Extensions of Switching Models for Gene Regulatory Networks

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Objective: to improve models for genetic systems. We use ODE models to describe concentrations of chemical species. Conventional models neglect actions of some species. We introduce additional equations to describe those actions.
Results: we present results proving that our modifications maintain certain properties necessary for these models' usefulness and proving that our modifications exhibit behavior not displayed by conventional models.

Gene Regulatory Networks
Qualitative descriptions of how concentrations of proteins affect one another.
1. Purpose of the model: to use mathematical techniques to predict long-term behavior of concentrations of proteins.
2. Questions of interest:
   a) How do concentrations behave in the long run?
   b) What are the steady states of the system?
   c) Does the final state depend on initial data? What are the consequences for the behavior of a population of cells?
   d) How do the steady states depend on environmental conditions (that is, on values of the parameters)?
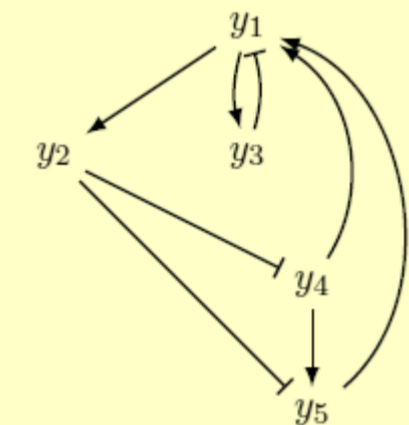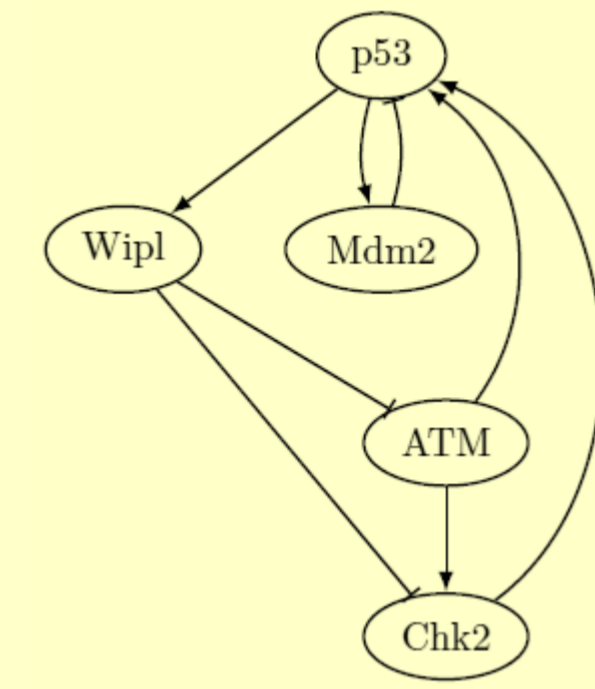
Switching System
A dynamical system consisting of N ordinary differential equations (ODEs), each describing the rate of change of a chemical species. Switching system models can address our questions for networks with 7 to 10 vertices. A switching system can describe behavior of proteins or mRNA but not both, motivating our extensions. Each ODE in the system has several key pieces:
1. The *step function* σ_i
2. The *logic function* M_i
3. The composite *switching function* Λ_i

$$\dot{y}_i = -\gamma_i + \Lambda_i(w), \quad i = 1, 2, \ldots, N$$

$$\Lambda_i = M_i \circ \sigma_i$$

$$\sigma_{i,s} = \begin{cases} l_{i,s} & \text{if } y_s < \theta_{i,s} \\ u_{i,s} & \text{if } y_s > \theta_{i,s} \end{cases} \text{ or } \sigma_{i,s} = \begin{cases} u_{i,s} & \text{if } y_s < \theta_{i,s} \\ l_{i,s} & \text{if } y_s > \theta_{i,s} \end{cases}$$

Extensions
We extend the regulatory network model to describe both mRNA and protein concentrations. We introduce a set of intermediaries between every pair of vertices that share an edge in the original graph. An extension is in some ways more biologically accurate than a typical regulatory network, and it often captures more dynamical behavior.
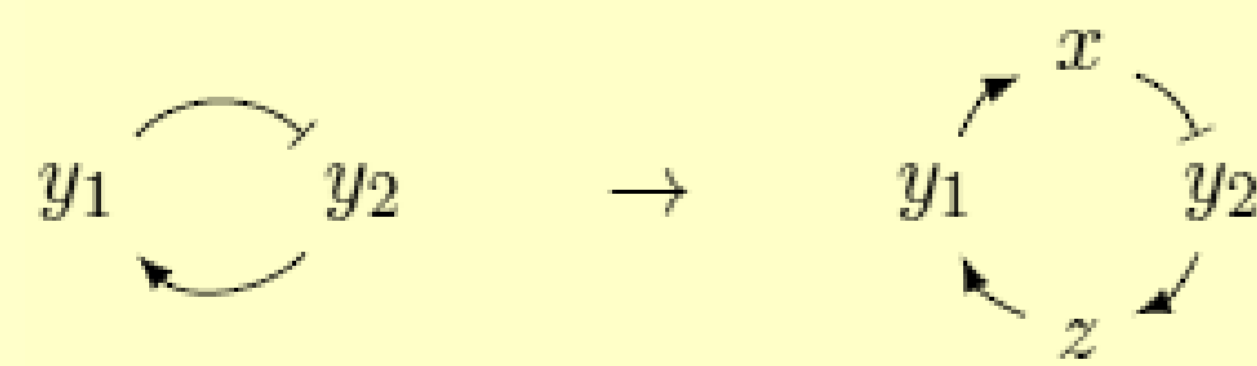
Extended System
We modify the switching system to describe the concentrations of species in an extension. We call this dynamical system an *extended system*. Note the original vertices are governed by similar equations to those in the switching system, albeit with modified step functions (and thus modified switching functions). The intermediaries are governed by linear ODEs.

$$\dot{y}_i = -\gamma_i y_i + \hat{\Lambda}_i(w), \quad i = 1, 2, \ldots, N$$
$$\dot{x}^1 = -a^1 x^1 + b^1 y_i$$
$$\dot{x}^k = -a^k x^k + b^k x^{k-1}, \quad k = 2, 3, \ldots, n$$

$$\hat{\Lambda}_i = M_i \circ \hat{\sigma}_i$$

$$\hat{\sigma}_{i,s} = \begin{cases} l_{i,s} & \text{if } x^n < \phi^n \\ u_{i,s} & \text{if } x^n > \phi^n \end{cases} \text{ or } \hat{\sigma}_{i,s} = \begin{cases} u_{i,s} & \text{if } x^n < \phi^n \\ l_{i,s} & \text{if } x^n > \phi^n \end{cases}$$
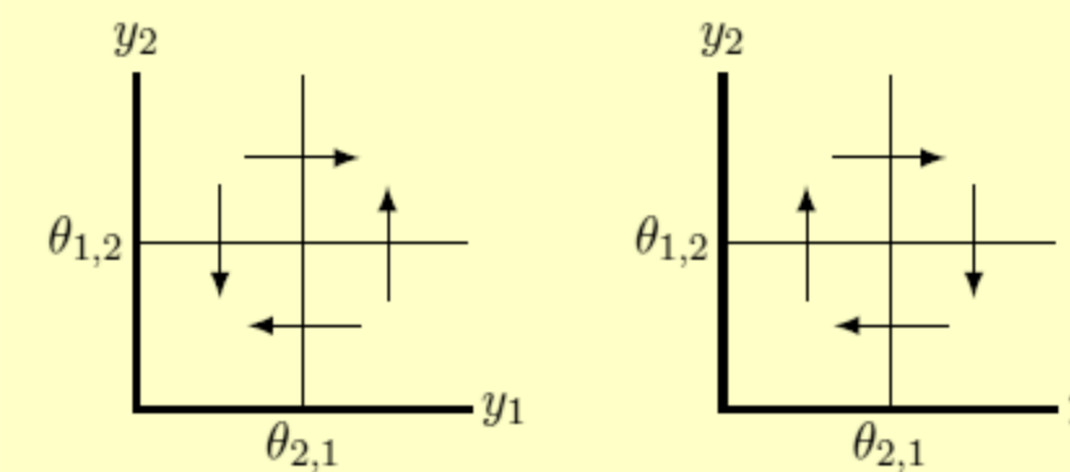
Phase Space
The phase space of the switching and extended systems. Each point in the space represents a state of the system, meaning a particular set of concentrations for each species. Each point also has an associated direction, which indicates the state to which the system tends from that initial point. Note that the thresholds associated to each vertex partition the phase space into a finite number of domains called *cells*. The cells each have a set of *faces* formed by the bounding portions of the hyperplanes on which a particular vertex is constantly equal to one of its thresholds. To the left is a projection of the phase space of the example network at left.
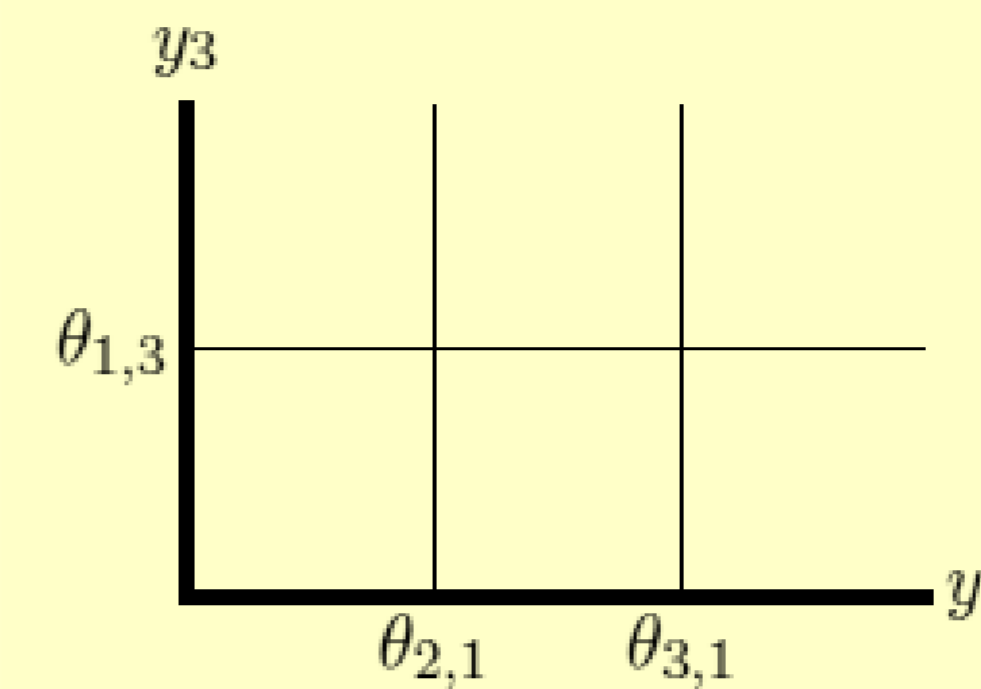
Methods: Using extensions of gene regulatory networks, mRNA-protein networks can be modeled using the same techniques as protein and mRNA networks, which allow fast computation and characterization of the systems' dynamics using Morse graphs over a parameter graph.

State Transitions
Given a particular parameter choice, the flow between states in the phase space implies flow between neighboring cells, which in most cases is monodirectional across each face. To the left are two two-dimensional examples. Note that even within the same system, the direction of flow between cells can change depending on parameter choice.

Domain Graph
We define a new directed graph on a set of vertices in bijection with the domains in the phase space. The edges preserve the direction of flow between the cells corresponding to the vertices at the endpoints, or take a vertex to itself if all neighbors of the corresponding cell flow into that cell. Note that unlike the gene regulatory network there is only one edge labeling in the domain graph. To the right are domain graphs for the two examples above.
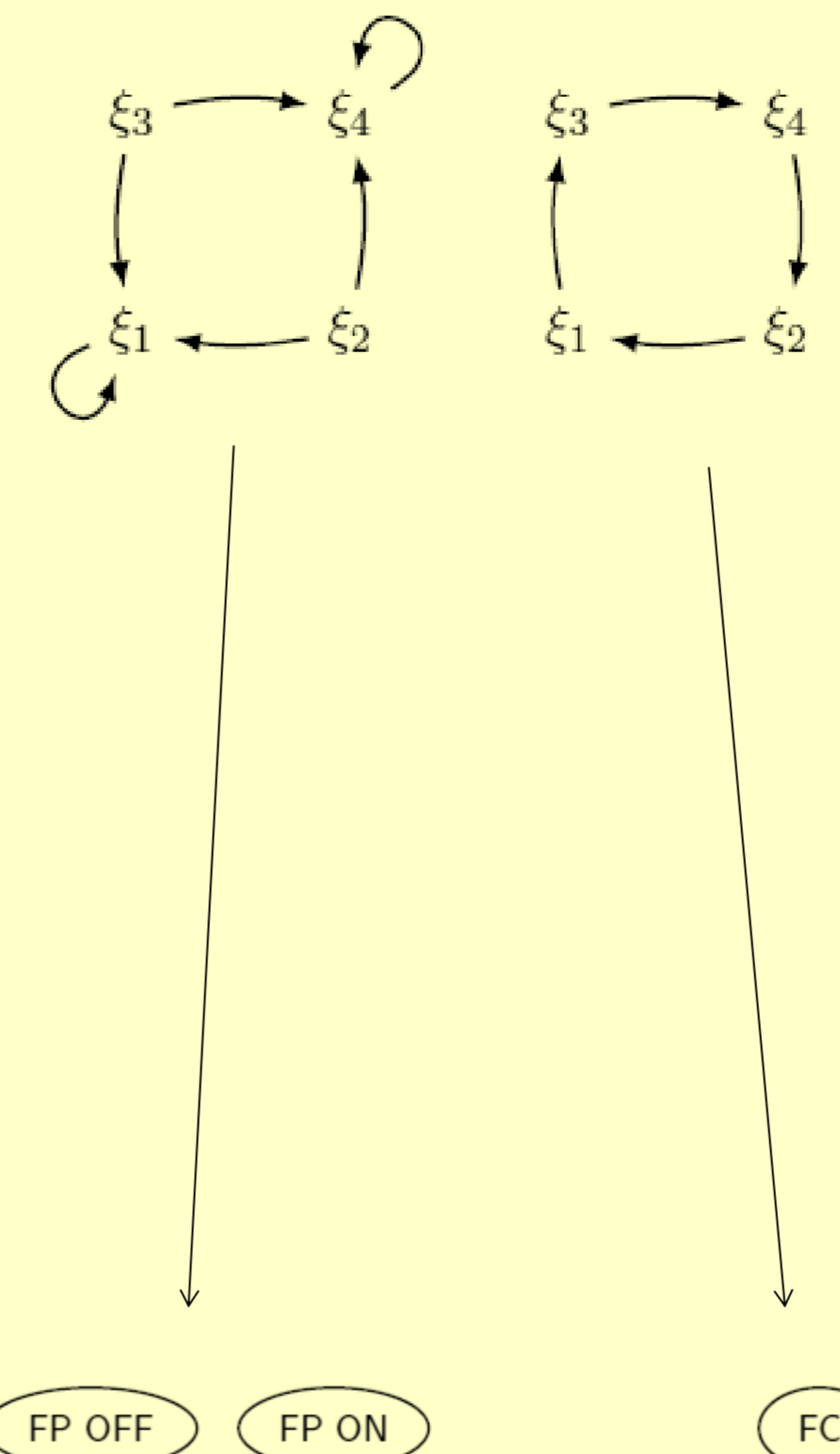
Morse Graph
Maintaining a parameter choice and the associated domain graph, we define a third directed graph. The vertices are in bijection with the set of *recurrent components* of the domain graph. A set C of vertices is recurrent if for each $u, v \in C$, there exists a path from u to v in C. An edge is inserted between two vertices if there exists a path in the domain graph between the corresponding recurrent components. The node labelings indicate the type of recurrent component. A Morse graph is a course description of the dynamical behavior of the switching system at the corresponding parameter.

Parameters
A *parameter* for the switching system associated to a particular gene regulatory network is a tuple (l, u, θ, γ) of sets of values associated to each vertex and each edge. It consists of a choice of numerical values for each of the following:
1. for each y_i in the gene regulatory network, the associated γ_i.
2. for each edge (y_s, y_t) in the gene regulatory network, the associated $l_{t,s}$, $u_{t,s}$, and $\theta_{t,s}$.
A parameter for an extended system consists of the same four sets as a parameter for the regulatory network, plus:
1. for each x^k ($k = 1,2,3,\ldots,n$), the associated a^k and b^k.

$$(l, u, \theta, \gamma)$$

$$(l, u, \theta, \gamma, a, b)$$

Parameter Graph
The parameter graph is an undirected graph, and it is the same for a regulatory network and any of its extensions. Each vertex represents a set of parameters for the switching system that give rise to the same domain graph. An edge exists between two vertices if the two corresponding sets of parameters differ by the order between two consecutive threshold values or the order between $\gamma_i \theta_{j,i}$ and Λ_i for some y_i and y_j. To the right is an example regulatory network (called the repressilator) and the associated parameter graph. The vertices are shaded according to the Morse graphs they generate. Each Morse graph consists of a single node:
1. No shading: FP
2. Light shading: FP ON
3. Medium shading: FC
4. Dark shading: FP OFF
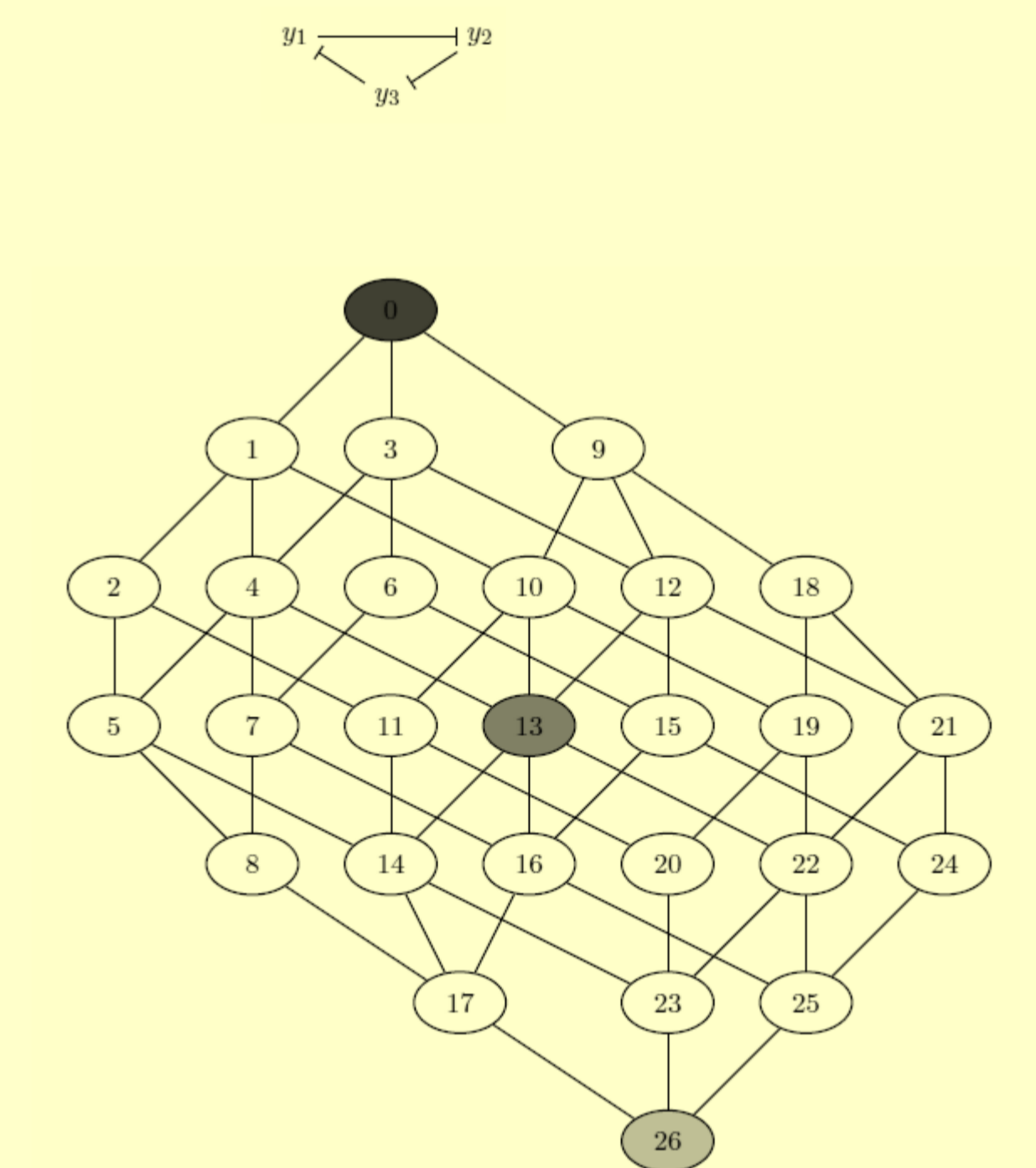
Non-isomorphic Morse Graphs
To the left are the domain and Morse graphs of an extension of a simple regulatory network at a particular parameter node. Although not shown, the Morse graph of the original regulatory network at the same parameter node consists of a single node labeled FC, meaning this extension exhibits additional dynamical behavior. There exist other examples of extensions whose Morse graphs are not only non-isomorphic to but are not even refinements of those of the original network.
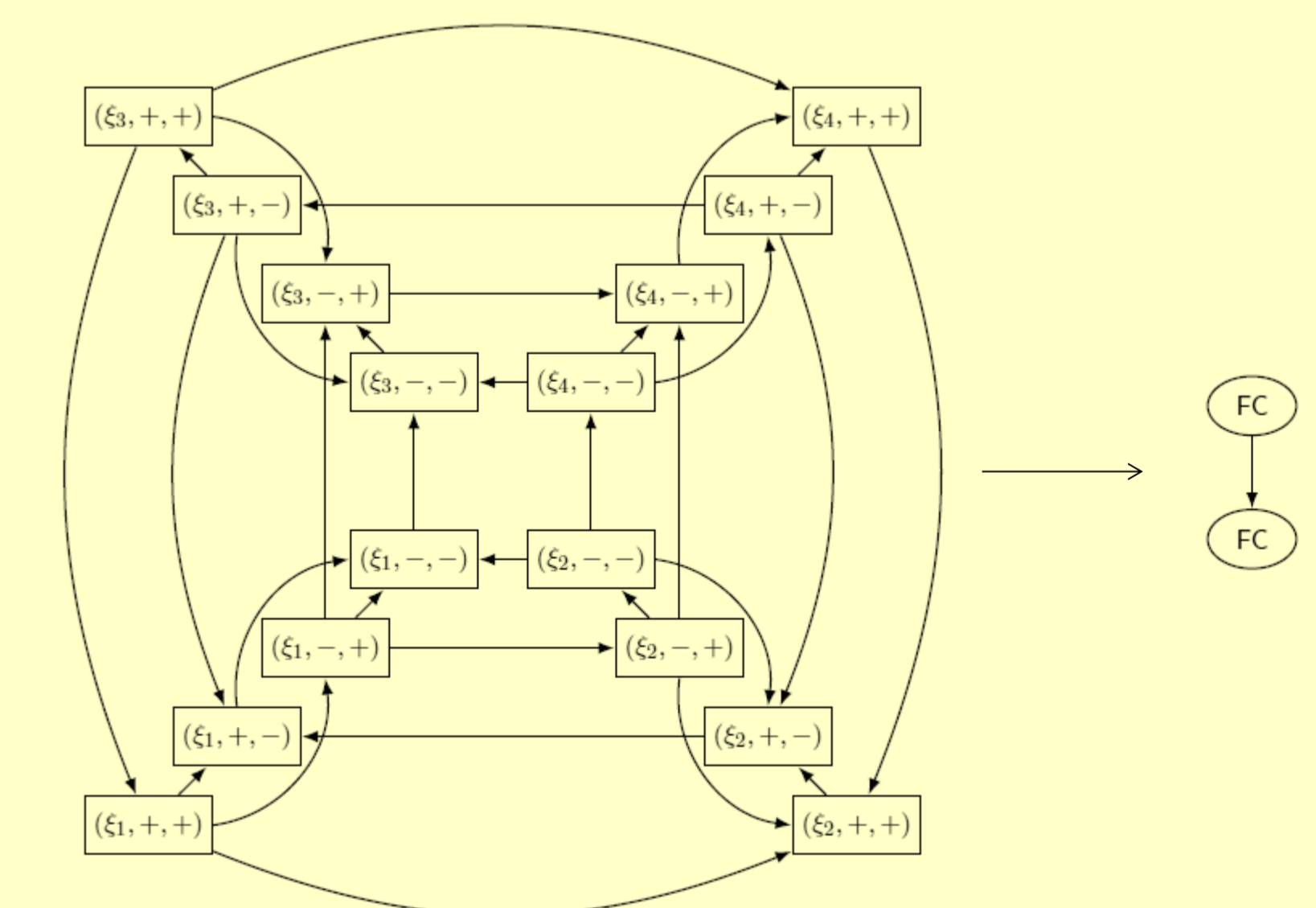
Applications
We intend to apply our work on extensions first to a test-bed network known as IRMA. This system was synthetically constructed in a species of yeast. We hope to establish that our modeling approach is viable for study of such networks in general. We will next apply our work to several networks relevant to cancer research.

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