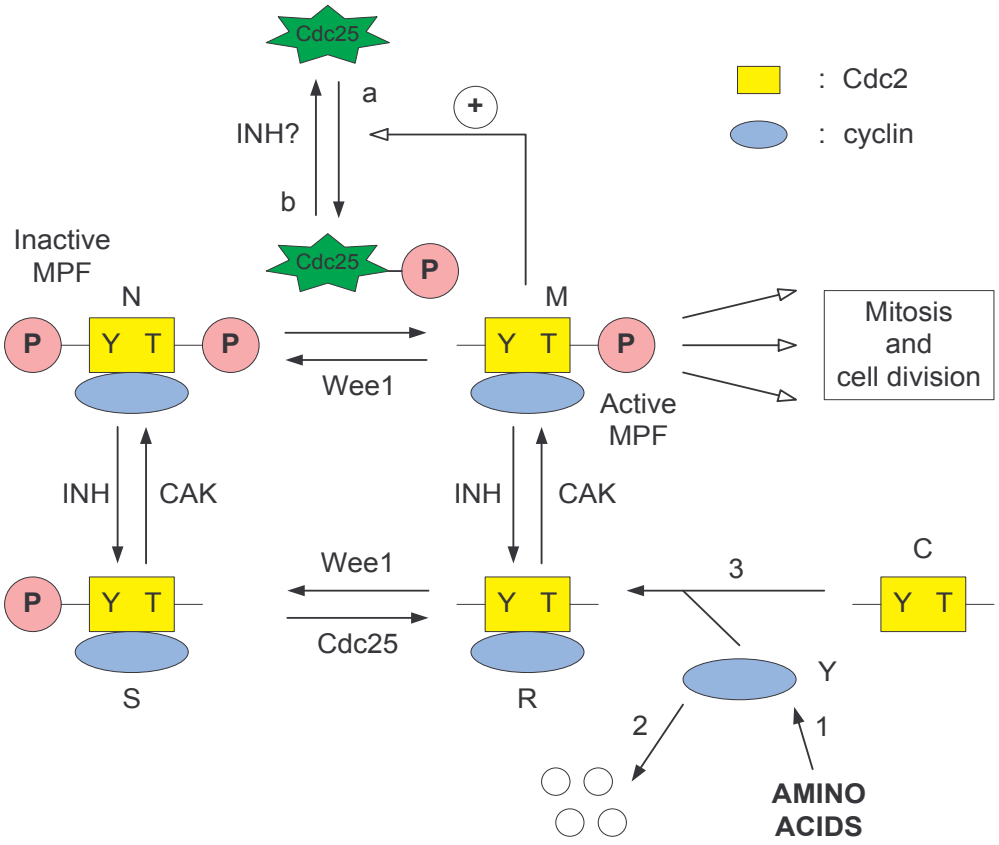
$$u = \frac{[active\ MPF]}{[total\ Cdc2]} = \frac{[M]}{[CT]}$$

$$v = \frac{[total\ cyclin]}{[total\ Cdc2]}$$

$$G = 1 + \frac{k_{INH}}{k_{CAK}},\ k_1' = \frac{k_1[AA]}{[CT]}$$

$$[CT] = [R] + [S] + [M] + [N] + [C]$$

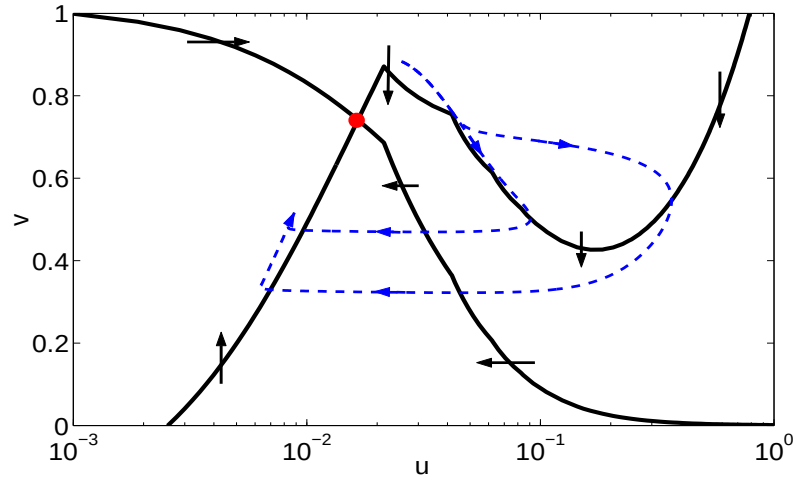
- ⋆ k_2', k_2'' - rate constants for low & high-activity form of cyclin degradation
- ⋆ k_{wee} - rate constant for inhibition of $Wee1$



BIFURCATION & PHASE-PLANE ANALYSIS

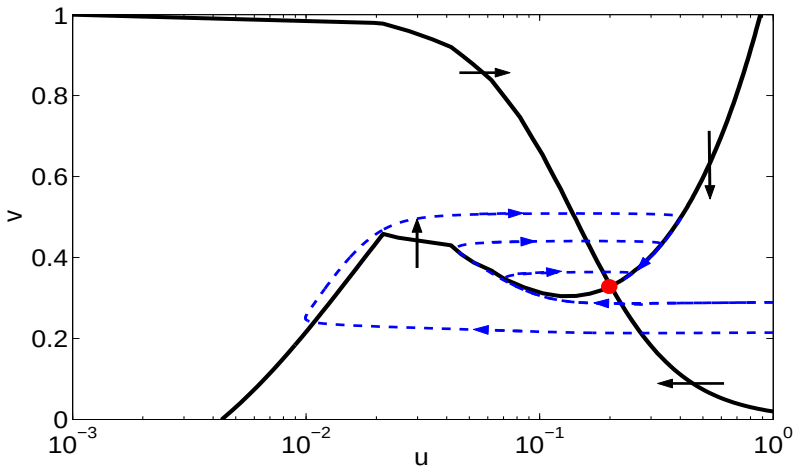
- **G2-arrested mode**

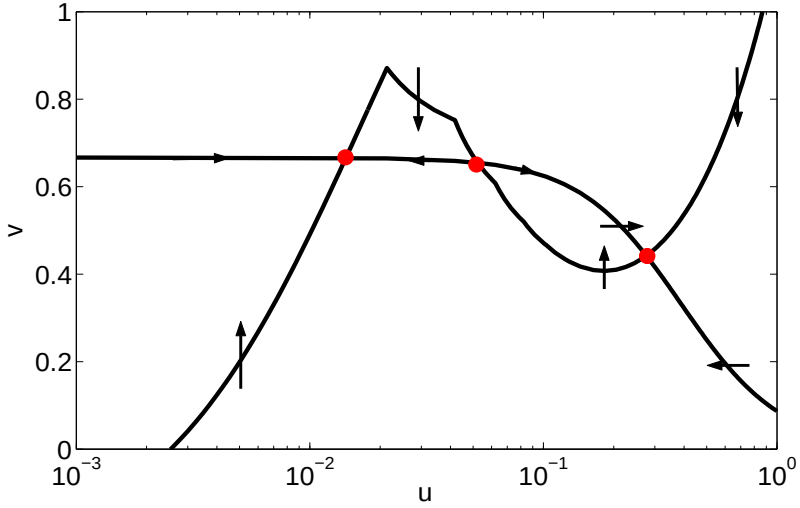
$(k_2' = 0.01,\ k_2'' = 10, k_{wee} = 3.5)$



- **M-arrested mode**

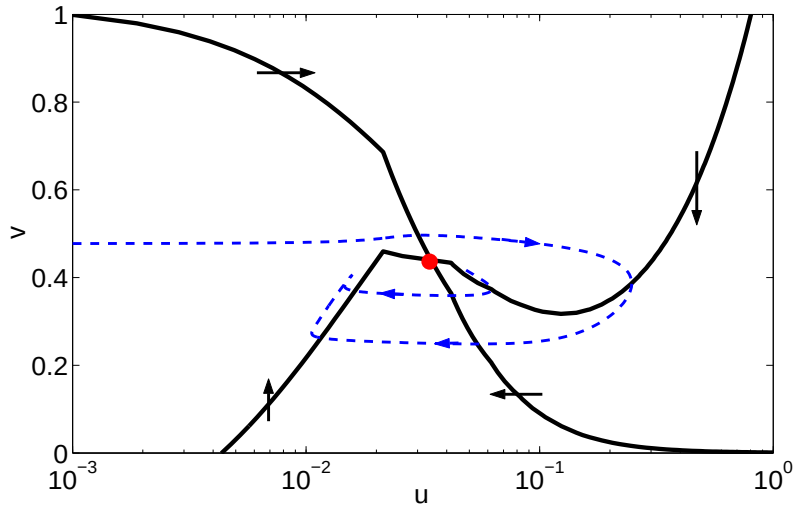
$(k_2' = 0.01,\ k_2'' = 0.5,\ k_{wee} = 2.0)$





- **Multiple steady-states**

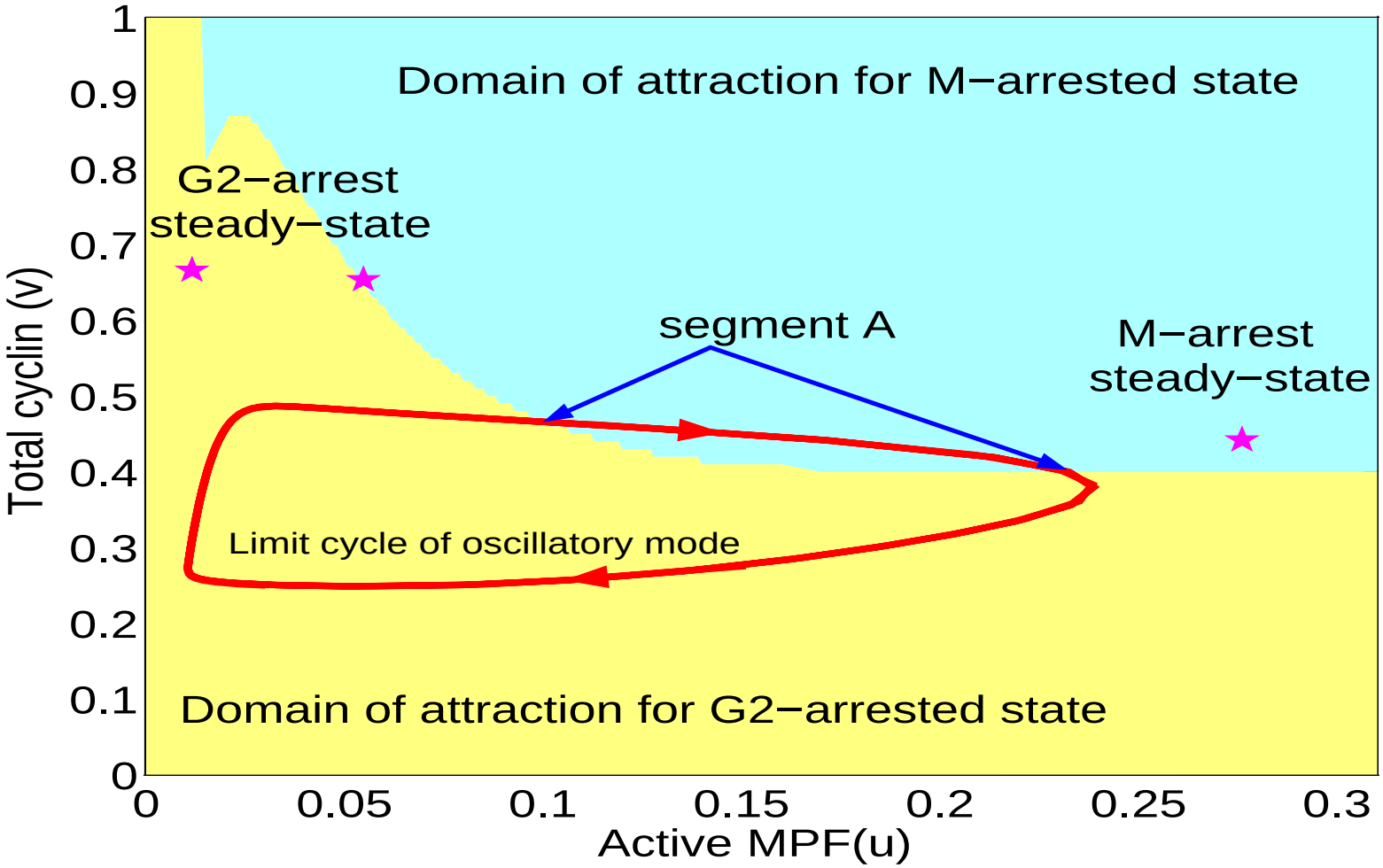
$(k_2' = 0.015,\ k_2'' = 0.1,\ k_{wee} = 3.5)$



- **Oscillatory mode**

$(k_2' = 0.01,\ k_2'' = 10,\ k_{wee} = 2.0)$

SWITCHING BETWEEN OSCILLATORY AND BI-STABLE MODES



- Construction of domains of attraction for G2- & M-arrested states:
  - ◇ Lyapunov function: $V = (u - u_s)^4 + 10(v - v_s)^2$
  - ◇ Limit cycle overlaps with both stability regions

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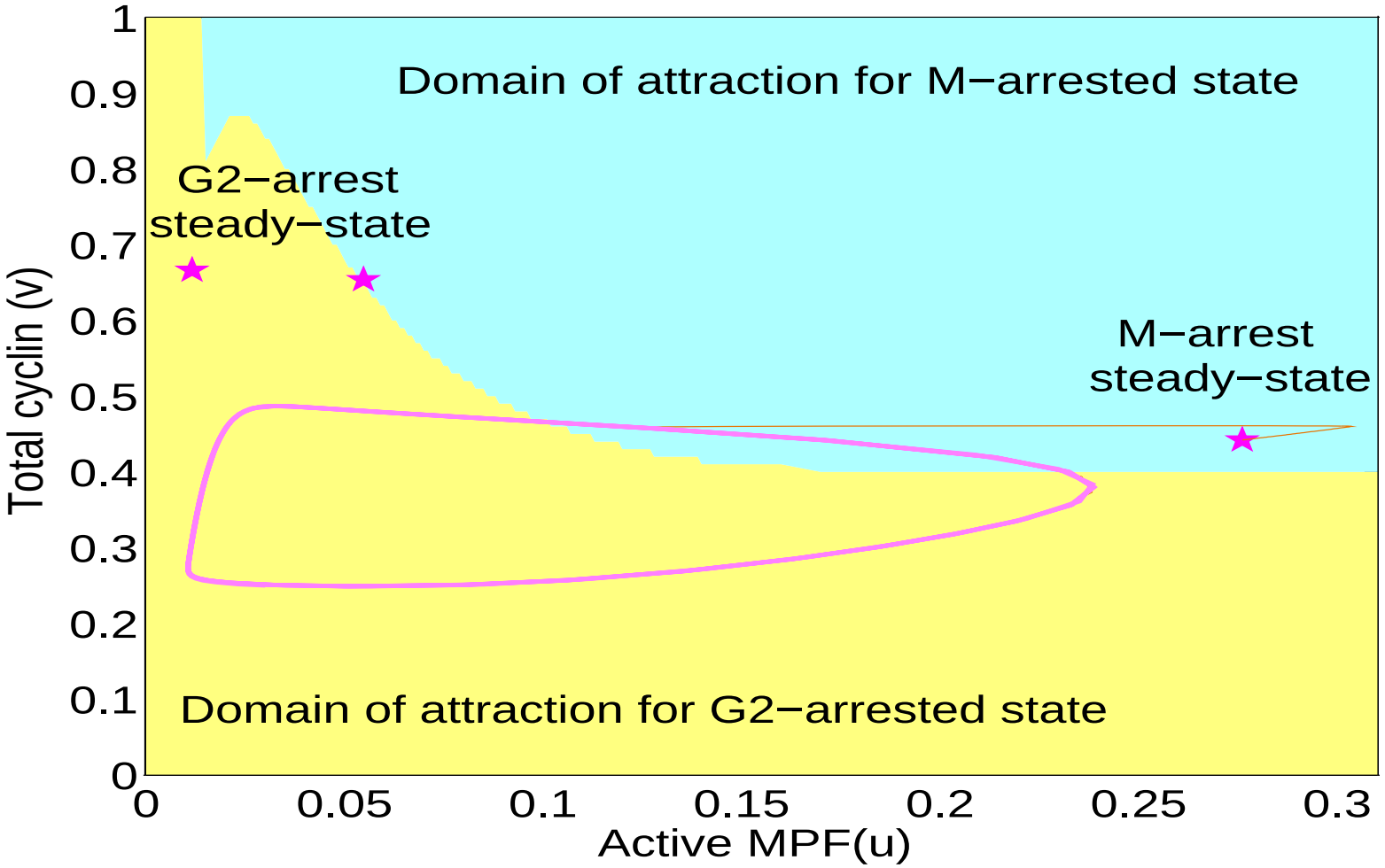

- Transition from oscillatory to bi-stable mode:
  - ◇ On segment A: $\Longrightarrow$ M-arrested state
  - ◇ At all other points: $\Longrightarrow$ G2-arrested state

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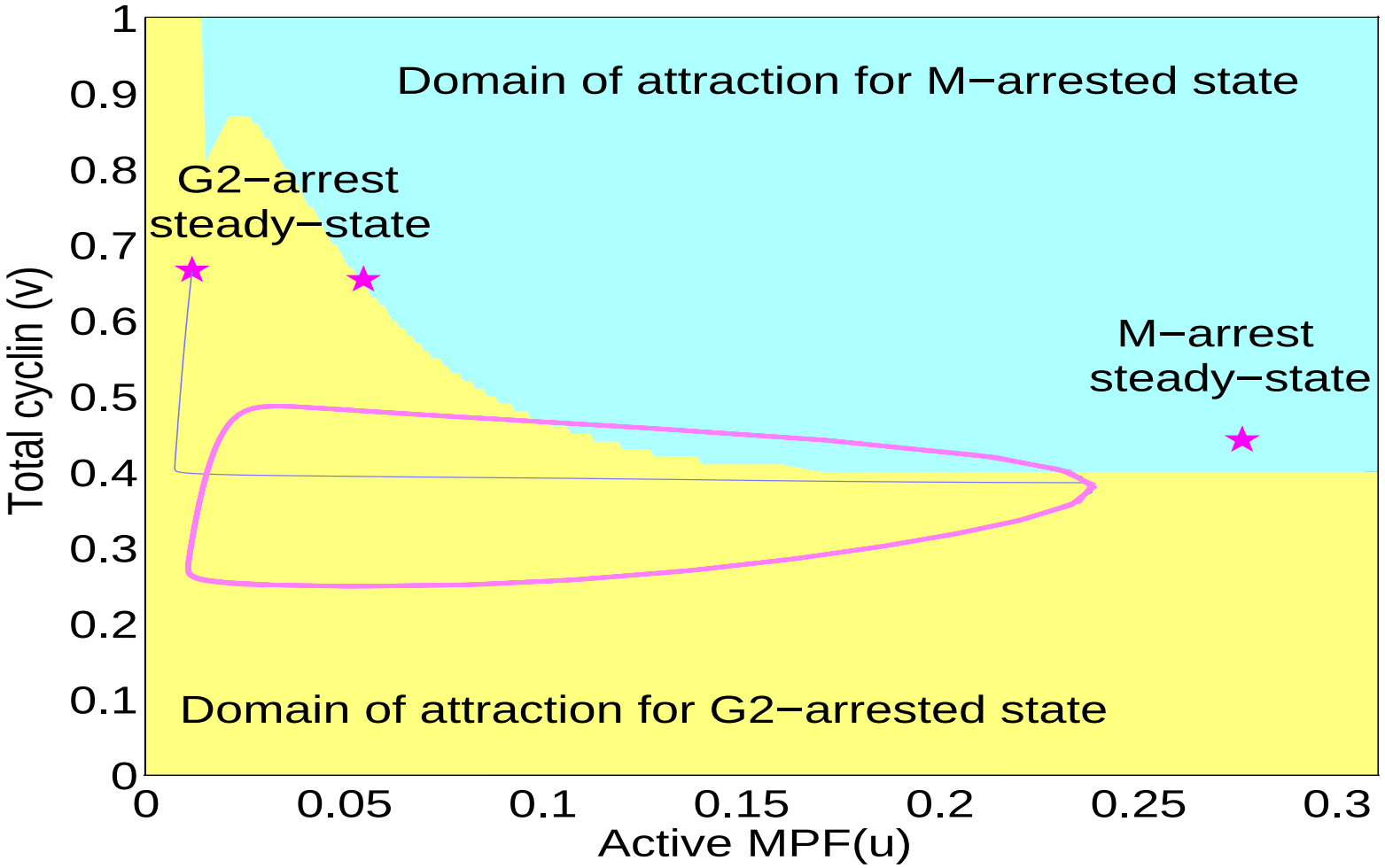

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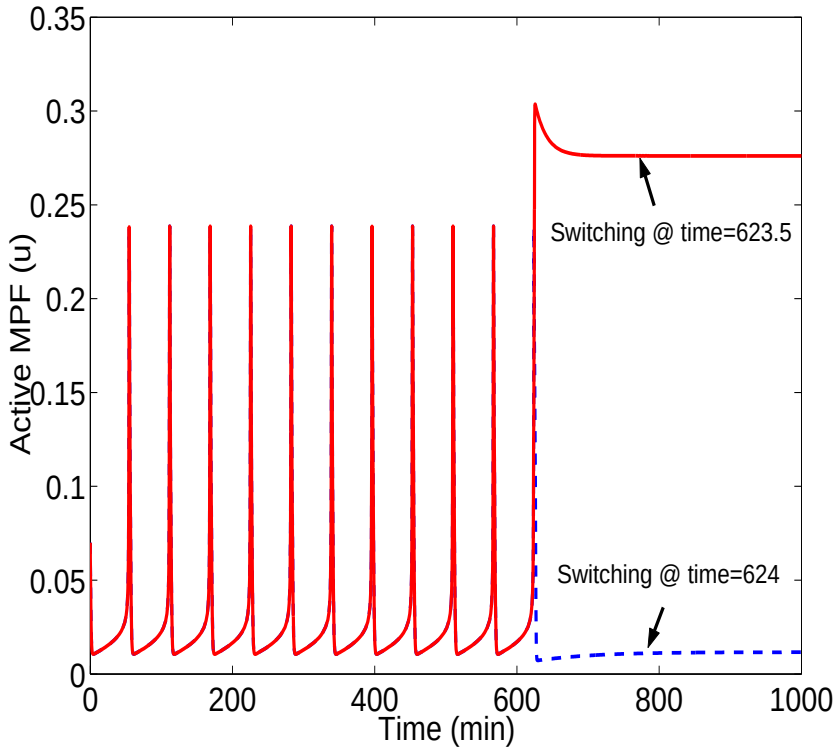
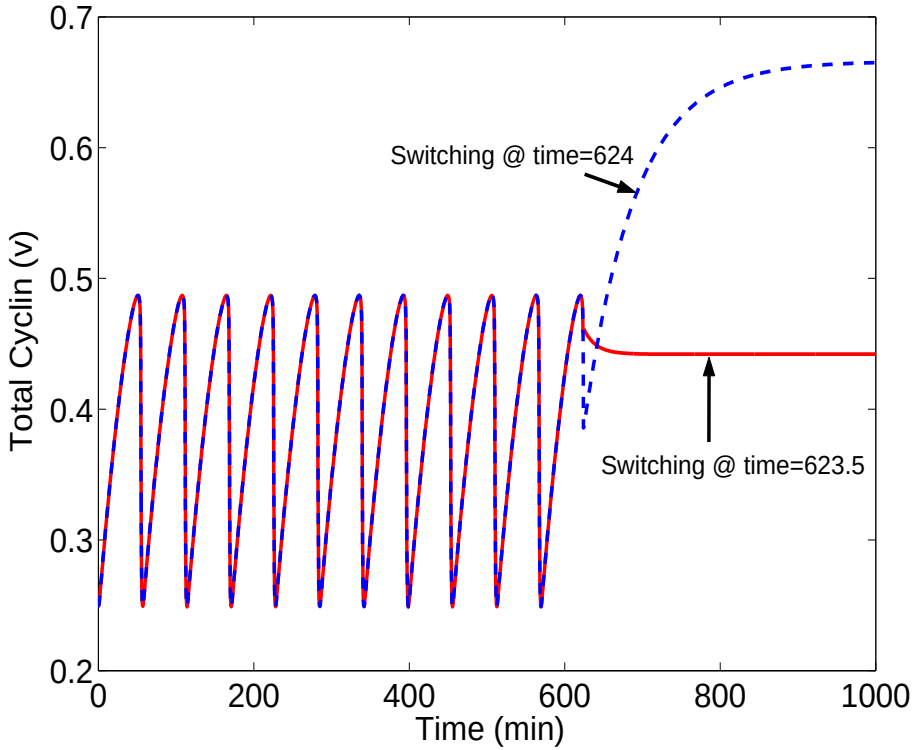
SWITCHING BETWEEN OSCILLATORY AND BI-STABLE MODES

- Temporal evolution of active MPF (u) and total cyclin (v) upon switching from oscillatory mode to bi-stable mode at different times





CONCLUSIONS

- Hybrid (combined discrete/continuous) dynamics in biological networks:
  - ◇ Naturally-occurring switches
  - ◇ Manipulation of network behavior (adding/deleting pathways)
- Hybrid systems framework for analysis & control of biological networks:
  - ◇ Modeling approach:
    - ⋆ Finite family of continuous nonlinear dynamical subsystems
    - ⋆ Discrete events trigger transitions
  - ◇ Analysis approach:
    - ⋆ Characterizing stability regions of constituent modes (Lyapunov tools)
    - ⋆ Accounting for the dynamics of mode transitions
  - ◇ "Control" implications:
    - ⋆ Provides predictions regarding feasibility of enforcing mode transitions

ACKNOWLEDGMENT

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